17th International Myeloma Workshop

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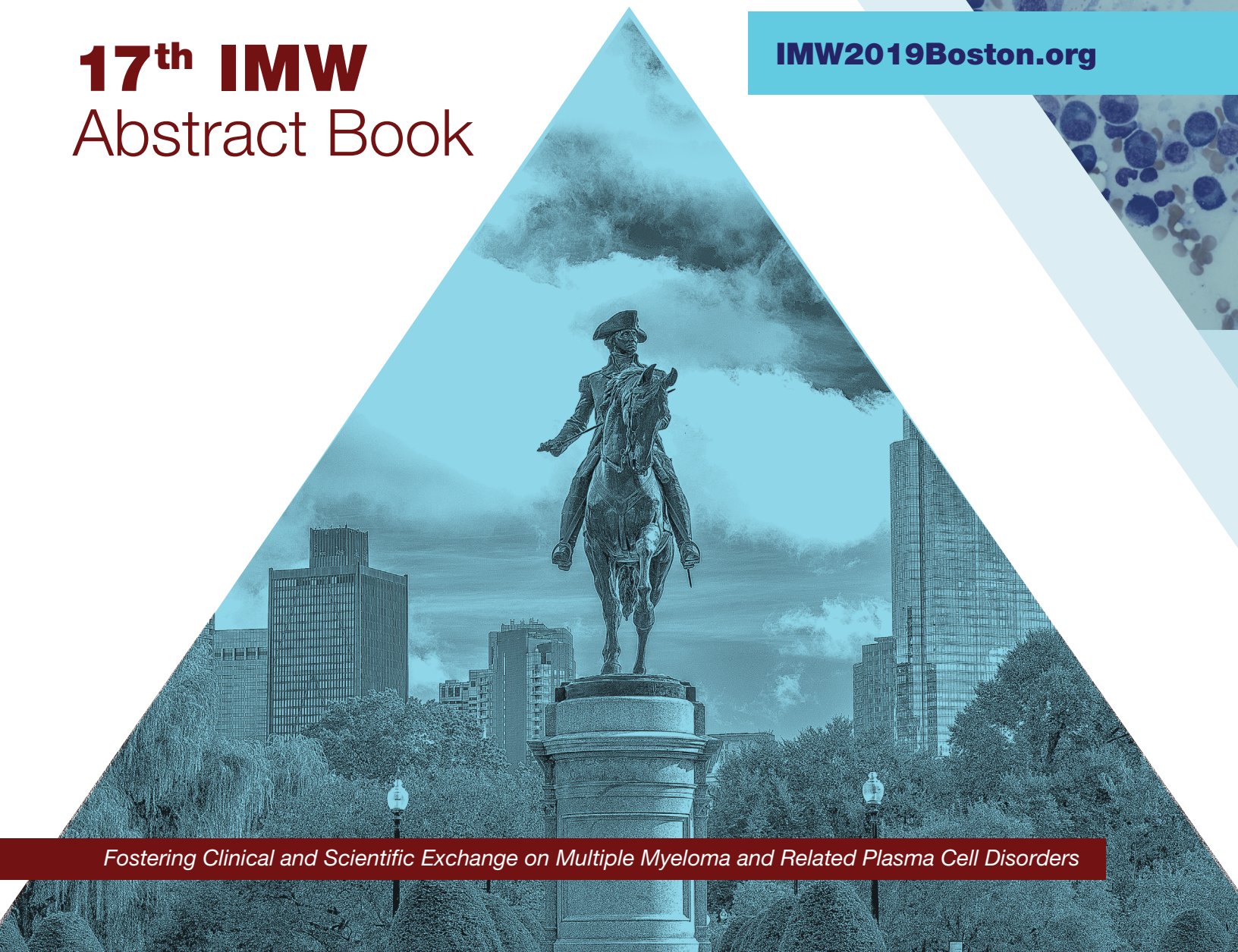

Fostering Clinical and Scientific Exchange on Multiple Myeloma and Related Plasma Cell Disorders

17th International Myeloma Workshop
Boston, MA, USA
September 12-15, 2019

About the 17th IMW

The 17th International Myeloma Workshop, under the auspices of the International Myeloma Society (IMS), is devoted to fostering scientific and clinical exchange on the latest breakthroughs in multiple myeloma and related plasma cell disorders. Scientific programming at the 17th IMW will cover the latest genomic advances, insights into immune and microenvironmental dysregulation, new drug targets and agents, immunotherapeutic approaches including Car T-cell therapies, and breaking results from early and large randomized clinical trials.

This book compiles the abstracts from oral and poster session presentations at the 17th IMW held at the Hynes Convention Center in Boston, Massachusetts from September 12-15, 2019. The abstracts are reproduced as submitted by the author and accepted by the Scientific Program Committee. They appear in order of abstract code and track. The presenting author of each abstract is underlined.

About the International Myeloma Society

The International Myeloma Society (IMS) is a professional, scientific, and medical society established to bring together clinical and experimental scientists involved in the study of myeloma.

The purpose of this society is to promote research, education, clinical studies (including diagnosis and treatment), workshops, conferences, and symposia on all aspects of multiple myeloma worldwide.

The IMS is a membership organization comprised of basic research scientists, and clinical investigators in the field along with physicians and other healthcare practitioners.

IMS is governed by a Board of Directors representing practices from around the world, and encourages and promotes the study of this expanding field through its biannual International Myeloma Workshop.

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ORAL PRESENTATIONS

OAB-001

Integrated Analysis of Bortezomib-Lenalidomide-Dexamethasone vs Bortezomib-Thalidomide-Dexamethasone in Transplant-Eligible Newly Diagnosed Myeloma

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Abstract:
BACKGROUND Although treatment (Tx) guidelines recommend VRD and VTD for TE NDMM, no randomized controlled trials (RCTs) have directly compared these regimens. Thus, an integrated analysis was conducted. METHODS Prospective phase 3 RCTs evaluating VRD or VTD induction (every 3 or 4 wks) in TE NDMM before ASCT meeting predefined eligibility criteria (including access to pt-level data) were included. Non-inferiority of ≥ VGPR rate after induction was the primary endpoint. Statistical methods were based on propensity score (PS). RESULTS Four studies met eligibility criteria-VRD: PETHEMA GEM (GEM) 2012 and IFM 2009; VTD: GEM2005 and IFM 2013-04. GEM studies, used for the primary analysis, had a symmetrical induction design (six 4-wk cycles, then ASCT). IFM studies were considered supportive due to pre-ASCT cycle number variability (3 VRD vs 8 VRD in IFM 2009 and 4 VTD in IFM 2013-04). IFM analyses compared IFM 2009 VRD non-ASCT vs IFM 2013-04 VTD arms. The VRD and VTD PS-stratified cohorts had no clinically meaningful differences in baseline characteristics. The integrated analysis met its primary endpoint (non-inferiority) and demonstrated a statistically significant and clinically relevant ≥ VGPR rate improvement after 6 induction cycles with VRD vs VTD (66.3% vs 51.2%; P = .00281) in GEM studies. IFM non-inferiority results had similar ≥ VGPR rates with VRD vs VTD by 4 cycles (12 wks; 57.1% vs 56.5%). Responses

deepened during induction in GEM studies. In the 378 VRD vs 111 VTD pts who started cycle 6, ≥ VGPR rate increased from 54.5% vs 35.1% by 3 cycles of induction to 62.7% vs 40.5% by 4 cycles and to 70.1% vs 55.9% by 6 cycles and 80.2% vs 59.5% post-induction, respectively. The ≥ VGPR rate post-ASCT (74.4% vs 53.5%) and MRD negativity (10−4) rates post-induction (46.7% vs 34.9%) and post-ASCT (62.4% vs 47.3%) support the benefit of VRD vs VTD. Safety was as previously reported for these studies. In GEM studies, SC vs IV administration of BORT may have contributed to lower rates of peripheral neuropathy (PN; grouped term) with VRD vs VTD (grade 3/4, 5.5% vs 15.4%; grade ≥ 2, 20.7% vs 44.6%). TEAEs led to dose reduction (21.6% vs 35.4%) and study or Tx discontinuation (3.1% vs 9.2%) less frequently in the VRD vs VTD cohorts. In IFM studies, TEAEs led to dose reduction more frequently (32.9% vs 18.3%) and Tx discontinuation less frequently (6.5% vs 11.2%) with VRD vs VTD. Grade 3/4 PN (grouped term) was 5.9% vs 15.4%, whereas grade ≥ 2 events were similar (30.3% vs 27.2%), which may reflect BORT administration in these IFM studies (IV for VRD vs SC for VTD, respectively). CONCLUSION Six cycles of VRD induction led to a significantly higher ≥ VGPR rate than VTD in TE NDMM. Deepened responses and MRD negativity further support the benefit of VRD over VTD. TEAEs with VRD compared well with VTD, with lower rates leading to discontinuation. This analysis supports the favorable benefit-risk profile of VRD over that of VTD as induction Tx in. METHODS Prospective phase 3 RCTs evaluating VRD or VTD induction (every 3 or 4 wks) in TE NDMM before ASCT meeting predefined eligibility criteria (including access to pt-level data) were included. Non-inferiority of ≥ VGPR rate after induction was the primary endpoint. Statistical methods were based on propensity score (PS). RESULTS Four studies met eligibility criteria-VRD: PETHEMA GEM (GEM) 2012 and IFM 2009; VTD: GEM2005 and IFM 2013-04. GEM studies, used for the primary analysis, had a symmetrical induction design (six 4-wk cycles, then ASCT). IFM studies were considered supportive due to pre-ASCT cycle number variability (3 VRD vs 8 VRD in IFM 2009 and 4 VTD in IFM 2013-04). IFM analyses compared IFM 2009 VRD non-ASCT vs IFM 2013-04 VTD arms. The VRD and VTD PS-stratified cohorts had no clinically meaningful differences in baseline characteristics. The integrated analysis met its primary endpoint (non-inferiority) and demonstrated a statistically significant and clinically relevant ≥ VGPR rate improvement after 6 induction cycles with VRD vs VTD (66.3% vs 51.2%; P = .00281) in GEM studies. IFM non-inferiority results had similar ≥ VGPR rates with VRD vs VTD by 4 cycles (12 wks; 57.1% vs 56.5%). Responses deepened during induction in GEM studies. In the 378 VRD vs 111 VTD pts who started cycle 6, ≥ VGPR rate increased from 54.5% vs 35.1% by 3 cycles of induction to 62.7% vs 40.5% by 4 cycles and to 70.1% vs 55.9% by 6 cycles and 80.2% vs 59.5% post-induction, respectively. The ≥ VGPR rate post-ASCT (74.4% vs 53.5%) and MRD negativity (10−4) rates post-induction (46.7% vs 34.9%) and post-ASCT (62.4% vs 47.3%) support the benefit of VRD vs VTD. Safety was as previously reported for these studies. In GEM studies, SC vs IV administration of BORT may have contributed to lower rates of peripheral neuropathy (PN; grouped term) with VRD vs VTD (grade 3/4, 5.5% vs 15.4%; grade ≥ 2, 20.7% vs 44.6%). TEAEs led to dose reduction (21.6% vs 35.4%) and study or Tx discontinuation (3.1% vs 9.2%) less frequently in the VRD vs VTD cohorts. In IFM studies, TEAEs led to dose reduction more frequently (32.9% vs 18.3%) and Tx discontinuation less frequently (6.5% vs 11.2%) with VRD vs VTD. Grade 3/4 PN (grouped term) was 5.9% vs 15.4%, whereas grade ≥ 2 events were similar (30.3% vs 27.2%), which may reflect BORT administration in these IFM studies (IV for VRD vs SC for VTD, respectively).CONCLUSION Six cycles of VRD induction led to a significantly higher ≥ VGPR rate than VTD in TE NDMM. Deepened responses and MRD negativity further support the benefit of VRD over VTD. TEAEs with VRD compared well with VTD, with lower rates leading to discontinuation. This analysis supports the favorable benefit-risk profile of VRD over that of VTD as induction Tx in TE pts with NDMM.

Keywords:
Induction therapy

newly diagnosed MM

RVD

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

OAB-002

Quadruplet KCRD (Carfilzomib, Cyclophosphamide, Lenalidomide and Dexamethasone) Induction for Newly Diagnosed Myeloma Patients

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Abstract:
Background Multiple myeloma (MM) has significant spatial and temporal clonal heterogeneity suggesting therapeutic agents with different mechanisms of action, delivered in combination or sequentially, are required to maximize the depth of response and improve outcomes. The UK NCRI Myeloma XI phase III randomized trial compared induction with the second generation proteasome inhibitor carfilzomib and lenalidomide containing quadruplet, KCRD, vs a response-adapted approach of sequential triplet therapies in newly diagnosed transplant eligible patients. Methods 1056 patients were randomized between KCRD (28 day cycles of carfilzomib (K) 36mg/m2 IV d1-2,8-9,15-16, cyclophosphamide (C) 500mg PO d1,8, lenalidomide (R) 25mg PO d1-21, dexamethasone (D) 40mg PO d1-4,8-9,15-16) and immunomodulatory drug (IMiD) triplet CTD/CRD prior to ASCT. Patients with a suboptimal response to CTD/CRD underwent response-adapted intensification randomization to a proteasome inhibitor (bortezomib, CVD) containing triplet or no CVD. A maintenance randomization at 3 months post ASCT compared lenalidomide to observation. Molecular high-risk (HiR) was classified by t(4;14), t(14;16), t(14;20), del(17p) or gain(1q) with ultra-high risk (UHiR) the presence of >1 lesions. Results KCRD was associated with a significantly longer PFS than IMiD triplet therapy (HR 0.63, 95%CI 0.51, 0.76, 3yr PFS KCRD 64.5% vs CTD/CRD 50.3%, p<0.0001). PFS2 was also significantly improved with KCRD (HR 0.75, 95% CI 0.56, 0.99, 3yr PFS2 KCRD 81.8% vs CTD/CRD 75.1%). Deeper response rates were seen in patients treated with KCRD vs CTD/CRD pre and post-transplant (p<0.0001). All regimens were well tolerated with no significant additional toxicity due to the quadruplet regimen. A higher proportion of patients receiving KCRD induction were able to undergo ASCT than those who received response-adapted induction and in an analysis restricted to those who had completed ASCT, KCRD induction was still associated with a significantly longer PFS. There was no significant heterogeneity in PFS outcome between molecular risk groups with a benefit for KCRD over triplets in all. In patients receiving KCRD there was no difference in response rate at the end of initial induction by risk group but UHiR disease was associated with significantly shorter PFS than both SR and HiR, whilst there was no

difference in outcome between patients with HiR (one adverse lesion only) and SR. An exploratory analysis compared the patients receiving KCRD to patients in the CTD/CRD arm who had received the optimum response-adapted approach (i.e. excluding those with a suboptimal response randomized to no CVD). KCRD was associated with significantly longer PFS than using a response adapted sequential triplet approach (HR 0.64, 95% CI 0.52, 0.78, p<0.0001). Conclusion KCRD was well tolerated with deep responses pre- and post-transplant and a significant PFS benefit compared to triplet therapy across all risk groups.

Keywords:
carfilzomib

carfilzomib-lenalidomide-dexamethasone

Lenalidomide

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

OAB-003

Daratumumab Plus Bortezomib, Thalidomide, and Dexamethasone (D-VTd) in Transplant-eligible Newly Diagnosed Multiple Myeloma (NDMM): Subgroup Analysis of High-risk Patients (Pts) in CASSIOPEIA

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Abstract:
Introduction: High-risk cytogenetic abnormalities and International Staging System (ISS) disease stage III confer poor outcomes in MM pts. In the phase 3 CASSIOPEIA study, at median follow-up of 18.8 mo, D-VTd significantly reduced the risk of progression/death by 53%, and improved rates of stringent complete response (sCR), CR or better (≥CR), and minimal residual disease (MRD) negativity vs VTd in transplant-eligible NDMM pts. We present a subgroup analysis of high-risk pts in CASSIOPEIA based on cytogenetic risk and ISS stage. Methods: Transplant-eligible NDMM pts were stratified by site affiliation (IFM or HOVON), ISS stage (I, II, or III), and cytogenetic risk status. High-risk cytogenetic pts had del17p (≥50% abnormal cells) and/or t(4;14) (≥30% abnormal cells) by centrally assessed FISH. Pts were randomized 1:1 to 4 pre-transplant induction and 2 post-transplant consolidation cycles with D-VTd or VTd. Primary endpoint was sCR post-consolidation (Day 100 post-ASCT), per IMWG. Additional

endpoints were MRD-negativity (multiparametric flow cytometry; 10^–5) and ≥CR rates, and PFS. Results: Of 1,085 pts randomized to D-VTd (n=543) or VTd (n=542), 15.5% had a high-risk cytogenetic abnormality. ISS staging was 39.8%, 45.0%, and 15.2% for stage I, II, and III, with more pts classified as stage II in D-VTd vs VTd (47.0% vs 43.0%) and similar pts classified as stage III in D-VTd vs VTd (15.5% vs 14.9%). Post-consolidation sCR rates were significantly higher with D-VTd vs VTd (28.9% vs 20.3%; odds ratio [OR], 1.60; 95% CI, 1.21-2.12; P=0.0010). Prespecified subgroup analyses of sCR showed consistent treatment effect of D-VTd over VTd across subgroups except in high-risk cytogenetic (OR, 0.83; 95% CI, 0.42-1.66) and ISS stage III (OR, 1.07; 95% CI, 0.54-2.12) pts. However, ≥CR rates favored D-VTd vs VTd (high-risk cytogenetic, 36.6% vs 32.6%; OR, 1.11; 95% CI, 0.58-2.10 and ISS stage III, 44.0% vs 33.3%; OR, 1.54; 95% CI, 0.83-2.88). MRD-negative rate was higher for D-VTd vs VTd (63.7% vs 43.5%; OR, 2.27; 95% CI, 1.78-2.90; P <0.0001), including in high-risk cytogenetic (59.8% vs 44.2%; OR, 1.88; 95% CI, 1.02-3.46) and ISS stage III (64.3% vs 45.7%; OR, 2.14; 95% CI, 1.15-4.00) subgroups. At median follow-up of 18.8 mo, D-VTd reduced the risk of progression/death vs VTd (HR, 0.47; 95% CI, 0.33-0.67; P<0.0001), including in high-risk cytogenetic (HR, 0.67; 95% CI, 0.35-1.30) and ISS stage III (HR, 0.66; 95% CI, 0.32-1.39) subgroups. Conclusions: Prespecified subgroup analyses of sCR demonstrated that the treatment benefit of D-VTd over VTd was consistent across subgroups except pts with high-risk cytogenetic abnormalities and ISS stage III disease; however, strict IMWG criteria were used for sCR. Importantly, D-VTd resulted in a benefit in terms of ≥CR and MRD-negative rates, as well as PFS, in these high-risk pt subgroups. The clinical benefit of these deeper responses will be evaluated with additional follow-up and in Part 2 of the study.

Keywords:
daratumumab

Multiple myeloma

transplant

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

OAB-004

Concordance of Post-consolidation Minimal Residual Disease Rates by Multiparametric Flow Cytometry and Next-generation Sequencing in CASSIOPEIA

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Abstract:
Introduction: Bortezomib, thalidomide, and dexamethasone (VTd) is a standard-of-care regimen in Europe for patients (pts) with newly diagnosed multiple myeloma (NDMM) who are transplant eligible. The combination of daratumumab (DARA), a CD38-targeted mAb, with VTd significantly reduced the risk of progression or death and improved stringent complete response (sCR), CR or better (≥CR), and minimal residual disease (MRD)-negative rates vs VTd alone in transplant-eligible NDMM pts in Part 1 of the phase 3 CASSIOPEIA study. Part 2 is ongoing. MRD status is emerging as a valuable prognostic tool to evaluate efficacy in MM. The development of multiparameter flow cytometry (MFC) and next-generation sequencing (NGS) techniques has enabled more sensitive and high-throughput detection of MRD. Here, we evaluated the concordance in post-consolidation MRD results between the MFC and NGS methodologies from Part 1 of CASSIOPEIA. Methods: Transplant-eligible NDMM pts were randomized 1:1 to 4 pre-ASCT induction and 2 post-ASCT consolidation cycles with D-VTd or VTd. MRD analyses were performed on bone marrow aspirates post-induction and post-consolidation (at Day 100 post-ASCT) in all pts, regardless of response. For the ITT population, any missing or indeterminate results were assumed to be MRD positive. MRD was assessed primarily by EuroFlow-based MFC (with multi-epitope CD38 mAb to mitigate DARA interference) and, based on sample availability, secondarily with NGS (Adaptive clonoSEQ® Assay). Here, we evaluated the concordance in the subset of pts tested by both assays at a standard threshold of 10^–5. Results: A cohort of 1,085 pts was randomized to D-VTd (n = 543) or VTd (n = 542). There were 346 pts (63.7%) in the D-VTd group versus 236 (43.5%; P <0.0001) in the VTd group who achieved post-consolidation MRD negativity by MFC (ITT population) and 210 pts (56.6%) vs 134 (36.8%; P <0.0001) who achieved post-consolidation MRD negativity by NGS (MRD-evaluable population). A total of 733 pts were evaluable by both MFC and NGS post-consolidation. Evaluation of concordance between MFC and NGS MRD results, regardless of response, showed good overall agreement (83.5%). Considering response of ≥CR, analysis of concordance between MFC+≥CR vs NGS+≥CR status showed minimal difference in evaluating MRD by either method (94.4% agreement). Additionally, the overall agreement between MFC and NGS by treatment group was similar between the 2 cohorts (82.7% for D-VTd vs 84.3% for VTd). Conclusions: The high overall concordance of MRD results (10^–5) by MFC and NGS, regardless of response and combined with pts achieving CR or better, indicates that both techniques performed similarly in evaluating MRD. Moreover, the agreement between MRD assessments was similar between the D-VTd and VTd cohorts, suggesting that the presence of DARA did not interfere with MRD evaluation by the MFC protocol used.

Keywords:
daratumumab

Multiple myeloma

transplant

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

OAB-005

A tale of two paradigms: fixed duration vs continuous therapy in routine clinical practice: An INSIGHT MM study analysis of duration of therapy

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Abstract:
Background: An increasing range of treatment options are available for newly diagnosed (ND) and relapsed/refractory multiple myeloma (RRMM); however, there remains no global standard-of-care. Despite clinical trials showing benefits of continuous vs fixed duration therapy, shorter treatment durations are seen in the real-world. MM patients (pts) are a heterogeneous population; several factors must be considered when choosing a pt's treatment course, including real-world tolerability and treatment sequencing. Methods: INSIGHT MM (NCT02761187) is the largest global, prospective, non-interventional, observational MM study to date. Adults with NDMM or RRMM (1–3 prior therapies) are being enrolled from 15 countries in Europe, US, Latin America, and Asia, and followed prospectively for ≥5 yrs. Data are being collected at baseline and every 3 mos. Here, we evaluate duration of therapy (DoT), reasons for discontinuation, and subsequent treatments with regimens of interest prescribed at 1st, 2nd, or 3rd line. Results: At data cut-off (Nov 22, 2018; median follow-up 10.4 mos), 1761 NDMM and 1440 RRMM pts were enrolled, including 1027/683 who had received 2nd/3rd line therapy, (pts could receive >1 line). Regimens evaluated included daratumumab-based therapy (n=32/121/105, lines 1/2/3), IRd (n=2/29/43), Kd (n=5/33/33), KRd (n=47/61/17), Rd (n=90/130/71), VCd (n=323/57/19), Vd (n=102/48/29), VMP (n=53/8/3), VRd (n=321/36/8), VTd (n=200/25/4); median DoTs were 4.0–9.4 (1st line), 3.0–11.2 (2nd line), and 1.6–16.5 mos (3rd line) with these regimens. For these regimens as 1st-line therapy, among 185 pts who had stopped treatment, 65 (35%) had completed planned DoT, 49 (26%) had discontinued due to adverse events (AEs) and 26 (14%) had discontinued due to relapse. For 2nd-line treatment (N=75 stopped), the most common reason for discontinuation was relapse (n=23; 31%), then AEs (n=21; 28%), and 13 pts (17%) had completed planned DoT. For 3rd-line treatment (N=52 stopped), discontinuation due to relapse was the most common reason (n=19; 37%), then AEs (n=13; 25%) and 7 pts (13%) had completed planned DoT. Among pts who received a PI-based regimen as 1st, 2nd, or 3rd-line therapy, 29% of pts at each line had another PI-based regimen as their next therapy, while 4%, 14%, and 21% had a daratumumab-based regimen, respectively. Conclusion: In this interim analysis the most common reason for stopping 1st-line therapy was reaching the end of planned therapy; reasons for discontinuation change as patients move through lines of therapy. Analyses by specific regimens and transplant status will be presented to determine impact on DoT and reasons for discontinuation. Through INSIGHT MM, we are characterizing the longitudinal treatment path for pts, and gaining a better understanding of how long-term regimens are used in routine clinical practice,

treatment sequencing, and reasons for discontinuation, highlighting the importance of real-world data.

Keywords:
discontinuation

INSIGHT

real-world evidence

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

OAB-006

Genomic profiling of smoldering multiple myeloma identifies patients at a high risk of disease progression.

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Abstract:

Introduction: Multiple myeloma (MM) is an incurable plasma cell malignancy that arises from two precursor states: Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering Multiple Myeloma (SMM). Some of those patients rapidly progress to MM, while others remain asymptomatic over their lifetime. However, the genetic and molecular profiles that underlie this heterogeneity in disease progression are not yet elucidated. Methods: In the largest to date study on SMM genetics, our cohort included 212 samples from 203 SMM patients. We performed whole exome sequencing (WES) on 78 Tumor-Normal pairs, WES and RNA-sequencing on 82 Tumor-only samples, deep targeted sequencing on 52 samples, and whole genome sequencing (WGS) on 13 samples. Genomic data was correlated with clinical variables and current risk models. Results: Somatic copy number alterations (SCNAs) were found in 80% of patients, while chromosomal translocations and single nucleotide variations (SNVs) were present in 42% and 36% of patients, respectively. SNVs in MAPK pathway genes (KRAS, NRAS, BRAF) were the most frequently observed (54%). SMM patients harboring MYC oncogene aberrations (translocations or copy number gains) had the shortest median time to progression (TTP) (8.4 vs. 52 months, $p < 0.001$), followed by those with MAPK pathway mutations (15 vs. 60 months, $p < 0.001$). Moreover, DNA repair pathway alterations (deletion 17p, TP53 and ATM SNVs) were associated with significantly shorter TTP (19 vs. 47 months, $p = 0.008$). Patients who had one or more of these three alterations had significantly shorter TTP, compared to those who did not (1.2 vs. 6 years, $p < 0.001$). Importantly, these alterations remained independent risk factors for progression, even in the presence of biomarkers currently used in clinical risk models. This finding suggests SMM genomics can improve the efficiency of risk stratification. Indeed, in our cohort, patients with any of these alterations, regardless their clinical risk group, progressed faster than patients who are considered high-risk by Mayo 2018 criteria (1.3 vs. 3.4 years, $p = 0.006$). Moreover, intermediate and high-risk patients with any of these alterations had significantly shorter TTP compared to those without. We are currently

developing a clinical/genomic model that is being validated in larger cohorts, while matched RNA-Seq data will be used to define an expression signature corresponding to our high-risk genotype. Phylogenetic analysis of serial patient samples has revealed different patterns of clonal evolution, with certain patients showing growing subclones at progression, and others showing acquisition of new clones. Conclusion: Genomic profiling of SMM patients can identify high-risk group of patients that can go undetected by purely clinical risk models leading to improved efficiency of SMM risk stratification.

Keywords:
Genetic profiling

Risk stratification

Smoldering Multiple Myeloma

Tracks:
Multiple Myeloma Genomics

OAB-007

Timing the initiation of multiple myeloma

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Abstract:
INTRODUCTION: Cancer pathogenesis is usually characterized by a long evolutionary process where genomic driver events accumulate over time, conferring advantage to distinct subclones, allowing their expansion and progression. METHODS: Here, to investigate the evolution and progression of multiple myeloma (MM) over time, we interrogated the landscape and timing of mutational processes on a large cohort of 89 whole genomes and 973 exomes. To improve the accuracy of mutational signatures analysis, we developed a novel fitting algorithm (name mm-sig) which fits the entire mutational catalogue of each patient with the mutational signatures involved in MM pathogenesis. To reconstruct the cancer-history of each patient we integrated two different approaches. In the first we divided all mutations in either clonal (i.e early) or subclonal (i.e late). Next, to investigate different time windows among clonal mutations, we took advantage of primary and secondary chromosomal gains where clonal mutations could be subdivided into: 1) duplicated mutations (i.e present on two alleles and therefore acquired before the duplication); or 2) non-duplicated mutations (i.e. detected on a single allele), reflecting either pre-gain mutations on the minor allele, or post-gain mutations acquired on one of the duplicated alleles. RESULTS Eight main mutational signatures were identified, seven of which showed significant similarity with one included in the most recent mutational signature catalogue (i.e SBS1, SBS2, SBS5, SBS8, SBS9, SBS13 and SBS18). Reconstructing the chronological activity of each mutational signature, we identified four different routes to acquire the full mutational spectrum in MM based on the differential temporal activity of AID (SBS9) and APOBEC

(SBS2 and SBS13). Our data indicate that AID activity is not limited to the first contact with the GC, but persists in at least a subset of patients, behaving similarly to a memory B-cells, capable of re-entering the germinal center upon antigen stimulation to undergo clonal expansion several times before MM diagnosis. Next, we confirmed the SBS5 constant mutation rate over time in MM (clock-like). Based on the SBS5 mutation rates and inferred molecular time, we could estimate when the first copy number gain was acquired during the life history of each MM patient. Intriguingly, the first MM chromosomal duplication was acquired on average 38 years (ranges 11-64) before the first sample collection. In 23 out of 27 (85%) cases with large trisomies, the first multi gain event occurred before 30 years of age, and in 13/27 (48%) before 20 years reflecting a long and slow process potentially influenced and accelerated by extrinsic and intrinsic features. DISCUSSION Our findings provide a framework to study the etiology of MM and explore strategies for prevention and early detection.

Keywords:
Initiation

Mutational Signatures

Whole genome sequencing

Tracks:
Multiple Myeloma Genomics

OAB-008

Identification and Molecular Characterization of High-Risk Multiple Myeloma Patients from the MMRF CoMMpass Study at Diagnosis and Progression

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Abstract:
Even though the incorporation of new treatment modalities has improved the overall survival (OS) of multiple myeloma patients, there remains a subset of high-risk patients that exhibit poor outcomes. Analysis of patients from the MMRF CoMMpass Study (NCT01454297), a fully accrued, longitudinal, observational clinical trial with 1143 newly diagnosed myeloma patients, has aided in the identification and characterization of high-risk patients. Tumor samples were analyzed using whole genome, exome, and RNA sequencing at diagnosis and each progression event, and clinical parameters were collected at baseline and every three months through the eight-year observation period. Consensus clustering of RNAseq data from 714 patients at diagnosis identified 12 expression subtypes of myeloma which generally correspond to known genetic subgroups. However, the proliferation (PR) subtype comprised 51 patients whose tumors had an array of genetic backgrounds but converged upon a similar gene expression profile. PR patients had extremely poor OS (median = 21 months, HR = 3.7, 95% CI = 2.5 - 5.6, $p<0.001$) outcomes compared to patients in other RNA subtypes and were enriched for gain of 1q ($p<0.001$), loss of 13q ($p<0.001$), and bi-allelic loss of MAX ($p<0.01$) or RB1 ($p<0.001$). Although the PR subtype was enriched for patients classified as ISS3 ($p<0.001$), 25 were classified as ISS1 or 2, highlighting that ISS underestimates disease severity in nearly half of high-risk patients. To permit classification of progression tumor samples, a prediction model was developed leveraging gene markers predictive of each RNA subtype. Analysis of 55 patients with RNAseq data at multiple time points identified 13 patients who transitioned to PR at progression. These patients had extremely poor outcomes, with a median OS of 88 days after the progression event. Three patients that transitioned to the PR subtype acquired complete loss-of-function (LOF) of a cyclin-dependent kinase inhibitor, with two and one patient acquiring LOF of CDKN2C and CDKN1B, respectively. Overall, molecular events associated with loss of G1/S cell cycle control were

commonly identified in PR patients at both diagnosis and progression. In silico mixing experiments revealed that the RNA subtype prediction model could detect a PR signature (≥0.05) if 5-20% of sequencing reads originated from cells of the PR subtype, signifying that the model could detect a subclonal population of PR cells within a bulk tumor sample. At diagnosis, there were 26 non-PR patients with a detectable PR signature (≥0.05, med = 50 mo) who exhibited OS outcomes intermediate to PR patients, and patients with a negligible PR signature (<0.05, med = 74 mo), suggesting that knowing both the tumor RNA subtype and PR probability may help assess patient risk throughout their disease. A model such as the one presented here may be a useful tool to stratify patients to test optimal treatment strategies for patients with high-risk disease.

Keywords:
genomics

High risk

Outcome

Tracks:
Multiple Myeloma Genomics

OAB-009

Utilisation of liquid biopsies in functional high-risk myeloma demonstrates a unique mutational pattern and extensive spatial heterogeneity

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Abstract:
Background: Our understanding of the mutational landscape in multiple myeloma (MM) is based on studies of diagnostic bone marrow (BM). Limited data is available in the relapsed setting and the impact of spatial heterogeneity (SH) on the utility of BM analysis during disease evolution is unclear. We evaluated a liquid biopsy targeted amplicon sequencing (TAS) strategy to characterise uniformly treated 'functional' high-risk (HR) patients and compared it to a BM-based approach. Methods: 50 patients failing bortezomib-based induction who then received carfilzomib-based salvage were studied. DNA was isolated from PBMC and BM CD138 enriched plasma cells (PC) at baseline. cfDNA was sequentially isolated from plasma (PL) using the QIAamp circulating nucleic acid Kit. TAS was performed with a 23-gene customised panel on an Illumina NextSeq sequencer using the 500 High Output v2 Kit. Mutational fractional abundance (FA) was defined as the relative frequency of a mutant allele at a particular locus and expressed as a percentage. Variants appearing in the germ line controls were excluded. Mutation specific droplet digital PCR (ddPCR) was undertaken on cfDNA using commercially available mutation detection assays (Biorad). Minimal residual disease (MRD) analysis was with the 8-colour EuroFlow platform. Results: Median duration from commencing induction to salvage therapy was 4 months. 49 patients had evaluable cfDNA (median 3 PL mutations [PLM], range, 0-10). Matched BM was available from 33 patients (median 4 mutations, range, 0-15). In the 44 patients positive for PLM the most prevalent (% of patients) were CDC27 (23%), DIS3 (16%), KRAS (16%), PIK3CA (9%) and MAX (9%) with FA from 0.3-50.1% (median 1.25%), with 4 PLM clones with FA>40% (DIS3 50.1%, PIK3CA 46.5%, KRAS 45.2%, CYLD 40.3%). Importantly, TAS of BM failed to demonstrate 73% of these dominant PLM (including 3 of the 4 clones with FA>40%), consistent with extensive SH in these HR patients. Five patients with RAS PLM who achieved BM MRD negativity (<1 x 10-5) while on treatment were tracked with

ddPCR - 3 cleared their PLM but 2 had persisting detectable PLM discordant with their MRD negative status. One demonstrated extra-medullary relapse 2 months following completion of salvage therapy, coincident with a rising NRAS Q61R FA (0.1% to 0.9%). The other remains clinically in remission but now with a rising NRAS Q61R FA (0.3% to 0.6%). Conclusions: These data reveal a unique mutational pattern in HR MM consistent with the emergence of resistant clones under treatment selection pressure, including loss-of-function mutations of the tumour suppressor CDC27 and targetable activating mutations of PIK3CA. CDC27 plays a significant role in cell cycle control via the ubiquitination of CCND1 and its potential role in HR MM warrants further evaluation. Importantly, our data confirm extensive SH in this patient population questioning the utility of isolated BM sampling for disease characterization in

Keywords:
High risk

Liquid biopsy

spatial heterogeneity

Tracks:
Multiple Myeloma Genomics

OAB-010

Genome wide chromatin accessibility profiling identifies chromatin signatures and novel transcription factor dependencies in multiple myeloma

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Abstract:
Multiple myeloma (MM) is a plasma cell malignancy characterized by clinical and genomic heterogeneity. Recurrent IgH translocations, copy number abnormalities and somatic mutations have been reported to participate in myelomagenesis but no universal driver of the disease has been identified. Here, we evaluate the transcriptional deregulation as a critical event in MM pathogenesis. In order to capture signatures of transcription factor (TF) engagement with the myeloma epigenome, we performed the assay for transposase-accessible chromatin sequencing (ATAC sequencing) in 77 primary myeloma samples and 5 normal plasma cells (NPC) from healthy donors along with whole genome sequencing and H3K27Ac ChIP-seq, SNParray and deep RNA sequencing in a cohort of these samples. We identified the variable accessible loci between MM and NPC and performed nuclease-accessibility footprint analysis to identify TF binding events. Thus, we characterized the myeloma-specific open chromatin landscape, and identified TF dependencies and potential new myeloma drivers. While we observed a vast amount of heterogeneous chromatin states across the sample cohort, we identified distinct variable chromatin accessibility signatures indicative of the MM chromatin state compared to NPC and within MM samples related to specific subgroups including hyperdiploid and non-hyperdiploid MM. Accessibility footprinting revealed MM-specific enrichment for TFs known to be essential for MM cell survival including Interferon Regulatory Factors (IRFs), Ikaros, and Sp1. Interestingly, we identify the myocyte enhancer factor 2 (MEF2) family of TFs as being specifically enriched in open chromatin regions in MM cells. Using a CRISPR-Cas9 knockout system, we identified the MEF2 family

member MEF2C, as essential for MM cell proliferation and survival and we performed chromatin immunoprecipitation with massively parallel sequencing (ChIP seq) in MM1S cell line to confirm MEF2C occupancy. MEF2C is significantly overexpressed at the RNA level in our study as well as in several independent cohorts and is a central enhancer-localized TF in MM core regulatory circuitry as determined by H3K27ac ChIP-sequencing profiles of primary MM samples. Finally, we used small molecule inhibitors targeting MEF2C activity via inhibition of MEF2C phosphorylation using inhibitors of salt-induced kinases (SIK) and microtubule affinity regulating kinases (MARK). SIK and MARK inhibition resulted in both dose- and time-dependent inhibition of MM cell growth and survival in a panel of MM cell lines with various genotypic and phenotypic characteristics, revealing a potential approach to targeting the dysregulated cis-regulatory landscape of myeloma. To conclude, we identify an altered chromatin accessibility landscape in multiple myeloma that likely contributes to oncogenic transcriptional state through the activity of transcription factors such as MEF2C, representing a new MM dependency and therapeutic target.

Keywords:
chromatin

Multiple myeloma

transcription factor dependency

Tracks:
Multiple Myeloma Genomics

OAB-011

Comparative effectiveness of lenalidomide, bortezomib, and their combination as first-line treatment of older patients with myeloma

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Abstract:
Background: Phase 3 trials show the RVD (lenalidomide, bortezomib, and dexamethasone) triplet to be superior to RD (lenalidomide/dexamethasone) for initial therapy of myeloma. However, among older transplant-ineligible patients [pts], RVD has not been directly compared with doublets (RD or VD[bortezomib/dexamethasone]), nor has RD been compared with VD, leaving an important gap in evidence. We used population-based data to compare these regimens among older patients (Medicare beneficiaries) with receiving first-line therapy for myeloma. Methods: We identified Medicare beneficiaries with myeloma receiving first line RD, VD, or RVD in 2007-2015, using Medicare claims linked to cancer registry data (SEER-Medicare). Using propensity score analysis, we generated pseudo-randomized cohorts balancing multiple baseline factors, including socio-economic and performance status, time from diagnosis, presence of baseline hypercalcemia, renal disease, anemia, neuropathy, DVT, and other comorbidities. After confirming the balance, we analyzed two survival endpoints: overall survival (OS) and time to treatment failure (TTF, defined as start of a 2nd line agent, hospice, or death; censored in case of an autologous transplant), reporting hazard ratios (HR) with 95% confidence intervals (CI). We also compared select identifiable toxicities within 6 months of starting therapy, reporting relative risk (RR). Results: Between 2007 and 2015, the proportion of beneficiaries (median age, 76 years [y]) receiving RD increased from 18% to 25% (total n = 1,541), VD from 17% to 26% (n = 1,672), and RVD from 1% to 26% (n = 891), yielding 4,104 patients available for comparative analyses. In the analysis of RVD vs doublets, RVD has shown better TTF (median 1.7 vs 0.8y; HR 0.68, 95%CI, 0.61-0.76) and OS (median 3.4 vs 2.7y; HR, 0.83; 95%CI, 0.72-0.95), at the expense of higher rates of hospitalization (RR, 1.17; 95%CI 1.03-1.32), anemia (RR, 1.16; 95%CI 1.09-1.23), and neuropathy (RR, 1.49; 95%CI, 1.14-1.96), but no increased risk of thromboembolism (RR, 1.06; 95%CI, 0.79-1.44). A

higher proportion of pts treated with RVD underwent consolidative transplant (26% vs 6%). In the analysis of RD vs VD, RD has demonstrated better TTF (median 1.0 vs 0.6y; HR, 0.74; 95%CI, 0.68-0.81) and OS (median 2.7 vs 2.3y; HR 0.91, 95%CI, 0.83-0.99). RD resulted in more frequent thromboembolism (RR, 1.44; 95%CI, 1.13-1.83), but less neuropathy (RR, 0.39; 95%CI, 0.29-0.53), without significant difference in the rates of hospitalization (RR, 0.96; 95%CI, 0.87-1.06) or anemia (RR, 0.95; 95%CI, 0.89-1.00). Conclusions: RVD offers TTF and OS benefit for older patients with myeloma who can tolerate higher potential short-term toxicity, confirming the results of the SWOG S0777 in a population-based setting. For patients receiving doublets, RD showed an unexpected advantage over VD, suggesting that RD may be the preferred doublet, despite the prevalent use of VD in this population.

Keywords:
comparative effectiveness

Elderly patients

Lenalidomide

Tracks:
Treatment of Newly Diagnosed Myeloma Non-Transplant

OAB-012

Lenalidomide and Dexamethasone in Newly Diagnosed Multiple Myeloma Patients: Meta-analysis of Efficacy in Pivotal Randomized Controlled Trials

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Abstract:
Introduction/Background: For patients with newly diagnosed multiple myeloma (NDMM) who are not candidates for autologous stem cell transplantation (ASCT), lenalidomide and low-dose dexamethasone (Rd) is an established, alkylator-free, treatment option. The FIRST trial demonstrated the efficacy and safety of Rd, showing a significant improvement in overall survival (OS) with Rd over the combination of melphalan, prednisone, and thalidomide. Rd is a recommended treatment option in the European Society for Medical Oncology (ESMO) guidelines (Moreau et al. Ann Oncol. 2017;28:iv52-61). Recent trials comparing Rd with Rd + bortezomib or Rd + daratumumab have contributed to the growing body of evidence regarding the efficacy of Rd in patients with NDMM. Using phase 3 registration trials, this meta-analysis aimed to obtain a consolidated median estimate for OS and progression-free survival (PFS) in NDMM patients receiving Rd who were not intended for ASCT. Methods: Baseline patient characteristics, trial characteristics, and outcomes were extracted from pivotal phase 3 registration trials looking at Rd in patients with NDMM. Kaplan–Meier curves for OS and PFS were digitized; patient-level data were estimated numerically. Estimated patient-level data were then pooled and analyzed using a Bayesian meta-analysis. To estimate the survival function, Weibull, Gompertz, and second-order fractional polynomial models were fit to the data. Results: There was some variance among the 3 trials included in this meta-analysis of randomized controlled trials, regarding inclusion criteria and baseline characteristics. In particular, patients enrolled in FIRST and MAIA were ineligible for ASCT, whereas those enrolled in SWOG S0777 were not intended for immediate ASCT. Median follow-up for MAIA was shorter than FIRST or SWOG S0777 (28 months vs 67 and 84 months, respectively). This variance prevented the stable estimation of heterogeneity, requiring use of a fixed-effects model. Using the best-fitting models, the median OS with Rd was estimated at 67.2 months (95% confidence interval [CI] 61.3–74.2 months) and the median PFS was estimated at 28.9 months (95% CI 26.8–31.3 months). Estimated

results aligned with the outcomes from the individual trials (median OS values for FIRST, SWOG S0777, and MAIA were 59.1, 64, and not reported, respectively; median PFS was 26.0, 30, and 31.9 months, respectively) and subgroups tested (where data were available). Across the 3 trials included, the adverse events reported were consistent with the known safety profile for Rd. Conclusion: This meta-analysis demonstrated a consistent treatment benefit for Rd in patients with NDMM not intended for ASCT, with estimated median OS and PFS exceeding 5 years and 2 years respectively. These results support Rd as a first-line standard of care in this setting as recommended by ESMO, and also its role in the development of novel combination regimens.

Keywords:
meta-analysis

Multiple myeloma

Tracks:
Treatment of Newly Diagnosed Myeloma Non-Transplant

OAB-013

PROGNOSTIC AND PREDICTIVE PERFORMANCE OF SKY92 COMBINED WITH R-ISS IN ELDERLY MULTIPLE MYELOMA PATIENTS IN THE HOVON-87/NMSG-18 STUDY

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Abstract:
Background The prognosis of multiple myeloma (MM) is highly dependent on cytogenetic abnormalities and gene expression. Currently, evidence to either start or withhold therapy is insufficient. Especially, in the eldest patient such a predictive tool is eagerly awaited as side effects of treatment are more pronounced and might be irreversible. In the HOVON-87/NMSG-18 trial elderly patients were treated with either thalidomide or lenalidomide, followed by maintenance therapy until progression, i.e. MPR-R vs MPT-T. In this cohort, we assessed the prognostic and predictive performance of the previously described SKY92-ISS and the revised ISS (R-ISS). Methods Purified plasma cells to perform the MMprofiler™ CE IVD assay were available for n=190 patients. This gene expression profiling (GEP) assay delivers the SKY92 risk score, as well as GEP derived IGH translocation status. ISS (n=186), treatment arm and R-ISS (n=176) were included in Cox survival analyses for progression free survival (PFS) and overall survival (OS) and assessed by the likelihood ratio test. Results The 186 newly diagnosed patients analyzed had a median age of 72 years (inter-quartile range: 69 – 76). At the time of analysis the median follow up was 6 years; 25% of patients had ISS I, 49% ISS II and 26% ISS III. Classification into the four-tier SKY92-ISS was applied dividing the patients into high- to low-risk categories: SKY92 high-risk (HR)-ISSI/II/III (13% of patients),

SKY92-standard risk (SR)/ISS III (45%), SKY92-SR/ISS II (21%) and SKY92-SR/ISS I (21%). The median PFS of these groups from high- to low-risk was 11, 21, 22 and 25 months (p=6.8x10-3) and median OS 18, 49, 56 and 88 months (p=1.7x10-4). R-ISS classification resulted in 7% R-ISS III, 74% R-ISS II and 18% R-ISS I patients with a median PFS of 12, 20 and 30 months (p=0.09); median OS of 25, 53 and 88 months (p=4x10-4). In a multivariate analysis (n=176), SKY92-ISS and R-ISS both remain independently related to PFS (p=1.6x10-3 and 4.7x10-2) and to OS (p=2.4x10-4 and 1.1x10-2). As the ISS term in SKY92-ISS was redundant when combined with R-ISS, the SKY92 and R-ISS were combined as follows from high- to low-risk: 11% SKY92 HR/R-ISS II/III, 73% SKY92 HR/R-ISS I or SKY92 SR with R-ISS II/III, 16% SKY92 SR and R-ISS I. Combining SKY92 with R-ISS suggests that high-risk patients (SKY92 HR and R-ISS II/III) may benefit from MPR-R as compared with MPT-T with median OS of 55 versus 13 months respectively. This is supported by a significant interaction term for OS between risk-group and treatment (p=0.01). Conclusion The SKY92-ISS and R-ISS are robust markers to identify HR patients, also in non-transplant eligible MM patients. Both markers have independent prognostic value in relation to OS and PFS. In addition, the SKY92-R-ISS combination demonstrates predictive value for treatment in this trial. This finding requires validation in independent datasets. Funding: MMpredict (Horizon 2020, 701143).

Keywords:
Elderly patients

Revised ISS

SKY92

Tracks:
Treatment of Newly Diagnosed Myeloma Non-Transplant

OAB-014

Long-term proteasome inhibition in newly diagnosed multiple myeloma (NDMM): US MM-6, a real-world study transitioning from bortezomib to ixazomib

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Abstract:
Long-term proteasome inhibition (LTPI) improves outcomes in NDMM vs non-proteasome inhibitor (PI)-based therapy. However, efficacy improvements seen in clinical trials are often not achieved in real-world (RW) settings, and duration of PI-based therapy is typically shorter in US non transplant NDMM RW patients (pts) vs in phase 3 trials. This may be due to poor treatment adherence, burden of parenteral administration, comorbidities, financial burden, distance from treatment center, physician/pt preference, or toxicity. Maintaining quality of life (QoL), minimizing toxicity, and increasing adherence are critical for NDMM pts receiving LTPI. US MM-6 is a RW US community-based phase 4 study investigating transitioning from a parenteral PI (bortezomib [btz]) to an oral PI (ixazomib) in NDMM to increase PI-based treatment adherence and duration, maintain QoL, and improve outcomes. We report preliminary demographics,

baseline characteristics, actigraphy, and electronic pt reported outcomes (ePRO) compliance data for pts receiving all-oral ixazomib lenalidomide-dexamethasone (IRd). US MM-6 (NCT03173092) is enrolling ~160 non-transplant pts (transplant-ineligible or transplant delayed >24 months) with ≥stable disease after 3 cycles of btz-based induction. Pts receive IRd (ixazomib 4mg on d 1, 8, and 15, lenalidomide 25mg on d 1–21, dexamethasone 40mg [20mg for pts aged >75 yrs] on d 1, 8, 15, and 22, of each 28 d cycle) until progression or toxicity for ≤26 cycles. QoL and monthly medication adherence are assessed via ePROs. Pts use wearable digital devices and smartphones to record daily medication adherence and actigraphy (average steps and sleep per day). Primary endpoint: progression-free survival (PFS); secondary endpoints: response, duration of therapy, ePRO compliance, overall survival (OS), safety. We report preliminary data for the first 25 pts enrolled. Overall, 80% of pts were aged ≥65 yrs, 40% were male, 13% were of non-white race, and 43% had International Staging System stage III disease. Comorbidities included renal and urinary disorders (48%), peripheral neuropathy (28%), and cardiac disorders (24%). At data cutoff, 3 pts had discontinued study treatment due to pt/physician preference. Pts have received a median of 5 (range 1–12) cycles of IRd to date (plus 3 cycles of pre-enrollment btz-based therapy). Average ePRO compliance was 92%. At data cutoff, 24 pts recorded actigraphy data (2086 compliant days [≥12 h of data]); mean (standard deviation) number of steps/day and sleep time were 3236 (3540) and 8.35 (3.21) h, respectively. Response, PFS, and OS were not available at data cutoff. Duration of PI-based therapy is similar to previously published reports of LTPI; US MM-6 pts are older with a higher rate of advanced stage disease vs previous LTPI studies, yet have high compliance rates. US MM-6 will provide useful data on pt/disease characteristics and outcomes, including QoL and actigraphy, for IRd-treated US NDMM RW pts receiving LTPI.

Keywords:
clinical trials

Multiple myeloma

Proteasome Inhibitor

Tracks:
Treatment of Newly Diagnosed Myeloma Non-Transplant

OAB-015

The clinical impact of frailty in transplant ineligible patients with multiple myeloma treated with bortezomib-based chemotherapy as front line therapy

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Abstract:
Background : Patients with frail, accounting for one third of the elderly multiple myeloma (MM) can not be included in clinical trials because of the presence of comorbidities, abnormal laboratory test results, and physical disability. So far, there have been few studies on patients with unfit or frail. Therefore, this study was planned to compare the survival outcomes of patients according to frailty who treated with bortezomib combined chemotherapy as an initial treatment. Methods : Data of four hundred and eleven patients with MM were collected retrospectively at six university hospitals in South Korea between December 2012 and Oct 2017. All of them have been treated with bortezomib, melphalan and prednisone (VMP) as a first-line treatment.

Clinical and laboratory data were collected retrospectively by review of medical records. The criteria for classifying all patients as fit, unfit, and frail were based on the revised Myeloma Comorbidity Index (R-MCI) and international myeloma working group (IMWG) frailty score. The R-MCI is consisted of impaired lung and kidney function, the Karnofsky Performance Status, frailty, age and unfavorable cytogenetics. The parameters are used as weighted factors within the R-MCI. Classification of risk groups were 0-3 points of low risk, 4-6 points of intermediate risk and 7-9 points of high risk. IMWG frailty score is consisted of age, Chalson comorbidity index, ADL and IADL score. Classification of risk groups were 0 point of fit, 1 of unfit and 2 or more than 2 of frail. But our retrospective data did not have ADL and IADL score so we replaced ADL and IADL score with ECOG performace status. At now, the standard frailty risk model in MM are R-MCI and IMWG frailty. Results : The median age was 69 years (range, 34-91 years). The 156 (38.0%) patients were low risk, 204 (49.6%) were intermediate risk and 51 (12.4%) were high risk by R-MCI criteria. However, the 97 (23.6%) were fit, 148 (36.0%) were unfit, and 166 (40.4%) were frail patients by IMWG frailty. The survival outcomes according to R-MCI risk groups, the 2-year PFS were 68.2%, 53.3% and 14.3% in low, intermediate and high risk groups, respectively ($p<0.001$). The 2-year OS were 90.0%, 86.2% and 52.7% in these groups, respectively ($p<0.001$). According to IMWG frailty, the 2-year PFS were 62.5%, 63.1% and 42.2% in fit, unfit and frail groups, respectively ($p<0.001$). The 2-year OS were 89.8%, 87.0% and 77.2% in these groups, respectively ($p=0.002$). Conclusions : In our study, frail patients showed a significant short survival in PFS and OS compared to fit patients. So, treatment of the unfit and frail patients needs more caution on toxicity management and appropriate dosing schedules to improve the survival outcome. Further well designed prospective study will be needed to improve the survival outcomes of frail patients who modify dosing and schedule and develop more appropriate frailty risk model.

Keywords:
bortezomib

frailty

Multiple myeloma

Tracks:
Treatment of Newly Diagnosed Myeloma Non-Transplant

OAB-016

RECURRENT SOMATIC ALTERATIONS IN THE NON-CODING GENOME ALTER GENE EXPRESSION LEVELS AND CORRELATE WITH CLINICAL OUTCOME

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Abstract:
Current DNA sequencing studies in Multiple Myeloma (MM) have predominatly evaluated the alterations and their impact on protein coding genes.

However coding part is only 2% of the entire genome and almost 99% of all somatic alterations reported in other malignancies occur in the non-coding regions. Very little is known about frequency and significance of these alterations and how they affect the disease. By have now performed a deep (average coverage > 80X) whole genome sequencing (WGS) on 376 MM samples (240 newly diagnosed, 52 first relapse and 84 rrMM) as well as RNAseq to comprehensively analyze recurrent somatic alterations in non-coding regions. We detected median 9,649 (Range 3,194-126,935) mutations and indels per sample with overall more than 4M total somatic mutations. Introns (> 2.5 mutations/per Mb) and intergenic regions (> 3 mutations/per Mb) had significantly higher number of mutations per megabase compared to Exons (~2 mutations/per Mb) ($p < 1e-5$). We observed 57 [range 7 - 376] structural variants (SVs) per sample with > 98% involving non-coding regions. We identified 48 SV hotspots that are targeting tumor suppressor genes or key regulatory elements such as TCF3 and TNFSF10 and these SVs were also associated with significantly altered expression of the target genes. We found that mutational load is associated with clinical outcome and 19 genes with mutation hotspots in the non-coding region do have significant expression changes. After false discovery rate correction, we identified 12 hot spots with significant impact on overall survival (OS). We identified 42 deletions and 6 translocations frequently observed (> 3%) and effect the target gene expression levels. 16 of these deletions were signifincatly associated with OS or PFS after FDR correction. Several hypodiploid only translocation hotspots impacted the gene expression level with positive effect on OS. Some of these SV hotspots were associated with chromothripsis reported in ~25 of newly diagnosed MM patients. In conclusion, the large deep whole genome sequencing data from newly-diagnosed MM patients have identified a vast majority of non-coding mutations with potentially significant functional and biological role in MM. Our integrative approach using both WGS and RNA-seq data from the same patients now provides us important tool to further characterize the impact of these mutations and develop opportunities for targeted therapeutics.

Keywords:
genomics

Multiple myeloma

Whole genome sequencing

Tracks:
Multiple Myeloma Genomics

OAB-017

A First In-Depth Analysis of Alternate Splicing Landscape in Multiple Myeloma with Significant Potential Biological and Clinical Implications

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Abstract:
Alternative splicing (AS) is a critical post-transcriptional event, which affects the number of cellular processes, including cell growth and survival. Aberrant splicing of numerous genes in multiple myeloma (MM) such as XBP1 affects the

disease biology. However, to date, no whole-transcriptome-wide AS study has been performed in MM. We used deep RNA-sequencing data from 16 normal plasma cells (NPC) and 360 newly diagnosed MM patients to describe the landscape of the splicing events and evaluate the transcriptomic repertoire focused on the abundance of various isoforms. A global splicing analysis showed that mutually exclusive exon (MXE) (n=510) and Skipped Exon (SE) (n=417) are the most frequent splicing events in MM compared to normal plasma cells. Among these events, ~54% were observed in genes which are not differentially expressed between MM and NPC and 46% of the AS events (SE, MXE, retained intron, alternative 3'/5' sites) were observed in differentially expressed genes targeting 203 unique genes. The AS events targeted RNA transcription regulatory genes such as IKZF1, IKZF3; key regulatory elements in MM including IRF3, IRF4, and key transcription factors such as MEF2C, XPB1, STAT2, and ILF3. In general, alternate splicing affected DNA replication, cell cycle, and apoptosis pathways. There was heterogeneous distribution of AS in various MM subgroups; monosomy 14, t(4;14), del1p and del17p had the highest number of unique (not observed in other subgroups) AS events compared to NPCs. We finally evaluated isoform switched which may be affected by AS pattern changes. Our initial comparison between NPC and MM cells showed 500 significant isoform switches that are described as different usage of isoforms in different conditions. 48% of these switches were on non-differentially expressed genes between NPC and MM, targeting functionally critical genes such as CCND3, a cell cycle associated protein, in which the gene expression was not different between NPC and MM, but isoform usage was significantly altered. Significant isoform switches on SCNM1, RBMS1, CHMP7, PTAR1, TRIM22, CPPED1, C20orf24, DIDO1 were observed in all MM subgroups; however, subgroups tend to have different patterns similar to AS events. Functional impacts of isoform switches were evaluated using Open Reading Frame (ORF), protein domains (via Pfam), signal peptides (via SignalP), coding potential (via ENCODE) and sensitivity to Non-sense Mediated Decay (NMD). We report that alternative isoforms tend to create more protein-coding isoforms, alter the binding domains, and create new ORFs to alter the function of the genes. In summary, we describe a detailed splicing landscape in myeloma and highlight the biological and clinical importance of alternative splicing events. Moreover, we report significant isoform switches with potential functional consequences and therapeutic implications.

Keywords:
Gene expression profiling

Multiple myeloma

splicing

Tracks:
Multiple Myeloma Genomics

OAB-018

Clinical and Biological Early Relapse Predictors in Multiple Myeloma: An Analysis from the MMRF CoMMpass Study

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Abstract:
Trial in progress Background and aims. Multiple myeloma (MM) patients' (pts) prognoses range from

few months to many years. Pts who relapse early after first-line treatment show dismal outcomes. We analyzed the Multiple Myeloma Research Foundation (MMRF) CoMMpass trial to study the clinical and biological characteristics of early relapsing pts. Methods. CoMMpass interim analysis 14 cohort was used. Data cut-off for pts co-enrolled in the NCT02203643 study was May 30 2018. Early progressors were defined as pts with a time-to-progression (TTP) ≤18 months. Non-synonymous mutations/indels from a customized 21-genes list occurring in at least 25 pts were analyzed. Cytogenetic data were defined according to Seq-FISH. LDH levels were considered high if above the upper limit value of normal (ULN) or above the 90th centile if ULN was not available. Therapy for each pt was categorized according to initial induction therapy, autologous stem-cell transplantation (ASCT) and maintenance therapy. A univariate analysis of clinical and biological factors in early progressors vs no early progressors was performed; factors with p-value <0.15 in univariate analysis were then tested in a multivariate logistic regression model. Results. 1151 pts were enrolled in the IA14 CoMMpass release, the median follow-up of our cohort was 41 months. Molecular and TTP data were available in 926 pts that were included in the subsequent analyses. The most frequent induction therapy was VRd (34%) followed by bortezomib + chemotherapy triplet (23%). ASCT was received by 53% of evaluable pts. Maintenance was received by 74% of evaluable pts. Early progression occurred in 191/926 (21%) pts. Among early progressors, 16.2% were primary refractory, 46.6% relapsed while receiving active treatment during the first year. The cohort was composed of 760 (82.1%) real world pts and 166 (17.9%) pts enrolled in clinical trials. To avoid bias, the multivariate logistic regression model was corrected for clinical trial participation. Independent factors increasing the risk of early progression were TP53 mutation (OR 3.63, p<0.001), high LDH levels (OR 2.23, p=0.026), amp1q positivity (OR 1.56, p=0.027) and IGLL5 mutation (OR 1.73, p=0.025). Independent factors lowering the risk of early progression were ASCT (OR 0.29 vs no ASCT, p<0.001) and maintenance (OR 0.52 vs no maintenance, p=0.017). Conclusions. TP53 mutation, high LDH levels, amp1q and IGLL5 mutation are independent predictors of early relapse in our cohort. With the limitations of a mixed real-world + clinical-trial population and a non-randomized evaluation, treatment intensification with ASCT and maintenance lowered the risk of early progression.

Keywords:
early relapse

predictive factors

treatment

Tracks:
Multiple Myeloma Genomics

OAB-019

Combinatorial CRISPR-knockout identifies interactions between key genes and regulatory pathways in myeloma

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Abstract:
Combination regimens informed by preclinical studies have been a major driver of therapeutic progress in multiple myeloma (MM) over the last decades. To help inform the development of future combination regimens, we applied CRISPR-based functional genomics to identify previously underappreciated synergistic interactions between candidate therapeutic targets in MM. Our previous CRISPR-based gene-editing studies identified a large set of genes which are preferentially essential for MM (compared to other neoplasias). To examine how MM cell survival/proliferation is impacted by CRISPR KO of each gene individually vs.

simultaneous KO of two genes, we performed a combinatorial CRISPR dual knockout (DKO) screen in MM.1S or KMS-11 cells, which express 2 orthologous Cas9 nucleases (from S. pyogenes and S. aureus), to increase the efficiency and specificity of DKO. We studied 105 select genes, including ~50 MM-preferential dependencies; additional genes with broad-spectrum roles as dependencies in MM and other neoplasias; tumor suppressors; and genes that are frequently expressed in, but are not major dependencies for, MM cells in single KO studies (e.g. ZBP1, ELL2). We also applied this DKO system in vivo using MM.1S cells implanted in a "humanized" scaffold-based BM-like model. We observed strong overlap, but also distinct results, between the two cell lines in vitro; and between in vitro and in vivo studies of MM.1S. Notable results included: a central role for recurrent synergistic KO pairs, in vitro and in vivo, for several transcription factors (TFs), including members of NF-κB pathway, or endoplasmic reticulum (ER)-stress pathways; lack of major synergy between IKZF1 and IKZF3 KO, but recurrent synergistic pairs of either of these genes with other TFs; significant time-dependent pattern of synergistic interaction: in early time-points of these studies, potent dependencies (e.g. IRF4) are highly recurrent partners in synergistic pairs, while later time-points uncover interactions between genes with less pronounced, if any, individual roles as essential genes. Indeed, many synergistic combinations contained genes that are not top dependencies when tested individually but have known or proposed roles in regulation of gene transcription and/or ER stress (e.g. ZBP1, XBP1, ELL2). We observed prominent synergistic interactions involving antiapoptotic BCL-2 family members such as MCL1 or BCL2L1 in both cell lines, especially in KMS-11 cells for which these genes are less pronounced individual dependencies than MM.1S. KO of major dependencies such as IRF4 and POU2AF1 overcame the effect of TP53 KO in TP53-WT MM.1S cells and the effect of PTEN KO in MM.1S and KMS-11 cells. Our combinatorial functional genomics studies provides insights into interactions between key MM genes/regulatory pathways, including previously underappreciated pairs of targets with biological and potential therapeutic implications for the design of future combination therapies for MM.

Keywords:
BCL-2

Dual Knockout

Transcription factors

Tracks:
Multiple Myeloma Genomics

OAB-020

Immunomodulatory therapy improves outcome in multiple myeloma patients with clonal hematopoiesis

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Abstract:
Background: Multiple myeloma (MM) is a clonal plasma cell malignancy that accounts for 10% of hematological neoplasms and is diagnosed most commonly in patients over 50 years of age. Somatic mutations in hematopoietic stem cells are commonly acquired during aging - a phenomenon referred to as clonal hematopoiesis of indeterminate potential (CHIP) - and negatively influence survival in patients with non-hematological neoplasms. We examined how CHIP influences outcomes of MM patients. Methods: We performed targeted sequencing of cryopreserved, growth factor-mobilized peripheral blood from 629 MM patients who underwent autologous stem cell transplantation (ASCT) between 2003 and 2011 at the Dana-Farber Cancer Institute. We used the Multiple Myeloma Research Foundation database of 986 MM patients as a validation cohort. Results: Of the DFCI cohort, 136 patients (21.62%) had CHIP at the time of ASCT. The most commonly mutated genes were DNMT3A, TET2, TP53, ASXL1 and PPM1D. Twenty- four patients (3.8%) developed a second hematological malignancy at a median of 4 years [range: 1-10] following ASCT, and 29% of these had CHIP. Twenty-two percent of all patients underwent at least 3 years [range: 0.06-12.8] of first-line immunomodulatory (IMiD) maintenance. Of those who did not receive IMiD maintenance, CHIP was associated with worse overall survival (OS) ($p=0.001$) and, even more interestingly, progression-free survival (PFS) ($p<0.001$). In patients receiving IMiDs, CHIP had no effect on OS or PFS. Conclusion: CHIP is common in MM and the use of IMiDs post ASCT may abrogate the deleterious effects of CHIP on PFS and OS.

Keywords:
autologous stem cell transplant

CHIP

immunomodulatory drugs

Tracks:

Multiple Myeloma Genomics

OAB-021

Elotuzumab plus lenalidomide/dexamethasone for relapsed/refractory multiple myeloma: Final overall survival results from the phase 3 ELOQUENT-2 trial

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Abstract:
Introduction: In the randomized, phase 3 ELOQUENT-2 trial (NCT01239797), the addition of elotuzumab to lenalidomide/dexamethasone (ELd) demonstrated a sustained improvement in progression-free survival (PFS) compared with lenalidomide/dexamethasone alone (Ld) in patients (pts) with relapsed or refractory multiple myeloma (RRMM) (Dimopoulos MA et al. Cancer 2018). An interim analysis (IA) of overall survival (OS) showed a trend in favor of ELd vs Ld (hazard ratio [HR] 0.77; 95% confidence interval [CI] 0.61, 0.97), with a median OS of 43.7 months vs 39.6 months (Dimopoulos MA et al. Br J Haematol 2017). Here we present the final OS analysis. Methods: 646 pts with RRMM and 1–3 prior lines of therapy (LoT) were randomized 1:1 to receive ELd or Ld until disease progression, unacceptable toxicity, or withdrawal of consent. OS was tested hierarchically to the co-primary endpoints of PFS and overall response rate, with the final OS analysis (secondary endpoint) pre-specified to occur after at least 427 deaths. The 2-sided alpha for statistical significance was 0.046, based on the observed number of deaths at IA in the group sequential tests. Results: At the pre-specified final OS analysis (data cut-off Oct 3, 2018; minimum follow-up 5.9 years), ELd demonstrated an 18% reduction in the risk of death vs Ld (HR 0.820; 95.4% CI 0.676, 0.995; p=0.0408). The median (95% CI) OS was 48.3 (40.3, 51.9) months with ELd and 39.6 (33.3, 45.3) months with Ld. The OS benefit was observed in most predefined subgroups of interest, including pts aged at least 75 years (HR 0.69), pts with International Staging System stage III disease at enrollment (HR 0.74), 2–3 prior LoT (HR 0.71), and del17p positivity (HR 0.71). At the time of final analysis, 10.3% (33/321) of pts randomized to ELd and 4.3% (14/325) to Ld remained on treatment. The safety profile of ELd was consistent with prior reports, with no new safety signals detected. Fewer deaths occurred with ELd (212/318; 66.7%) vs Ld (225/317; 71.0%), with most deaths attributed to disease progression (ELd 41.2% vs Ld 44.8%). Grade 1–2 and grade 3 infusion reactions occured in 9.4% and 1.6% of pts who received ELd, respectively. Serious adverse events were reported in 74.8% (ELd) and 61.2% (Ld) of pts, most commonly infection (ELd 39.3% vs Ld 28.4%). The incidence of second primary malignancies was 12.3% (ELd) and 8.8% (Ld). Adverse events leading to discontinuation of any study drug occured in 35.8% (ELd) and 32.8% (Ld) of pts. Conclusion: ELd demonstrated a statistically significant and clinically meaningful 18% reduction in the risk of death vs Ld in the ELOQUENT-2 trial. ELd is the only approved antibody-based regimen shown to significantly prolong OS in pts with RRMM and 1–3 prior LoT.

Keywords:
elotuzumab

Overall survival

relapsed/refractory multiple myeloma

Tracks:
Antibody Based Approaches to MM

OAB-022

Subcutaneous (SC) Daratumumab (DARA) in Combination With Standard Multiple Myeloma (MM) Treatment Regimens: An Open-label, Multicenter Phase 2 Study (PLEIADES)

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Abstract:
Background: Intravenous (IV) DARA is approved as monotherapy and in combination with standard-of-care (SoC) regimens for relapsed or refractory MM (RRMM) and transplant-ineligible newly diagnosed MM (NDMM). A SC co-formulation of DARA with recombinant human hyaluronidase PH20 (rHuPH20; ENHANZE® drug delivery technology, Halozyme, Inc.) can be administered in 3-5 minutes. This phase 2, open-label, multicenter study (PLEIADES) assessed efficacy and safety of DARA SC (D) combined with bortezomib, lenalidomide, and dexamethasone (VRd), bortezomib, melphalan, and prednisone (VMP), or lenalidomide and dexamethasone (Rd) in NDMM or RRMM patients (pts). Methods: Transplant-ineligible NDMM pts received D-VMP, and RRMM pts with ≥1 prior line of therapy received D-Rd; both cohorts were treated until disease progression. Transplant-eligible NDMM pts received 4 cycles of D-VRd induction therapy (subsequent therapy/autologous stem cell transplant performed off-study). Primary efficacy endpoints were overall response rate (ORR) for D-VMP and D-Rd and very good partial response or better (≥VGPR) rate for D-VRd. Secondary endpoints included ≥VGPR for D-VMP and D-Rd, ORR for D-VRd, and complete response or better (≥CR) rate, duration of response, minimal residual disease (MRD)-negativity rate, and DARA serum concentrations for all cohorts. Safety data included rates of treatment-emergent adverse events (TEAEs) and infusion-related reactions (IRRs). Results: 199 pts were enrolled (D-VMP, n=67; D-Rd, n=65; D-VRd, n=67). As of the data cutoff (4 March 2019), median duration of follow up was approximately 7 months for D-VMP and D-Rd and 4 months for D-VRd. Primary endpoints were met for all cohorts. Rate of ORR for D-VMP was 88.1% (90% CI, 79.5%-93.9%) and for D-Rd was 90.8% (90% CI, 82.6%-95.9%). Rate of ≥VGPR for D-VRd was 71.6% (90% CI, 61.2%-80.6%). Rate of ≥VGPR for D-VMP was 64.2% (90% CI, 53.5%-73.9%) and for D-Rd was 64.6% (90% CI, 53.7%-74.5%). ORR for D-VRd was 97% (90% CI, 90.9%-99.5%). At the time of the primary analysis, ≥CR rates, duration of response, and MRD-negativity rates were immature. DARA mean Cmax was comparable across cohorts at Cycle 1, Day 4 and consistent with historical DARA SC data. Rates of any grade IRRs and injection-site reactions were each 7.5% across all cohorts (1 grade 3 IRR for D-VRd; no grade 4 reactions in any cohort). Median duration of administration was 5 minutes for all cohorts. Grade 3 or 4 TEAEs were reported by 46 (68.7%), 51 (78.5%), and 39 (58.2%) pts in the D-VMP, D-Rd, and D-VRd cohorts, respectively. TEAEs leading to treatment discontinuation were <5% in all cohorts. Safety profiles in all cohorts were consistent with DARA IV in combination with these backbone SoC regimens. Conclusions: DARA SC in combination with SoC regimens demonstrated comparable clinical activity and safety to corresponding DARA IV regimens, with considerably lower IRR rates and substantially shorter durations of administration.

Keywords:
CD38

daratumumab

Multiple myeloma

Tracks:
Antibody Based Approaches to MM

OAB-023

Isatuximab, Carfilzomib, Lenalidomide and Dexamethasone (I-KRd) in front-line treatment of high-risk Multiple Myeloma: Results of the Safety Run-In cohort in the phase II, multicenter GMMG-CONCEPT trial

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Abstract:
High-risk multiple myeloma (MM) disease still has a significant impaired prognostic outcome. Achievement of minimal residual disease (MRD) negativity correlates with favorable progression-free (PFS) and overall survival (OS) including high-risk patients. Combination treatment with proteasome inhibitor, immunomodulating agent and dexamethasone in first-line treatment results in high response rates and deep remissions. It was shown, that addition of monoclonal anti-CD38 antibody further improves depth of response and MRD-negative rates. The multicenter, phase II GMMG-CONCEPT trial investigates combination treatment with Isatuximab, Carfilzomib, Lenalidomide and Dexamethasone (I-KRd) for front-line, high-risk MM. Here, we report on the results of the safety run-in cohort. 153 patients with newly-diagnosed MM are planned to be included into the trial and receive 6 cycles of I-KRd induction followed by high-dose melphalan, 4 cycles of I-KRd consolidation and I-KR maintenance. The safety-run in phase included the first 10 patients to assess dose-limiting toxicities during the first two I-KRd cycles. In addition, early responses are reported. 10 patients (42-67 years) contributed to the analysis. All patients experienced at least one treatment-emergent adverse event (TEAE), in total 49 TEAE were reported, 15 were classified as Grad 1, 14 as Grade 2, 17 as Grade 3 and 3 as Grade 4. Main ≥ Grade 3 toxicities were hematologic with neutropenia in 6 patients, leukopenia in 5 patients, lymphopenia in 2 patients, anemia in 2 patients and thrombocytopenia in 1 patient. Non-hematological toxicities Grade ≥ 3 were cerebral vascular disorders in 2 patients, self-limiting ventricular tachycardia in 1 patient and diarrhea in 1 patient. 3 patients experienced infusion reaction grade 2 during the first Isatuximab infusion. In total, 5 SAE occurred. The 2 cerebral events were classified as non-related due to preexisting comorbidities. 9/10 patients completed 6 cycles of induction. 10/10 patients had documented responses during induction phase with all patients achieving ≥ VGPR. Conclusions: The 4-drug combination of I-KRd was administered for the first time for treatment of MM patients. Overall, toxicity was manageable with an overall safety profile consistent with prior experience with KRd and anti-CD38 antibody treatment. After completion of the safety run-in, the trial continued as planned. First response rates are encouraging and will be followed continuously.

Keywords:
High risk

isatuximab

Tolerability

Tracks:
Antibody Based Approaches to MM

OAB-024

Potent Targeting of the Glycoantigen CD75s on Myeloma by the Tetravalent, Fc-Engineered Antibody 'EBU-141 Tetra'

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Abstract:
Background: Daratumumab and elotuzumab are powerful treatment options in myeloma therapy but resistance and relapse still represent major challenges. Novel target structures may open alternative avenues to develop effective antibody therapies. Here, we present the monoclonal antibody 'EBU-141 Tetra' directed against the glycoantigen CD75s (alpha-2,6-sialylated lactosamines on glycoproteins and glycolipids) as a potent agent with potential application in myeloma therapy. CD75s is present on plasma cell tumors and mature B cell lymphomas, including Burkitt's lymphoma, FL, DLBCL, MCL and CLL. To evaluate CD75s as a target for a therapeutic antibody we generated a tetravalently binding Fc-engineered chEBU-141 IgG1 antibody with enhanced avidity for CD75s and potent effector functions. Methods: 'EBU-141 Tetra' was designed in a format enabling tetravalent antigen binding and improved recruitment of immune cells as well as the complement system by applying Fc-protein engineering. The antibody was produced by transient transfection and purified by affinity chromatography. Direct anti-tumor effects and Fc-mediated effector functions were investigated in cell proliferation assays, by fluorescence microscopy, and in 51Cr release experiments using myeloma cell line U266 and Burkitt's lymphoma cell line Daudi as well as freshly isolated tumor cells. Peripheral blood mononuclear cells (PBMC), monocyte-derived macrophages and serum of healthy donors were used in the functional assays. Results: The Tetra-Fab design of 'EBU-141 Tetra' improved binding to CD75s on cell surface of malignant plasma cells as well as mature B cell lymphoma cells compared to the conventional bivalent antibody chEBU-141 IgG1. The higher avidity for CD75s and the applied Fc-engineering strategy resulted in markedly improved antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) of 'EBU-141 Tetra' compared to chEBU-141 IgG1 against myeloma and Burkitt's lymphoma cells. Of note, also freshly isolated B-CLL tumor cells were efficiently killed by 'EBU-141 Tetra' and PBMCs with EC50 values in the low nanomolar range. In addition, 'EBU-141 Tetra' induced potent antibody-dependent cellular phagocytosis (ADCP) of myeloma and lymphoma cells. Thus, the novel tetravalent, Fc-engineered antibody 'EBU-141 Tetra' efficiently activated immune effector cells and the complement system for tumor cell lysis.
Conclusions: Our findings demonstrate that highly potent IgG-based antibody-derivatives against glycan-structures can be generated that harbor four antigen-binding sites and are Fc-engineered for improved ADCC, ADCP and CDC activity. In conclusion, 'EBU-141 Tetra' may represent a new candidate for clinical application in myeloma and lymphoma therapy.

Keywords:
Fc-engineering

glycoantigen

immunotherapy

Tracks:
Antibody Based Approaches to MM

OAB-025

The anti-BCMA Bispecific T-cell Engager (BiTE®) Molecule AMG 420 Induced MRD-Negative Complete Responses in R/R Multiple Myeloma in a FIH study

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Abstract:
Background: BCMA, a TNFR family member, is expressed on multiple myeloma (MM) cells and plasma cells (PC). Objectives of this study included assessing safety and activity per IMWG 2006 of the BiTE molecule AMG 420/BI 836909, which binds BCMA (B-Cell Maturation Antigen) on MM cells and CD3 on T cells, thus engaging T cells to malignant cells in R/R (relapsed and/or refractory) MM. Methods: In this FIH study (NCT02514239), 6-week cycles of AMG 420 were given for ≤5 cycles or until disease progression (PD), toxicity, or consent withdrawal; 5 more cycles could be given for benefit. Single-patient cohorts [0.2 1.6 µg/day (d)] were followed by cohorts of 3-6 patients (3.2 800 µg/d). Eligible patients had progression after ≥2 lines (including proteasome inhibitor and IMiDs). Excluded were PC leukemia, extramedullary relapse, CNS involvement, or prior allo-SCT. Minimal residual disease (MRD) was defined for this study as <1 tumor cell / 10-4 bone marrow cells per flow cytometry using antibodies to cytIgλ, cytIgκ, CD19, CD56 or CD138, CD38, and CD45. Results: As of April 8, 2019, 42 patients received AMG 420 (0.2-800 µg/d). Median age was 65 y, median MM duration 5.2 y, and median # prior therapies 4. Patients discontinued for PD (n=25), adverse events (AE, n=7, incl 3 dose-limiting toxicities [DLTs]), death (4), completed 10 cycles (3), and consent (1). Patients were treated for a mean (SD) of 2.8 (2.9) cycles. Serious AEs (SAEs, n=20, 48%) occurring in >1 patient were infections (14) and polyneuropathy (PN, 2). Treatment-related SAEs included the 2 cases of grade 3 peripheral PN and 1 case of grade 3 edema. There were 2 deaths from AEs, acute respiratory distress from flu / aspergillosis and fulminant hepatitis related to adenovirus infection; neither treatment related. Grade 2-3 CRS was seen in 3 patients. No anti-AMG 420 antibodies were detected. In this study, 800 µg/d was determined to not be tolerable as 2/3 patients had DLTs, 1 grade 3 CRS and 1 grade 3 PN; both events required hospitalization and subsequently resolved. There also was 1 grade 3 DLT of PN among the 10 patients receiving 400 µg/d, which also resolved. At 400 µg/d, there were 5 MRD-negative CRs, 1 VGPR, and 1 PR, for a response rate of 7/10 (70%); at April datacut, responses lasted for 5.8-13.6 months with 2 patients ongoing on treatment. Overall in the study, there were 13/42 responders (6 MRD-negative CRs, 3 CRs, 2 VGPRs, 2 PRs). Median time to any response was 1 month, with 11 of 13 patients responding in the first cycle. Conclusions: In this FIH study, AMG 420, a short half-life BiTE molecule targeting BCMA, showed encouraging evidence of activity in patients with R/R MM. At 400 µg/d, there was a 70% response rate (7/10) with 5 out of 7 responders achieving MRD-negative CRs. DLTs at 800 µg/d were CRS and PN. Other than 1 DLT of PN at 400 µg/d, no major toxicities were observed up to 400 µg/d; this dose is being investigated further.

Keywords:
B-cell maturation antigen

BiTE® (Bispecific T-cell Engager) molecule

Minimal residual disease

Tracks:
Antibody Based Approaches to MM

OAB-026

Synthesis, preclinical analysis, and first-in-human phase I imaging of 89Zr-DFO-daratumumab for CD38 targeted imaging of myeloma

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Abstract:
Introduction: Currently, there is a lack of imaging-based assays to determine disease burden in patients diagnosed with multiple myeloma. Daratumumab is an FDA-approved antibody therapy for myeloma, that targets CD38, an antigen expressed on nearly all myeloma cells. We report here the synthesis, preclinical analysis, and first-in-human imaging of 89Zr-DFO-daratumumab for noninvasive CD38-targeted imaging of myeloma. Methods: Daratumumab was radiolabeled with 89Zr via desferrioxamine (DFO) conjugation, producing 89Zr-DFO-daratumumab. Western blot, flow cytometry, saturation binding assays, and internalization assays characterized CD38 expression and binding of 89Zr-DFO-daratumumab in an OPM2 myeloma cell line. A murine xenograft model of the OPM2 cell line was generated for in vivo studies. Mice with OPM2 xenografts and healthy mice were administered 200 microCi of 89Zr-DFO-daratumumab and PET/CT imaging was performed. Following successful preclinical imaging, an IRB protocol and IND from the FDA were obtained for first-in-human phase I imaging. Ten myeloma patients received 2 mCi of intravenous 89Zr-DFO-daratumumab in 3, 20, or 50 mg of total antibody mass. Each patient underwent 4 PET/CT scans over the next 8 days, as well as blood draws and whole-body counts, to determine tracer biodistribution, pharmacokinetics, and radiation dosimetry. Results: 89Zr-DFO-daratumumab was produced with >99% radiochemical purity and high stability. Flow cytometry demonstrated >90% antibody immunoreactivity in OPM2 cells. PET/CT of murine xenograft models demonstrated background 89Zr-DFO-daratumumab distribution in the blood pool, liver and spleen. Substantial bone marrow uptake was seen in OPM2 mice, but not in healthy mice, consistent with targeted imaging of OPM2 myeloma cells engrafted in this cancer model. Phase I first-in-human 89Zr-DFO-daratumumab PET/CT imaging demonstrated distribution in the blood pool, liver and spleen. Focal 89Zr-DFO-daratumumab uptake was visualized in previously known as well as unknown sites of osseous myeloma, consistent with successful CD38-targeted immunoPET imaging of myeloma in human patients. Conclusions: 89Zr-DFO-daratumumab provides successful whole-body PET visualization of myeloma in both a murine myeloma xenograft model and in a first-in-human phase I trial of myeloma patients. This novel PET antibody will be tested for its potential to provide sensitive detection of myeloma, predict the effectiveness of daratumumab therapy, and serve as the basis of theranostic constructs for patients with myeloma.

Keywords:
CD38

Imaging

PET-CT

Tracks:
Antibody Based Approaches to MM

OAB-027

Progression signature underlies clonal evolution and dissemination of Multiple Myeloma

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Abstract:
Multiple Myeloma (MM) is a genetically complex and evolutionary process whereby transformed cells continuously acquire genetic and/or epigenetic lesions to generate heterogeneous cell populations composed of functionally distinct clones in the bone marrow (BM). A small number of detectable pre-malignant clones are present in early stage and will continue to acquire more abnormalities leading to overt disease. In order to accurately predict the course of the disease with the presence of BM environment, we require methods to estimate clone-specific growth rates and define clones that have the propensity of dissemination. Methods: We developed a PrEDiCT (Progression through Evolution and Dissemination of Clonal Tumor cells) xenograft mouse model, enabling both molecular profiling and functional tracking of clonal dissemination of MM tumor cells by performing tumor-bearing bone chip implantation subcutaneously to SCID-beige mice and examining tumor clones present in the implanted bone chips (primary sites) compared to those in the distant BM sites (disseminated sites). By intersecting differentially expressed genes at primary and disseminated sites, we identified a set of genes that are either down-regulated or up-regulated during dissemination and designated this set of gene expression profiles as 'progression signature'. Results: We found that 15 fluorescent color labeled tumor clones were present with equal distribution in the primary sites but not at the disseminated sites. Specific clones (winner clones) had a greater advantage of growing in the disseminated sites. Confocal imaging showed the difference in cluster structures between primary and disseminated tumors. Most of the clusters in the disseminated sites consisted of cells of single colors. RNA sequencing analysis of two human MM cell lines derived from PrEDiCT model demonstrated a distinct gene expression profile. Gene Set Enrichment Analysis of the progression signature in publicly available MM patient datasets (GSE6477, GSE2113 and GSE24080) demonstrated that this signature significantly correlated with overall survival and with clinical progression from MGUS/smoldering MM to overt myeloma and relapsed disease. 36 genes were computationally predicted to be master regulators of MM progression, HMGA1, TRIM28 and PA2G4 were selected and validated in PrEDiCT model using CRISPR mediated loss of function screen which prioritized HMGA1 and PA2G4 as the key regulators in MM dissemination. Conclusions: Here, we demonstrate that in vivo clonal evolution can be characterized using an in vivo model of MM. The data defines specific clones that have a higher progression potential and are likely driver clones for tumor dissemination in MM. A progression signature was discovered and HMGA1 and PA2G4 were validated as potential regulators of MM progression. Overall, our model successfully deciphered key characteristics of human MM progression and identified potential therapeutic targets.

Keywords:
clonal evolution

dissemination

progression signature

Tracks:
Multiple Myeloma Signaling

OAB-028

REIIBP is a histone methyltransferase overexpressed in T(4;14) multiple myeloma with oncogenic potential

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Abstract:

Multiple Myeloma (MM), characterized by the uncontrolled proliferation of malignant plasma cells in the bone marrow, occurs mainly in the elderly population. Recurrent chromosomal translocations are central to the pathogenesis of MM, with t(4;14) being the second-most common and associated with poor prognosis. The histone methyltransferase (HMTase) MMSET is overexpressed in MM as a result of the t(4;14) translocation. MMSET is capable of producing 3 major isoforms, MMSET II, REIIBP and MMSET I. MMSET II encodes the full-length protein of 1365 amino acids and possesses HMTase activity for H3K36 and H4K20. MMSET I, a short isoform with 647 amino acids, is identical to MMSET II N-terminus. REIIBP, a short isoform with 584 amino acids, has an identical sequence of MMSET II C-terminus. Although the short isoform REIIBP is overexpressed universally in t(4;14) MM, its role in t(4;14) MM remains poorly understood. In this study, non-t(4;14) MM cell line RPMI8226 was transfected with REIIBP vector and selected with puromycin, thereby generating a cell line with ectopic expression of REIIBP. Overexpression of REIIBP in MM cells leads to an aberrantly high global level of H3K9me3, H3K27me3 and H3K79me3, which were subsequently confirmed with liquid chromatography-mass spectrometry (LC-MS) analysis. In vitro HMTase assay indicated that the SET domain is required for REIIBP methyltransferase activity, specifically H3K27me3. We further investigated genes and pathways regulated by REIIBP in MM cells. Gene expression array analysis after REIIBP overexpression showed that REIIBP increased BTK (Bruton's tyrosine kinase) mRNA levels significantly. BTK is involved in B-cell receptor signaling in which it activates NFkB signaling pathway via phosphorylation of NFkBp65 and anti-apoptotic protein Bcl2. REIIBP upregulates BTK level, which in turn activates BTK downstream target Bcl2, leading to increased cell proliferation and reduced cell apoptosis in MM cells. REIIBP also promotes in vivo tumor formation of MM cells. MM cells overexpressing REIIBP are sensitive to BTK inhibitor, Ibrutinib. Our results indicated that H3K27me3 is the primary product generated by REIIBP and suggests that REIIBP might act as an oncoprotein in t(4;14) MM cells.

Keywords:
BTK

REIIBP

Tracks:
Multiple Myeloma Signaling

OAB-029

Cooperative impact of Utx loss and Braf V600E mutation induces myeloma in mice

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Abstract:
Dysfunction of the epigenetic modifiers has been implicated in multiple myeloma (MM). The histone H3K27 demethylase UTX was found to be affected by inactivating somatic mutations in 3-10% of myeloma samples. Importantly, patients with a mutation or deletion in UTX had shorter overall survival. These reports suggest that UTX acts as a

tumor suppressor in MM. However, no studies have investigated the role of UTX loss in MM in vivo. In addition, overexpression of EZH2, that catalyzes the generation of H3K27me3, was found to correlate with myeloma disease progression and poor prognosis. We previously showed that dual inhibition of EZH2 and its homolog EZH1 alone and in combination with proteasome inhibitors constitute a novel therapeutic strategy in MM (Rizq et al. Clin Cancer Res. 2017). On the other hand, the activating mutations in the RAS/RAF/MEK/ERK/MAPK pathway were identified in up to 50% of newly diagnosed MM patients with V600E as the predominant BRAF variant. In this study, we investigated the function of UTX in MM and the interplay between UTX loss and the activating BRAF V600E mutation in myelomagenesis. We used a conditional mouse model with knock-out allele of Utx and/or knock-in allele of Braf V600E combined with Cγ1-Cre allele. We found that UTX loss together with the activating Braf V600E mutation shortened the survival of mice, particularly UtxΔ/Δ Braf V600E females, compared with either single mutation and control mice. We observed plasma cell neoplasms in a significant number of UtxΔ/Δ Braf V600E, UtxΔ/+ Braf V600E, and UtxΔ/Y Braf V600E mice (6/17, (35%); 5/16, (31%) and 12/20 (60%), respectively). Mice that developed MM-like disease showed a marked increase in BM plasma cells, large M spikes in serum protein electrophoresis, and anemia. Importantly, the malignant plasma cells were readily transplantable into recipient mice with high penetrance. Interestingly, gene set enrichment analysis of RNA seq data of mice that developed MM-like disease revealed that Myc was a major driver of tumorigenesis in our mouse model. ChIP-seq for H3K27me3 could not detect a meaningful change in Utx/Braf-mutant mice compared with control ones. Next, we studied the sensitivity of a murine cell line developed from our mouse model to novel and conventional anti-myeloma agents. Consistent with our data from human cell lines, dual inhibition of EZH2 and EZH1 was more effective than specific EZH2 inhibition. Interestingly, we found that concurrent loss of Utx and the activating Braf V600E mutation conferred resistance to proteasome inhibitors, which was overcome by dual inhibition of EZH2 and EZH1. Importantly, restoration of Utx expression in the Utx knock-out cell line markedly inhibited the growth of the cells. Taken together, Utx insufficiency cooperates with the activating Braf V600E mutation in mice to induce myeloma. We believe that our mouse model is a useful tool to understand the pathogenesis of myeloma and test novel therapeutic agents.

Keywords:
BRAF

epigenetic

UTX

Tracks:
Multiple Myeloma Signaling

OAB-030

PHF19 Promotes Drug Resistance via Increased EZH2 Phosphorylation in Multiple Myeloma

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Abstract:
Introduction:Multiple myeloma (MM) is an incurable hematological malignancy characterized by the clonal proliferation of plasma cells. Besides genetic abnormalities, epigenetic aberrations affecting histone modifications also play a critical role in MM pathogenesis. However, it remains largely elusive. Methods:We investigated the expression of PHD finger protein 19(PHF19), a component of the polycomb repressive complex 2, and outcomes of MM patients in clinical databases and sequential patient samples. The effects of PHF19 on cell growth and drug resistance were confirmed by overexpression or shRNA knock-down models both in vitro and in vivo. Co-IP and western blot assay further confirmed molecular mechanism involved in PHF19 functional activity. Dual luciferase assay was applied to explore the direct regulation of miRNA-15a on PHF19. Results: Enhanced PHF19 expression is highly associated with high-risk cytogenetic profiles and inferior outcomes of MM patients. We overexpressed full-length human PHF19 cDNA into ARP1 and OCI-My5 MM cell lines via lentivirus infection. PHF19-OE significantly enhanced cell proliferation compared to cells transfected with an empty vector (EV) in both ARP1 and OCI-My5 MM cell lines. Moreover, overexpression of PHF19 led to suppression of apoptosis in ARP1 and OCI-My5 cells exposed to commonly using anti-MM reagents, such as bortezomib (BTZ), epirubicin (EPI), and melphalan (MEL). We also investigated the effects of PHF19 overexpression in vivo using a xenograft mouse model. We found that mice engrafted ARP1-OE cells had a significantly larger tumor volume than the control mice engrafted with ARP1-EV cells. Consistent with our in vitro data, bortezomib injection could not inhibit ARP1-OE cell growth. PHF19 promotes MM cell growth and drug resistance both in vitro and in vivo. We also knocked down PHF19 in ARP1 and OCI-My5 MM cell lines through a doxycycline-inducible shRNA lentivirus delivery. Upon the induction of doxycycline, PHF19 protein expression was remarkably downregulated. PHF19 Knock-down significantly suppressed cell growth and sensitizes myeloma cells to chemotherapeutic drugs both in vitro and in vivo. RNA-sequencing and western blot analysis confirms that PHF19 enhances PI3K/AKT activity, which subsequently leads to phosphorylation of EZH2 at Ser21. EZH2 phosphorylation suppresses H3K27me3, resulting in upregulation of downstream targets (BCL-xL, MCL-1 and HIF-1α) that promote cell growth. Importantly, PHF19 overexpression is not caused by DNA amplification of chromosome 9q, but by the direct downregulation of miR-15a. Conclusions: Deregulation of miR-15a/PHF19/phosphorylation EZH2 patterns participates in disease pathogenesis and progression of MM. PHF19 is a potential therapeutic target to overcome drug resistance, and improve outcome of MM patients. Our data provides preclinical rational to support the treatment targeting PHF19 to suppress growth and overcome drug resistance in MM and other cancers.

Keywords:
Drug resistance

Multiple myeloma

PHF19

Tracks:
Multiple Myeloma Signaling

OAB-031

Determining resistance mechanisms in BRAF-mutated multiple myeloma

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Abstract:
Introduction: Evolution and outgrowth of clones that harbor resistance mutations likely contribute to the emergence of drug-resistant disease in multiple myeloma (MM). In this study, we investigate resistance to the BRAF inhibitor dabrafenib in the context of BRAF-mutated MM which accounts for about 5-12% of all patients with relapsed/ refractory MM. Methods: Resistance to dabrafenib was modeled in vitro in the BRAF-mutated MM cell lines (MMCL) U266 (K601N-mut) and DP6 (BRAFV600E-mut). Low-pass whole genome sequencing (LPWGS), RNA sequencing, ChIP sequencing and immunoblotting were performed for genomic, transcriptomic, epigenomic and molecular characterization. Functional validation was performed by genome editing using CRISPR/Cas9 technology. Results: Modeling of dabrafenib resistance in vitro revealed an initial decline of cell numbers, followed by a plateau phase and a gradual outgrowth of resistant cells after ~80 days of treatment. As expected, exposure of BRAF-mut MMCL to dabrafenib led to initial downregulation of pERK and pMEK. At later timepoints, upregulation of pERK and pMEK was observed, suggesting that re-activation of the ERK/MEK pathway ultimately overcomes BRAF inhibition. This outgrowth was associated with highly distinct copy number profiles in each resistant clone. This implies clonal selection with outgrowth of genetically resistant clones as one mechanism of drug resistance in MM. In a next step, we found that BRAF inhibition of BRAF-mut MMCL promotes changes of the transcriptional circuitry that is independent from clonal outgrowth of genetically resistant clones. These transcriptional changes were highly homogenous, occurred as early as after 7-14 days of treatment and were associated with de-differentiation of MMCL into a more immature B lymphocytic phenotype. This phenotype was associated with greater mRNA expression of CD19 and CD81, as well as upregulation of the B-lymphocyte activation antigen B7-2 (CD86) and PI3K pathway genes. Chromatin immunoprecipitation for H3K27ac indicated increased enhancer marks near PIK3CD, PIK3CG and B7.2. We next investigated if targeting the PI3K pathway and B7.2 can be exploited for effective killing of dabrafenib-resistant BRAF-mut MMCL. Studies for the PI3Kδ inhibitor idelalisib in dabrafenib-persistent MMCL revealed higher sensitivity as compared to dabrafenib-naïve controls. Genome editing suggests a survival advantage for CD86-wt as compared to CD86-ko MMCL. Conclusions: Resistance to BRAF inhibition in vitro is mediated by two distinct mechanisms: 1) clonal outgrowth of genetically distinct resistant clones, and 2) transcriptional rewiring that leads to activation of alternative signaling pathways. The latter is characterized by a de-differentiated B-cell phenotype and upregulation of PI3K and CD28/CD86 signaling. These concepts may provide a framework for revealing therapeutic vulnerabilities and to overcome drug resistance mediated by genetic heterogeneity in MM.

Keywords:
BRAF

clonal evolution

Genomic instability

Tracks:
Multiple Myeloma Signaling

OAB-032

Copy number gain of the MCL1 gene locus (1q21) and acquisition of BCL2 mutation mediate resistance to venetoclax in multiple myeloma (MM) patients

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Abstract:
Background: Venetoclax (VEN) induces deep responses in relapsed MM, however acquired resistance frequently occurs. With the challenges secondary resistance poses there is a need to investigate the mechanisms mediating this resistance to VEN. Methods and Results: Bone marrow aspirates were collected from patients (n=8) treated with VEN prior to initiation of therapy and at progression. Ex-vivo profiling of VEN sensitivity was performed on CD138+ cells. Unbiased mRNA and DNA profiling was conducted by single-cell RNAseq and copy number analysis (scCNV) on pre- and post-VEN CD138+ cells. Cell Ranger, Seurat and Monocle were used for sequencing data analysis. Ex-vivo apoptosis studies revealed a shift of the IC50s of VEN from ~100 nM in pretreatment to >1000 nM at disease progression. scCNV profiling identified a significant expansion of a pre-treatment subclonal (<1%) cluster with 1q21 gain to become the predominant clone (>70%) at relapse. The scale of the 1q CNV gain varied from 3 Mb to a focal gain of 100 kb encompassing the MCL1 locus. scRNA confirmed the gain in the MCL1 transcript. Single cell trajectory analysis and pseudotime ordering of cells revealed the emergence of a highly proliferative clone and of a MCL1 dependent clone as the disease evolved from its original BCL2 dependent cluster at pseudotime t0. Ex-vivo apoptosis profiling revealed an acquired sensitivity to the MCL1 inhibitor (S63845).. In order to functionally confirm whether the gain in MCL1 is sufficient to induce resistant to VEN, we stably overexpressed MCL1 in the KMS12PE BCL2-dependent MM cell line (KMS12PE_MCL1) and examined its sensitivity to VEN relative to control (KMS12PE_EV). Of interest, co-immunoprecipitation of BIM in KMS12PE_MCL1 demonstrated a shift in BIM loading and co-IP with MCL1 and BCL2 while it was restricted to BCL2 in KMS12PE_EV cells. Importantly, VEN IC50 increased by 200 folds in KMS12PE_MCL1 cells with acquired sensitivity to S63845. In one patient, scCNV analysis did not identify any gain in the 1q locus at the time of disease progression. Mutation analysis however identified a de novo BCL2 mutation [c.332A>C, p.(Asp111Ala)]. To determine whether the Asp111Ala mutation alone is sufficient to confer resistance to VEN, the mutant was overexpressed in KMS12PE cells. While BIM binding to BCL2 was unaffected, Aps111Ala largely abrogated VEN-induced BIM displacement from BCL2 and reduced KMS12PE cells sensitivity to VEN by ~7.5 folds. Conclusion: We have discovered a novel BCL2 mutation that confers resistance to VEN. In addition we have identified an enrichment of MM clones with MCL1 locus 1q copy number gain at the time of acquired VEN resistance. These findings (1q gain) may explain the worsened overall survival seen in VEN relapsing patients. Early detection and dynamic monitoring of these abnormalities (BCL2 mutant or 1q gain) with early therapeutic interventions targeting these clones may enhance VEN efficacy and improve patients' survival

Keywords:
BCL-2

Drug resistance

Venetoclax

Tracks:
Multiple Myeloma Signaling

OAB-033

Clinical Responses and Pharmacokinetics of fully human BCMA Targeting CAR T Cell Therapy in Relapsed/Refractory Multiple Myeloma

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Abstract:

Background: Previous studies indicate that patients with relapsed/refractory multiple myeloma (RRMM) who receive high-dose BCMA-targeting CAR-T cells may achieve better remission but have worse adverse events. Moreover, once the disease progresses again, the re-infusion of CAR-T cells is not effective. To solve this dilemma, we have developed a novel BCMA-targeting CAR-T (CT103A) with a lentiviral vector containing a CAR structure with a fully human scFv, CD8a hinger and transmembrane, 4-1BB co-stimulatory and CD3z activation domains. Methods: ChiCTR1800018137 is a single-center and single-arm trial of CT103A in patients with RRMM. The primary objectives are to characterize the safety and tolerability in patients with R/R MM. The secondary objectives include evaluation of anti-myeloma activity, cytokines, CAR-T cell persistence, and pharmacokinetics. Between September 21, 2018, and June 18, 2019, twelve patients (including 4 patients having relapsed after being given a murine BCMA CAR-T and 5 patients having extramedullary disease and/or plasma cell leukemia) received CT103A in 3+3 dose-escalation trial (four doses at 1, 3, 6 ×106/kg) after a conditioning chemotherapy regimen of cyclophosphamide and fludarabine. All Patients had received a median of 4 prior lines (range 3 - 6) of MM therapy. Results: At the time of the June 18, 2019 data analysis, the overall response rate was 100%, and 4/12 patients achieved CR within two weeks post-infusion (Table1). The sCR was 64%, and VGPR was 36% for 11 evaluable patients. In 4 patients who have participated in a prior CAR-T trial, three have achieved sCR, and 1 achieved VGPR. The pharmacokinetics of CT103A were assessed by a digital polymerase chain reaction. Rapid and robust CAR- T cell expansion in all dose levels. The median Tmax is 14 days (ranging from 9 to 25) after infusion, indicating rapid expansion of the CT103A. CT103A persist in 10/11 patients; the longest CART persistence time has reached 260 days. In addition, Cmax and AUC0-28 reached levels comparable to reported CD19 CAR-T. In the first two dose groups, the grade of cytokine release syndrome (CRS) was 0 - 2. A grade 4 CRS appeared at six ×106 /kg dose group and was considered as a dose-limiting toxicity DLT. No neurotoxicity was observed in all dose groups. Conclusions: Data from this early-stage clinical study showed the unparalleled safety and efficacy of CT103A in heavily pretreated R/R multiple myeloma patients. Major AEs were transient, manageable, and reversible. Highly active (ORR 100%) and rapid response within two weeks, suggests CT103A could be developed as a competitive therapeutic to treat patients with RRMM.

Keywords:
B-cell maturation antigen

clinical trials

myeloma

Tracks:
Immunotherapeutic Approaches to MM

OAB-034

Off-the-shelf AlloCAR T™ cells targeting BCMA for the treatment of multiple myeloma

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Abstract:
Autologous chimeric antigen receptor (CAR) T cells targeting B-Cell Maturation Antigen (BCMA) have achieved clinical responses in patients with relapsed or refractory multiple myeloma. Development of autologous CAR T therapies is however limited by logistical challenges and manufacturing constraints. Allogeneic CAR T (AlloCAR T™) therapies may overcome these innate limitations of autologous CAR T therapies, potentially expanding patient access by providing a readily available off-the-shelf product. ALLO-715 is an anti-BCMA allogeneic CAR T cell product manufactured using healthy

donor-derived peripheral blood mononuclear cells. Activated T cells are transduced with a lentiviral vector containing the anti-BCMA CAR and subsequently transfected with mRNAs encoding Transcription Activator-Like Effector Nucleases (TALEN®) designed to inactivate the T cell receptor alpha constant (TRAC) and CD52 genes. These genetic modifications are intended to reduce the risk of TCR-mediated graft-versus-host disease (GvHD) and confer resistance to ALLO-647, an anti-CD52 antibody that can be used to deplete host immune cells prior to ALLO-715 infusion, potentially enabling expansion and persistence of the AlloCAR T™ cells. To further enhance the safety profile of ALLO-715, an off-switch activated by rituximab is incorporated within the CAR, providing a means to ablate AlloCAR T™ cells on-demand. In preclinical studies, ALLO-715 showed robust cell expansion and low levels of CAR tonic signaling, resulting in minimal T cell differentiation and high potential for antigen-dependent proliferation. Moreover, ALLO-715 demonstrated long-term antitumor activity in vitro, which was not significantly affected by soluble BCMA. In vivo, ALLO-715 exhibited dose-dependent efficacy that was comparable to that of T cells expressing CARs with clinically-validated anti-BCMA single chain variable fragments (scFvs). To evaluate potential off-target binding of the ALLO-715 scFv, human tissue-cross-reactivity studies were conducted using a recombinant protein consisting of the extracellular domain of the ALLO-715 CAR fused to an IgG backbone. The fusion protein stained patient-derived multiple myeloma cells but no appreciable staining was observed across a panel of 36 human tissues, except for cytoplasmic staining of some epithelial cells in sweat glands and tonsil. Finally, we tested the efficacy of ALLO-715 manufactured under GMP-like conditions in an orthotopic xenograft model of multiple myeloma as well as its sensitivity to rituximab through complement-dependent cytotoxicity assays. ALLO-715 exhibited potent activity in vivo and was rapidly depleted by complement in the presence of rituximab, demonstrating preservation of key attributes following scale-up manufacturing. Taken together, these results support clinical investigation of ALLO-715 for the treatment of multiple myeloma.

Keywords:
Allogeneic

BCMA

CAR T cells

Tracks:
Immunotherapeutic Approaches to MM

OAB-035

EXPLORING NKG2D AND BCMA-CAR NK-92 FOR ADOPTIVE CELLULAR THERAPY TO MULTIPLE MYELOMA.

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Abstract:
Background: Despite impressive preliminary efficacy of CAR-T cells in multiple myeloma (MM), NK cell engineering has emerged as a competitive and safer approach. NK-92 is a universal, cheap and fast cellular therapy previously used in clinical trials. Although modest responses with these cells have been reported in MM, their oncolytic potential can be enhanced by genetic modification. So far, two preclinical studies have been performed with CAR NK-92 against MM, targeting CD138 or CS1

(SLAMF7). However, there are still reasonable doubts about its clinical outcomes due to on-target off-tumor effect or fratricide, respectively. Thus, the aim of our study is to generate and compare two novel CAR NK-92 products for MM treatment. Materials and methods: NK-92MI cells were lentivirally transduced with the full-length ectodomain sequence of the human native NKG2D receptor or with an anti-BCMA scFv, both containing identical 4-1BB costimulatory and CD3-ζ signaling domains. To compare the efficacy between these 2nd generation NKG2D-CAR and BCMA-CAR, the same MOI 10 was used to transduce cells; both populations were then purified by FACS sorting to obtain stable modified cell lines and vector copy number was measured by qPCR to ensure similar CAR expression. Cytotoxicity assays were performed by 3-hours Calcein-AM analysis. We used MM cell lines with different expression of target ligands: U266 and ARP-1, BCMAhigh and NKG2DLhigh; XG-1, BCMAhigh and NKG2DLlow; NCI H929 R20, NKG2DLlow. K562, BCMAnegative and NKG2DLhigh, a leukemia cell line. Results: NKG2D-CAR NK-92MI cells consistently showed much higher in vitro antitumor activity than the parental line NK-92MI against U266 (84 ± 2% vs 40.7 ± 4% at a 1:1 E:T ratio), ARP-1 (82.1 ± 4% vs 21.3 ± 9.2% at a 16:1 E:T ratio), XG-1 (67.9 ± 9% vs 18.5 ± 4% at a 16:1 E:T ratio) and NCI H929 R20 (50.9 ± 6% vs 23.7 ± 2% at a 16:1 E:T ratio) cell lines. Next, we compared cytotoxicity between NKG2D and BCMA-CAR NK-92MI against U266 (84 ± 2% vs 91.9 ± 3% at a 1:1 E:T ratio), ARP-1 (82.1 ± 4% vs 80.4 ± 3.7% at a 16:1 E:T ratio), XG-1 (67.9 ± 9% vs 89.9 ± 2% at a 16:1 E:T ratio) and K562 (94 ± 3% vs 25.74 ± 4% at a 1:1 E:T ratio) cell lines. Strikingly, there were no significant differences between NKG2D-CAR NK and the gold standard BCMA-CAR against MM cell lines with high and similar BCMA and NKG2DL expression. In addition, correlation between target ligands expression on the tumor and efficacy of both CARs was also shown. None of the CAR NK-92MI studied populations showed toxicity against PBMCs from healthy donors and in vivo MM orthotopic xenograft mouse model experiments are ongoing. Conclusions: We have generated two novel and stable CAR NK-92 immunoproducts that improve the oncolytic efficacy of the parental cell line. Indeed, NKG2D-CAR cells are as equally efficient as BCMA-CAR cells to eradicate diverse MM cells. To summarize, all these data show the feasibility to use this 'off-the-shelf' approach for MM.

Keywords:
CAR NK-92

Chimeric Antigen Receptor

NKG2D-CAR

Tracks:
Immunotherapeutic Approaches to MM

OAB-036

In vivo efficacy of BCMA-iNKT-CAR is enhanced by NT-I7, a long-acting IL-7

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Abstract:
B-cell maturation antigen (BCMA) targeted chimeric antigen receptor-T (CAR-T) cells generate short-lived responses in multiple myeloma (MM) with high risk of cytokine release syndrome and neurotoxicity. Expressing CAR proteins on alternative cell types could lead to a less toxic cure. Invariant natural killer T-cells (iNKTs) express a monomorphic T cell receptor that recognizes glycolipids displayed by the MHC-like molecule CD1d. iNKTs do not cause graft versus host disease (GvHD), making them a useful alternative cell type for an allogeneic, "off the shelf" CAR product, including a BCMA-CAR . Prior to testing efficacy of BCMA-iNKT-CAR we generated and tested BCMA-CAR-T. Human T-cells were transduced with a lentivirus encoding a 3rd generation CAR targeting BCMA or CD19 (negative control). In vivo

efficacy was tested by engrafting 5X105 MM.1S cells (BCMA+; expressing luciferase and GFP; MM.1S-CG) i.v. into NSG mice (day 0) followed by treatment with 2x10^6 BCMA-CAR-T or CD19-CAR-Ts (day 28). All BCMA-CAR-T (n=7) treated mice were tumor free at day 150, while all CD19-CAR-T treated mice died of tumor (median survival 40 days; n=4), demonstrating our BCMA-CAR is active and useful for testing in iNKTs. iNKTs isolated from normal human PBMCs were stimulated with matched donor irradiated negative fraction PBMCs. We generated BCMA-iNKT-CAR and CD19-iNKT-CAR (CD19-iCAR) and found efficient killing of MM.1S-CG by BCMA-iCAR and negligible killing by CD19-iCAR in Chr51 killing assays. Since iNKT's express the IL-7R, we used NT-I7 (a long-acting IL-7) to enhance expansion and efficacy of BCMA-iCARs. Mice were engrafted as above (day 0) and treated with 10X106 1) BCMA-iCAR/vehicle (VEH; n=10) 2) CD19-iCAR/VEH (n=5) 3) BCMA-iCAR/NT-I7 (n=10) 4) CD19-iCAR/NT-I7 (n=5) or 5) nothing. Median survival of mice treated with CD19-iCAR/VEH and CD19-iCAR NT-I7 was 45 and 49 days, respectively. Median survival of BCMA-iCAR/VEH treated mice was 163 days while 7 of 10 BCMA-iCAR/NT-I7 treated mice lived >200 days with no tumor detected by BLI. BCMA-iCAR/NT-I7 treated mice had an avg. of 92 iNKT+CAR+/μL blood on day 62 and 0 by day 90; no CARs were detected in BCMA-iCAR/VEH treated mice at either time point. Thus, NT-I7 enhanced BCMA-iCAR antitumor efficacy and prolonged iNKT-CAR cell survival in vivo. To assess long lived functional BCMA-iCARs, we re-challenged the 7 living BCMA-iCAR/NT-I7 mice with 5X105 MM.1S-CG cells and treated them with VEH (n=3) or NT-I7 (NT-I7#2; n=4). Two of four NT-I7#2 treated mice were tumor free 5 weeks later while NSG control (n=5) and VEH had high tumor burden, demonstrating NT-I7's potential anti-tumor effect. Future experiments focus on repeating preliminary results and testing CS1 (SLAMF7), a priority CAR-T candidate, on iNKTs and CS1 CRISPR/cas9 gene edited iNKTs. iNKTs hold promise as an alternative cell source for off-the-shelf CAR therapies and combination with NT-I7 extended CAR-cell and overall survival in a MM mouse model.

Keywords:
B-cell maturation antigen

Chimeric Antigen Receptor

iNKT

Tracks:
Immunotherapeutic Approaches to MM

OAB-037

Single cell Dissection of Resistance to anti-BCMA CAR-T cell Therapy

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Abstract:
Despite advances in therapy, multiple myeloma remains incurable in most patients. Immunotherapies may possess unique mechanism(s) of action to overcome drug resistance, potentially providing long-term tumor surveillance and durable disease control. Anti-B-cell maturation antigen (BCMA) CAR-T cell therapy has recently emerged, with dramatic clinical responses seen. Nevertheless, primary and acquired resistance is observed with the current generation of anti-BCMA CAR-T cells. The mechanisms that govern the expansion, persistence, and effector function of these cells are unknown. Further, the interaction of CARs with the myeloma bone marrow (BM) microenvironment remains uncharted, which hampers the ability to modulate the immune response to an optimal safe and efficacious zone. We utilized single-cell approaches to identify mechanisms of resistance to CAR-T cells. Methods:

Bone marrow aspirates and peripheral blood from MM patients (N=17) were assessed fresh, at different time points, before and after anti-BCMA CAR-T infusion. CAR-T cells were enriched by flow cytometry and were identified in silico for further analysis. scRNA-seq was performed using 10x genomics 5' technology in conjunction with assessment of T-cell clonality. To gain insight into the BM microenvironment role in resistance, CD45+ CD3- CD19- subsets were sorted from paired blood and BM samples, and BM enriched clusters were further analyzed. Mass cytometry was performed on the same samples with a tailored panel. Results: At time of analysis, 5/17 patients achieved very good partial response or better, 6/17 had progressed and 6/17 were <3 months post CAR-T infusion. T-cells from responders compared to non-responders had a more restricted T-cell receptor repertoire; overexpressed stem and memory markers such as TCF7 (1.9 log[fold change of normalized mean unique molecular identifier per cell], p<10^-5, Wilcoxon rank-sum t test); and unexpectedly overexpressed exhaustion markers, i.e. TIGIT (2.53 log[fold change(mean UMI/cell)], p<10^-5). BM microenvironment cells in patients with disease progression showed an enrichment of specific CD14+ myelo-monocytes subsets within the BM compared to the blood. Those cells were negative for the tumor-associated macrophage marker CD163, and overexpressed early growth response genes, i.e. EGR2 (4.9 log[fold change(mean UMI/cell)], p<10^-5) and IL1β (2.56 log[fold change(mean UMI/cell)], p<10^-5). Together, our results uncover both T cell-intrinsic and microenvironment factors associated with clinical response to anti-BCMA CAR-T cells in refractory myeloma. Our findings suggest that dominant CAR-T cell clones drive the anti-tumor immune response, blunted by myeloid cells in the myeloma niche. Dissection of CAR-T cell dynamics and functional states will allow for improved CAR-T generation and/or combination immune therapies.

Keywords:
Chimeric Antigen Receptor

immunotherapy

Single cell genomics

Tracks:
Immunotherapeutic Approaches to MM

OAB-038

Checkpoint expression on immune cells in the patients with multiple myeloma or pre-malignant diseases: Therapeutic Implication for Combination Immu

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Abstract:
Background: Characterization of various immune-mediated or regulatory cell subsets and costimulatory or checkpoint molecules in the patients with Monoclonal Gammopathy of Undetermined Significance (MGUS), Smoldering Multiple Myeloma (SMM) or active Multiple Myeloma (MM) will provide the framework for development of novel immunotherapeutic strategies. Methods: Evaluation of T cell subsets, myeloid derived suppressor cells (MDSC), CD4+ regulatory T cells (Treg), primary CD138+ myeloma cells and their expression of immune checkpoint and costimulatory molecules which may contribute to regulation of tumor-specific responses was performed by flow cytometry. Results: Using freshly isolated bone marrow mononuclear cells (BMMC) or peripheral blood mononuclear cells (PBMC), we found increased G-type MDSC (CD11b+CD33+HLA-DRlow CD14- CD15+) and CD4+ Treg (CD3+CD4+/CD25+FOXP3+) and decreased CD4+ T helper cell frequencies in active MM patients including newly diagnosed [ND], relapsed [R] or relapsed/refractory [R/R], as compared to MGUS/SMM patients or healthy

donors. Increased PD1 but not LAG3, OX40 or GITR expression was detected on CD3+ T cells (both CD4+ Th cells and CD8+ Tc cells) in active MM patients. In parallel, we observed an increased expression of PD-L1 but not PD-L2, PD1 nor LAG-3 on CD138+ cells, G-type MDSC (not M-type MDSC) and CD4+ Treg (not CD8+ Treg), in active MM patients' BMMC or PBMC. Interestingly, in MGUS and SMM patients, CD4+ Treg but not CD8+ Treg expressed high levels of PD-L1. Treatment of MM patients' BMMC with specific clinical grade antibody targeting checkpoint molecules (anti-PD1, anti-LAG3) or stimulating costimulatory molecules (anti-OX40, anti-GITR) increased the proliferation of CD3+ T cells, both CD4+ Th and CD8+ Tc cells. However, these treatment strategies also induced the proliferation of CD4+ Treg cells or CD3+ T cells expressing another checkpoints, which may contribute to resistance to tumor cell cytotoxicity of immunotherapies. Finally, we evaluated the impact of checkpoint inhibitor or immune agonist treatment on the poly-functional anti-myeloma activities of XBP1/CD138/CS1-specific CTL. The XBP1/CD138/CS1-specific CTL generated in vitro demonstrated robust anti-tumor activities against myeloma cells; importantly, the blockade of PD1, LAG3 or TIM3 enhanced their cytotoxic activities, as assessed by CD107a degranulation, granzyme B upregulation, and IFN-γ cytokine production in response to MM cells. Conclusions: An increased level of immune regulatory cells and upregulation of checkpoint molecules were detected in patients with active MM (ND, R, R/R) compared to MGUS and SMM. Treatment with an immune agonist or checkpoint inhibitor increased the proliferation of MM patients' T cell with enhanced functional activity of antigen-specific CTL activity against myeloma. Our results provide the framework for combination approaches to overcome resistance and enhance activity of immune therapies in MM.

Keywords:
immune checkpoint

immune modulation

Immuno-oncology

Tracks:
Immunotherapeutic Approaches to MM

OAB-039

Single-cell RNA sequencing reveals compromised immune microenvironment in precursor stages of multiple myeloma

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Abstract:
In multiple myeloma (MM), despite well-characterized precursor states such as monoclonal gammopathy of undetermined significance (MGUS)

and smoldering multiple myeloma (SMM), there is a lack of sufficient biomarkers to predict mechanisms of disease progression. Most genomic analyses have sought biomarkers by study of the malignant plasma cells, however, cancers form a complex ecosystem with the immune and stromal microenvironment. Thus, to characterize the cellular composition and transcriptional programs of each component of the tumor and microenvironment at different stages of MM progression, we employed a single-cell RNA sequencing on a cohort of 30 patients at different stages of disease progression (from MGUS to MM) and 11 healthy donors. Expression profiles of plasma cells revealed clear tumor-specific differences including known oncogenic drivers in MM (MMSET/FGFR3, CCND1 and MAFB) as well as Lysosome-associated Membrane Protein 5 (LAMP5), Histone Cluster 1 H1 Family Member C (HIST1H1C) and Amphiregulin (AREG) distinguishing them from healthy plasma cells. We identified a subset of cycling plasma cells, observing a range of proliferative activity of the malignant fraction. Furthermore, our approach allowed a unique head-to-head comparison of gene expression changes in normal and malignant plasma cells in the MGUS and SMM patients within an individual, excluding inter-individual variation. We were able to discriminate malignant from non-malignant plasma cells and identify transcriptional alterations including known drivers and novel disease associated genes. Additionally, we report striking changes in the diseased microenvironment, including changes in the cell composition with a drastic influx of NK cells, increased non-classical monocytes and T-cell populations. By studying changes in NMF-derived gene expression programs, we observed a substantial skewing of CD8+ T-cells towards activated Granzyme (Gr) B/H- expressing states away from healthy-associated GrK populations, as well as subclasses of patients with marked interferon type-1 response. In CD14+ monocytes we find dysregulated expression of MHC type II genes and a corresponding loss of antigen presentation. In vitro assays show that MM cells drive this loss of MHC type II presentation thus inducing the T-cell suppressive phenotype in monocytes. Together, we provide a comprehensive view at the complex interplay of the immune and malignant cells in different stages of the disease. Significant transcriptional alterations in the PCs compartment as well as compositional changes in the tumor immune microenvironment may characterize myeloma already at the MGUS stage of disease. Our results hint at mechanisms of anti-tumor immune response as well as immune evasion. Importantly, the immune patterns observed are often heterogeneous across patients, and thus may prove important biomarkers when considering risk assessment and therapeutic strategies for prevention of progression in MM.

Keywords:
Immune Tumor Microenvironment

Immunosuppression

RNA-Seq

Tracks:
Multiple Myeloma Microenvironment

OAB-040

High dimensional profiling of the immune microenvironment in smoldering multiple myeloma

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Abstract:
Multiple myeloma (MM) is a malignancy of plasma cells that arises from premalignant Monoclonal

Gammopathy of Undetermined Significance (MGUS) and often progresses through an asymptomatic Smoldering (SMM) phase lasting months or years before manifesting clinical symptoms warranting therapy. Current research indicates that the immune microenvironment (IME) in the bone marrow may play a significant role in governing progression to symptomatic disease. Therefore, understanding of the interactions between malignant plasma cells and the IME in early disease states is critical in the pursuit of therapies that will prevent progression to symptomatic disease. We performed high dimensional genomic and immunologic analysis of bone marrow specimens from 73 subjects with SMM. We performed RNAseq on the malignant plasma cells isolated by anti-CD138 magnetic bead positive selection, mass cytometry and T cell receptor sequencing of CD138-depleted bone marrow mononuclear cells, and proteomics, seromic, and grand serology analysis of bone marrow plasma. These samples and assays provided a broad view of the tumor cells and the cellular and soluble components of the IME. Analysis of RNASeq, mass cytometry, and proteomic data identified self-organizing clusters of subjects, indicating that subgroups of SMM patients shared common characteristics in the tumor or IME populations. We then applied novel bioinformatic methods to compare data from pairs and triads of assays to determine if multiple high dimensional data sets identified common communities of subjects. Notably, TCRSeq and mass cytometry identified a group of subjects with high TCR productive clonality that was driven by CD8+ effector and memory T cell subsets, suggesting that the state of the T cell compartment is a strong distinguishing feature in this population. Integrated analysis of proteomics with either seromics and RNASeq or TCR Seq and mass cytometry demonstrate that features of both the tumor and IME identify diverse communities. These results suggest that the continuum from MGUS to MM does not consist of a single pathway in either the tumor cells or the IME, and that complex interactions ultimately determine progression. Understanding the key tumor and immune determinants of non-progressing patients may lead to rationally designed therapy to replicate these conditions to the general population and prevent progression to symptomatic disease.

Keywords:
immunotherapy

microenvironment

Smoldering Multiple Myeloma

Tracks:
Multiple Myeloma Microenvironment

OAB-041

High-dimensional Clonal Heterogeneity and Immune Landscape in Multiple Myeloma

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Abstract:
Multiple myeloma (MM) represents prototypical disease model to study tumor heterogeneity due to the high frequency of intra-clonal diversity within malignant clone of plasma cells (PC) in the bone marrow (BM). To better understand the myeloma heterogeneity within complex myeloma pathophysiology, we performed large-scale mass cytometry (CyTOF) analysis in the cohort of BM samples from MM patients (n=188) compared to 10

age-matched healthy donors (HD). We designed a pipeline for deep characterization of PC within the immune ecosystem of the myeloma microenvironment enrolling bone marrow of 16 MGUS, 25 smoldering MM (SMM), 43 newly diagnosed (NDMM) and relapsed or relapsed/refractory MM patients (n=104). Our study was focused on profiling of PC based on molecular perturbations of transcriptional factors and signaling regulators ensuring B cell development and stemness-controlling markers within B myeloma lymphomagenesis by 2 CyTOF panels. Cell frequency of B cell clusters showed that switched memory B cells and plasmablast clusters were upregulated in MGUS compared to HD. Similar observations were detected in SMM and NDMM vs. HD, with the highest abundance of PC clusters in NDMM. The downregulation of cell distribution in B cell progenies, immature and transitional B cells, and un-switched memory B cell clusters was observed in NDMM patients. To evaluate intra and inter-tumor heterogeneity, significant variations were detected in PC clusters of MM cohort based on different expression of IRF4, c-Myc, CD28, CD117, and FGFR-3, however with homogenous expression of sXBP1 and MMSET, which differ in all 4 MM stages compared to HD. Significant upregulation of CD47 was showed in all PC clusters of MM cohort. Moreover, PC clusters differ in intra-clonal expression of self-renewing/stemness markers CD184, Notch-1, Oct3/4, KLF-4, Sox-2, Nestin and Nanog, supporting the idea of sub-clonal variations insight of MM tumor. In addition, interaction of PC with myeloma immuno-ecosystem showed that immune clusters differ with significant abundance in subsets of T helper cells, non-canonical monocytes, and subsets of myeloid lineage, whereas decrease of cell distribution in immature T and B cells, pro-monocytes and cytotoxic T cell subsets was observed in MM cohort compared to HD. The upregulation of KIR expression was more pronounced in adaptive immune clusters, whereas PD-1 immune checkpoint was mostly increased in innate immune clusters. However, downregulation of PD-L1 was detected in innate and adaptive immunity in MM cohort compared to HD. MM patients treated with Revlimid-Velcade-Dexamethasone had decrease frequency of specific PC clusters and un-switched and transitional B cell clusters. This study might provide the rational for prediction of MM patient status and design of targeted and immune therapy in MM on personalized bases. This work was supported by REA grant agreement No. 609427-SASPRO 0064/01/02, TRS-2015-00000170, APVV-16-0484 and VEGA 2/0076/17.

Keywords:
Clonal Heterogeneity

High dimensional analysis

Immune Tumor Microenvironment

Tracks:
Multiple Myeloma Microenvironment

OAB-042

Accumulation of CD69+ Terminal Effector CD8+ T cells occurs in the bone marrow of newly diagnosed Myeloma patients who lack protective clonal Vb expanded cytotoxic T cells

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Abstract:
The investigation of the differentiation of terminal effector CD8+CD57+T cells (TTE) in multiple myeloma (MM) and its premalignant stage, monoclonal gammopathy of undetermined significance (MGUS), is essential for understanding myeloma immune escape. We have previously shown that patients with clonal expansions of cytotoxic TTE cells have better outcomes than those who do not, but have not examined the underlining differentiation of TTE cells that leads to these distinct states. We hypothesised that a lack of clonally expanded TTE cells in myeloma patients could be due to myeloma induced alterations of TTE cell differentiation. To define TTE cell differentiation at high resolution, we have analysed paired bone marrow (BM) and peripheral blood (PB) samples from patients with newly diagnosed Myeloma (NDMM) and MGUS using time of flight mass cytometry and unsupervised clustering algorithm Flow Self-organizing Map (FlowSOM). We designed a 39 antibody panel, including antibodies to TCR-Vβ families custom-labelled with heavy metals, allowing the detailed characterization of the phenotype of clonally expanded TTE cells. We found that in contrast to TTE cells in MGUS, TTE cells in BM of NDMM failed to display the phenotype typical of terminal effector cell differentiation and were enriched in atypical tissue resident CD69+, CD28+ and CD27+ subsets. They also failed to display the expected upregulation of CD45RA and downregulation of CD45RO expression. Moreover the accumulation of atypical CD69+ TTE cells was prevalent in myeloma patients without clonally expanded TTE cells. FlowSOM clustering discovered 4 metaclusters (MC) contributing to the accumulation of CD69+ TTE cells in the BM of NDMM patients. Phenotypically, two MC were in the memory stage based on CD27, CD28 and CD45RO expression and another two MC showed evidence of progression to the effector stage by downregulating CD27, CD28, CD45RO and upregulating CD45RA expression. Progression to the effector stage was associated with downregulation of CD38 and PD-1 expression, but did not affect persistent TIGIT expression. Vβ expanded TTE cells did not contribute to the accumulation of CD69+ TTE cells and occupied phenotypically different MC with low or undetectable CD69 expression. When comparing phenotype of Vβ expanded TTE cells to remaining TTE cells, effector and memory CD8+T cells they had higher Tbet, Perforin, Granzyme B, and lower levels of Eomes, TIGIT and PD-1 expression arguing against their exhaustion stage and confirming our previous observations that they resemble senescent cells Our results suggest that accumulation of atypical tissue resident CD69+ TTE cells in myeloma infiltrated BM could prevent differentiation and expansion of clonal myeloma specific CD8+TTE cells and ultimately contribute to myeloma immune escape.

Keywords:
Immuno-oncology

T-Lymphocytes

Tracks:
Multiple Myeloma Microenvironment

OAB-043

Expansion of effector memory CD27+ T cells and tolerogenic type 2 classical dendritic cells regulate myeloma patients' sensitivity to daratumumab & IMiDs

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Abstract:
CD38 targeting MoAbs in combination with IMiDs induce durable responses in MM; however the mechanisms that underlie acquired resistance to this combination remain to be elucidated. We interrogated the tumor microenvironment (TME) of daratumumab & IMiDs treated patients in order

delineate the mechanisms of resistance and identify potential means to reinstate sensitivity. Serial BM aspirates (n=40) were collected from patients treated with daratumumab and/or pomalidomide prior to initiation of therapy, C3D1 and at relapse. Mononuclear fractions were isolated through density gradients coupled with magnetic sorting of CD138+ cells. Unbiased mRNA profiling of BM CD138- cells was performed by single-cell RNA-seq. Single cell ATACseq was also performed on BM infiltrating CD3+ T cells. Cell Ranger pipelines, Seurat and Cicero were used for data analyses. Significant differences were observed in the TME of resistance (R) and sensitive (S) patients. With regard to CD8+ T cells: 1) Effector memory cytotoxic T cells (Tem: CD27+, CD28+, IL7R+, GZMK+) are significantly more expanded in S patients at baseline and C3D1 compared to R; 2) cytotoxic T cells in R patients are terminally exhausted (CD28-, GZMB+, GZMH+) with high expression of the checkpoint inhibitor LAG3; 3) chromatin accessibility (scATACseq) and mRNA analyses showed TCF7 and GATA3 expression in CD27+ Tem cells, in contrast with RUNX3, Eomes and TBX21 in exhausted T cells. Key differences were also observed in dendritic cells (DC). Classical type 2 DCs (cDC2) CD1C+_A & CD1C+_B (Villanil, Science 2017) had a significantly higher expression of MHC class II genes in S compared to R patients. In contrast cDC2 in R patients highly expressed interferon response genes. cDC2 preferentially initiate CD4+ Tconv responses in several conditions including antitumor immunity and this cDC2-mediated Tconv differentiation function is repressed by Treg. TMEs with high classical type 2 dendritic cells and low Treg (cDC2high/Treglow) are capable of mounting a more efficient and sustained responses to immune therapies such as checkpoint inhibitors blockade (Binnewies, Cell 2019). Of interest, in our cohort the ratio of cDC2/Treg was significantly higher in S compared to R patients. This finding, coupled with the low MHCII expression on cDC2 in R patients, clearly implicate dysfunctional cDC2s as mediators of the tumor tolerance seen in R patients. CD14+ monocytes type I were significantly expanded pre-C3D1 compared to baseline in the TME of S but not R patients. Similarly FCGR3A+ monocytes were more present in the TME of S patients at baseline but were depleted to similar levels to that of R patients pre-C3D1. Lastly, we observed a significant depletion of FCGR3A+ NK cells post C3D1 with retained population of cytotoxic NK cells (CD27high, NCR3high, PRF1+). Our study defined the TME immune profile of anti-CD38 & IMiDs treated patients and identified an unsuspected tolerogenic role of type 2 classical dendritic cells

Keywords:
Daratumumab resistance

Immune Tumor Microenvironment

Single cell genomics

Tracks:
Multiple Myeloma Microenvironment

OAB-044

High throughput 3D bioprinting of patient-derived multiple myeloma organoid models for niche recapitulation and chemosensitivity assessment.

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Abstract:
Background: The intricate interactions of multiple myeloma (MM) cells with the bone marrow (BM) niche are key in tumor growth and chemoresistance. Current 2D pre-clinical models fail to replicate this interaction and are suboptimal at studying MM biology and susceptibility to treatments. Nevertheless, a boom in treatments have become available with no head-to-head comparison studies to identify the optimal combination. The purpose of

this study is to create a 3D organoid model from patient-derived BM aspirates to better replicate natural conditions and study chemosensitivity and plasma cell interaction with its microenvironment. Methods: MM patients scheduled for BM biopsy were consented and 3-5 ml of aspirate was collected. Mononuclear cells from BM aspirates were assessed for viability (>90%) and CD138+ content (>10%) to qualify to testing. The cell pellets were resuspended in hydrogel containing growth factor, thiol-fibronectin, and PEGSSDA to create a bio-ink mixture. Individual 40-50µm 3D organoid constructs were high throughput bioprinted into 48-well plates and exposed to UV light. Each organoid contained 200,000 cells. Culture media was used to keep cells alive and changed on day 2 and 4. The following tests were performed at baseline and day 7: viability with ATP quantification, immunohistochemistry, flow-cytometry, fluorescence in situ hybridization, chemosensitivity assays, and sell sorting using StemPro® (only at baseline). Statistical analysis was performed in Prism 8.0 software. The primary objective was to bioprint 3D organoid models using patient-derived MM cells and stroma. Secondary objectives were to maintain cell viability long enough to assess chemosensitivity using established regimens. Results: Forty-five patient-derived BM aspirate samples have been collected and used for this study. The initial 35 samples were used to test hydrogel compositions and culture media to optimize organoid lifespan. A combination of GM-CSF, IL-6, and RPMI was able to keep constructs above 70% viability up to 7 days. Of the 10 remaining samples, 5 were used to create organoids with 100% success rate. The remaining viable samples were cell sorted and cryopreserved for future testing. All but the clotted sample had the potential to yield enough organoids for chemosensitivity testing based on sample nucleated cell count > 2.4 million. The number of organoids produced from each sample ranged from 60 to 200 (median of 122). Three samples underwent chemosensitivity testing in triplicate fashion with a control. Live/dead cell testing showed differences among the regimens tested. Conclusion: This is the first 3D MM organoid model from patient-derived samples using high throughput bioprinting. The ability to generate durable organoids enable chemosensitivity testing. Further studies to compare with responses in the clinical setting are needed to validate this model for clinical application.

Keywords:
Bone marrow microenvironment

organotypic models

relapsed/refractory multiple myeloma

Tracks:
Multiple Myeloma Microenvironment

OAB-045

A Phase 3 Study of Venetoclax or Placebo in Combination with Bortezomib and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma

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Abstract:
Background: Venetoclax (Ven) is a BCL-2 inhibitor that induces apoptosis in multiple myeloma (MM) cells and has shown synergistic activity with bortezomib (B) and dexamethasone (d). Ven±d had encouraging efficacy in t(11;14) MM and in a broader pt population administered with B, with a tolerable safety profile in Phase 1 studies. We present results from a Phase 3 trial of VenBd vs Bd in relapsed/refractory (RR) MM. Methods: BELLINI (NCT02755597) was a randomized, double-blind, multicenter Phase 3 study of Ven or placebo (Pbo) + Bd in pts with RRMM who received 1-3 prior therapies and were sensitive or naïve to proteasome inhibitors (PIs). Pts were randomized 2:1 to receive Ven 800 mg/day or Pbo + Bd. Cycles 1-8 were 21-day with B 1.3 mg/m2 on Days 1, 4, 8, 11 + d 20 mg on Days 1, 2, 4, 5, 8, 9, 11, 12. Cycles 9+ were 35-day with B 1.3 mg/m2 on Days 1, 8, 15, 22 + d 20 mg Day 1, 2, 8, 9, 15, 16, 22, 23. The primary endpoint was progression-free survival (PFS). Results: As of the data cut-off of 26 Nov 2018, 291 pts were randomized, 194 to Ven and 97 to Pbo. Median age was 66; 53% had ISS II/III disease; 54% received 2 or 3 prior lines of therapy; 59% had prior stem cell transplant; 70% had prior PI, 68% had prior immunomodulatory drug, 41% had both; 18% had high-risk cytogenetics; 13% were t(11;14); and 79% were BCL-2 high by immunohistochemistry. Median PFS was 22.4 months (mo) in Ven vs 11.5 mo in Pbo (HR=0.630, p=0.01), with a median follow-up of 18.7 mo. Higher overall response (ORR, 82% vs 68%, p<0.01), very good partial or better response (≥VGPR, 59% vs 36%, p<0.01) and minimal residual disease negativity (MRD [10-5], 13% vs 1%) rates were observed in Ven vs Pbo. Median overall survival (OS) was not reached but favored Pbo (HR 2.027, 95% CI=1.042-3.945). Median PFS was not reached for t(11;14) pts receiving VenBd (HR=0.110), or pts with high BCL-2 expression (HR=0.502). Subgroup analyses show that low BCL-2 expression, high-risk cytogenetics, or ISS III were associated with decreased PFS and OS in the Ven arm. There were 51 deaths in the safety population, 40 (21%) in the Ven arm and 11 (12%) in Pbo, with progressive disease (PD) the most common cause (40% Ven, 64% Pbo). Among 14 treatment-emergent (TE) deaths, 13 were in the Ven arm (8 due to infection, 2 due to PD), and 1 (PD) was in the Pbo. The most common TE adverse events (TEAEs; VenBd/Bd) were diarrhea (58%/48%), nausea (36%/22%), constipation (34%/31%), and fatigue (31%/32%); most common Grade 3/4 TEAEs were neutropenia (18%/7%), pneumonia (16%/9%), thrombocytopenia (15%/30%), and anemia (15%/15%); 16%/8% discontinued Ven due to a TEAE. Serious AEs (48%/50%) and serious infections (28%/27%) were comparable between arms. Conclusion: Ven+Bd significantly improved PFS, ORR, ≥VGPR, and MRD negativity rates, but had an increase in deaths. Pts with t(11;14) had consistent clinical benefit when treated with Ven+Bd, and a biomarker-driven approach with Ven is the most appropriate in MM

Keywords:
BCL-2

relapsed/refractory multiple myeloma

Venetoclax

Tracks:
Treatment of Previously Treated Myeloma

OAB-046

Safety and efficacy of once-weekly carfilzomib (K) dosing in frail patients (pts): a subgroup analysis from the phase 3 A.R.R.O.W. study

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Abstract:
Background: A.R.R.O.W. demonstrated superior progression-free survival (PFS) with once-weekly K (70 mg/m2)-dexamethasone (Kd70) vs twice-weekly K (27 mg/m2)-dexamethasone (Kd27) in pts with relapsed and refractory multiple myeloma (RRMM), regardless of age. Weekly Kd70 is US-approved for relapsed or refractory MM (1–3 prior therapy lines). For a comprehensive fitness measure, frailty scales were developed incorporating age, comorbidities, and functional status. (Palumbo Blood 2015; Facon Blood 2015). Here we assessed post hoc patient outcomes by frailty status. Methods: PFS and safety were assessed by treatment arm and a frailty algorithm incorporating age, medical history–derived Charlson Comorbidity Index, and ECOG performance status; pts with frailty scores of 0, 1, or ≥2 were classified as fit, intermediate (int), or frail, respectively. PFS was assessed with the Kaplan-Meier method. Safety was assessed in pts who received ≥1 treatment dose. Results: Patient distribution by frailty status was generally balanced between once-weekly (QW) Kd70 and twice-weekly (BIW) Kd27 arms, respectively (fit: 60 pts and 66 pts; int: 89 pts and 103 pts; frail: 80 pts and 61 pts). QW Kd70 vs BIW Kd27 resulted in median PFS for fit, int, and frail pts of 15.7 vs 5.7 mos (hazard ratio [HR], 0.53; 95% confidence interval [CI], 0.33–0.86), 11.1 vs 7.7 mos (HR, 0.81; 95% CI, 0.55–1.19), and 10.3 vs 6.6 mos (HR, 0.76; 95% CI, 0.49–1.16), respectively. Rates of grade ≥3 treatment-emergent adverse events of interest were similar between treatment arms across frailty subgroups. One grade ≥3 peripheral neuropathy (PN) event was reported in fit pts treated with BIW Kd27 while there was no PN event in the remaining subgroups. The grade ≥3 acute renal failure rates for QW Kd70 and BIW Kd27 were 0 and 5% for fit pts, 7 and 6% for int pts, and 4 and 7% for frail pts, respectively. The grade ≥3 cardiac failure rates for QW Kd70 and BIW Kd27 were 2 and 2% for fit pts, 3 and 3% for int pts, and 4 and 8% for frail pts, respectively. The grade ≥3 ischemic heart disease rates for QW Kd70 and BIW Kd27 were 2 and 0% for fit pts, 0 and 1% for int pts, and 0 and 2% for frail pts, respectively. Only one grade ≥3 pulmonary hypertension event was observed in frail pts treated with BIW Kd27 across the study. Conclusions: Once-weekly Kd70 resulted in PFS benefits vs twice-weekly Kd27 with a favorable benefit-risk profile regardless of frailty score. These results support weekly Kd70 as a treatment option for both fit and frail patients with RRMM.

Keywords:
carfilzomib

frailty

Relapsed Refractory MM

Tracks:
Treatment of Previously Treated Myeloma

OAB-047

Pomalidomide + Bortezomib + Dexamethasone After One Prior Line of Therapy in Bortezomib-Pretreated Multiple Myeloma: Subanalysis of OPTIMISMM

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Abstract:
BACKGROUND Results of OPTIMISMM (NCT01734928) demonstrated significantly improved progression-free survival (PFS) with pomalidomide (POM), bortezomib (BORT), and dexamethasone (DEX; PVd) vs BORT and DEX (Vd) after lenalidomide (LEN)-based therapy in relapsed refractory multiple myeloma (RRMM) pts (100% LEN-pretreated; 70% LEN-refractory; 1-3 prior lines of therapy [LOT]). Because LEN and BORT are often used upfront in MM, we analyzed the efficacy and safety of following frontline LEN ± BORT with second-line PVd or Vd.

Methods:
Eligible pts received (1:1) PVd or Vd in 21-day cycles (C): POM 4 mg/day, days 1-14 (PVd arm only), bortezomib (BORT) 1.3 mg/m2, days 1, 4, 8, and 11 C1-8 and on days 1 and 8 C9+, and DEX 20 mg/day (10 mg/day if > 75 yrs), days of and after BORT. The primary endpoint was PFS. BORT-refractory pts (defined as refractory to once-weekly 1.3 mg/m2 BORT or a lower dose) were included.

Results:
As of Oct 26, 2017, 226 of 559 pts enrolled had 1 prior LOT (111 PVd; 115 Vd); 59.3% had prior BORT (67 PVd; 67 Vd) and 40.7% did not have prior BORT (44 PVd; 48 Vd). In PVd vs Vd pts previously treated with BORT, median age was 63 vs 64 yrs, 16.4% vs 10.4% were refractory to BORT, and 53.7% vs 46.3% were refractory to LEN. In PVd vs Vd pts without prior BORT, median age was 74 vs 70 yrs and 63.6% vs 70.8% were refractory to LEN. After 1 prior LOT, PVd vs Vd significantly improved PFS (median, 17.8 vs 12.0 mos; HR 0.47 [95% CI, 0.26-0.82]; P = .0068) in pts with prior BORT. Of note, median PFS values did not change after excluding pts refractory to BORT. In pts without prior BORT, median PFS was 20.7 mos with PVd vs 9.5 mos with Vd (HR 0.62 [95% CI, 0.35-1.11]; P = .1055). PVd significantly improved ORR vs Vd: 89.6% vs 49.3% (P < .001) in pts with prior BORT and 90.9% vs 62.5% (P = .002) in pts without prior BORT. Rates of very good partial response or better were 62.7% vs 16.4% and 59.1% vs 31.3%, respectively. The safety population included 131 pts with prior BORT (67 PVd; 64 Vd) and 90 pts without prior BORT (44 PVd; 46 Vd). The most common hematologic grade 3/4 treatment-emergent AEs with PVd vs Vd were neutropenia (44.8% vs 10.9% prior BORT, 22.7% vs 8.7% no prior BORT) and thrombocytopenia (23.9% vs 26.6% prior BORT, 13.6% vs 13.0% no prior BORT). Grade 3/4 infections occurred in 26.9% vs 15.6% (pneumonia 7.5% vs 4.7%) in pts with prior BORT and 31.8% vs 15.2% (pneumonia 11.4% vs 6.5%) in pts without prior BORT. Grade 3/4 peripheral sensory neuropathy occurred in 10.4% vs 0% and 6.8% vs 8.7%, respectively.

Conclusion:
After 1 prior LOT, PVd significantly reduced the risk of progression or death by 53% vs Vd in pts previously treated with BORT. Second-line PVd also significantly improved ORR, regardless of prior BORT treatment, and led to deeper responses vs Vd. Data demonstrate that PVd is an effective second-line treatment in pts who previously received BORT and LEN. The safety of PVd was consistent with the known profiles of each agent.

Keywords:
bortezomib

Pomalidomide

Relapsed Refractory MM

Tracks:
Treatment of Previously Treated Myeloma

OAB-048

Efficacy of isatuximab/pomalidomide/dexamethasone in relapsed/refractory multiple myeloma: ICARIA-MM high-risk cytogenetics subgroup analysis

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Abstract:
Background: High-risk cytogenetic abnormalities (HR CAs) negatively impact on the prognosis of patients (pts) with multiple myeloma (MM). ICARIA-MM was a randomized, open-label, active-controlled, multicenter phase 3 study that investigated the anti-CD38 monoclonal antibody isatuximab (Isa) in combination with pomalidomide and dexamethasone (Pd) in pts with relapsed/refractory MM (RRMM) who had received ≥2 prior lines of therapy (NCT02990338). Progression free survival (PFS) was significantly improved with Isa-Pd vs Pd (11.5 vs 6.5 months; hazard ratio [HR] 0.60 [95% confidence interval (CI) 0.44–0.81]). This subgroup analysis of ICARIA-MM examined efficacy in pts with HR CAs. Methods: Pts were considered of high cytogenetic risk if they had ≥1 del(17p), t(4;14), or t(14;16) abnormalities at study entry. Cytogenetic analysis was performed by a central laboratory using cut-offs of 50% for del(17p), 30% for t(4;14) and t(14;16). Isa (10 mg/kg IV) was given on days 1, 8, 15, and 22 (cycle 1), and days 1 and 15 in subsequent 28-day cycles. All pts received pomalidomide 4 mg on days 1 to 21 of each cycle and dexamethasone 40 mg (20 mg for pts ≥75 years old) on days 1, 8, 15, and 22 of each cycle. The primary endpoint was PFS in the intent to treat (ITT) population. Results: In the ITT population, 24/154 (15.6%) pts in the Isa-Pd group and 36/153 (23.5%) in the Pd group had ≥1 HR CA (high-risk pts). In the Isa-Pd and Pd arms, respectively, there were 14 and 23 pts with del(17p); 12 and 14 pts with t(4;14), and 1 and 4 pts with t(14;16). A similar benefit of treatment on PFS was observed for high-risk pts (Isa-Pd 7.5 vs Pd 3.7 months; HR 0.66 [95% CI, 0.33–1.28]) and standard-risk pts (Isa-Pd 11.6 [n=103] vs Pd 7.4 months [n=78]; HR 0.62 [95% CI 0.42–0.93]). Among pts with del(17p) in the Isa-Pd and Pd arms, respectively, median PFS was 9.1 and 7.4 months (HR 0.76 [95% CI 0.30–1.92]), and for pts with t(4,14), median PFS was 7.5 and 2.8 months (HR 0.49 [95% CI, 0.19–1.31]). Overall response rate (ORR) in high-risk pts (Isa-Pd 50.0% vs Pd 16.7%) had an odds ratio (OR) of 5.00 (95% CI, 1.33–19.79) compared with standard-risk pts (Isa-Pd 65.0% vs Pd 42.3%) with an OR of 2.54 (95% CI, 1.33–4.86). Very good partial response or better in high risk patients (Isa-Pd 29.2% vs Pd 2.8%) had an odds ratio of 14.41 [95% CI, 1.57–667.48]) compared with standard-risk pts (Isa-Pd 32.0% vs

Pd 9.0%) with an OR of 4.78 [95% CI, 1.90–13.57]). In the safety population, grade ≥3 treatment-emergent adverse events were reported in 22/23 (96%) and 23/34 (68%) high-risk pts, and 88/103 (85%) and 58/76 (76%) standard-risk pts, respectively. Few pts discontinued Isa-Pd treatment due to adverse events (high-risk, 9%; standard-risk, 7%). Conclusion: The addition of Isa to Pd improved PFS and ORR in pts with RRMM and benefit was maintained among pts with high-risk cytogenetics.

Keywords:
CD38

High-risk cytogenetics

Multiple myeloma

Tracks:
Treatment of Previously Treated Myeloma

OAB-049

Efficacy and Safety of Carfilzomib-Pomalidomide-Dexamethasone in Relapsed and/or Refractory Multiple Myeloma: Pooled Analysis of 2 Single Arm Studies

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Abstract:

Introduction: Treatment with regimens containing pomalidomide may be an option for patients with relapsed and/or refractory multiple myeloma (RRMM) progressing on or previously refractory to lenalidomide. The triplet combination of carfilzomib, pomalidomide and dexamethasone (KPd) has been shown to be well-tolerated and active in RRMM in two phase 1/2 studies (NCT01665794 [n=65], NCT01464034 [n=118]); however, both studies were single arm with a relatively small number of enrolled patients. A pooled analysis of individual patient data would provide an overall assessment of clinical outcomes for KPd. This meta-analysis will assess the efficacy and safety of KPd in RRMM. Methods: Patient-level data from two single-arm phase 1/2 studies of KPd in RRMM were combined. Patients were treated in 28-day cycles of KPd: carfilzomib (most received 20/27 mg/m2, days 1,2,8,9,15,16), pomalidomide (4 mg, days 1-21), and dexamethasone (40 mg, days 1,8,15,+/-22. Reduced to 20 mg after cycle 4). During maintenance phase (cycle 7+ in first trial, cycle 9+ in second trial), carfilzomib was administered on days 1,2,15,16. Treatment was continued until disease progression or unacceptable toxicity. The primary endpoint was to estimate overall response rate (ORR) and secondary endpoints included assessments of progression-free survival (PFS), overall survival (OS), and safety. Results: 183 patients were included in the analysis. The median number of prior lines of therapy in the pooled population was 4 (range, 1–15). ORR for the individual studies was 77% and 70%, respectively with a pooled rate of 73% (95% CI, 67–79). The pooled proportion of patients who had very good partial response or better (≥VGPR) was 35% (95% CI, 28–42). Median OS was 29.6 months (95% CI, 26–34), and 12 and 24-month PFS rates were 49% and 20%, respectively in the pooled population. ORR was 79% (95% CI, 62–96) and the rate of ≥VGPR was 45% (95% CI, 25–66) in patients at first relapse (n=22). In patients with 1-3 prior lines of therapy (n=89), ORR was 80% (95% CI, 72–88) and ≥VGPR was 40% (95% CI, 30–50). In patients with ≥2 prior lines of therapy (n=160), ORR was 72% (95% CI, 65–79) and ≥VGPR was 34% (95% CI, 26–41). ORR was 70% (95% CI, 62–77) and

≥VGPR was 30% (95% CI, 23–38) in patients with ≥2 prior lines of therapy who had received both prior lenalidomide and prior proteasome inhibitor (n=141). Overall, 143 patients (78%) reported at least one grade 3 or 4 treatment-emergent adverse event (TEAE). The frequency of grade ≥3 TEAEs in the pooled KPd population was consistent with that reported for other carfilzomib containing regimens. Conclusion: As the need for lenalidomide sparing regimens is increasing, KPd is an important, effective, and well-tolerated option for lenalidomide exposed patients in both early and later relapse settings. Future research should assess these promising results against sound clinical benchmarks.

Keywords:
carfilzomib

Pomalidomide

relapsed/refractory multiple myeloma

Tracks:
Treatment of Previously Treated Myeloma

OAB-050

Fracture Risk Assessment in Patients with Monoclonal Gammopathy of Undetermined Significance: Value of Bone Mineral Density and Trabecular Bone Score

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Abstract:
Background: Monoclonal gammopathy of undetermined significance (MGUS) is a common finding in clinical practice affecting greater than 3% of adults age 50 years or older. Despite evidence that patients with MGUS suffer from increased fracture risk, there are no guidelines for evaluation and/or management of skeletal health in these patients. Trabecular bone score (TBS), a texture index derived from standard lumbar spine (LS) DXA images, provides information about the underlying trabecular bone microarchitecture independent of the bone mineral density (BMD). We hypothesized that patients with MGUS have a reduced trabecular microarchitecture that would reflect in a lower TBS, and that the latter can have implications for the treatment of these patients in the future. Methods: We retrospectively identified 115 adult patients diagnosed with MGUS (cases) between 2005 and 2018 that had a lumbar spine DXA starting 24 months prior to the MGUS diagnosis. The MGUS diagnosis was ascertained using the 2003 IMWG criteria. A control group was identified, matched 1:1 for sex, age (±5 years) and BMI (± 2 kg/m2). Exclusion criteria included presence of primary or metastatic bone malignancy, multiple myeloma, exposure to anti-resorptive or anabolic agents, or exposure to steroids for > 3 months. TBS analysis was performed retrospectively using TBS iNsight v3.0 software. TBS values were categorized as low (<1.20), intermediate (1.20 – 1.35) or normal (>1.35). Results: Patients had a median age of 69.7 years (IQR 63.7 – 75.8; p=0.98 for cases vs. controls) and predominantly Caucasian (96%; n=111) men (77%; n=89) with a median BMI of 28.3 (25.5 – 32.4; p=0.92). BMD was performed after a median of 24 months from the time of MGUS diagnosis (0 – 68 months). Cases had significantly higher incident fractures compared to controls (14 vs. 7, respectively, p<0.05). There was no difference between cases and controls as to the distribution of TBS categories (low 23 vs. 15%; intermediate 42 vs. 41%; normal 35 vs. 44%; p=0.22) or LS T-scores (-0.30 vs +0.22, p=0.16). Although fractures occurred in controls who had a significantly lower TBS value (1.17 vs. 1.34 in controls with vs. without fracture, respectively, p <0.01), this was not the case in patients with MGUS (TBS 1.28 vs. 1.31 in cases with vs. without fractures p=0.97). Similarly, there was no difference in LS T-scores in cases with or without fractures (0.29 vs. -0.4, respectively, p=0.3). Conclusion: Despite a significantly increased risk of fractures in patients with MGUS compared to age-, sex- and BMI-matched controls, neither BMD nor TBS, obtained within 2 years of MGUS diagnosis, were able to risk stratify patients. Indeed, unlike controls, patients with MGUS tend to fracture despite a normal BMD and an intermediate or

normal TBS value. More advanced non-invasive measures of bone quality and finite element analysis may be needed to capture this risk.

Keywords:
Fracture

Metabolic Bone Disease

MGUS

Tracks:
Multiple Myeloma Bone Disease

OAB-051

Fractures and Survival in Multiple Myeloma: Results from a Population-Based Study

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Abstract:
Background Multiple myeloma (MM) causes lytic bone lesions and fractures, which increase the morbidity of MM patients. The impact of fractures on MM survival is unclear. The aim of the study was to evaluate the association of fractures and survival at MM diagnosis, as well as after diagnosis, in MM patients diagnosed in Sweden in the years 1990-2013. Methods Patients diagnosed with MM were identified from the Swedish Cancer Register. Information on date of birth, MM diagnosis, fractures, and death were collected from central registries. Cox regression model was used to estimate the effect of fracture at diagnosis (within 30 days before or after MM diagnosis) on survival after the time of MM diagnosis. Another Cox regression model was used with fractures as time-dependent variables to assess the effect of fracture after MM diagnosis. The effect of fracture was assessed for any fracture or a specific subtype of fracture. Either first fracture or the first subtype of fracture was used in the analysis. To compare the difference in the association of fracture and survival between the two calendar periods 1990-1999 and 2000-2013, the interaction effect of the calendar period and fracture was assessed in a Cox regression model. Results were adjusted for age, sex, time of diagnosis and previous fractures. Results A total of 14,013 patients were diagnosed with MM during the study, thereof 1,213 (8.7%) were diagnosed with a fracture at MM diagnosis, and 3,235 (23.1%) after diagnosis. Patients with a fracture at diagnosis were at a significantly increased risk of death (hazard ratio (HR)=1.28; 95% confidence interval (CI): 1.19-1.37). The risk of death was significantly increased for patients that developed a fracture after the time of MM diagnosis (2.00; 1.90-2.10), for all fractures combined. The risk of death was significantly increased in patients who developed all subtypes of fractures after MM diagnosis; pathological fracture (2.17; 2.03-2.32), vertebral fracture (1.74; 1.61-1.87), hip fracture (1.99; 1.82-2.18), femoral fracture (2.62; 2.32-2.98), humerus fracture (2.57; 2.31-2.85), forearm fracture (1.24; 1.05-1.46), rib fracture (1.52; 1.31-1.77), pelvis fracture (1.99; 1.74-2.29), except ankle fracture (1.07; 0.79-1.44). The impact of fractures on survival did not change significantly between the two calendar periods 1990-1999 and 2000-2013 (0.98; 0.89-1.08). Conclusion Our large study, including over 14,000 patients diagnosed with MM in Sweden in the years 1990-2013, shows that patients with a fracture at diagnosis have a 28% higher risk of dying compared to patients without a fracture. Furthermore, MM patients that develop a fracture after the time of MM diagnosis are at twofold risk of dying compared to MM patients that do not develop a fracture, and this risk has not decreased significantly after the introduction of more effective treatment agents in MM. Our results stress the importance of preventing bone disease in MM.

Keywords:
Fracture

myeloma bone disease

survival

Tracks:
Multiple Myeloma Bone Disease

OAB-052

Bone marrow MRI versus 18F-FDG-PET/CT for detecting multiple myeloma lesions: diagnostic performance and clinical relevance

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Abstract:
Purpose To compare the diagnostic performance of MRI and 18F-FDG-PET/CT in detecting bone marrow involvement (BMI) in patients with multiple myeloma (MM). Materials and Methods This retrospective study was approved by our Institutional Review Board. Two radiologists and two nuclear medicine specialists independently and blindly reviewed 84 pairs of MRI and PET/CT scans obtained in 73 MM patients. Readers assessed the presence and patterns of BMI. The best valuable comparator (BVC) for BMI was established by a panel review of all baseline and follow-up imaging, biological and pathological information. Intra- and inter-reader agreement and correlation between MRI and PET/CT were assessed using the prevalence-adjusted bias-adjusted kappa (k) coefficient. Diagnostic performance of MRI and PET/CT in detecting BMI was evaluated from ROC characteristics. Association between imaging and biological, pathological and clinical findings was assessed using Wilcoxon rank-sum and chi-square tests. Results Intra- and inter-reader agreement was very good for MRI (k = 0.90 [0.81; 1.00] and 0.88 [0.78; 0.98]). Intra- and inter-reader agreement was substantial for PET/CT (k = 0.80 [0.69; 0.91] and 0.71 [0.56; 0.86]). The sensitivity of MRI to detect BMI (97% [90%; 100%]) was significantly superior to that of PET/CT (76% [64%; 85%]). The specificity of MRI (86% [57%; 98%]) was lower than that of PET/.CT (93% [66%; 100%]), without reaching statistical significance. There was a strong correlation between decisions regarding patient management and PET/CT findings. Conclusion WB-MRI is significantly more sensitive than PET/CT to detect BMI in MM. Patient management is more strongly correlated with PET/CT findings.

Keywords:
Magnetic Resonance Imaging

Multiple myeloma

PET-CT

Tracks:
Multiple Myeloma Bone Disease

OAB-053

CXCR4 positron emission tomography for the detection of bone disease in newly diagnosed myeloma

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Abstract:
Background: Preliminary studies of positron emission tomography (PET) using [68Ga]-Pentixafor, a novel radiolabelled CXCR4 ligand, show favourable imaging characteristics in humans

with relapsed multiple myeloma. Theranostic applications have also been reported with evidence of activity in advanced, treatment-refractory disease. Little is known about the utility of this tracer as a diagnostic tool to detect myeloma bone lesions in newly diagnosed disease. Aim: To assess the diagnostic performance of CXCR4 PET in a cohort of untreated myeloma patients using whole-body magnetic resonance imaging (WB-MRI) as the gold standard. Methods: Newly diagnosed patients with biopsy-proven myeloma/plasmacytoma were enrolled prior to initiation of therapy. Simultaneous WB-MRI (T1, T2 STIR) and [68Ga]-Pentixafor PET were performed using the Siemens Biograph mMR with unblinded image interpretation by two independent assessors. Focal lesions >5mm on MRI displaying T1 hypointensity/T2 hyperintensity, and PET lesions with SUVmax>2.5, were classified as positive. Lesion counts were categorised as discrete variables of 0, 1-5, 6-20 or >20. The primary outcome was test accuracy of CXCR4 PET compared to MRI. Results: Ten patients were recruited between March 2017 and March 2019, with median age 69.5 years. ISS staging included stage 1 (n=3), stage 2 (n=4) and stage 3 (n=2). High-risk cytogenetics (del17p, t(4;14) or t(14:16)) were detected in two patients. [68Ga]-Pentixafor PET identified focal bone lesions in 7/10 patients compared with 9/10 using WB-MRI. The one patient with negative WB-MRI was found to have a single bony lesion on PET. The other three discordant cases had low-risk clinical features with few and/or small lesions on WB-MRI. The sensitivity of [68Ga]-Pentixafor PET was therefore 6/9 (67%). No extramedullary lesions were detected. Mean SUVmax for the positive PET scans was 16.2 with good tracer uptake at pathological fracture sites and favourable lesion-to-background characteristics. The most avid PET study occurred in a patient with heavy bone marrow disease and adverse cytogenetics (17p deletion). Conclusion: [68Ga]-Pentixafor PET identifies bone disease in a majority of cases but underestimates lesion count compared with WB-MRI, with sensitivity of 67% in this patient series. PET showed concordance with WB-MRI for all major findings, including pathological fractures. Lesion pickup rate and SUVmax appeared higher in patients with high-risk clinical features. These preliminary findings provide hypothesis-generating data for future staging and theranostic applications of this molecule.

Keywords:
CXCR4

Newly diagnosed multiple myeloma

PET

Tracks:
Multiple Myeloma Bone Disease

OAB-054

Prospective evaluation of a quantitative MRI biomarker to assess treatment response for patients with multiple myeloma

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Abstract:
Purpose To investigate the capability for assessment of treatment response for multiple myeloma patients of a quantitative measurement of bone marrow changes in magnetic resonance (MR) images. Method and Materials This study evaluated the generalizability of a new MRI biomarker in an ongoing two-site prospective study. With IRB approval and informed consent, 32 pairs of pre- and post-treatment spinal MRI scan with an average interval of 2.4±1.1 months were collected from 32 MM patients who underwent first induction therapy in Peking University and University of Michigan in China and USA. We developed a 3D dynamic intensity entropy transformation (DIET) method to transform MR signal to a voxel wise quantitative entropy enhancement value, from which predictor

variables were derived and combined into a DIET response index (qERI) to assess treatment response. We applied the DIET method to the pairs of MRI scans of 32 patients to predict clinical outcomes. Results Of 32 patients, in which 16 from China and 16 from USA, 19 and 16 were clinically diagnosed as responders (PR and more than PR) and non-responders, respectively, by using International Myeloma Working Group Uniform Criteria (IMWG-URC) in more than 6-months follow-up. Using a decision threshold previously chosen with the development set, the qERI correctly predicted 17 responders (89.47% sensitivity) and 10 non-responders (76.92% specificity) at an AUC of 0.79. Of 17 responders, IMWG-URC initially determined 2 as non-responders at 3-month time point and re-assessed them as responders in 6-month follow-up. The agreement between the DIET method and the clinical outcome reached 0.84 with a kappa value of 0.67. Conclusion The substantial agreement between qERI prediction and clinical outcomes demonstrated that qERI has the potential for early assessment of the clinical outcome of MM response, allowing clinicians to optimize therapy of individual patients.

Keywords:
MRI biomarker

Response Criteria

Tracks:
Multiple Myeloma Bone Disease

OAB-055

Glutamine addiction of myeloma cells shapes the metabolic features of the bone microenvironment and impairs osteoblast differentiation

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Abstract:

Introduction. We have recently found that the metabolism of multiple myeloma (MM) cells is peculiarly characterized by high glutamine (Gln) dependency leading to decreased levels of the amino acid in the bone marrow (BM) plasma of patients (Bolzoni M. et al. Blood 2016). However, the potential impact of the MM-related alterations of Gln metabolism on the bone microenvironment and the development of osteolytic lesions is still unknown. Since osteoblast suppression is the hallmark of MM bone disease, in this study we investigated if the low-Gln microenvironment, imposed by MM cells, affects osteoblastogenesis. Methods. The effect of changes in extracellular Gln levels on osteoblast formation and activity was checked. Several human MM (HMCLs), BM mesenchymal stromal (hMSCs) and osteoblastic (HOBIT and HOB-01) cell lines were used. Gln extracellular levels were measured by a commercial kit or mass spectrometry, and amino acid uptake was assessed as previously described (Bianchi et al. Neuroscience 2008). The expression of osteoblastic markers (ALP, COL1A1 and RUNX2), ALP activity and expression were assessed to evaluate the osteogenic differentiation of hMSCs. Results. We found that HMCLs consumed large amounts of Gln (750 ± 50 nmol/106 cells/day) and exhibited fast initial uptake of the amino acid. When co-cultured with hMSCs or osteoblasts, HMCLs accelerated the depletion of extracellular Gln (+25%/day, compared to monocultures of MSC/osteoblasts), promoted the expression of Gln Syntethase (GS) by hMSCs and hindered viability of osteoblasts but not of hMSCs. Consistently, osteoblasts were more sensitive to Gln depletion than hMSCs. The expression and the activity of the Gln transporter SNAT2 (SLC38A2) were induced during human osteoblastogenesis, while other transporters, such as ASCT2 and SNAT1, were unchanged. SNAT2 induction was also associated with the increased expression of Glutaminase 1 (KGA, long-transcript form), suggesting a link between higher Gln consumption and osteogenic differentiation. Moreover, osteogenic differentiation by hMSC was affected by limitation of extracellular Gln. While this was suppressed in the absence of the amino acid (a condition associated with GS induction), the decrease of extracellular Gln

from 0.6 mM (the average physiological BM plasma concentration) to 0.4 mM (the average concentration found in BM plasma of MM patients) negatively affected the expression of osteoblastic markers as well as of ALP activity and staining. Finally, to further investigate the role of GS in osteoblastogenesis we either downregulated or upregulated GS expression in hMSC by lentivirus vectors. Conclusions: These results suggest that Gln addiction of MM cells and the consequent reduction of extracellular Gln levels in the bone microenvironment impair osteoblast differentiation and viability and are potentially involved in the development of bone lesions in MM.

Keywords:
Metabolic Bone Disease

microenvironment

Multiple myeloma

Tracks:
Multiple Myeloma Bone Disease

OAB-056

Transcriptional profiling of cortical bone after mechanical loading in the MOPC315.BM myeloma bone disease model

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Abstract:
Introduction Eighty percent of the newly diagnosed patients with multiple myeloma (MM) already suffer from MM bone disease, exhibiting osteolytic bone destruction. Currently available therapeutics have not yet succeeded in regenerating eroded bone even in the absence of active disease. We recently showed in a mouse model for MM bone disease (MMBD) that mechanical loading has anabolic effects and slows disease progression and MM spread. To identify underlying molecular events, we performed RNA sequencing analysis of mechanically-loaded cortical bone. We hypothesized that osteocytes as the main mechanosensors in bone, mediate the anabolic responses and alter the tumor microenvironment. Methods The 8-week old female Balb/c mice were injected in the left tibia with either syngeneic MOPC315.BM MM cells (36 mice), PBS (36 mice) or were not injected (18 mice). At 14 days post injection, the left tibiae from half of the mice in the MM and PBS groups and from all of the noninjected mice were subjected to a single session of compressive loading (-10N) (right tibia as nonloaded control). The other half of the mice from MM and PBS groups served as nonloaded controls. Mice were sacrificed 1h, 8h or 24h following loading (n=5-7 mice/group), total RNA was isolated from the cortex of dissected tibiae and RNA sequencing was performed. Differential gene expression was analyzed using the EdgeR software package and gene ontology (GO) enrichment analysis was done with the Gorilla tool. Results Comparison of all loaded and nonloaded groups at each time point revealed two sets of genes, which drive the early (1h after loading) and the later (8h after loading) osteocytic response to loading in MOPC315.BM mice. This core mechanotranscriptome consists of already known mechanoresponsive genes (such as Early Growth Response 2 and Wnt Family Member 1) as well as new factors, such as Activity-Regulated Cytoskeleton-Associated Protein. In addition, expression levels of genes such as Prostaglandin-Endoperoxide Synthase 2, known as immediate mechanoresponse genes were decreased in presence of MM cells indicating that the tumor affects mechanotransduction cascades. Notably, the strongest effect of loading on this gene set is seen eight hours after loading in MM mice while in healthy mice similar effects could be detected as early as one hour after loading. Further, ECM-related genes were among the gene sets most

downregulated by MM, revealed by GO analysis. Changes in ECM proteins such as Collagen Type VI Alpha 1 Chain is related to MM growth and metastasis. Mechanical loading counter-regulated this effect suggesting osteocytes could restore MM-impaired bone matrix. Conclusion Using a high-throughput approach we explored the transcriptional response of osteocytes to tumor and mechanical loading. We identified ECM changes after loading as a key event that affects the metastatic potential of MM cells.

Keywords:
bone target

extracellular matrix

high-throughput analysis

Tracks:
Multiple Myeloma Bone Disease

OAB-057

Progression risk stratification of Asymptomatic Waldenström Macroglobulinemia

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Abstract:
Background. Waldenström macroglobulinemia (WM) is a low-grade non-Hodgkin's lymphoplasmacytic lymphoma associated with overproduction of monoclonal IgM protein. It is preceded by an asymptomatic stage, called Asymptomatic WM (AWM), whose risk of progression to symptomatic disease is not well defined. Methods. In the largest to date study of AWM, we studied 439 patients with AWM at time of diagnosis, who were diagnosed and followed up at Dana-Farber Cancer Institute between 1992 and 2014. Results. During the 22-year study period, with a median follow-up of 7.8 years, 317 patients progressed to symptomatic WM (72%). IgM $\geq$ 4,500 mg/dL, bone marrow lymphoplasmacytic infiltration $\geq$ 70%, β2-microglobulin $\geq$ 4.0 mg/dL, and albumin < 3.5 g/dL were all associated with a 2-year progression risk of 60% and were identified as independent predictors of disease progression. To avoid discretizing these predictors based on arbitrary thresholds, we used them in a proportional hazards model as continuous variables instead. The model divided the cohort into 3 distinct risk groups: a high-risk group with a median time to progression (TTP) of 1.8 years, an intermediate-risk group with a median TTP of 4.8 years, and a low-risk group with a median TTP of 9.3 years. We successfully validated our model in two external cohorts, one from Mayo Clinic and one from the University of Athens, demonstrating its robustness and generalizability. For the purposes of clinical applicability and ease of use, we made the model available as a web page calculator (www.awmrisk.com). Importantly, high-risk AWM patients were shown to have inferior disease-specific survival (log-rank test, p = 0.029). What is more, by combining two cohorts, we were powered to identify wild-type (WT) MYD88 as an independent predictor of progression (HR: 2.7, p-value <0.001). In our cohort, all WT MYD88 patients progressed within 5 years. Conclusion. Drawing from the largest AWM study to date, this classification system is positioned

to inform patient monitoring and care, and for the first time, identify high-risk asymptomatic WM patients who may need closer follow up or benefit from early intervention.

Keywords:
Asymptomatic Waldenstrom Macroglobulinemia

Progression risk

Waldenström macroglobulinemia

Tracks:
Other Plasma Cell Disorders and Amyloidosis

OAB-058

Impact of Chromosome 6q Deletions in Multiple Myeloma and Waldenström's Macroglobulinemia by Next Generation RNA Sequencing

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Abstract:
Deletions of the long arm of chromosome 6 (del6q) are highly recurrent in MYD88 mutated Waldenström's Macroglobulinemia (WM) and impact regulatory genes for NF-kB, BTK, BCL2, and apoptotic signaling. Clonal del6q appear mutually exclusive of CXCR4 and may promote disease progression from IgM MGUS to overt WM (Hunter et al, 2016; Guerrera et al, 2018). Here, we aimed to explore the transcriptional impact of del6q in multiple myeloma (MM) and compare the 6q-related transcriptional signatures across the two diseases.

Methods:
We analyzed RNASeq data from 163 MM and 71 WM patients. Patient samples were isolated using bone marrow CD138+ plasma cells from MM and CD19+ lymphoplasmacytic cells from WM patients. The patient cohort included 94 hyperdiploid MM (H-MM) and 69 nonhyperdiploid MM (NH-MM) patients, 23 (24%) and 11 (16%) of whom showing del6q, respectively. Fifty-eight (82%) WM patients were MYD88 mutated, 19 (33%) of whom also carried CXCR4 mutations. Del6q were observed in 14 and 10 of MYD88MUT CXCR4 WT and MYD88MUT CXCR4 MUT cases, respectively. No del6q were present in MYD88WT WM. RNASeq data were analyzed using Bioconductor in R using limma/voom with Camera used for gene set enrichment based on MSigDB from the Broad Institute.

Results:
In H-MM, 15,847 genes were differentially expressed in the presence of del6q compared to only 105 genes in NH-MM. Interestingly, H-MM showed a strong and unique 6q-related gene signature characterized by downregulation of genes involved in apoptosis, the predominant upregulation of MYC targets, and the selective downregulation of KRAS signaling. In addition to having a differential impact based on MM subtype, del6q induce upregulation of IFN-α and downregulation of TNF-α signaling in MM patients, whereas they have the opposite transcriptional modulation in the context of WM. This observation indicates that, outside of the directly impacted genes on chr6q, the downstream signaling effects may depend heavily on the active signaling networks and epigenomic states specific to each disease.

Conclusion:
Our study indicated the existence of a strong and unique transcriptional regulation induced by del6q in H-MM patients. MM and WM showed different del6q-related transcriptional profiles, thus suggesting the potential cooperation of additional and disease-specific genomic and epigenomic events. Further efforts are warranted to clarify the

significance and clinical implications of del6q in MM patients.

Keywords:
6q deletion

RNA-Seq

Waldenström macroglobulinemia

Tracks:
Other Plasma Cell Disorders and Amyloidosis

OAB-059

Multicenter prospective phase II study of venetoclax in patients with previously treated Waldenstrom macroglobulinemia

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Abstract:
Background: The role of the oral BCL2 antagonist venetoclax in Waldenstrom macroglobulinemia (WM) is unknown. Immunophenotypic and genomic sequencing studies have shown that BCL2 is highly expressed and activated in WM cells. We initiated a phase II study to evaluate the safety and efficacy of venetoclax monotherapy in previously treated patients with WM (NCT02677324). Methods: The study was approved by the IRB at each participating institution, and all patients provided informed consent. Venetoclax was given in the outpatient setting and followed a ramp-up of 200 mg daily days 1-7, 400 mg daily days 8-14, then 800 mg daily thereafter, for maximum of 2 years, for the first 6 patients. For the following 24 patients, venetoclax was given at 400 mg daily days 1-7, then 800 mg daily thereafter, for maximum of 2 years. Patients were closely monitored for tumor lysis syndrome (TLS) during the first 24 hours of each dose escalation. Toxicity was graded per CTCAE v.4.03. Response was assessed based on IWWM-6 criteria. Results: 31 patients were enrolled. Median follow-up time is 18 months. Median age was 66 years and 17 patients (55%) were men. Median number of previous lines of therapy was 2 (range 1-10); 16 patients (52%) were previously exposed to BTK inhibitors (BTKi). MYD88 L265P was detected in all patients, and CXCR4 mutations in 17 (55%). At baseline, median serum IgM was 3,524 mg/dl (range 642-7,970 mg/dl), median bone marrow involvement was 40% (range 4-95%) and median hemoglobin was 10.6 g/dl (range 6.4-13.5 mg/dl). All patients were successfully escalated to target dose of 800 mg. At 12 months, serum IgM declined to 1,071 mg/dl (range 89-4,770 mg/dl), bone marrow involvement declined to 3% (range 0-50%) and hemoglobin increased to 13.1 g/dl (range 8.9-14.9 g/dl). At best response, VGPR was attained in 6 patients (19%), PR in 19 (61%), minor response in 2 (6%), stable disease in 3 (10%) and no response in 1 (3%), for overall response rate of 87% and major response rate of 81%. Patients with refractory disease had lower major response rate than patients with relapsed disease (p=0.005). Median time to response (TTR) was 1.9 months (95% CI 1.1-3.1 months) and was slower in patients with prior BTKi exposure (p<0.001). The 2-year PFS rate is 76% (95% CI 52-89%). Refractory disease was associated with worse 2-year PFS (p=0.003). Ten patients are off therapy; 4 completed treatment protocol, 4 had disease progression on treatment, 1 withdrew consent and 1 due to non-compliance. Grade 4 neutropenia occurred in 5 patients. Grade 3 adverse events included neutropenia (n=15), anemia (n=4) and diarrhea (n=4). One instance of laboratory TLS occurred. Venetoclax was dose reduced due to neutropenia (n=2), fatigue (n=1), diarrhea (n=1) and self-reduction (n=1). No IgM flare or clinical TLS were observed, and there have been no deaths. Conclusion: Venetoclax is a safe and effective treatment option for patients with symptomatic, previously treated WM.

Keywords:
clinical trials

Venetoclax

Waldenström macroglobulinemia

Tracks:
Other Plasma Cell Disorders and Amyloidosis

OAB-060

A Prospective Phase II of Daratumumab in Previously Treated Systemic Light-Chain (AL) Amyloidosis: Updated Results

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Abstract:
INTRODUCTION: Daratumumab (DARA) is a high-affinity human monoclonal antibody that specifically recognizes CD38. It has emerged as a breakthrough targeted therapy for multiple myeloma patients (pts). Monoclonal plasma cells in AL amyloidosis (AL) express CD38. We report here updated results of a prospective multi-center, phase 2 study of DARA in AL (NCT02816476).
METHODS: This trial was planned to recruit 40 pts with evaluable AL (dFLC > 50 mg/L) with ≥1 major organ involvement, ECOG 0-2, supine blood pressure > 100 mmHg and NT-proBNP < 8500 ng/L. Pts should have received ≥1 prior therapy and should not be in very good partial response (VGPR) or better. DARA was infused in a standard schedule and dose for a total of six 28-day cycles: 16 mg/kg weekly in cycles 1-2 and every other week in cycles 3-6. Hematologic responses were measured after 1 injection of DARA, at day 1 of each cycle, at the end of treatment visit (EOT) and every 3 months thereafter. The main objectives were to determine hematologic responses at EOT and Best Response Achieved (BRA), organ responses and safety.
RESULTS: 40 pts were enrolled between 9/2016 and 4/2018 in 14 centers. The median age was 69 years (45-83). The median number of organ involvement was 2 (1-5), 27 pts (68%) have cardiac and 25 pts (63%) renal involvement. The median time from diagnosis to accrual was 24.0 months (3.5-122) with a median of 3 prior therapies (1-5): 20 pts (50%) have received melphalan, 38 pts (95%) bortezomib, and 23 pts (58%) IMiDs. At data cut-off (02/2019), all pts ended therapy and 34 pts received the planned 6 cycles. Six pts discontinued therapy earlier because of disease progression and 2 because of an adverse event, 3 pts died while on therapy (cardiac progression, lung cancer, cardiac arrest). All pts are evaluable for response (at least 1 cycle) and for safety (received 1 dose). VGPR or better was observed in 19 pts (47.5%), and partial response (PR) in 3 pts (7.5%). The global response rate was 65% with 22 pts in ≥VGPR (BRA). Responses were rapid with 13 pts in ≥VGPR after a single dose of DARA. In the responding pts, median dFLC decrease after 1 injection was 67% (146 mg/l to 39 mg/L). Regarding organ responses, we observed 15 (60%) renal and 8 (29.5%) cardiac responses. Concerning safety, 9 pts (22.5%) had at least one SAE. The most common drug-related AE was infusion reaction in 16 pts (40%), all of grade 1/2. Overall, 215 AEs were reported in 37 pts and 18 were grade ≥3, all considered as non-drug related.

Median follow-up is 22 months. Among 18 pts in response at the EOT, at data cut-off only 5 pts needed another line of therapy. Further data on PFS and duration of response will be provided during the meeting. CONCLUSIONS: Monotherapy with DARA demonstrates encouraging efficacy in previously treated pts with AL amyloidosis with deep and rapid hematological responses with a good safety profile. The Andromeda phase 3 study comparing CyborD with or without DARA is ongoing.

Keywords:
amyloidosis

daratumumab

Tracks:
Other Plasma Cell Disorders and Amyloidosis

OAB-061

A Prospective Phase II Trial of Lenalidomide and Dexamethasone in POEMS Syndrome

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Abstract:
Background. POEMS syndrome is a rare form of B cell dyscrasia with multiple clinical signs including polyneuropathy and osteocondensing bone lesions. Vascular endothelial growth factor (VEGF) plays a major role. Depending on bone marrow involvement and number of sclerotic bone lesions first line therapy should be radiation or systemic therapy, the most effective being high dose chemotherapy with autologous stem cell transplantation (ASCT). Lenalidomide seems to have a particular efficacy in this disease. We report the final results of a prospective phase II trial using Lenalidomide and Dexamethasone (Len-Dex) in 50 patients (pts), 2 cycles preceding radiation or ASCT or 9 cycles followed by 1 year Len alone in pts who cannot receive radiation or ASCT. Methods. Newly diagnosed or relapsing pts with POEMS syndrome were eligible. Pts eligible to radiation or ASCT received two 28 day cycles of Len 25 mg PO Days 1-21 and Dex 40 mg PO Days 1,8,15,22 before radiation or intensive treatment (Group 1), the other pts received 9 cycles of the same Len-Dex (Group 2) and then 12 cycles of continuous low dose Len (10 mg). Len and Dex dose was tapered for pts with renal failure or above 75 years of age or frail. All pts had a diagnosis of POEMS syndrome according to criteria by Dispenzieri et al (Am J Hematol 2012;87(8):80414). The primary endpoint was evaluation of the effectiveness of Len-Dex combination using biological responses (decrease of monoclonal protein and VEGF level) and secondary endpoints were clinical and particularly neurological responses and safety. Results. Fifty pts have been included in 19 centres, median age at inclusion was 58 (range 32-77), the median follow-up is 3.4 years (range 0.1-6.6). Thirty-three pts were included in group 1, with radiotherapy in 10 pts and ASCT in 23 pts; 17 pts were included in group 2. Thirty-nine pts were in first line and 11 pts already treated. Main

adverse events due to Len-Dex were 2 arterial thrombotic events. No engraftment syndrome was noted in the 22 pts treated with ASCT. To date, 4 pts have died, 1 in the ASCT group and 3 in group 2. PFS at 3 years is 73%, 84% in the ASCT group, 90% in the radiation group and 49% in group 2. After 2 cycles VEGF values in serum and plasma were normal in 15 and 21 pts, median values at inclusion were 2316 pg/ml in serum and 382 pg/l in plasma, after 2 cycles (n=49, post C1 in 2 pts) it was 743 pg/ml and 76 pg/ml respectively. Neurological improvement was very rapid in some pts, based on ONLS and 10 meters walking test assessment, 21/45 and 11/18 evaluable pts had a neurological improvement after 2 cycles. After ASCT 1 pt relapsed and received a second ASCT, 1 pt relapsed after radiation, in the group 2 7 pts had a progression after 9 cycles. Conclusion. This prospective trial of Len-Dex combination in POEMS syndrome showed a good tolerance , a strong efficacy on VEGF measurement and led to rapid neurological improvement in the majority of pts.

Keywords:
Lenalidomide

POEMS syndrome

Tracks:
Other Plasma Cell Disorders and Amyloidosis

OAB-062

Profound MRD negativity rates after frontline tandem autologous-allogeneic stem cell transplantation followed by bortezomib maintenance in high-risk or young myeloma patients

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Abstract:
Introduction: Prior studies suggest that allogeneic (allo) stem cell transplant (SCT) can overcome high-risk (HR) cytogenetics associated with poor outcome in multiple myeloma (MM). Despite being the only potentially curative therapy for MM, the use of allo SCT remains controversial due to unacceptably high nonrelapse mortality (NRM; 10-15%), morbid extensive chronic graft-versus-host disease (cGVHD; 50-80%) and high relapse rates (50-60%). We hypothesized that bortezomib (BTZ) after allo SCT might decrease both relapse and cGVHD in HR disease and young MM patients (pts) who have the greatest loss in years of life from MM. We also sought to determine the predictive value of bone marrow minimal residual disease (MRD) on progression using a validated next-generation flow cytometry protocol. Methods: A prospective phase II trial included newly diagnosed MM pts with an 8/8 sibling/unrelated donor who were ≤ 65 years with HR cytogenetics, ISS 3, primary plasma cell leukemia or ≤ 50 years regardless of biologic risk. After a BTZ-based induction and autologous SCT, a nonmyeloablative allo SCT was performed, followed by BTZ maintenance at 1.3 mg/m^2 SC every 2 weeks for 1 year. Responses were assessed by IMWG criteria. MRD was evaluated on 10x10^6 cells by flow cytometry (sensitivity ≥ 10^-5) using the 8-color EuroFlow protocol prior to allo SCT, prior to BTZ and every 3 months thereafter for 2 years. Results: Thirty-nine pts (median age 54 years) were enrolled and allotransplanted (41% had sibling donors); 35 had received BTZ at time of datalock. ISS 3 was found in 44% and HR cytogenetics in 65%. With a median follow-up of 30 months, NRM, PFS and OS at 36 months were 6% (95%CI: 1-16), 46% (26-65) and 92% (77-97), respectively. After allo SCT, BTZ was shown to improve ≥ CR from 64% to 77% and immunophenotypic (i) CR (defined as stringent CR plus 2 consecutive negative MRDs) from 28% to 61%. Identification of < 50 MM cells/10x10^6 bone marrow cells 6 months after

initiation of BTZ was associated with a significantly lower incidence of progression at 2 years (27%) compared to ≥ 50 MM cells (82%, p=0.0075). Incidences of overall, moderate/severe and severe cGVHD at 24 months were 56%, 46% and 11% with predominance of skin, mouth and liver involvement. Compared to 42 similarly treated historical controls without BTZ maintenance, the overall (56% vs 83%, p=0.002) and moderate/severe (46 vs 69%, p=0.01) cGVHD incidences were lower in BTZ recipients. Conclusion: Tandem auto-allo SCT followed by BTZ maintenance results in a remarkably high rate of iCR and could improve cure rates. BTZ following allo SCT contributes to decrease both incidence and severity of cGVHD. For the first time in allo SCT recipients, we report that < 50 MM cells using an 8-color EuroFlow protocol 6 months after initiating BTZ is predictive of a better outcome. If confirmed, this landmark could be used to design future therapeutic interventions to further lessen the risk of relapse.

Keywords:
Allogenic stem cell transplant

bortezomib

Multiple myeloma

Tracks:
Myeloma Transplant and Maintenance Strategies

OAB-063

Maintenance therapy with either Lenalidomide or Bortezomib equally improves PFS and OS in High Risk Myeloma initially treated with Autotransplant.

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Abstract:
Introduction: Autologous stem cell transplantation (SCT) remains a frontline standard in eligible multiple myeloma (MM) patients (pts). Maintenance with Lenalidomide (Len) following SCT improves progression free survival (PFS). In del17p MM bortezomib (Bort) pre and post transplant was shown to improve PFS and OS. This led to the approval of len maintenance for all pts and of bort maintenance as an option for pts with high risk cytogenetics (HRC) in 2014 in British Columbia. Uptake of maintenance options was dependent on pt and physician preference. We compare the influence of maintenance regimen on outcome in pts with HRC after their first SCT for MM and compared this group to non-HRC MM pts. Methods: We identified 550 newly diagnosed MM pts in BC between January 2012 and July 2018 who underwent bort based induction followed by SCT with melphalan conditioning for frontline therapy. A retrospective chart review using our LBMT Database was used. 103 pts with HRC were identified (defined as del17p, t(4;14), and t(14;16)). 51 pts had del17p vs 52 with non del17p HRC. Continuous data were reported as medians with the Wilcoxon rank-sum test used for comparison. Categorical variables were compared using Fisher's exact test. Survival estimates were obtained using Kaplan-Meier method. Cox Proportional Hazards analysis was used to assess significance. Results: Baseline characteristics were similar between groups with a median followup of 24 mos in HRC subgroups. Among HRC pts 61(59%) pts did not receive maintenance therapy, 21(20%) received len and 21(20%) pts received bort as maintenance. Pts with HRC who received maintenance therapy post SCT had a significantly better PFS and OS compared to no maintenance therapy (PFS:30.2 vs 12.6 mos, p=.001, OS:not reached (NR) vs 39.8 mos, p=0.04. There were no statistically significant differences between bort and len maintenance among pts with HRC (PFS:len 30.2 vs bort:27.9 mos, p=0.9, OS len:43.6 mos vs bort NR, p=0.7). When we compared pts with del17p as the high risk feature vs.

all other HRC, the results were the same with equivalence for bort and len with both improving PFS and OS vs no maintenance (17p:PFS:len 30.2 mos vs Bort NR, p=0.9 (len vs bort), vs none 10.5 mos) (non 17p HRC:len NR, Bort 27.3 mos, p=0.85 (len vs bort), vs none 15.6 mos) As compared to all pts, HRC pts on maintenance had a shorter PFS as compared to non-HRC pts, although this was not statistically significant (non-HRC:45.6 vs HRC:30.2 mos, p=.085) Pts with HRC who did not receive maintenance had significantly shorter PFS (non-HRC:27.7 vs HRC:12.6 mos, p=<.001). In the whole group neither paraprotein response to maintenance or normalization of the lymphocyte count predicted PFS or OS. Conclusion: Maintenance therapy with either Bort or Len improved both PFS and OS for pts with HRC following SCT. Pts with del17p and other HRC both had a benefit. Prospective studies may be helpful to further define optimal maintenance for HRC subsets.

Keywords:
bortezomib

High-risk cytogenetics

maintenance

Tracks:
Myeloma Transplant and Maintenance Strategies

OAB-064

Comparison of bortezomib versus lenalidomide maintenance therapy in newly-diagnosed, transplant-eligible multiple myeloma: results from the phase III GMMG-HD4 and -MM5 trials

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Abstract:
Background: Maintenance therapy (MT) in newly-diagnosed, transplant-eligible multiple myeloma (MM) is a standard of care. Comparisons of single agent MT from distinct substance classes are not available. The present retrospective study analyzed post-transplant MT for 2 years with either bortezomib (BTZ) or lenalidomide (LEN) from two

subsequently conducted, multicenter phase III trials (HD4/MM5) of the German-speaking Myeloma Multicenter Group (GMMG). Patients and methods: The analysis included n=138/183 patients from the HD4/MM5 trials, respectively. In the HD4 trial (German part of the HOVON65/GMMG-HD4 trial), all patients were intended to receive an upfront tandem high-dose melphalan/autologous stem cell transplantation (HDM/ASCT) followed by BTZ MT (1,3mg/m2 i.v. every 2 weeks) for 2 years (HD4 study arm B). Patients in the MM5 trial received a single HDM/ASCT and only in case of less than near complete response (3 copies), elevated LDH (LDH>ULN), renal impairment (RI, serum-creatinine ≥2mg/dl) and age (>60 years). Analyses on progression-free/overall survival (PFS/OS) were carried out from start of BTZ MT (HD4) or LEN CONS (MM5). Results: Patient cohorts were well balanced regarding baseline characteristics. Tandem HDM/ASCT was applied in 90.6/33.3% of patients (p<0.001) in the HD4/MM5 trial, respectively. Rates of nCR/CR prior to MT were higher in the MM5 vs. HD4 trial (52.0 vs. 38.8%, p=0.02). The median time on study from start of MT/CONS was 21.5/24.0 months in the HD4/MM5 trial. Neither PFS (LEN vs. BTZ, hazard ratio [HR]=0.83, p=0.18) nor OS (HR=0.70, p=0.15) from start of BTZ MT/LEN CONS significantly differed between the two MT strategies. Multivariate analyses adjusted for response status prior to start of MT (CR/nCR vs. 1 favors BTZ) were observed according to RI (RI no/yes: HR=0.59/2.77; interaction p [i-p]=0.008), any adverse cytogenetics (no/yes: HR=0.41/1.62, i-p=0.049), deletion17p (no/yes: HR=0.58/2.56; i-p=0.018) and ISS (ISS I/II/III: HR 0.96/0.39/1.40; i-p=0.045). Conclusions: PFS and OS for LEN vs. BTZ MT were not significantly different in our cohort. Differential treatment effects for OS in relevant disease subgroups were observed. Randomized controlled trials comparing distinct substance classes as MT are highly warranted to offer risk-adapted MM therapy strategies.

Keywords:
bortezomib

Lenalidomide

maintenance

Tracks:
Myeloma Transplant and Maintenance Strategies

OAB-065

Maintenance with Weekly Carfilzomib in Elderly newly Diagnosed Multiple Myeloma (IFM 2012-03).

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Abstract:
Backgroung. Prolonged treatments have significantly improved survival in newly diagnosed multiple myeloma (NDMM). Lenalidomide (IMiDs), is currently approved in this indication, but remains a daily treatment, although oral, and may favor side effects in the long run. Furthermore, the use of a proteasome inhibitor (PI) is warranted in

certain type of MM, such as high-risk. Carfilzomib, a second generation PI, has proved active combined with an acceptable security profile, although its added benefit when given continuously is unknown. We thought to study maintenance Carfilzomib for elderly NDMM (eNDMM). Methods. The IFM 2012-03 multicenter phase I KMP (Carfilzomib, Melphalan, Prednisone) weekly study for eNDMM (≥ 65 years old) determined the maximal tolerated dose of weekly Carfilzomib at 70mg/m². We focus herein on the second part of the study with IV Carfilzomib monotherapy given at 36mg/m² for 13 cycles maintenance on an every 2 weeks schedule. Results. Thirty eNDMM were recruited in IFM 2012-03. Median age is 75, with 56% R-ISS 2 or 3 and 11% high-risk cytogenetic. With K weekly from 36 to 70mg/m², ORR is reported at 93.3%, including 46.7% ≥CR.; median PFS is 35.8 months and median OS was not reached.Twenty-two (73%) patients started K maintenance and 16 (73%) completed it. Four patients progressed and 2 stopped for AEs (renal amylosis, sensory neuropahty) during the maintenance phase. At maintenance completion, 50% were ≥CR. From the start of maintenance, in landmark analysis, median PFS is 28.1 months and the estimated 36-months OS approximately 70%. Moreover, 3 patients (14%) improved their responses during maintenance Conclusion. Carfilzomib monotherapy can be used safely in maintenance for 1 year in eNDMM, including for patients above 75 years. K maintenance may lead to deep response rate, certainly a most relevant prognostic factor for prolonged survival. Therefore, Carfilzomib maintenance, characterized with a simple administration modality, might be considered as an alternative to Lenalidomide and integrate the armamentarium of prolonged therapy in eNDMM.

Keywords:
carfilzomib

Elderly

maintenance

Tracks:
Myeloma Transplant and Maintenance Strategies

OAB-066

Measuring serological response to vaccination before and after autologous hematopoietic cell transplantation in multiple myeloma

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Abstract:
Introduction Patients with multiple myeloma (MM) are susceptible to infections due to impaired cellular and humoral immunity. To further investigate humoral, and indirectly cellular, immunocompetence, we analyzed anti-pathogen titers and response to polyvalent vaccinations pre and post autologous hematopoietic cell transplantation (HCT). Patients and methods We measured anti-pathogen titers pre, and at approximately day 100 post, HCT and again post-vaccination in 131 MM patients who had a first HCT at Roswell Park (RP) from 2013-2016. Anti-pathogen titers were quantified using commercially available kits according to manufacturer's instructions. Vaccinations were given against diphtheria, tetanus, bordetella (DTap), hemophilus influenzae type B (HIB), hepatitis A/B (hep A/B), influenza A/B, rubella, mumps, rubeola (MMR), meningococci (Men), polio, streptococcus pneumoniae (Strep), varicella zoster virus (VZV). We analyzed factors that might influence completion of planned vaccination, and investigated conversion of negative to positive serology to pathogens post-HCT and vaccination. Results Of 131 patients, 59% were >60 yrs, 55% male and 54% IgG MM. Over 90% were mobilized with G-CSF+Plerixafor, received melphalan 200 mg/m2 pre-HCT and had lenalidomide-based maintenance therapy post-HCT. Complete response rates increased from 17% pre-HCT to 53% post-HCT. About 75% of patients had

at least one dose of planned vaccines. There were no significant differences in diagnostic, treatment or response characteristics between patients who did and did not complete vaccinations. Conversion from negative to positive serostatus to pathogens occurred in up to 47% of patients post-HCT and before starting vaccines. The pathogens that patients are most likely to encounter in community settings had lower conversion rates post-HCT of 2% Strep, 8% rubeola/VZV, 9% Men, 14% HIB. However, receipt of at least 1 dose of scheduled vaccine post-HCT resulted in sero-conversion rates of 30% hepB, 62% Strep, 64% hepA, 65% Men, 78-83% polio, 94% HIB, 71-100% DTap. Most patients did not receive the MMR and VZV vaccines as they are not administered until 2 yrs post-HCT. Additionally, because the Shingrix vaccine was not released until 10/2017, analysis of this vaccine is beyond the scope of this study. No patient or disease factors predicted sero-conversion post-HCT or vaccination. Hypogammaglobulinemia pre-AHT was not correlated with pre-HCT serostatus against pathogens. Conclusion Conversion of sero-status post-HCT and pre-vaccination suggests that HCT can reset the immune system. Additionally, vaccination post-HCT is effective at further enhancing immunity to the analyzed pathogens. Analyses are ongoing of additional factors that may predict sero-conversion and whether sero-conversion is associated with progression-free/overall survival.

Keywords:
autologous stem cell transplant

Immunorecovery

vaccination

Tracks:
Myeloma Transplant and Maintenance Strategies

OAB-067

Detection and Prevalence of Monoclonal Gammopathy of Undetermined Significance: A study utilizing mass spectrometry-based monoclonal immunoglobulin rapid accurate mass measurement

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Abstract:
Aim: To determine the incidence and evolution of monoclonal gammopathy of undetermined significance (MGUS) in a cohort of patients from Southeastern Minnesota. Methods: We identified patients in the Mayo Clinic database who were clinically diagnosed with MGUS or related monoclonal gammopathy but had a prior negative work up for monoclonal proteins as part of the Olmsted County MGUS screening study. We performed a sensitive mass spectrometry-based monoclonal immunoglobulin rapid accurate mass measurement (miRAAM) assay on the baseline serum sample that was interpreted as negative for monoclonal protein in the initial screening study, as well as the sample obtained at the time of clinical monoclonal gammopathy diagnosis. We also performed serum immunofixation on all baseline samples obtained at the time of the screening study to enable comparison of sensitivity to the miRAMM method. We then determined the proportion of patients who developed clinical MGUS or related monoclonal gammopathy in whom the origin of the monoclonal protein could be detected years prior to the diagnosis through the sensitive miRAMM assay. Results: In the Olmsted County screening study, MGUS (IgM, non-IgM, or light chain types) was detected in 738 of 17,367 identifiable persons, resulting in a prevalence of 4.24%. Of the 16,629 persons who were negative for MGUS during the initial screening period, a monoclonal gammopathy was clinically diagnosed during subsequent follow up in 300 patients, and we studied 228 persons in whom cryopreserved serum samples from the initial screening available for testing with the miRAMM assay. The median time to first clinical diagnosis of monoclonal gammopathy was 10.1 years (range 0.3-18.4 years). In 150 of 228 persons (65.8%), a

monoclonal protein could be detected by miRAMM assay in the baseline sample that had been considered negative. Only 25 of 228 samples (11%) had a detectable monoclonal protein on immunofixation. From the time of clinical monoclonal gammopathy diagnosis, samples for testing were available in 216 of the 228 persons, and miRAMM confirmed presence of monoclonal protein in 198 persons (91.7%). Using the sensitive miRAMM we show that MGUS is present in 888 of 17,367 persons from the Olmsted County screening cohort, translating into a prevalence of 5.1% among persons 50 years of age and older. This represents the most accurate prevalence estimate of MGUS thus far.

Keywords:
MALDI Mass Spectrometry

Monoclonal Gammopathy of Undetermined Significance

Tracks:
Myeloma Response Assessment including MRD

OAB-068

Sequential minimal residual disease (MRD) monitoring: results from the UK Myeloma XI trial

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Abstract:
MRD is a powerful predictor of survival outcomes in multiple myeloma but treatment regimens show increasing duration and complexity for both TE and TNE populations. For this reason, sequential assessments are preferable to single timepoints. This has been evaluated in the Myeloma XI trial, which was a phase 3 trial with three potential randomisations to determine induction therapy, consolidation therapy and maintenance in both TE and TNE patients. Bone marrow aspirates were obtained after induction, post consolidation (if given), post ASCT for TE patients and 6 months post maintenance randomisation. MRD was assessed using flow cytometry (minimum sensitivity 0.004%). This analysis represents a subset of 1630 samples that represent all patient groups and therapeutic timepoints. Overall MRD-negativity post-induction was 164/722 (22.7%). 70.1% of patients randomised to CCRD were MRD-negative compared to 19.6% after CTD or RCD in TE patients and 12.7% after CTDa and 19.2% after RCDa ($p < 0.001$) in TNE patients. Levels of residual disease in MRD-positive patients were lower following CCRD induction; median 0.08% of leucocytes (range 0.001-9.5%), compared to medians of 0.31%, 0.23%, 0.38% and 0.42% following CTD, RCD, CTDa and RCDa respectively. MRD-negativity was demonstrated in 16/54 (29.7%) of patients who received bortezimib-based consolidation following a suboptimal response to induction. Post ASCT, 257/413 (62%) of samples were MRD-negative, with a significant increase in MRD-negativity rate relative to post induction seen with CTD (59.2% vs 19.6% post induction) and RCD (53.6% vs to 19.6% post induction). The level of conversion from MRD-positive post induction to MRD-negative post-ASCT was lower in the CCRD cohort (83.3% MRD-negative post ASCT compared to 70.1% following induction). Amongst the patients who underwent maintenance randomisation, MRD-

negativity was demonstrated in 238/413 (57.6%). Conversion to MRD-negativity was seen in 32% of MRD-positive patients on lenalidomide maintenance, whilst those patients who became MRD-positive during maintenance had poor outcome. For those patients that remained MRD-positive, lower levels of residual disease were noted in those receiving maintenance (median 0.15% on maintenance vs 0.39%, p=0.04). Sequential MRD monitoring allows for the assessment of individual components of complex myeloma therapeutic strategies. It enables comparison of induction regimens, possibly identifying patients that may not require ASCT. Consolidation or maintenance strategies can also be assessed. This data suggests a potential future role for flow cytometric MRD assessment in individual patient management. A full dataset of >4000 samples and mature outcome data will be presented at the meeting.

Keywords:
Flow Cytometry

Minimal residual disease

Tracks:
Myeloma Response Assessment including MRD

OAB-069

Stem Cell Mobilization and Autograft Purity with Novel Induction Regimens in Multiple Myeloma

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Abstract:
High-dose chemotherapy and autologous stem cell transplantation (ASCT) remains the standard-of-care in transplant-eligible patients with multiple myeloma (MM). Bortezomib with lenalidomide and dexamethasone (VRD) is the most common triplet induction regimen for patients with newly diagnosed MM in the US. Carfilzomib with lenalidomide and dexamethasone (KRD), however, has shown promising efficacy and may ultimately supplant VRD. We performed a comparative analysis of stem cell collection yields and autograft purity after VRD vs KRD induction. Deeper responses (VGPR or better), including bone marrow (BM) minimal residual disease (MRD) negativity by 10-color flow cytometry, were higher with KRD. Pre-collection BM cellularity, the interval from the end of induction therapy to start of stem cell collection, and the method of stem cell mobilization were similar for the two cohorts. Average time to stem cell collection completion (collection target = 10 x 106 CD34+ cells/kg) was slightly greater with KRD (VRD 1.85 vs KRD 2.2 days), as was the fraction of patients requiring ≥3 days to complete collection (20.29% vs 39.84%, p<0.0007). Viable CD34+ cell content (cells/μL) was significantly higher with VRD (108.6 vs. 61.33, p=0.0002), which associated with higher total stem cell yield after VRD (VRD 11.13 x 106 vs KRD 9.18 x 106, p=0.0245). Collection failure was rare but higher with KRD (4 patients, 3.25%) than with VRD (1 patient, 0.8%). Age (≥70) was a common factor predictive of lower stem cell yields for both cohorts (<60: 11.19 x 106 vs. 60-69: 9.69x106 vs. ≥70: 6.53 x 106, p=0.0004). In a subset of subjects with available samples, stem cell autograft purity/MRD negativity was higher with KRD (82.35%) than with VRD (57.5%) (p=0.01). For both cohorts, a greater proportion of autografts than pre-collection BMs were MRD negative. For patients who proceeded to transplant, mean time to engraftment after ASCT was comparable (VRD 9.96 vs. KRD 10.08 days). Although patients in the KRD cohort received an average of one additional cycle of treatment (VRD 4.9 vs. KRD 5.9), subgroup analysis of patients who received six cycles of VRD and KRD showed similar trends to overall study population, including

increased stem cell MRD negativity with KRD. In summary, KRD induces deeper clinical responses and greater stem cell graft purity than VRD without compromising stem cell yield or post-transplant engraftment kinetics, despite decreased viable CD34+ content of sample at the time of stem cell mobilization and lower stem cell collection totals. Longer follow-up is needed to evaluate the progression-free and overall survival of these patients.

Keywords:
Autograft products

Minimal residual disease

Multiple myeloma

Tracks:
Myeloma Response Assessment including MRD

OAB-070

Prognostic implications of MRD assessment in multiple myeloma patients: comparison of Next-Generation Sequencing and Next-Generation Flow

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Abstract:

Despite the deeper level of responses that new agents have brought to myeloma patients, some of them will eventually relapse due to the presence of resistant cells (minimal residual disease, MRD). Detecting MRD-positive cases allows the identification of patients with an increased risk of relapse, progression or death. In this context, Next-Generation Flow (NGF) and Next-Generation Sequencing (NGS) have emerged as potential tools to evaluate MRD. Because of that, we wanted to validate a commercial NGS strategy (LymphoTrack®), comparing it with NGF in the context of the Spanish Myeloma Group GEM2012MENOS65 clinical trial (ClinicalTrials.gov access number: NCT01916252). For this purpose, 202 bone marrow paired samples obtained from 101 patients at diagnosis and follow-up (3 months after ASCT, n=83, or at the end of induction, n=18) time points were used. For survival analysis, we considered the 83 patients for which MRD was evaluated after transplant; additionally, 5 patients achieving stringent complete response after the end of induction were also considered. Applicability of the NGS panel for clonality assessment was high: VDJH-FR1 (83.2%), VDJH-FR2 (79.2%), VDJH-FR3 (62.4%) and VJL-Kappa (86.1%), providing a 100% in total, quite comparable with that of Sanger sequencing (100/101 sequences were identified). In contrast, the applicability for MRD evaluation was biased by the quality of the initial sample and the concentration step using the ethanol precipitation method. This caused a fictitious lower sensitivity for NGS than NGF in our study (10-4-5·10-6 versus 3·10-5-3·10-6, respectively). MRD correlation between NGS and NGF was high (R2=0.987). Of note, there were 13 discordant cases (4 NGF+/NGS-; 9 NGF-/NGS+), but none of these patients have relapsed yet. By contrast, the 21 relapsing patients in our cohort (four of them in stringent complete response after induction) were MRD-positive using both methodologies. MRD-negative patients showed a significantly better PFS rate than MRD-positive patients (median not reached versus 55.16 months, respectively; $p<0.005$). This difference was maintained irrespectively of the response after induction ($p<0.05$), thus demonstrating a significant

advantage of MRD over conventional response for patient stratification. When patients were compared combining cytogenetics and MRD, we only detected differences in PFS between high-risk and standard-risk MRD-positive cases (p<0.001). All these findings were similar either using NGS or NGF. In the multivariate analysis, NGF positivity (p=0.004, HR: 9.13, 95% CI: 2.05-40.66) was the only independent prognostic factor of dismal PFS. In conclusion, comparison between NGS and NGF in this trial confirmed a major role for MRD detection in patient prognosis, and highlighted the need for considering MRD as a potential endpoint in more clinical trials.

Keywords:
Flow Cytometry

Minimal residual disease

Next Generation Sequencing

Tracks:
Myeloma Response Assessment including MRD

OAB-071

Dynamic monitoring of minimal residual disease reveals its superior prognostic significance in multiple myeloma

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Abstract:
Minimal residual disease (MRD) test is a promising approach for tailoring treatment of patients with multiple myeloma (MM). However, many questions remain to be addressed before integrating into daily practice. To this end, we evaluated the prognostic value of kinetic changes of MRD status at the sensitivity level of 10-4~10-5. In a total of 131 patients, 63.4% achieved MRD negativity (MRD-), among which 82% occurred within 6 months, with a median time-to-MRD- of 4 months from beginning of induction therapy. MRD- was significantly associated with prolonged PFS (p = 0.002), while MRD persistence (MRD+) represents an independent factor for poor prognosis, in terms of PFS (univariate, p = 0.002 ; multivariate, p = 0.003, HR = 2.214, 95% CI = 1.307~3.749) or OS (univariate, p = 0.05; multivariate, p = 0.056, HR = 2.043, 95% CI = 0.981~4.254). MRD– duration ≥ 12 months was strongly related to prolonged survival (p < 0.001 for both PFS and OS), in association with a marked reduction in risk of relapse or death (for PFS, p < 0.001, HR = 0.886, 95% CI = 0.845~0.930; for OS, p < 0.001, HR = 0.844; 95% CI = 0.768~0.928). In contrast, loss of MRD- status (MRD reappearance) was associated with poor PFS (p < 0.001) and OS (p = 0.003), with a median PFS of 19 months, which was close to, if not worse than, MRD persistence (median PFS = 20 months). In patients carrying high-risk cytogenetic abnormalities (HRCAs), the MRD status remained its value to predict PFS and OS (p < 0.001 for both). Interestingly, MRD- somehow overrode the adverse effect of HRCA, while there was no significant difference in both PFS and OS between MRD- patients carrying HRCAs and MRD+ patients without HRCAs. Treatment with the bortezomib-based regimens as well as ASCT was associated with increased MRD- rate (p = 0.014 and p = 0.017, respectively). Maintenance therapy prolonged OS of MRD- patients (p = 0.003), but not PFS (p = 0.350), while it also improved PFS and OS of MRD+ patients. Last, 16.9%, 30.1%, and 48.2% of MRD- patients achieved stringent CR, CR, and VGPR respectively, suggesting that approximately half of MRD- patients had VGPR or even PR (4.8%). MRD- patients also exhibited better outcome than those who achieved >= CR (PFS, p = 0.002; OS, p = 0.050). In conclusion, our results support several notions as follows: a) the MRD status is an independent prognostic factor in MM patients, including those carrying HRCAs; b) MRD- duration plays an additional and rather important role in prognostic estimation, while loss of MRD- could serve as an early marker for disease relapse; c) MRD negativity predicts favorable prognosis of MM patients more accurately than CR; d) MRD test might need to be carried out when patients achieved

>= VGPR, instead of >= CR. Together, monitoring of MRD kinetics could not only predict prognosis more precisely, but also be helpful to guide treatment decision, particularly for deciding when to start re-treatment of relapsed patients.

Keywords:
dynamic monitoring

Minimal residual disease

Multiple myeloma

prognostic impact

Tracks:
Myeloma Response Assessment including MRD

OAB-072

CRISPR studies identify genes preferentially essential for myeloma cells vs. other neoplasias: implications for future therapies selective against MM

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Abstract:
Improved clinical outcomes for MM in the last 2 decades have been driven by therapeutics which have limited activity in non-MM neoplasias; do not target specific oncogenic mutations in MM cells, but rather pathways which are critical for plasma cells (PCs), yet dispensable for normal or malignant cells of most other lineages. We performed genome-scale CRISPR gene-editing studies to systematically characterize the molecular vulnerabilities of 19 MM cell lines and define which genes are more pronounced and/or recurrent dependencies for MM vs. (n=657) lines from other blood cancers and solid tumors). We hypothesized that these studies would "re-identify" targets of currently used "PC-selective" anti-MM therapies and also pinpoint additional, previously underappreciated, genes critical for MM cells, but not other tumor types. We identified 90+ genes whose function was significantly more essential for MM lines than other neoplasias, including a large collection of transcription factors (e.g. IRF4, PRDM1, MAF, NFKB1, RELB, IKZF3, IKZF1, TCF3, CCND2, CBFB, MEF2C; transcriptional cofactors (e.g. POU2AF1); epigenetic regulators (e.g. EP300, DOT1L, HDAC1, ARID1A, CARM1); kinases such as IKBKB and CHUK/IKKa (both upstream of NF-κB), PIM2, IGF1R, SIK3, STK11; genes related to endoplasmic reticulum (ER) or Golgi function (e.g. HERPUD1, SYVN1, UBE2J1, SEC23B); as well as BCL2 and SMAD7. Results for several of these genes were further supported by in vitro studies with individual sgRNAs for gene editing or activation; "addback" experiments with CRISPR-resistant cDNAs; shRNA studies in MM lines; use of small molecule inhibitors (e.g. against PIM kinases, CBFB, CARM1); and a focused in vivo CRISPR screen with MM.1S cells implanted in mice with BM-like scaffolds harboring a "humanized" stromal compartment: this study examined 46 MM-

preferential dependencies which are also essential for MM.1S cells in vitro and observed that 41 of these genes were also essential for MM.1S cells in the "humanized" BM-like in vivo system. Some MM-preferential dependencies are essential for subsets of leukemia or lymphoma lines, but most have more pronounced/recurrent essentiality in MM vs. other blood cancers. In terms of overexpression (in high- vs. standard-risk MM; MM vs. normal PCs; or MM vs other cancers); frequency of mutations, DNA copy number gain or proximity to superenhancers, most of the MM-preferential dependencies harbor no such alterations or are not ranked in the top 100 genes for these alterations. The reassuring observation that MM-preferential dependencies include prominent known targets for therapeutics with relatively MM-selective clinical activity (e.g. thalidomide derivatives [IKZF1/IKZF3], proteasome inhibitors [NF-kB, ER function] or panobinostat [HDAC1]) underscores the promising therapeutic implications of the large number of previously underappreciated / understudied MM-preferential dependencies identified in our CRISPR-based functional studies.

Keywords:
CRISPR

preferential essential genes

Tracks:
Multiple Myeloma Novel Drug Targets

OAB-073

Gain-of-function studies with CRISPR-based transcriptional activation at endogenous genomic loci reveals genes with critical roles for myeloma cells

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Abstract:
Functional genomic studies (e.g. with RNAi or CRISPR) in multiple myeloma (MM) or beyond have generally focused on loss-of-function (LOF) studies. We reasoned though that important complementary information can be obtained from systematic gain-of-function (GOF) studies with transcriptional activation at endogenous genomic loci. We thus performed genome-scale CRISPR activation studies in 4 MM lines (MM1S, KMS11, LP1, L363) transduced with the dCas9-P65-HSF transcriptional activation system and the Calabrese genome-scale sgRNA library (2 pooled sub-libraries; total of ~110,000 sgRNAs targeting promoters of ~18000 genes; initial coverage ~800-1000 cells/sgRNA). Next generation sequencing quantified the sgRNA abundance in MM cells at baseline and various timepoints (e.g. 2-12 weeks of culture) and rank aggregation algorithms identified genes with statistically significant enrichment or depletion of their sgRNAs, reflecting positive vs. negative, respectively, effect of GOF of these genes on MM cell survival/proliferation. These studies identified several positive regulators of MM cell growth, including IRF4, IKZF3, IKZF1 and the transcriptional co-factor POU2AF1; known oncogenes, e.g. KRAS and MYC; NF-kappaB pathway members (e.g. RELA); and signal transduction regulators (e.g. IGF1R and its downstream effectors IRS1 and AKT2): these results were consistent with our observations that these genes are essential in LOF CRISPR studies in 20 MM cell lines. Interestingly, we identified several other genes which are not essential for MM cell survival/proliferation in LOF studies, but whose GOF stimulates MM cells, e.g. the transcription factors POU2F2 (Oct2) and PAX2, the TRAF interacting protein TIFA or the Toll-like receptor TLR4. We validated these results for several such genes (e.g. POU2F2, POU2AF1) with individual sgRNAs for CRISPR activation and/or cDNA overexpression (vs. isogenic controls) in competition experiments, cell cycle analyses and transcriptional profiling studies. We also identified several genes whose GOF potently suppresses MM cells, while

their LOF has limited impact on MM cells, including YAP1 (reported as oncogene for solid tumors but tumor suppressor for blood cancers); the pro-death TNFRSF10A, TP73, CDKN1A, MXI1 (negative regulator of c-Myc) or the pro-apoptotic Bcl2 family member BAK1. Most positive regulators of MM cell growth identified in this study are not among the top 50-100 genes in terms of transcriptional overexpression (in MM vs. normal PCs; late vs. early MM), mutation or amplification rates or proximity to superenhancers. CRISPR activation provide data complementary to those derived from CRISPR LOF interventions; and allowed us to both validate previously known genes and identify promising new candidate regulators of MM cell biology, including genes whose potential biologic and therapeutic implications may not be readily identifiable through standard analyses of the MM genome, transcriptome, or epigenome.

Keywords:
cell cycle

CRISPRa

gain-of-function

Tracks:
Multiple Myeloma Novel Drug Targets

OAB-074

Multiple myeloma with amplification of chromosome 1q is highly sensitive to MCL-1 targeting

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Abstract:
Introduction: Pro-survival BCL-2 family proteins are potent inhibitors of apoptosis and are often overexpressed in lymphoid malignancies. In multiple myeloma (MM), BCL-2 inhibitor Venetoclax induces cell death, particularly in presence of t(11;14) and high BCL-2 expression. The most prominent BCL-2 family member in MM is MCL-1, whose expression contributes to survival of malignant plasma cells and overexpression correlates with poor prognosis. Amplification of 1q21, the chromosome region that contains the MCL1 locus, occurs in approximately 40% of newly diagnosed MM, and 70% at relapse. This chromosomal abnormality is associated with poor disease prognosis. In this study, we investigate whether sensitivity to the novel MCL-1-inhibitor S63845 can be predicted using cytogenetics, thereby focusing on amplification of 1q21. In addition, we study the relation of MCL-1 inhibitor sensitivity with other diagnostic characteristics, and with BCL-2 family protein expression. Methods: In 31 human myeloma cell lines and in bone marrow aspirates from 47 newly diagnosed MM patients, we measured the effect of S63845 alone, or combined with BCL-2 inhibitor ABT-199 (Venetoclax), and BCL-XL inhibitors A-1155463 or A-1331852, on cell viability. Results: We demonstrate for the first time that MM patients with 1q21 amplification are significantly more sensitive to inhibition of MCL-1 in vitro. We propose that this increased sensitivity results from increased MCL1 expression due to amplification of 1q21. Additionally, and independent from 1q21 status, increased serum β2m level and presence of renal insufficiency correlated with increased sensitivity to MCL-1 inhibitor treatment. Using both 1q21 status and serum β2m level, we identified a MM subset with very strong dependence on MCL-1. Combining S63845 with other BH3-mimetics synergistically increased apoptosis compared to single inhibitors, and sensitivity to inhibitor combinations was found in a large proportion of MCL-1-independent MM. Conclusion: Collectively, our data indicate that amplification of 1q21 identifies a poor prognosis MM subset that is highly sensitive to MCL-1 inhibitor treatment.

Keywords:
Chromosomal abnormalities

Mcl-1 inhibitor

Newly diagnosed multiple myeloma

Tracks:
Multiple Myeloma Novel Drug Targets

OAB-075

Founding precision therapy for 1q-amplified multiple myeloma

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Abstract:
Introduction Amplification of the long arm of chromosome 1 (Amp1q) is one of the few frequent genetic alterations in Multiple myeloma (MM) and has a confirmed adverse effect on survival. While the region between 1q21 and 1q23 has been described as a probable target of the amplification, the actionable gene dependencies in that region have not been explored so far. Here, we employed a large number of in-house and publicly available CRISPR, shRNA and drug screens, in the largest to date effort to characterize the genetic dependencies of Amp1q MM and discover drugs that target them. Methods To assess the genetic dependencies of Amp1q MM cell lines, we analyzed publicly available dependency data from Dependency Map (CRISPR & RNAi) and performed a genome-wide CRISPR screen and a C911-corrected shRNA screen targeting the 1q21-1q23 region. Integrative analysis of all dependency screens was performed using a linear model, weighed for each screen's technical quality. In parallel, we performed two drug screens, one utilizing the Broad Institute's Drug Repurposing Library of over 5,000 drugs that have cleared varied stages of clinical testing, and another with ~200 compounds guided by the Connectivity Map (CMap), which we queried with an Amp1q gene expression signature derived from patient data. Results Gene-set enrichment analysis of our genome-wide screens revealed Amp1q MM to be dependent on Myc and cell cycle-related pathways, as well as PI3K-mTOR and ubiquitin-related pathways. Upon integration of all four dependency screens, potential new targets for drug development were identified, including S100A11, a gene involved in proliferation and metastasis, and CLK2, a cell cycle kinase involved in RNA-splicing. MCL-1 was the main directly targetable dependency of Amp1q MM, suggesting a potential for fast clinical translation. Two specific MCL-1 inhibitors, S63845 and AZD5991, were tested in vitro, and Amp1q MM lines were shown to be markedly more sensitive to MCL-1 inhibition. Further linking this phenotype to Amp1q, MCL1 gene expression was shown to increase linearly with increasing 1q copy number, while BCL2/BCL2L1 expression decreased. Furthermore, and in accordance with results indicating PI3K-mTOR as a major Amp1q addiction, PI3K and VEGFR2 inhibitors were the most common hits across both, the Drug Repurposing and the CMap-guided drug screen. Collectively, response to MCL-1, PI3K and VEGFR2 inhibitors that cleared in vitro validation allowed for distinct clustering of Amp1q lines in an unsupervised manner. Conclusion We have shown that Amp1q MM does have its own vulnerabilities and those can be targeted through small molecule inhibitors. This discovery has the exciting potential to establish precision therapy for Amp1q MM and affect change in a large number of patients.

Keywords:
1q amplification

Mcl-1

Multiple myeloma

Tracks:
Multiple Myeloma Novel Drug Targets

OAB-076

Synthetic lethality in multiple myeloma harboring double oncogenic hits of 17p13(del) and 1q21(amp)

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Abstract:
Background: Recurrent chromosomal aberrations are the main hallmark of multiple myeloma (MM). A recent large scale genome-wide analysis has unveiled that the co-occurrence of 17p13(del) and 1q21(amp) lesions constitute a novel high-risk disease group. Within 17p13, lies TP53 that maintains the genomic integrity by keeping the double stranded DNA damage (DSB) pathway in check. On the other hand, ADAR1 is a critical gene within 1q21 and we have recently reported that its direct RNA editing mechanism on NEIL1 (base-excision repair (BER) gene) caused defective single stranded DNA breaks (SSB) repair, resulting in CHK1 activation. With DNA damage abnormalities being a long standing player in cancer/MM, we aim to elucidate how p53 and NEIL1 aberrancy (associated with 17p13(del) and 1q21(amp), respectively) has potential collaborating role in affecting DNA damage response and their sensitivity to CHK1 inhibitor, and to identify novel biomarkers for patients with the double oncogenic hits. Methods: For clinical association, we analysed the publicly available patient dataset, CoMMpass. For biological studies, we synthetically and pharmacologically inhibited CHK1 with its specific siRNA, CHK inhibitor (AZD7762) and ATR inhibitor (VE821). The effects of CHK1 inhibition were determined with standard molecular assays. Results: We identified that MM patients with double oncogenic hits are closely associated with genomic instability and poorer response to standard MM treatments. CHK1, a DNA damage marker, was overexpressed in the double hit patients, having close association with overall survival, suggesting that it may be a good therapeutic target in these patients. This was proven when AZD7762 and VE821 showed greater efficacy against MM cell lines with the double chromosomal lesions as compared to single abnormality. When we further elucidated if this was related to the aberrancy in NEIL1 and deficiency in p53, indeed, cells with NEIL1-editing and loss of p53 function demonstrated increased sensitivity to shRNA-mediated and pharmacological inhibition of CHK1, and the cells having both genes compromised, were the most sensitive. There was an increased amount of unrepaired DSB, involuntary cell cycle progression and enhanced apoptosis. Biologically, we identified that defective BER in NEIL1-edited cells synergizes with CHK1 inhibition to render an accumulation of unrepaired SSB that was then converted into DSB. Coupled with inefficient DSB repair from the loss of p53, there was a massive build-up of DSB, overwhelming the repair machineries, thus, resulting in eventual cell death. Conclusion: Our data indicates that genomic instability could serve as the Achilles heel in the double hit patients and could thus be manipulated for targeted treatment using the synthetic lethality approach.

Keywords:
DNA damage

double hit

GENOME STABILITY

Tracks:
Multiple Myeloma Novel Drug Targets

OAB-077

APOBEC3B is induced by activation of DNA damage pathway and regulates the survival and treatment response in human multiple myeloma

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Abstract:
Apolipoprotein B mRNA editing catalytic polypeptide-like 3B (APOBEC3B), a DNA cytosine deaminase causing cytosine-to-uracil (C-to-U) deamination in single-stranded DNA, plays a prominent role in inducing mutations in multiple human cancers. In MM, high APOBEC3B activity is associated with a poor prognosis and expression of APOBEC3B is significantly up-regulated in MM patients with t(14;16) and t(14:20). However, only approximately 23 % of patients with high APOBEC3B are linked to MAF/MAFB/MAFA translocations. Here, we further studied mechanisms modulating APOBEC3B expression and functional consequences of molecular manipulation of APOBEC3B in MM cells. Quantitative RT-PCR and immunoblotting show that APOBEC3B expression is significantly higher than other members of the APOBEC3 gene family in MM cell lines. APOBEC3B protein levels are also higher in the MM cell lines with higher ongoing DNA damage levels. Next, we examined whether DNA damage response affects APOBEC3B expression in MM cells. Sub-lethal doses of Melphalan (Mel) or ionizing radiation (IR) induced APOBEC3B transcript and protein in a dose- and time-dependent manner in multiple MM cell lines ($n > 6$). Bortezomib (btz), which at sub-lethal doses triggers DNA damage signaling, also induced APOBEC3B expression. Since DNA replication stress activates the ATR/ATM pathway, we next investigated whether these kinases mediate APOBEC3B induction following Mel- or IR- or btz-induced DNA replication stress. H929 and MM1S cells were treated with Mel or IR in the presence or absence of ATM or ATR inhibitors, following which they were then lysed and assayed for APOBEC3B expression. The presence of ATM or ATR inhibitors blocked phosphorylation of H2AX induced by Mel, IR, or btz. Importantly, inhibition of ATR or ATM activation blocked Mel- or IR or btz-induced APOBEC3B, indicating that replication stress induced by Mel, IR, or btz, upregulated APOBEC3B expression via an ATM/ATR-dependent pathway. Next, we used gene-specific CRISPR knock out (KO), shRNA knockdown (KD), and inducible-shRNA KD to study the functional impact of APOBEC3B perturbation in MM cells. Both KO and KD of APOBEC3B decreased growth and survival in MM cell lines (MM1S, RPMI8226, and KMS11). Using zombie aqua and annexin V-based flow cytometric analysis, APOBEC3B inhibition further increased growth arrest followed by apoptosis in these MM cells. Moreover, downregulation of APOBEC3B enhanced resistance to pomalidomide in RPMI8226 MM cells. These data suggest that increased APOBEC3B levels plays an important role in MM cell survival and drug responses. Taken together, DNA replication stress triggered by Mel, IR, or btz upregulates APOBEC3B expression via ATM/ATR pathway, which in turn increases subclonal diversity leading to drug resistance. The role of APOBEC in disease pathogenesis and progression, coupled with its role mediating treatment response, suggest potential utility of targeting APOBEC3B in novel MM therapies.

Keywords:
DNA damage

Drug resistance

Multiple myeloma

Tracks:
Multiple Myeloma Novel Drug Targets

OAB-078

A phase 1b study of once-weekly carfilzomib combined with lenalidomide and dexamethasone (wKRd) in patients (pts) with newly diagnosed multiple myeloma (NDMM)

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Abstract:
Introduction: Twice-weekly KRd is approved for the treatment of relapsed or refractory multiple myeloma (RRMM). Previously it was shown that wKRd is active with manageable toxicity in RRMM pts. Here we present results from a cohort of NDMM pts who received wKRd. Methods: NDMM pts were enrolled regardless of transplant eligibility. Treatment was given in 28-day (D) cycles (C) for up to 18 C. Carfilzomib (30-min IV) was given on D1, 8, and 15; lenalidomide 25 mg on D1–21; and dexamethasone 40 mg on D1, 8, and 15 (also D22 for C1–8). NDMM pts were initially enrolled for treatment with carfilzomib 20/70 mg/m2 (20 mg/m2 on C1D1; 70 mg/m2 thereafter) in a dose-expansion arm. After serious adverse events (AEs) occurred in 2 of the first 4 NDMM pts, enrollment was suspended. A protocol amendment specified that NDMM pts were to be enrolled in a dose-evaluation cohort, with a 2-step-up KRd dosing schedule (20 mg/m2 on C1D1; 56 mg/m2 on C1D8/C1D15; 70 mg/m2 thereafter) followed by a cohort safety review committee (CSRC) meeting to evaluate dose-limiting toxicities (DLTs) and recommend the NDMM dose-expansion dose. After evaluation of available DLT data, the CSRC elected to open a NDMM dose-expansion arm with carfilzomib at 20/56 (20 mg/m2 on C1D1; 56 mg/m2 thereafter). Treatment interruption or termination for autologous stem cell collection and/or transplant (SCT) was allowed after C4. Results: 51 NDMM pts enrolled between March 2016 and October 2017, 9 initially in the carfilzomib 70-mg/m2 NDMM dose-expansion arm, which was discontinued when 2 serious AEs (both thrombotic microangiopathy) occurred. Nine pts then enrolled in the 2-step-up dose-evaluation arm, and based on CSRC recommendations, a new NDMM dose-expansion arm at carfilzomib 56 mg/m2 was opened. Results are presented for pts who received weekly carfilzomib 56 mg/m2 (n=33) with Rd. Median administered carfilzomib dose was 52.8 mg/m2. Median number of cycles pts received carfilzomib was 7; 6 pts received carfilzomib through C18. Twenty-five pts underwent stem cell collection; 19 went on to autologous SCT. Pt incidence of grade ≥3 treatment-emergent AEs (TEAEs) was 60.6%. Common grade ≥3 TEAEs were anemia (12.1%), hyponatremia (12.1%), and increased ALT (9.1%). There were no fatal TEAEs. Nine pts had a dose reduction to 45 mg/m2. Median PFS was not reached. By C4 the overall response rate (ORR) in the safety population (n=33) was 97.0% (very good partial response [VGPR] or better by C4, 69.7%; complete response [CR] or better by C4, 3.0%). Among pts who did not receive autologous SCT (n=14), best overall responses at any time during the study were 78.6% (≥VGPR) and 50.0% (≥CR); ORR was 92.9%. Conclusions: Once-weekly KRd (carfilzomib 56 mg/m2) demonstrated promising activity with an acceptable safety profile in NDMM. These results merit additional evaluation of a convenient wKRd regimen in NDMM.

Keywords:
carfilzomib

Newly diagnosed multiple myeloma

once-weekly

Tracks:
Multiple Myeloma Novel Agents

OAB-079

A Phase 1b/2a Study of the CELMoD Iberdomide (CC-220) in Combination With Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma

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Abstract:
Background: Iberdomide (IBER) is a novel CELMoD cereblon E3 ligase modulator with enhanced tumoricidal and immunostimulatory activities. Preclinically, IBER overcomes IMiD immunomodulatory drug resistance and has synergy with daratumumab (DARA), bortezomib (BORT), and dexamethasone (DEX). This phase 1b/2a multicenter, open-label, dose-escalation study (NCT02773030) was conducted to evaluate the maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), safety and preliminary efficacy of IBER in combination with DEX, in patients with relapsed/refractory multiple myeloma (RRMM). Methods: Eligible patients had RRMM and must have received ≥ 2 prior regimens including lenalidomide (LEN) and/or pomalidomide (POM), and a proteasome inhibitor (PI). All patients had progressed on or within 60 days of last MM therapy. Escalating doses of IBER were given on days 1–21, in combination with DEX 40 mg (20 mg in patients aged > 75 years) on days 1, 8, 15, and 22, of each 28-day cycle. Dose escalation was reviewed by a dose escalation committee. Results: As of January 2019, 58 patients had received IBER + DEX. Median age was 64.5 years (range 33–79), and median number of prior regimens was 5 (2–12). Prior therapies included autologous stem cell transplantation (79%), LEN (100%), POM (69%), PIs (100%), and DARA (66%). IBER dose ranged from 0.3 to 1.2 mg; MTD/RP2D was not reached. Median duration of therapy was 12+ weeks (range 4–109). Grade 3–4 adverse events (AEs) were reported in 41 (72%) patients and were not related to dose. Grade 3–4 neutropenia, thrombocytopenia, neuropathy, and fatigue occurred in 26%, 11%, 2%, and 0% patients, respectively. Three patients discontinued treatment due to AEs. Clinical activity occurred early and was observed across all dose levels. Of the 51 efficacy-evaluable pts, 16 achieved an overall response rate (ORR; partial response or better), 26 a minimal response (MR) or better, and 45 achieved disease control (stable disease [SD] or better); 20 of the 51 patients remained on treatment (2–27+ cycles). Conclusions: IBER + DEX showed favorable efficacy and safety in heavily pretreated patients with RRMM who failed multiple prior therapies. This study is ongoing, including combinations of IBER with DARA or BORT.

Keywords:
clinical trials

immunomodulatory drugs

Relapsed Refractory MM

Tracks:
Multiple Myeloma Novel Agents

OAB-080

A Phase 1, First-in-Human Study of AMG 176, a Selective MCL-1 Inhibitor, in Patients

With Relapsed or Refractory Multiple Myeloma

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Abstract:
Background: The antiapoptotic protein myeloid cell leukemia sequence 1 (MCL-1) is highly expressed in many human cancers and has been implicated in the development of resistance to anti-cancer therapy. AMG 176 is a novel, selective, small molecule MCL-1 inhibitor. Here we report preliminary results from a phase 1, first-in-human trial to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and efficacy of AMG 176 in relapsed or refractory multiple myeloma (RRMM). Methods: This is an ongoing phase 1, dose-escalation study conducted at sites in the USA, Germany, Australia, and Canada. Patients ≥ 18 years old with RRMM (≥ 2 lines of prior therapy) received intravenous AMG 176. Primary endpoints included safety, tolerability, and PK of AMG 176; secondary endpoints included pharmacodynamic evaluation of MCL-1 inactivation and multiple myeloma response assessment. Treatment continued until intolerance, progression, death, or consent withdrawal. Results: At the data cutoff date (March 15, 2019), 26 RRMM patients had received AMG 176 (median age, 63.5 years). Patients had a median of 5 prior lines of therapy, and 20 patients (77%) received ≥ 5 prior therapy lines. Patients received a median (range) of 2 (1–8) cycles of study treatment. Most patients discontinued treatment due to progressive disease (n = 22 [85%]). Treatment-emergent adverse events (TEAEs) of any grade occurred in 25 patients (96%); common TEAEs (≥ 20%) were neutropenia (n = 10 [38%]), nausea (n = 8 [31%]), diarrhea (n = 7 [27%]), and anemia (n = 6 [23%]). Grade ≥ 3 TEAEs occurred in 16 patients (62%); common grade ≥ 3 TEAEs (≥ 5%) were neutropenia (n = 9 [35%]), anemia (n = 4 [15%]), and hypertension (n = 2 [8%]). Treatment-related AEs of any grade or grade ≥ 3 occurred in 18 patients (69%) and 7 patients (27%), respectively. Fatal AEs occurred in 2 patients (tumor lysis syndrome [related to study treatment] and hepatic failure [related to disease progression]). AMG 176 plasma concentrations generally increased with increasing doses, and no appreciable drug accumulation was observed across the dose range evaluated. Evidence of pharmacodynamic impact was observed through release of pro-apoptotic protein Bax and activation of the effector caspase 3 in peripheral blood monocytes, and a subsequent reduction in monocyte counts. At the time of this analysis, 11 patients had stable disease as best overall response. Data reported here are preliminary and a maximum tolerated dose has not yet been reached; updated results will be provided at the meeting. Conclusions: Initial results from this first-in-human study suggest that the MCL-1 inhibitor AMG 176 may have acceptable tolerability in RRMM, with toxicity predominantly hematologic and gastrointestinal. Early evidence of pharmacodynamic activity was suggested by biomarker analyses. Further investigation of the safety profile and efficacy of AMG 176 is ongoing.

Keywords:
Mcl-1 inhibitor

Pharmacokinetics

Tolerability

Tracks:
Multiple Myeloma Novel Agents

OAB-081

AMG 701, a half-life extended anti-BCMA BiTE®, potently induces T cell-redirected lysis of human multiple myeloma cells and can be combined with IMiDs to overcome the immunosuppressive bone marrow microenvironment

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Abstract:
AMG 701 is an anti-BCMA BiTE® with characteristics suitable for once-weekly dosing in multiple myeloma (MM) patients. We here evaluated AMG 701-mediated (i) T cell-dependent cellular cytotoxicity (TDCC) of MM cells with or without MM-supporting cells from the bone marrow (BM) microenvironment, (ii) changes in T cells and (iii) TDCC in combination with immunomodulatory drugs (IMiDs). AMG 701 induced TDCC of (i) BCMA+ MM cells resistant or sensitive to current anti-MM agents including bortezomib (PIs) and IMiDs, (ii) lenalidomide (len)- and pomalidomide (pom)-resistant MM cells in the presence of osteoclasts (OCs), BM stromal cells (BMSCs), or a proliferation-inducing ligand (100 ng/ml). Significantly, AMG 701 induced lysis of autologous patient MM cells from relapse and refractory patients. AMG 701-mediated TDCC caused changes in T cells, including CD107a degranulation, IFNγ and TNFα production, and proliferation in a higher percentage of CD8+ than CD4+ T cells. Transient expression of immune checkpoint markers and costimulatory markers on CD4+ and CD8+ T cells suggests that AMG 701 induced activation rather than exhaustion of T cells. The percentage of central memory (CM) and effector memory (EM) T cells was increased consistently after AMG 701 treatment (median % of CM+EM on CD4+ T cells: 74.8% (d1), 82.5% (d5), and 91.5% (d8), $p<0.01$; median % of CM+EM on CD8+ T cells: 54.4% (d1), 83.6% (d5), and 91.1% (d8), $p<0.001$). In parallel, the ratios of CD8+/CD4+ T cells were significantly increased by 1.21 to 3.48-fold at d1 to d5 ($p<0.001$) and 1.97 to 8.64-fold at d1 to d8 ($p<0.001$). Pretreatment of effector PBMC cells with either len or pom enhanced AMG 701-induced TDCC of MM cells at earlier time points, lower E/T ratios, lower AMG 701 concentrations and in the presence of OCs or BMSCs. Importantly, enhanced killing by combination treatment vs single agent was seen when autologous patient MM cells were used. The combination index of < 1 further indicated synergistic effects. In an NCI-H929 xenograft model, AMG 701, dose-dependently, blocked tumor growth 5d after the first injection and completely eradicated tumor growth after 3 injections at all dose levels (0.02, 0.2, 2 mg/kg), without drug-related adverse effects in the host. Next, mice were treated, from d15 until end of study, with (i) len once daily, (ii) AMG 701 once weekly or (iii) a combination of len and AMG 701. Statistically significant anti-tumor activity ($p<0.001$; Tukey's multiple comparison) was observed at 2d after treatment with AMG 701, len or combination while monotherapy treatment of AMG 701 or len resulted in tumor growth delay. Importantly, combination of AMG 701 and len resulted in significantly superior antitumor activity compared to either monotherapy, inducing tumor regression and prevention of relapse.

Taken together, these results further support AMG 701-based clinical studies, as monotherapy (NCT03287908) or in combination with IMiDs, to improve patient outcome in MM.

Keywords:
B-cell maturation antigen

BiTE® (Bispecific T-cell Engager) molecule

immunotherapy

Tracks:
Multiple Myeloma Novel Agents

OAB-082

CT053, Anti-BCMA CAR T-cell therapy for Relapsed/Refractory Multiple Myeloma: Proof of Concept Results from a Phase I Study

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Abstract:
Background: B-cell maturation antigen (BCMA)-specific chimeric antigen receptor (CAR) T cells (CT053) are autologous T cells genetically modified with a second-generation CAR incorporating a fully human anti-BCMA single chain fragment variant, a 4-1BB co-stimulatory domain and a CD3-zeta signaling domain. CT053 was studied in a single-arm, open-label, 3-site phase I study (NCT03716856, NCT03302403, and NCT03380039). Methods: Patients with relapsed/refractory multiple myeloma (rrMM) who received at least 2 prior lines of therapies and between 18-79 years of age, received 1 single CT053 infusion after fludarabine/cyclophosphamide treatment. The primary objective was safety. Adverse Event (AE) was graded per CTCAE 4.0. Tumor response was assessed per IMWG 2016. Results: A total of 24 consecutive patients (7 from NCT03302403, 6 from NCT03380039, and 11 from NCT03716856) (median age of 62.2 years, median of 4.5 prior lines of therapy, 11/24 with extramedullary diseases, 16/24 with ECOG 0-1, 6/24 with ECOG 2, and 2/24 with ECOG 3) were administered with a dose of 1.5 x 10E8 CT053 cells except 3 patients who received 0.5 x 10E8, 1 x 10E8, and 1.8 x 10E8 cells, respectively. The data cutoff date was February 28, 2019. Hematologic toxic effects were the most common events of grade (G) 3 or higher, including white blood cell count decreased (95.8%), neutrophil count decreased (87.5%), lymphocyte count decreased (79.2%) and thrombocytopenia (66.7%). 1 subject died of bone marrow failure and neutropenic infection. A total of 15 patients (62.5%) had cytokine release syndrome (all G1/2). 3 patients (12.5%) had neurotoxicity (2 G1, 1 reversible G3). The objective response rate was 87.5% (21/24) including 17 patients (70.8%) with complete responses (CR). Higher CAR T-cell expansion was associated with better responses, and the longest CAR T cells persisted more than 1 year after the infusion. Extramedullary diseases were associated with relapse. 16 patients were still in CR/very good partial response after a median follow-up of 295 days. Conclusion: This study demonstrated that CT053 had an excellent efficacy and a good safety profile in patients with rrMM.

Keywords:
BCMA

CAR T cells

Multiple myeloma

Tracks:
Multiple Myeloma Novel Agents

OAB-083

Safety and Efficacy of the Combination of Selinexor, Lenalidomide and Dexamethasone (SRd) in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

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Abstract:
Introduction: The nuclear export protein Exportin 1 (XPO1) is overexpressed in a wide variety of cancers including multiple myeloma. Selinexor (SEL) is a novel, first-in-class selective inhibitor of nuclear export (SINE), which blocks XPO1, forcing the nuclear retention and activation of tumor suppressor proteins. SEL in combination with dexamethasone (DEX) has demonstrated an overall response rate (ORR) of 26.2% in patients (pts) with triple class refractory MM. Lenalidomide (LEN) in combination with DEX is approved for the treatment of RRMM with an overall response rate (ORR) of 60-76%. The combination of SEL and LEN showed at least additive activity in preclinical models of MM. We therefore hypothesized that the all oral combination of SEL/LEN/DEX may result in improved response rates. Methods: We conducted a multicenter, open-label study with dose escalation (phase 1) and expansion (phase 2) to assess the maximum tolerated dose, recommended phase 2 dose (RP2D), efficacy and safety of the combination of SEL, LEN, and DEX (SRd) in pts with RRMM. Pts were eligible if they had received ≥ 1 prior therapy. SEL was dosed escalated in two regimens: once weekly (QW) 80 mg and twice weekly (BIW) 60 mg plus LEN 25 mg once daily (QD x 21 days) and DEX 20 mg BIW or 40 mg QW each week. In the expansion phase, pts received the RP2D of QW SEL 60 mg plus DEX 40 mg, and QD LEN 25 mg. Enrollment in the study is now complete. Results: A total of 24 pts were enrolled. The median age was 67 (range: 49-84 years) and median number of prior treatments was 1 (range: 1–8). Of the 24 pts, 13 pts received the RP2D. Common treatment related adverse events (AEs) which were typically grade 1/2 and reversible, included nausea (58%), decreased appetite (42%), fatigue (38%), decreased weight (38%), vomiting (33%), constipation (25%), and diarrhea (25%). Common grade ≥3 AEs were thrombocytopenia and neutropenia (63% each). Of 24 pts, 2 pts (8%) discontinued treatment due to related AEs. Twenty pts were evaluable for response. Among pts without prior LEN treatment (n=12, median number of prior treatments 1 [range: 1-5], the ORR was 92% including 1 complete response, 2 very good partial responses, 8 partial responses [PR], and 1 stable disease [SD]). Among pts with prior LEN treatment (n=8), 1 PR, 2 minimal responses, 4 SD and 1 progressive disease were observed. With a median follow up of 7.8 months, median PFS was 10.3 months overall; median PFS had not been reached in pts without prior LEN treatment compared with 2.8 months in pts with prior LEN treatment, including LEN-refractory disease. Conclusions: With an ORR of 92%, the all oral combination of SRd has significant activity in pts with RRMM who have not received prior LEN.

No new or unexpected safety signals were observed. This study demonstrated that SEL can be combined safely with LEN and DEX to produce durable responses warranting further investigation, especially in pts without prior LEN treatment.

Keywords:
Lenalidomide

novel agents

relapsed/refractory multiple myeloma

Tracks:
Multiple Myeloma Novel Agents

POSTER SESSION I

MULTIPLE MYELOMA GENOMICS

FP-001

The CureCloud Research Initiative, a Next-Gen Direct-To-Patient Clinico-Immuno-Genomic Registry

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Abstract:
More than ever, there is an urgent need for a deeper understanding of the clinical, molecular and immunologic parameters involved in multiple myeloma (MM) disease initiation, progression and response to treatment. Such rich information, collected at the population level, is crucial to generate the evidence needed to ultimately make Precision Medicine a reality for all multiple myeloma patients. To this end the Multiple Myeloma Research Foundation (MMRF) has launched the MMRF CureCloud Research Initiative (NCT03657251), an Institutional Review Board (IRB) approved Direct-to-Patient (DTP) research effort aimed at enrolling 5,000 individuals from whom comprehensive molecular and immune analyses will be generated from blood specimens and the resulting data aggregated with the correlating clinical information. Blood is collected from all participants after electronic online consenting via a mailed blood kit designed for a mobile phlebotomy appointment. To support the molecular characterization of liquid biopsies, a MM-specific hybrid selection panel was developed that captures commonly altered genes in a patient's circulating-free DNA (cfDNA). Deep sequencing (80,000x depth) is performed. Because this liquid biopsy cfDNA assay may potentially be used by treating physicians for management of care, a clinical-grade (CLIA) pipeline is being established. A suite of immune profiling assays is also employed to characterize the MM blood microenvironment. Samples and derivatives generated through the CureCloud Research Initiative are banked to establish a rich collection of biospecimens for future research under the oversight of a Steering Committee created for this effort. Through the consenting process, participants also authorize linkage to their electronic medical records (EMRs) information. EMR retrieval on behalf of the consenting patient and data abstraction for use in the CureCloud Research Initiative is performed by a commercial partner. An important deliverable of the MMRF CureCloud Research Initiative is a curated dataset of integrated genomic, immune and correlating clinical data that will be made available to support scientific investigations through the MMRF CureCloud, a cloud-based platform with tools and capabilities for the seamless aggregation, integration and analysis of large collections of myeloma datasets. Truly making patients active participants in the research is also an important focus of the CureCloud Research Initiative. To that end,

participants will regularly receive messages alternating between newsletters and invitation to engage in new educational modules and surveys. At the time of abstract submission, 65 participants have been enrolled onto the CureCloud Research Initiative in pilot mode and initial results will be presented. By creating a next-gen DTP real-world registry of fully linked datasets, new, not previously possible, types of queries will be enabled to improve MM patient treatments and outcomes.

Keywords:
genomics

Immune Tumor Microenvironment

Real-World Data

Tracks:
Multiple Myeloma Genomics

FP-002

Aberrations of chromosome X in patients with multiple myeloma

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Abstract:
Aberrations of chromosome X are reported as less common abnormalities in patients with multiple myeloma (MM). Genetic studies revealed monosomy X in women, deletions of Xp and duplications of Xq27-Xq28 region, which seems to be translocated to unidentified autosomes. Patients with partial alternations of chromosome X have a higher incidence of structural chromosomal changes and tendency to a worse outcome, compared to complete losses of the whole chromosome. Genes for cancer testis antigens (CTAs), namely MAGE-C1/CT7 and MAGE-C2/CT10, are localized in duplicated region Xq27-Xq28.These genes represent family of tumor antigens expressed in MM, melanomas and several other tumours, whereas their expression in normal tissues is restricted to placenta and testis. The aims of the present study were to analyze aberrations of chromosome X in a cohort of 80 patients with active MM using array comparative genomic hybdridization (arrayCGH) (Agilent, Technologies, Santa Clara, CA) and to correlate these results with immunohistochemical analysis of MAGE C1/CT7 expression (MAGE-C1-CT-33, Santa Cruz biotechnology, Santa Cruz). Abnormalities of chromosome X were found in 29/52 (56 %) female patients: monosomy X (partial or whole chromosome) was found in 23/52 (44 %) patients, gain of Xq in 4/52 (7.7%) and loss of heterozygozity (LOH) of Xq in 2 female patients. Duplication of Xq (consistently involving Xq27-Xq28) was detected in 14/28 (46 %) male patients. Expression of MAGE-C1/CT7 was detected in the nucleus and in the cytoplasm in all women with Xq gain and 11/14 (79 %) male and in female with partial monosomy X and LOH of Xq. Expression of MAGE-C1/CT7 has not been found in females with whole monosomy X. Our results show, that abnormalities of chromosome X and MAGE-C1/CT7 expression are much more frequent events in MM than previously reported. It seems that they are promising myeloma associated aberrations suggesting possible pathogenic role in the evolution of MM. This work was supported by grant IGA_LF_2019_001, MZ ČR – RVO (FNOl, 00098892).

Keywords:
arrayCGH

cytogenetic abnormality

immunohistochemistry

Tracks:
Multiple Myeloma Genomics

FP-003

DNA methylation reprogramming in relapsed/refractory myeloma converges with loci prognostic of survival in newly diagnosed patients

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Abstract:
The genetic and transcriptional program of multiple myeloma is being studied in unprecedented detail leading to the identification of molecular markers of poor prognosis. However, there remains a significant gap between prospective identification of high-risk patients and our ability to determine all patients that experience poor outcomes. In contrast to genetic mechanisms, epigenetic alterations in myeloma have been less studied, but have significant potential as a translatable biomarker. Here, we analyzed the DNA methylome of 120 myeloma specimens from the MMRF CoMMpass study (NCT01454297) by whole genome bisulfite sequencing generating data at 21,393,650 CpG loci. Compared to plasma cells from healthy individuals that had an average methylation level of 64%, myeloma exhibited extensive genomic hypomethylation such that the median level was 42% (range 21-67%). This 3-fold range in methylation level was investigated by principle component analysis. The largest component of variation corresponded with hypomethylation that occurred in megabase domains, which were devoid of gene expression. In contrast, DNA methylation was retained in the bodies of expressed genes. Principle components 2 and 3 separated samples with t(4;14) translocations from others. This may be due to overexpression of WHSC1 driving excessive histone 3 lysine 36 di-methylation (H3K36me2), which in turn impacts the function of PWWP-domain containing DNA methyltransferases (DNMT3A, DNMT3B). Given the variability observed in the myeloma methylome, we sought to understand if these information provide prognostic value. Analysis of 87 specimens from newly diagnosed patients identified 7,266 loci where DNA methylation status was prognostic of outcome (FDR $\leq$0.01). These prognostic loci were clustered into contiguous regions often organized around genes and could be used to stratify patients by progression-free and overall survival (P <1e-7; hazard ratio >8). Importantly, the prognostic value of these CpG were independent of t(4;14) status, which is a known high-risk marker. Analysis of 24 relapse specimens from 22 patients indicated epigenetic remodeling with a median of 1.9 million differential methylated CpGs upon relapse. These, however, were asymmetrically distributed such that approximately 1 in 3 patients underwent dramatic DNA methylation reprogramming upon relapse. These relapse/refractory DNA methylation changes included hypomethylation of loci that were also prognostic of outcome in baseline specimens including regions proximal to PRKCE, MGMT, FHIT, WWOX, and HDAC9. Cumulatively, these data identify myeloma epigenetic markers of outcome that undergo reprogramming in relapsed samples suggesting they may be indicative of therapeutic resistance.

Keywords:
epigenetic

genomics

High risk

Tracks:
Multiple Myeloma Genomics

FP-004

A detailed exploration of using RNA-Seq data in established multiple myeloma gene expression profile microarray based risk scores

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Abstract:
Multiple myeloma (MM) newly diagnosed patients have a wide range of prognoses, which are traditionally been defined by key translocations and microarray-based gene expression profiling (GEP). In diseases that can differ greatly in prognosis based on initiating genomic events, such as MM, GEP is reliably used to establish risk. Several prognostic scores based on microarray data have been developed to identify high-risk MM patients, which include EMC-92, GEP-70, GEP-17, GEP-80, IFM-15, MRC-IX-6, and GPI-50. Microarrays are inexpensive and give consistently reproducible results, but with the wide adoption of next-generation sequencing, reduced costs, and improved algorithms, RNA-Seq is long overdue to replace microarrays. The goal of this study was to show the efficacy of replacing microarray expression data with RNA-Seq data in well-established MM prognostic risk-scores. We took 167 MM samples that had both RNA-Seq and microarray data and recapitulated each of the prognostic scores. Microarray probes used in each of the signatures were mapped back to genes. In many instances there was not a one-to-one conversion and resulted in fewer genes in the corresponding RNA-Seq score. The new cutoff was achieved in two-ways: 1) we ranked the samples by risk score and empirically determine the best RNA-Seq cutoff, and 2) using the running log rank tests on progression free survival (PFS) and overall survival (OS) separately in the training set and identify optimal cutoffs. The agreement between the calls generated with microarray and RNA-Seq take the microarray based call as being the truth set. GEP70 risk scores from RNA-Seq correlated with the Microarray risk scores with an R-squared value of 0.854. Sensitivity and specificity of the RNA-Seq risk scores had values of 0.83 and 0.93 respectively. The RNA-Seq based scores were validated on the CoMMpass dataset of 615 MM samples with RNA-Seq data with corresponding clinical data. RNA-Seq GEP70 scores classified 30% of the patients in the validation dataset as high-risk. Survival analysis showed that the RNA-Seq based scores was able to classifying samples as high-risk as demonstrated with a significant difference in PFS and OS in the validation dataset (p-value<0.001, p-value=0.002). It is extremely important to accurately identify high-risk patients early so that they can receive the most aggressive treatment and enter into appropriate clinical trials. This preliminary work demonstrated that with adjusted cutoffs, RNA-Seq expression data can be used in place of microarray data to classify patients as either high-risk or low-risk using established clinically relevant risk signatures.

Keywords:
Gene expression profiling

Risk stratification

RNA-Seq

Tracks:
Multiple Myeloma Genomics

FP-005

Mate pair sequencing outperforms fluorescence in situ hybridization and improves diagnostic yield in the genomic characterization of multiple myeloma

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Abstract:
Fluorescence in situ hybridization (FISH) is currently the gold-standard assay utilized to detect recurrent genomic abnormalities of prognostic significance in multiple myeloma (MM). High-risk abnormalities include IgH translocations t(4;14), t(14;16), t(14;20),TP53 deletions and 1q duplications, while standard-risk abnormalities include hyperdiploidy, t(11;14) and t(6;14). MYC rearrangements are associated with disease progression. Since most translocations in MM involve a position effect with heterogeneous breakpoints, we hypothesize that FISH has the potential to miss translocations involving these gene regions. We evaluated 70 bone marrow samples from patients with plasma cell dyscrasia by FISH and whole-genome mate-pair sequencing (MPseq) to determine the accuracy of FISH to MPseq. For each primary and secondary abnormality that was identified by either MPseq or FISH, 39 (55.7%) of cases displayed concordance between FISH and MPseq. Thirty one (44.3%) of cases displayed at least one instance of discordance between FISH and MPseq. Nine of these 31 discordant cases had abnormalities detected by FISH that went undetected by MPseq. Of these nine cases, 6 had a tetraploid clone that was not detectable by MPseq and in three cases MPseq failed to detect CNAs that were identified by FISH (trisomy 3, trisomy 9 and 1q gain). In contrast, 19 of the 31 discordant cases had abnormalities detected by MPseq that went undetected by FISH. Of these 19 cases, 17 were MYC rearrangements and two were 17p deletions and translocations involving the TP53 gene. MPseq identified 36 MYC abnormalities, 17 (47.2% of MYC abnormal group) of which displayed a false negative result by FISH. MPseq also identified 10 cases (14.3%) with IgL rearrangements, a recent marker of poor outcome, and 10 cases (14.3%) with abnormalities in genes associated with lenalidomide resistance (CRBN, IKZF1 and IKZF3) that are not evaluated by FISH. In summary, MPseq was superior in the characterization of rearrangement complexity and identification of secondary abnormalities. In addition, MPseq resolved atypical FISH findings and identified novel abnormalities of prognostic significance not targeted by traditional FISH panels, thus demonstrating increased clinical value of MPseq compared to FISH.

Keywords:
FISH

Genetic profiling

MYC

Tracks:
Multiple Myeloma Genomics

FP-006

Analysis of the genomic and transcriptomic landscape of chemoresistant multiple myeloma

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Abstract:
INTRODUCTION AND AIMS In Multiple myeloma (MM) no treatment has a curative potential

and even complete response to proteasome inhibitors (PIs) and immunomodulatory agents (IMiDs) are followed by relapse over time. Next generation sequencing (NGS) has showed how MM at diagnosis is defined by several somatic mutations, but only few drivers, even fewer "druggable" mutations, and many found at a subclonal level. At relapse, NGS can inform on cases where drug resistance is mediated by mutations of drug targets or by activation of alternative oncogenic pathways. The aim of this study is therefore to provide a better understanding of the genomic and transcriptomic determinants of chemoresistance in MM. MATERIALS AND METHODS We selected 40 MM patients with refractory or relapsed-and-refractory disease to both lenalidomide and bortezomib. Whole exome sequencing was performed in all of them and RNAseq in 27/40. Clinical annotation was available for all patients. RESULTS Patients received a median of 3 lines of treatment, with median progression free survival of 182 days. We found more mutations than what reported at diagnosis. 100% of samples showed evidence of subclonality, and 37% of them exhibited a higher number of subclonal than clonal variants. Therefore, even at this advanced stage the MM genome is evolving and is composed of different subclones that may display different chemosensitivity. The mutational landscape was also different. TP53 was the most frequently inactivated gene: 17/40 patients showed mutations and/or deletions (35,3% and 64,7%, respectively). On the contrary, mutations of the genes associated with resistance to IMiDs and PIs were rare and always found at a subclonal level, e.g. CRBN was mutated in 1/40 and IKZF3 in 2/40. Refractory cases were also uniquely characterized by a novel signature described to be linked to exposure to alkylating agents, whose role in chemoresistance and disease progression remains to be elucidated. RNAseq analysis did not show any influence of treatment or mutational data on the clustering of samples, which was mainly influenced by karyotypic events. The main cluster was composed by non-hyperdiploid patients with both amp(1q) and del(13): these showed CCND2 and MCL1 upregulation, the latter representing a novel target of experimental treatments. Overall, classical high-risk features or CRBN pathway mutations were found in 83% of the cohort. However, none predicted survival in our cohort. DISCUSSION In double-refractory MM we describe a higher prevalence of high-risk features. Their lack of prognostic value is likely explained by a global prevalence of such features in late stages. Our data suggest that gene mutation is not a preferred mode of evolution of drug resistance in MM. Chemoresistance of the bulk tumor population is likely attained though differential, yet converging evolution of different subclones that are overall highly variable from patient to patient and within the same patient.

Keywords:
Drug resistance

Next Generation Sequencing

Relapsed Refractory MM

Tracks:
Multiple Myeloma Genomics

FP-007

Long-term Analysis Of Multiple Sequential Samples Reveals Patterns Of Progression In Smoldering Myeloma

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Abstract:
Smoldering myeloma (SMM) is an asymptomatic plasma cell disorder, distinguished from monoclonal gammopathy of undetermined significance (MGUS) by a much higher risk of progression to symptomatic multiple myeloma (MM). We postulated that a better understanding of the molecular makeup of SMM may help identify new risk factors for progression that may be used to define new inception strategies. Sequential samples from 9 SMM patients (9 controls and 54 tumors) with a median follow-up of 7 years (range: 3.5 to 12.8 years) were analysed. DNA was obtained from either CD138+ cells from the bone marrow of SMM patients through time (tumor) or from non-tumor cells from the same patient (control). 100 ng of DNA was fragmented, end-repaired, and adapters ligated, before hybridization using NimbleGen's MedExome with an additional capture for the IGH, IGK, IGL, and MYC loci. After PCR amplification hybridized libraries were sequenced on a NextSeq500 (Illumina) using 75 bp paired end reads. The median coverage was 93x (IQR 86-105) and 100x (IQR 95-103) for tumors and controls, respectively. The number of mutations per sample increased with time from diagnosis. There was a trend suggesting the mutation rate of progressors (n=6) was higher than the one of non-progressors (n=3) (F=3.9, p=0.052). Samples with hyperdiploidy had a higher rate of mutations over time than the others (F=9, p=0.009). Bi-allelic events were a common finding immediately before progression. We detected translocations in 7/9 patients. In most cases, they were seen at every time point. In one case, a t(8;14) was detected during follow up, 5.9 years from diagnosis. Using ddPCR, we quantified the rearranged MYC allele and compared the frequency to the IGH rearranged locus. This t(8;14) was not present at diagnosis, appeared in a small fraction (1%) 4.1 years after initial diagnosis and steadily increased over time reaching 37% in the last sample, 8.2 years from the initial diagnosis. Clonality analysis was available for eight patients and identified a median of seven clones per patient, most of them from branching evolution (7/8) but one yielding a linear pattern (1/8). Dramatic changes in clonal structures could be seen in all samples up to one year prior to the biological or clinical progression. Driver events were seen in 7/9 patients. Four patients had more than one driver, which were in different clones in two patients and in the same clone in two patients. In summary, comprehensive analysis of multiple SMM samples over time offers greater insight into the mechanisms of progression of SMM to MM including both novel events (such as MYC translocations and biallelic events) and changes in the clonal architecture. All these changes occurred several months before progression suggesting they could be used as early progression markers.

Keywords:
sequencing

Smoldering Multiple Myeloma

Tracks:
Multiple Myeloma Genomics

FP-008

Clinicopathologic characteristics and clinical outcome of multiple myeloma with del(17p): A retrospective analysis of single center experience for 12 years.

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Abstract:
Background Although novel agents have markedly improved the outcome of multiple myeloma (MM), patients (pts) with del(17p) still have dismal prognosis and their predictive biomarker and satisfactory treatment strategy remain unclear. We aimed to determine the treatment outcome and prognostic factors in MM pts with del(17p). Methods We reviewed a prospective MM database to identify all pts with del(17p) detected by fluorescence in situ hybridization (FISH). Data regarding baseline characteristics, treatment and survival outcomes were obtained. Results Out of 549 MM pts treated between Sep 2006 and Feb 2019, 428 (78.0%) underwent FISH testing, and 28 (6.5%) with del(17p) were identified. The median age was 61 years (range, 44-82) with males comprising 46.4% (n=13). According to the International Scoring System (ISS), 4 pts were stage I (14.3%), 10 pts stage II (35.7%) and 14 pts stage III (50.0%). The most common co-existing cytogenetic abnormality was del(13q) (n=21, 75.0%), followed by 1q gain (n=8, 34.8%), CCND1 gain (n=7, 25.0%), MAF loss (n=6, 21.4%), t(11:14) (n=6, 21.4%), and t(4:14) (n=6, 21.4%). With a median follow-up of 21.1 months, median overall survival (OS) was 18.0 months. High ISS stage (II, III vs. I; 9.0 vs. not reached; P=0.036) plasmacytoma (vs. absence; 5.4 vs. 68.5 months, P=0.050), elevated serum LDH (vs. normal; 5.3 vs. 68.5 months, P=0.011), platelet count < 100K/uL (vs. ≥ 100K; 5.2 vs. 68.5 months, P=0.067) were associated with shorter OS. By cytogenetics, pts with t(4:14) (vs. without t(4:14); 5.4 vs. 68.5 months; P=0.126) and 1q gain (vs. without 1q gain; 5.4 vs. 68.5 months; P=0.11) were likely to have poorer OS, but this was not statistically significant due to the small number of pts. Regarding treatment, in transplant-eligible pts (age≤65), bortezomib, thalidomide and dexamethasone (VTD) was associated with better outcome with median OS of 25.8 months, compared with thalidomide plus dexamethasone (TD, 4.6 months) or cytotoxic agent (5.2 months; P=0.030). Also, pts who underwent autologous stem cell transplantation (ASCT) after achieving at least partial response to 1st line treatment had significantly longer OS (median, not reached) compared with those who underwent ASCT for refractory disease (9.0 months), or who did not undergo ASCT (5.3 months; P=0.007). In transplant-ineligible pts (age>65), 1st line lenalidomide plus dexamethasone (Rd) tended to be related with more favorable outcome than bortezomib, melphalan and prednisone (VMP; median OS, 68.5 vs. 2.2 months; P=0.307). Conclusion In MM pts with del(17p), high ISS stage, presence of plasmacytoma, elevated serum LDH, low platelet count, as well as additional cytogenetic abnormalities like t(4:14) or 1q gain was still associated with poor prognosis. Pts who proceeded with ASCT after achieving objective response on 1st line treatment showed long-term survival, which elicit the importance of developing proactive therapeutic approach for pts with del(17p)

Keywords:
del(17p)

Multiple myeloma

prognostic factors

Tracks:
Multiple Myeloma Genomics

FP-009

Validation of SKY92 high and low risk prognostication in a retrospective, multinational cohort of 155 non-trial multiple myeloma patients

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Abstract:

Background: Genetic hallmarks of multiple myeloma (MM) patients have been extensively studied based on biobanked samples that have been collected as part of clinical trials. For example, the gene expression profiling (GEP) based SKY92 signature, which identifies ~15-20% of patients as high risk, has been independently validated in more than ten trials as a prognostic factor for progression free survival (PFS), and overall survival (OS). Limited evidence is available outside of trials, and here we present the first analysis of SKY92 and other markers on real-world MM data. Methods: As part of the HORIZON2020 funded MMpredict project, a total of n=155 samples (136 newly diagnosed, 19 relapsed) from non-trial MM patients were collected from the National University Hospital System (Singapore, n=73), Münchner Leukämielabor (Germany, n=37) and the University of Turin (Italy, n=45). Median age was 65 years (range 32-90), and treatments were diverse. MMprofilers were performed on all samples, providing SKY92 risk status results. Interphase FISH, and ISS results were collected from health records. Hazard ratios (Cox proportional hazards model) were calculated and evaluated by the likelihood ratio test to assess the significance of each marker. We also stratified the risk groups by combining SKY92 and ISS as proposed before. Results: There were 34/155 patients with SKY92 high risk (22%) with hazard ratio of 2.7 (p=6.5E-05 with 95% CI 1.66 – 4.41) for PFS and 3.2 (p=1.7E-04 with 95% CI 1.74 – 5.88) for OS. Other markers that were univariately significant for both PFS and OS, were: Clusters MF and PR, virtual gain(1q) and interphase del(13p). In a multivariate Cox proportional hazards model, SKY92 and Cluster PR remained significant for both PFS and OS among all univariately significant markers (interphase del(13p) excluded since 35% of data was missing). Surprisingly, ISS II compared to ISS I had very similar survival (PFS: HR 0.9, p=0.78; OS: 1.0, p=0.98), whereas ISS III had worse, but not significantly different, survival compared to ISS I (PFS: HR 1.2, p=0.56; OS: 2.2, p=0.15). The three class SKY92–ISS classifier identifies high risk (HR; SKY92 high risk), intermediate risk (IR; SKY92 standard risk and ISS II or III) and low risk (LR; SKY92 standard risk and ISS I). Using these classes for PFS resulted in IR vs LR (HR 1.77; p=0.28) and HR vs LR (HR 4.81; p=0.004). For OS the results were IR vs LR (HR 1.69; p=0.48) and HR vs LR (HR 6.47; p=0.01). Conclusions: Real-world evidence confirms that SKY92 is prognostic for PFS and OS in the non-trial setting. In addition, we found indications that despite the poor association of ISS with outcome, the LR class (SKY92 SR ISS I) tends toward the low risk in the non-trial setting as was seen previously. Funding: This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 701143

Keywords:
Gene expression profiling

prognostication

real-world

Tracks:
Multiple Myeloma Genomics

FP-010

Epigenetic silencing of miR-340-5p in multiple myeloma: mechanisms and prognostic impact

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Abstract:
Background miR-340-5p, localized to 5q35, is a tumor suppressor miRNA implicated in multiple cancers. As a CpG island is present at the putative promoter region of its host gene, RNF130, we hypothesized that the intronic miR-340-5p is a tumor suppressor miRNA epigenetically silenced by promoter DNA methylation of its host gene in multiple myeloma. Results By pyrosequencing-confirmed methylation-specific PCR, RNF130/miR-340 was methylated in 8/15 (53.3%) myeloma cell lines but not normal plasma cells. Methylation correlated inversely with the expression of both

miR-340- 5p and RNF130. In completely methylated WL-2 and RPMI-8226R cells, 5- AzadC treatment led to demethylation and re-expression of miR-340-5p. In primary samples, RNF130/miR-340 methylation was detected in 4 (22.2%) monoclonal gammopathy of undetermined significance, 15 (23.8%) diagnostic myeloma, and 7 (23.3%) relapsed myeloma. RNF130/miR-340 methylation at diagnosis was associated with inferior overall survival (median 27 vs. 68 months; P = 3.944E−5). In WL-2 cells, overexpression of miR-340-5p resulted in reduced cellular proliferation [MTS, P = 0.002; verified in KMS-12-PE (P = 0.002) and RPMI-8226R (P = 2.623E−05) cells], increased cell death (trypan blue, P = 0.005), and enhanced apoptosis by annexin V-PI staining. Moreover, by qRT-PCR, overexpression of miR-340-5p led to repression of both known targets (CCND1 and NRAS) and bioinformatically predicted targets in MAPK signaling (MEKK1, MEKK2, and MEKKK3) and apoptosis (MDM4 and XIAP), hence downregulation of phospho-ERK1/2 and XIAP by Western blot. Furthermore, by qRT-PCR, in CD138-sorted primary samples (n = 37), miR-340-5p and XIAP were inversely correlated (P = 0.002). By luciferase assay, XIAP was confirmed as a direct target of miR-340-5p via targeting of the distal but not proximal seed region binding site. Conclusions Collectively, tumor-specific methylation-mediated silencing of miR-340-5p is likely an early event in myelomagenesis with adverse survival impact, via targeting multiple oncogenes in MAPK signaling and apoptosis, thereby a tumor suppressive miRNA in myeloma.

Keywords:
DNA methylation

miR-340-5p

XIAP

Tracks:
Multiple Myeloma Genomics

FP-011

Circulating cell free DNA is a biomarker for GEP70 risk score and tumor burden in myeloma

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Abstract:
Background: Multiple myeloma (MM) is a heterogeneous disease with variable outcomes. In the past several years, serum proteins, cytogenetics and gene expression profiling (GEP) have been used to predict outcomes of MM patients. Patients identified by the prognostic GEP70 gene signature as high risk (HR) have more aggressive disease and shorter survival compared to patients identified as low risk (LR). We have analyzed cfDNA levels in LR and HR patients and determined its correlation to GEP70 risk score. In a subset of patients, we performed low-pass whole genome sequencing (LP-WGS) and targeted sequencing to determine genomic alterations in cfDNA. Methods: GEP was performed on CD138+ plasma cells from bone marrow using Affymetrix U133 Plus 2.0 arrays. Low-risk (n=38) and high-risk MM patients (n=44) as determined by GEP70 score were selected. Plasma cells in bone marrow aspirate were ascertained for tumor burden by flow cytometry. cfDNA was extracted from plasma using QIAamp circulating nucleic acid kit (Qiagen) and was measured using Qubit fluorometer. In a subset of patients, plasma cfDNA, matched tumor DNA and matched white blood cell genomic DNA were sequenced using a targeted panel covering key driver genes and immunoglobulin regions involved in translocations in myeloma. Targeted sequencing was performed on NextSeq500 (Illumina) to a depth of 400-600x. LP-WGS was performed at 0.1X

coverage. Sequencing data were analyzed using Strelka and ichor. Results: Total cfDNA (ng/ml plasma) was significantly higher in the HR group compared to the LR group, median cfDNA LR=18.76 ng/ml range 0.2-140 ng/ml plasma vs. HR=33 ng/ml plasma range 7.3-726.66 ng/ml; p=0.02. cfDNA levels among different GEP subgroups did not reach significance, however patients in the PR subgroup had higher cfDNA in plasma compared to other subgroups. Ranked cfDNA levels correlated with GEP risk score r=0.32, p=0.0029 (Spearman's test). cfDNA levels also correlated with tumor burden r=0.41, p<0.0001 (Pearson's test). Additionally, LP-WGS analysis performed in a subset of patients showed that circulating tumor DNA (ctDNA) fraction correlated strongly with GEP70 risk score (Spearman r=0.83, p=0.0012). Monitoring of cfDNA levels in patients before and after chemotherapy showed an increase in cfDNA levels between 3-5 days after chemotherapy and fell to baseline levels a week later. Variant allele frequencies of NRAS and KRAS mutations were higher immediately post-chemotherapy compared to baseline in 3/4 patients. Conclusions: cfDNA levels correlate with GEP70 risk score. In the small subset of sequenced patients, ctDNA fraction also correlated with GEP70 risk score. Molecular monitoring of myeloma using cfDNA can capture the mutational landscape in myeloma and can be a potential prognostic biomarker for MM disease.

Keywords:
cell-free DNA

Gene expression profiling

Whole genome sequencing

Tracks:
Multiple Myeloma Genomics

FP-012

The prognostic value of 1q21 gain does not rely on the copy numbers, clone size and concurrence with t(4;14)

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Abstract:
Background Multiple myeloma (MM) is characterized by genetic heterogeneity. Chromosome 1q21 aberrations in MM have attracted much attention for a long time, however, the prognostic value is still under investigation. Methods Cytogenetic aberrations were detected by a panel of DNA probes, including CKS1B at 1q21, RB1 at 13q14, TP53 at 17p13, IgH split at 14q32 and IgH translocations with CCND1 at 11q13, FGFR3/MMSET at 4p16, MAF at 16q23 or MAFB at 20q11 by fluorescence in situ hybridization. Comprehensive method was used to integrate the intra-tumoral heterogeneity of 1q21 gain and analyze the prognosis of patients with concurrent aberrations. Results Additional copies and larger clonal size of 1q21 gain did not worsen the outcome. 1q21 gain facilitated the acquisition of new chromosome abnormalities and contributed to the genomic instability, evidenced by the strong correlation between 1q21 gain and complex karyotypes or the acquisition of more than two cytogenetic aberrations. 1q21 gain retained unfavorable even when stratified by concurrent presence of t(4;14), especially in the bortezomib

arm. Finally, although bortezomib might benefit patients with 1q21 gain, it could not completely overcome its adverse effects. Conclusion The prognostic value of 1q21 gain does not rely on the copy numbers, clone size and concurrence with t(4;14). Patients with 1q21 gain need more effective therapies.

Keywords:
bortezomib

Chromosomal abnormalities

Outcome

Tracks:
Multiple Myeloma Genomics

FP-013

Plasma Cell-free DNA chromosomal instability score as early predictor to monitor tumor burden in response to therapeutic in multiple myeloma patients

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Abstract:
Background: Multiple myeloma (MM) is a plasma cell malignancy characterized by chromosomal instabilities (CIN), including complex cytogenetic and molecular abnormalities. Cell-free DNA (cfDNA) offers the potential for minimally invasive genome-wide profiling of tumor alterations in monitoring tumor burden without tumor biopsy and may be associated with cancer precision medicine and patient prognosis. The better response is associated with improved overall survival (OS) in MM, but data on early response at treatment two cycle to predictor the prognosis are limited. Here we investigate the potential of cfDNA CIN as minimal invasive biomarker to predict early response for MM treatments. Methods: In this prospective cohort study, we recruited 30 patients from 11 relapsed/refractory (RRMM) and 19 newly diagnosed (NDMM) patients at our institution Changzheng Hospital. Plasma samples were freshly collected after finished two cycles or one months (for RRMM) of therapy, with matched baseline plasma samples collected before the current regimen. Cell-free DNA was extracted followed by chromosomal copy number imbalance analyses by using a customized bioinformatics workflow, ultrasensitive chromosomal aneuploidy detector (UCAD). Criteria for response and progression were according to the IMWG（Durie BG et al. 2006）. Results: Among the 30 patients, 7 (23%) of them (5 RRMM and 2 NDMM) showed high cfDNA CIN regard as strong positive after two cycles of treatments. Plasma cfDNA CIN profiling found complex clonal evolution compared two cycles to baseline. Multiple genomic regions, including chromosome 7, 17p (surrounding TP53 locus), 12q and 3p, were found involved in MM clonal evolution. Further analysis showed that the degree of chromosomal instabilities in cfDNA correlated with myeloma stage and overall survival. Remarkably, of the 5 heavily treated RRMM patients and 1 primary refractory newly diagnosed patient, 3 died within 60 days after the last time of cfDNA detection. Nine patients (30%) of patients shows positive cfDNA CIN after two cycles of treatment, which response rate was 11% (n=1) with SD, 33% (n=3) with MR, and 56% with PR, respectively. Fourteen patients with 5 RRMM and 9 NDMM were detected marginal or negative cfDNA CIN after two cycle's treatment. The overall response rate in 14 patients was 100%, including 14.3% with a complete response, 14.3% with a very good partial response (VGPR), 57.1% with a PR, and 14.3% with a MR. Of these patients, 3 RRMM who received with more than six lines of therapy, showed positive cfDNA CIN. Subsequently these three heavily treated RRMM patients have chance to enroll the chimeric antigen receptor T-Cell immunotherapy (CAR-T) therapy (enrolled NCT03093168). Surprising, all of them were benefit of the CAR-T therapy to improve responses dramatically, meanwhile, the dynamics of total cfDNA concentration correlated with tumor

burden to negative. Conclusion: We provide evidence that cfDNA level co

Keywords:
chromosomal instability

Plasma Cell-free DNA

predictor to monitor tumor burden

response to therapeutic

Tracks:
Multiple Myeloma Genomics

FP-014

L-type amino-acid transporter 1 (LAT1) expression is predictive of response to autologous stem cell transplantation for multiple myeloma

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Abstract:
Introduction: L-type amino acid transporter 1 (LAT1) plays a key role in cell growth and survival. Overexpression is a common feature of many malignancies to support increased protein synthesis demand. Among patients with multiple myeloma, high LAT1 expression has been shown to be associated higher risk disease but also a higher response rate following treatment with oral melphalan in clinical and pre-clinical models (Isoda, et al, Cancer Sci, 2014; Hathi, et al, J Nucl Med, 2018). Oral melphalan is infrequently used in today's clinical practice; however, high-dose intravenous melphalan is the standard of care for conditioning prior to autologous stem cell transplantation (ASCT). In this study, we sought to determine if LAT1 expression was predictive of response to melphalan-based ASCT for multiple myeloma. Methods: We performed a secondary analysis of data from the MMRF CoMMpass study (IA14). CoMMpass is a longitudinal study of over 1000 MM patients which incorporates both clinical and genomic data. As part of the CoMMpass study, RNA-seq on CD138-enriched bone marrow cells was performed using Illumina TruSeq RNA library kits. LAT1 expression > 0.5 standard deviations above the mean was considered high-expression. The association of high LAT1 expression with myeloma stage, response rate post-treatment, and progression-free survival (PFS) were compared using bivariate and multivariate statistics. Results: 762 patients were included in the analysis. The median age at diagnosis was 63 (range 27-93) and 50% were male. Mean LAT1 expression was 3.00 logs (± 0.95); 30% were considered to have high LAT1 expression. High LAT1 was observed in 40% of patients with Stage III disease, compared to 27% of those with Stage I or II disease ($p < .001$) 296 patients underwent ASCT during first-line treatment with 39% having a complete response (CR). 49% of those with high LAT1 obtained a CR compared to 35% of those without ($p = .030$). 16% of the 466 patients who did not undergo ASCT also obtained a CR. 21% of those with high LAT1 obtained a CR compared to 14% of those without, which was not statistically significant. Overall, high LAT1 expression was associated with a 34% increase risk for PFS (aHR 1.34; 95% CI 1.07-1.69; $p = .012$) after controlling for ASCT, CR, and ISS stage. However, the risk was mitigated in patients undergoing ASCT. For those with high LAT1, receiving an ASCT resulted in a 47% decrease in risk (aHR 0.53; 95% CI 0.37-0.74; $p < .001$) and PFS was similar to those with normal LAT1 expression. Discussion: Melphalan-based ASCT may mitigate the higher risk associated with high LAT1 expression at diagnosis of multiple myeloma. While ASCT is generally recommended for all eligible patients with multiple myeloma, those with high LAT1 may receive an even larger benefit.

Keywords:
autologous stem cell transplant

gene expression

High risk

Tracks:
Multiple Myeloma Genomics

FP-015

Next-generation optical mapping reveals numerous previously unrecognizable structural variants in multiple myeloma

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Abstract:
Multiple myeloma (MM) is characterized by high genetic heterogeneity, which in turn affects not only the development of the disease but also the therapeutic response. To further characterise the genetic heterogeneity in MM, we applied a novel approach of next-generation optical mapping to study a genomic architecture of MM cells. We analysed samples of bone marrow from two patients with newly diagnosed MM using optical mapping together with standard methods (karyotype, FISH, and arrayCGH) and compared the results of these approaches. For optical mapping, high-molecular weight DNA was isolated from sorted MM cells, labelled by DLS chemistry and visualised on Saphyr system (BioNano Genomics). The optical genome maps (480 Gbp, coverage 124X) were aligned to a human reference genome (GRCh38) and the detected structural variants (SVs) were compared against the database of healthy controls; only rare de novo variants were analysed. In Patient 1 (male, 77 years, MM IgG kappa, stage IIIA (Durie-Salmon, DS), International Staging System (ISS) 2, revised ISS (R-ISS) 2) numerous genetic aberrations were detected by both optical mapping and arrayCGH (trisomy 4, 11, 18, 19, 21, monosomy 13 and tetrasomy 15). Optical mapping revealed additional 47 deletions, 16 insertions, 14 inversions, 4 duplications and 4 translocations. All translocations were within unusual chromosomes 3 and 6. We also identified 587 bp insertion in 17p13 chromosome and 8.1 kbp deletion in 18q21 chromosome, both regions affecting the activation of cancer genes tumor suppressors and oncogenes. Additionally, several large SVs were located on chromosome 3, including duplication, inversion, intra- and inter-chromosomal translocations t(3;6). In Patient 2 (male, 74 years, MM IgA kappa, st. IIIA (DS), ISS 2, R-ISS 2), both optical mapping and arrayCGH detected trisomy 3, 5, 9, 11, 15, 18, 19 and tetrasomy 21. Optical mapping revealed additional 35 deletions, 22 insertions, 11 inversions, 2 duplications and 8 intrachromosomal translocations affecting chromosomes 3, 4, 14, and 18. Although no IGH locus rearrangements were detected by standard methods, monosomy on chromosome 14 and 20.5 kbp deletion were found within IGH locus by optical mapping. As conclusion, a large number of additional novel genomic rearrangements was detected in MM using next-generation mapping technology, showing a high potential of optical maps for refinement of genomic variability in MM. The study on larger patient cohort and longer follow-up of patients may identify structural variants associated with the clinical course and therapy response. Support: research grant Celgene, MZ ČR VES16-32339A, NV18-03-00500, MZ ČR – RVO (FNOl, 00098892)

Keywords:
genomic architecture

optical mapping

Tracks:
Multiple Myeloma Genomics

FP-016

Fusion gene detection across a large cohort of multiple myeloma patients

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Abstract:
Gene fusions are an important class of genetic variation relevant across cancer types. We detected gene fusion events from a cohort of 742 patients from the Multiple Myeloma Research Foundation CoMMpass Dataset, combining sequencing data from RNA and DNA with clinical information to form a landscape of fusion events. From the 742 patients, 53 had data from multiple time points for a total of 806 samples in this study. We ran five fusion detection tools on each sample's RNA sequencing data and required fusions to pass several filtering criteria. From RNA-seq, we also quantified gene expression levels to find relationships between gene fusions and gene expression. Whole genome sequencing data provided evidence of genomic changes such as translocations and deletions that lead to gene fusions as well as a way to validate fusion events. Several genes involving fusions show upregulated expression in comparison to non-fusion samples, including FGFR3, WHSC1, MYC, and NTRK1. We performed breakpoint and expression analysis of t(4;14) events leading to IGH--WHSC1 fusions and overexpression of FGFR3 and WHSC1. We compared fusions detected in our cohort to those reported in pan-cancer analyses to illustrate overlapping events but also highlight myeloma-specific events. We analyzed the structure and expression patterns of 3' kinase fusions with intact kinase domains, including druggable fusions involving NTRK1. We further analyzed fusions detected from samples with serial time points, illustrating changes in the fusion and mutational landscape over time. Finally, we present a novel use of single-cell RNA-sequencing data by detecting chimeric transcripts related to fusions events in multiple myeloma at single-cell resolution.

Keywords:
Bioinformatics

Fusion

Single cell genomics

Tracks:
Multiple Myeloma Genomics

FP-017

Defining the differentiation states of multiple myeloma at single cell resolution – Identifying opportunities for immunotherapy

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Abstract:
Non-genetic cellular plasticity has recently emerged as a basis for therapeutic resistance in cancer. Therefore, a better understanding of cellular plasticity and adaptive state changes in myeloma cells and the immune microenvironment is critical to develop effective therapeutic approaches that can overcome drug resistance. We performed fluorescence activated cell sorting and full-length single-cell RNA sequencing of myeloma cells and CD45+ immune cells from the bone marrow of 8 patients with relapsed/refractory multiple myeloma (RRMM) treated on a clinical trial with elotuzumab,

pomalidomide, bortezomib and dexamethasone (Elo-PVD; NCT02718833) before and after treatment. We discovered that the transcriptional states of single myeloma cells are highly distinct between individual patients, despite the presence of the same established genomic classifiers, such as t(11;14). Furthermore, distinct transcriptional states co-exist within individual patients. Leveraging the single-cell RNA sequencing data to reconstruct differentiation trajectories of the myeloma cells, we found that transcriptional states diverge from normal plasma cells towards more immature cells, of the B lymphoid lineage or entirely different hematopoietic lineages. Since cell states are controlled by a small set of interconnected transcriptional regulators, we investigated expression of transcription factors and epigenetic modifiers and found widespread deregulation. Using SCENIC to define gene-regulatory relationships, we identified a shared core regulatory network between RRMM patients with transcription factors, such as MYC, MEF2C and TCF3. However, we further detected patient-specific regulons, which provide critical insight into mechanisms driving inter-patient heterogeneity. Interestingly, these altered transcriptional states were associated with up-regulation of potential immunotherapeutic targets, such as CD20, CD19, CD33. Subsequently, we defined the effect of immunomodulatory treatment with Elo-PVD on the immune microenvironment with single cell resolution. A high degree of variation in NK cell subsets in RRMM patients is reflected in patient-specific subclusters, with CD56bright NK cells ranging from 2%-69%. Importantly, NK cell differentiation trajectories revealed a shift with treatment, indicating there is substantial plasticity in NK cell subsets. Differential expression of more than 2000 genes (qval < 0.01), including CD16 and effector molecules PRF1, GNLY and GZMB, was indicative of widespread transcriptional reprogramming, which is therapeutically relevant. In conclusion, we find that higher transcriptional diversity and activation of alternate gene regulatory programs facilitate the emergence of altered transcriptional states in myeloma cells and the immune microenvironment. Interestingly, these altered states are associated with up-regulation of putative immune-therapeutic targets in myeloma cells, thus providing novel therapeutic vulnerabilities.

Keywords:
Immune Tumor Microenvironment

Single cell genomics

Transcriptional profiling

Tracks:
Multiple Myeloma Genomics

FP-018

MicroRNA analysis in multiple myeloma and extramedullary disease

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Abstract:
Background: MicroRNAs (miRNAs) are short non-coding RNA molecules that are involved in many physiological and pathological processes. Multiple myeloma (MM) is the second most common hematological malignancy of plasma cells (PCs). Survival of patients is negatively affected by extramedullary disease (EM). EM occurs when PCs migrate out of the bone marrow (BM) and lose the dependence to its microenvironment. The mechanism by which the EM occurs is not yet

elucidated. The importance of miRNA in the pathogenesis of MM has been demonstrated by several studies. We assume that they are involved in the development of EM. Aims: The aim of this work was to analyze different expression of miRNA in BM PCs of EM vs MM patients. Materials and methods: In exploration phase, 36 BM PCs samples from MM patients and 9 BM PCs samples from EM were analyzed using next generation sequencing (NGS). Validation phase was performed by qPCR and included 23 MM samples and 14 EM patients. Results: NGS analysis showed 2278 different miRNAs that were present in analyzed samples; 635 miRNAs had more than 20 reads per sample and were included in subsequent analysis. Analysis showed that there are 10 miRNAs (miR-26a-5p, miR-26b-5p, miR-30e-5p, miR-424-3p, miR-503-5p, let-7i-3p, miR-548ag, miR-5696, miR-450b-5p, miR-4746-5p) with adjusted $p<0.005$ that differ significantly in expression between MM and EM patients. We validated 8 miRNAs – 6 based on NGS analysis (miR-26a-5p, miR-26b-5p, miR-30e-5p, miR-424-3p, miR-503-5p, miR-450b-5p) and another 2 based on literature (miR-767-5p and miR-105-5p). All validated miRNAs were significantly deregulated ($p<0.05$) in EM compared to MM patients. Furthermore, we performed ROC analysis to determine sensitivity and specificity of analyzed miRNA for EM detection. The best results were reached for miR-105-5p (cut-off: ≥ 0.002; AUC: 0.820; sensitivity: 84.62%; specificity: 82.61%). Summary: This study showed that there are 10 significantly ($p<0.005$) differentially expressed miRNA between MM and EM. This work was supported by AZV 17-29343A.

Keywords:
extramedullary disease

microRNA

Next Generation Sequencing

Tracks:
Multiple Myeloma Genomics

FP-019

DETERMINATION OF CNVs BY NGS BASED DIGITAL MLPA IN MULTIPLE MYELOMA AND THEIR EFFECT ON CLINICAL OUTCOME

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Abstract:
Introduction Copy Number Variations (CNVs) at specific cytogenomic segments in Multiple Myeloma (MM) are known to influence disease progression and response to therapy. Recent high throughput technologies such as digital MLPA (dMLPA) have enhanced the ability to target larger repertoire of CNVs with greater confidence. The aim of the study was to determine CNVs at multiple key genomic regions of relevance in MM and their effect on clinical outcome. Methods Genomic DNA extracted from enriched plasma cells obtained from 243 newly diagnosed MM patients was subjected to dMLPA assay using D006-X2-0717 MM dMLPA probemix (MRC Holland). The dMLPA libraries were sequenced on Illumina MiSeq and the '.fastq' files were analyzed with an in-house software. Data was normalized and interpreted as wild type, deletion or duplication states. Patients' clinical data were co-evaluated using Kaplan Meier survival and Cox proportion hazard regression analysis. Results The dMLPA assay consisted of a total of 507 dMLPA probes (160 for key CNVs, 219 karyotyping and 129 internal controls and BRAF V600E specific probe). Sequence read numbers in excess of ≥600, minimal variability (SD<0.1 per probe) and normal probe read ratios between0.8 to 1.2 were achieved. At least ≥1 CNVs (in key target genes) were identified in 59% patients and an average of 9 CNVs (range 0 to 24) were observed per patient. Median

PFS and OS of the total cohort were 50 and 63 weeks respectively. The most frequent deletions were those in 13p (~14%), 13q, 1p, 22q, 16q and 22q (~7-10%), 14q, 8p, 4p and 17p (~4 to 6%). Likewise, most frequent gains were in 15q, 1q, 11q, 9q (~18 to 20%), 5q, 3p, 11p and 7p (~9 to 16%). BRAF V600E mutation was identified in 13 patients of which 10 were randomly checked by targeted NGS and found to be congruent. Biallelic deletions were observed at genes located in 11q and 1p. Survival analysis revealed a significant correlation of progression free survival with deletions at CDKN1B (HR=3.5; 95%CI= 1.2 - 9.6, p= 0.014), 17p (HR=2.16; 95%CI=0.99 – 6.92, p=0.05), NF2 (HR=2, 95%CI= 1.03 – 4.09, p=0.04). Significant correlations were observed for overall survival with deletions at CHD4 (median OS 36 weeks vs not reached (NR); HR=4.6, 95%CI= 1.8 – 11.8, p=0.001), TFB1M (median OS 57 weeks vs NR; HR=4.3; 95%CI = 1.7 – 10.9, p=0.002), MTA1 (median OS 36 weeks vs NR; HR=3.1; 95%CI= 1.4 – 6.8, p=0.005), NEFL (median OS 34 weeks vs NR; HR=3, 95%CI= 1.2 – 6.9, p=0.011) and COL11A (median OS 57 weeks vs NR; HR=2.5, 95%CI= 1.03 – 6.4, p=0.04). Conclusion Digital MLPA allows detailed mapping of CNVs across multiple loci. Cytogenomic aberration profiles obtained by dMLPA could be useful for molecular classification and risk stratification in MM. Acknowledgements We thank the MRC-Holland team for all the support and Department of Biotechnology (BT/ MED/ 30/ SP11006/ 2015), Ministry of Science & Technology, Government of India for research funding.

Keywords:
copy number aberrations

digital MLPA

Multiple myeloma

Tracks:
Multiple Myeloma Genomics

FP-020

Inferring Biological Pathways in Multiple Myeloma after Missing Value Imputation

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Abstract:
Background: Gene expression data obtained from microarray or RNA-Seq can harbor missing values that affect accurate interpretations. It is preferable to first impute missing values via robust computational methods rather than repeating the whole experiment to re-capture gene expression data which is an expensive and time-consuming process. In this study, a novel but easy method of imputing missing values in both microarray and RNA-sequencing data has been proposed. Materials & Methods: Missing value imputation was carried out on microarray (GSE47552 GEO dataset for 99 samples, 33297 probe-ids) and RNA-Seq data obtained from MMRF researcher gateway (57998 genes for 881 subjects). Missing values were first introduced at different percentages ranging from 10% to 90% in microarray data and incomplete matrices were then imputed using proposed method of missing value imputation. It is a two-stage method utilizing Discrete Cosine Transform (DCT) based sparsity and then nuclear norm for denoising. Quantitative results on normalized mean square error (NMSE) between ground truth and imputed data were computed with state-of-the-art matrix completion methods, namely, LogDet, RPCA-GD, and LMaFit. Significance of imputation was validated by classification between normal versus cancer subjects on incomplete and imputed matrices followed by biological pathway analysis of top 500 candidate tumor drivers identified using SPARROW algorithm followed by gene enrichment analysis. Results: For microarray data, quantitative NMSE results of the proposed method were observed to be better compared to the existing state-of-the-art methods even at low observability of data. Results on classification with imputation were superior as compared to the classification results obtained on missing data matrix

as well as matrix imputed with existing methods. Cancer affected pathways obtained from KEGG analysis were discovered with higher significance in the data imputed with the proposed method compared to those discovered with the missing data matrix. For RAS signaling pathway, at 50% observed data, p-value was found to be 0.15 (insignificant) but after imputation, p-value became 0.028, indicating significant enrichment of this pathway. Similarly, at 70% observed data, p-value was 0.24 that decreased to 0.047 after imputation. RNA-Seq data had 55% missing values. The proposed matrix imputation method was able to impute all but 0.19% percent entries in RNA-Seq. Conclusion: Missing values in Gene expression data from microarray as well as RNA-sequencing is a persistent problem that can be resolved with a novel method of missing value imputation as proposed in this study. Acknowledgements We gratefully acknowledge GEO and MMRF CoMMpass network for providing datasets; Department of Biotechnology (BT/ MED/ 30/ SP11006/ 2015) and Department of Science and Technology (DST/ICPS/CPS-Individual/2018/279(C)), Ministry of Science & Technology, Government of India for research fundings

Keywords:
gene expression

missing value imputation

pathway analysis

Tracks:
Multiple Myeloma Genomics

FP-021

Super-enhancer profiling of multiple myeloma in search of novel oncogenes and therapeutic targets

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Abstract:
Background Multiple myeloma (MM) is an aggressive neoplastic plasma cell cancer characterized by complex heterogeneous cytogenetic abnormalities. Recently, super-enhancers (SEs) are defined as large clusters of cis-acting enhancers, marked by high-level bindings of acetylation of histone H3 lysine 27 (H3K27ac) and mediator, which have been shown to control genes for maintaining cellular identity and also key tumor drivers in various malignancies. Methods In this study, by collecting primary MM patient samples, MM cell lines, normal plasma cell and lymphoma cell lines for H3K27Ac ChIP-seq and RNA-seq analysis. We systematically compared SEs and their associated genes of normal and cancerous tissue. Besides, THZ1 as a CDK7 inhibitor can efficiently cause down-regulation of SE-associated genes. Combined analysis of THZ1-sensitive and SE-associated gene uncovered a number of promising MM oncogenes. With the CRISPR/Cas9 gene editing system and gene overexpression vector infection, a variety of cellular functional assays were performed to determine the effects of candidate SE-genes on MM tumorigenesis. Results SE analysis alone uncovered many cell lineage-specific transcription factors and well-known oncogenes. Several key TFs (including IRF4, PRDM1/BLIMP1, and XBP1) were recurrently identified in most MM samples, confirming the origin of MM cells and suggesting that SE establishment is a key component of MM biology. The acquisition of SEs around oncogene drivers is widely observed during tumorigenesis. ST3GAL6 and ADM were two known oncogenic drivers in myeloma cells, which were associated with super-enhancers in all MM samples but not in normal plasma cell and lymphoma cells. We also found SEs marked multiple key drivers in defined clinical subgroups of MM, such as CCND1 in t(11;14) cells, C-MAF in t(14;16) cells, and WHSC1 and FGFR3 in t(4;14) cells. Furthermore, THZ1, which is a small-molecule CDK7 inhibitor, showed prominent antineoplastic

effect against MM cells. SE-associated genes were more sensitive to THZ1 compared with those genes associated with typical enhancers (TEs). We then performed a combined analysis of THZ1-sensitive and SE-associated genes and found a number of novel MM oncogenes, including MAGI2, EDEM3, HJURP, LAMP5, MBD1, and UCK2 being a potentially druggable kinase. Finally, MAGI2 was related to myelomagenesis with gradually increased expression from MGUS, SMM to newly diagnosed and relapsed MM cases. MAGI2 silencing in MM cells suppressed cell proliferation and lead to cell apoptosis. Interesting, HJURP was confirmed as a novel SE-associated oncogene in t(4;14) cells, which could be regulated by MMSET. Knockdown of HJURP induced cell apoptosis, whereas overexpression of this gene promoted cell growth. Conclusion Mapping these acquired SEs and their associated genes may provide novel insight into both the understanding of MM biology and the development of novel therapeutic targets.

Keywords:
Multiple myeloma

super enhancer

t(4;14) translocation

THZ1

Tracks:
Multiple Myeloma Genomics

FP-022

The adverse double-hit effect of combining cytogenetic abnormalities and ISS stage III on the outcome of patients with newly-diagnosed multiple myeloma

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Abstract:

Emerging evidence suggests poor outcome of multiple myeloma (MM) patients carrying multiple adverse factors including high risk cytogenetic abnormalities (HRCA) and ISS stage III, thereby termed double-hit MM (DHMM). However, it remains uncertain how to define DHMM and its clinical significance due to lack of confirming study. To this end, our study aims to examine the prognostic values of co-occurrences of multiple HRCAs or their combination with ISS stage III in patients with newly-diagnosed MM (NDMM). A total of 307 NDMM patients who had baseline information of CAs detected by FISH and ISS staging, as well as received at least 4 cycles of treatment were included in this study. According to the consensus of the IMWG in 2016, 1q gain, del(17p), t[4;14], and t[14;16] were defined as HRCA, while del(13q14) was considered as a non-independent adverse CA. DHMM was defined as co-occurrences of either a) >= 2 HRCAs or b) at least 1 HRCA plus ISS stage III. In 180 cases harboring HRCAs, 23.3% and 10.5% patients carried only 1 HRCA or >= 2 HRCAs with a median PFS of 32.2 and 12.1 months ($p = 0.0004$), as well as a median OS of 65.6 and 29.3 months ($p = 0.027$), respectively. Interestingly, another subgroup of patients (17.2%) carrying 1 HRCA plus del(13q14) also displayed significantly shorter PFS (19.1 months, $p = 0.046$) and OS (29.6 months, $p = 0.055$), compared to those who had only 1 HRCA. In 140 cases harboring 1q gain, patients who carried >= 1 additional HRCAs had a median PFS of 11.2 months and a median OS of 18.9 months, significantly worse than those who had only 1q gain (PFS, 30.1 months, $p = 0.0009$; OS, 65.6 months, $p = 0.0008$). Patients carrying del(17p) with >= 1 additional HRCAs had a median PFS of 12.1 months and a median OS of 31.5 months. Moreover, patients carrying both 1q gain and del(17p) had significantly shorter PFS and OS than either 1q gain or del(17p) alone (PFS, $p = 0.008$ or $p = 0.001$; OS, $p = 0.001$ or $p = 0.006$), respectively. In 89 ISS III cases, patients with >= 1 HRCAs had a median PFS of 13.2 months and a median OS of 15.2 months, clearly worse than those without HRCA (PFS, 21.0 months, $p = 0.032$; OS, 43.8 months, $p = 0.057$). Last, ISS III patients carrying both 1q gain and del(17p) had the worst

outcome with a median PFS of 2.3 months and a median OS of 4.5 months, compared to those with only one of these two HRCAs (PFS, 15.8 months; OS, 24.5 months). In conclusion, our findings argue that patients either carrying two or more HRCA or at ISS III stage with at least one HRCA, so called DHMM, have significantly worse outcome (both PFS and OS), than those carrying only one HRCA or at ISS III stage, respectively. They also suggest that integration of the DHMM features into the current risk stratification criteria is helpful for more precisely identifying patients with high-risk or even worse disease at diagnosis, whose outcomes remain grim even in the era of novel therapies.

Keywords:
cytogenetic abnormality

Multiple myeloma

prognostic factors

Tracks:
Multiple Myeloma Genomics

FP-023

IGH and IGK Rearrangement and IGH Somatic Hypermutation Analysis Using Next-generation Sequencing for the Detection of Clonality in High-risk Korean Multiple Myeloma Patients

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Abstract:
Introduction: Clonality assessment in patients with multiple myeloma (MM) is important both for initial diagnosis and detecting minimal residual disease. Next-generation sequencing (NGS)-based immunoglobulin gene rearrangement assays may be useful for assessing clonality, although their applicability has not been convincingly demonstrated. Hence, we evaluated the primer set most widely used with the only commercially available NGS-based clonality assay in high-risk MM patients for the first time. Methods: Thirty bone marrow aspirate samples were included in the study (9 IgG, Kappa; 4 IgG, Lambda; 7 IgA, Kappa; 3 IgA Lambda; 1 IgD, Lambda; 2 Kappa light chain; 4 lambda light chain). The samples were from 28 patients with MM including 2 follow-up samples collected at the time of relapse or disease progression. The samples were evaluated for IGH rearrangements and IGH somatic hypermutation using the LymphoTrack® IGH-FR1 assay (InVivoScribe, San Diego, CA) on a MiSeqDx instrument (Illumina, San Diego, CA). When kappa-type cases showed negative IGH rearrangement (and somatic hypermutation), LymphoTrack® IGK assay (InVivoScribe) was performed. Results: IGH-FR1 and/or IGK assay detected clonality (demonstrated by rearrangements) in 22 out of 26 MM cases (84.6%) who were not lambda light chain disease. IGH clonality were observed in 20 of the 26 samples (76.5%), and among them 17 cases (85.0%) showed IGH somatic hypermutations. By testing IGK clonality on 5 kappa samples which didn't show any IGH clonality including 1 kappa light chain disease, 2 samples (40.0%) showed IGK clonality. One out of 2 kappa light chain disease cases and 1 out of 3 lambda light chain disease cases showed IGH clonality, suggesting that the heavy chain clonality could have been missed in immunofixation electrophoresis assay. The IGH or IGK clonality was not statistically associated with heavy chain or light chain, even though all the 10 IgA cases showed either IGH or IGK clonality. The median percentage of IGH clonality (in relation to the total lymphoid cells) was 68.12% (range: 4.85–86.60%). While 2 samples showed biclonality, the remaining 19 showed monoclonality(including the relapse of 1 of the 2 samples with biclonality). Two samples which showed no rearrangement in IGH assay, but positive rearrangements in IGK assay showed biclonality, and they were from the same patients. Neither the existence of IGH clonality nor its quantity (expressed as a percentage) was associated with the percentage of plasma cells in the specimens. The quantity of IGH clonality was not influenced by the

percentage of bone marrow plasma cells, ISS stage, or karyotype. Conclusion: By combining the IGH-FR1 assay and/or IGK assay, we detected clonality in approximately 85% of high-risk Korean MM patients. Somatic hypermutations of IGH gene was observed in 85% cases with IGH clonality. Different sets of primers of immunoglobulin genes might increase the clonality detection rate in MM.

Keywords:
clonality

Tracks:
Multiple Myeloma Genomics

FP-024

Delineating association between polymorphic variants of vitamin D receptor (VDR) gene and multiple myeloma disease in Indian population.

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Abstract:
Background and objectives Multiple myeloma (MM) is characterized by excessive proliferation and accumulation of abnormal plasma cells infiltrating the bone marrow microenvironment. It is characterized by secretion of atypical monoclonal immunoglobulin (M protein) by plasma cells in blood or urine, anemia, hypercalcemia, renal dysfunction, and bone pain accompanied with pathological fractures. Approximately 70% of MM patients display skeletal abnormalities at diagnosis and after diagnosis nearly 85% patients develop bone lesions during the course of disease. Bone disease represents a major cause of morbidity and mortality in MM. Vitamin D is an important regulator of calcium and phosphate homeostasis. Serum vitamin D levels regulate bone mineralization and its deficiency leads to reduced calcium absorption thereby increasing bone resorption in MM. Recent studies demonstrated significant association between VDR gene polymorphism and increased likelihood of diseases including cancers such as breast, colorectal, prostate etc. Thus, the objective of this maiden study was to ascertain association between VDR gene variants (ApaI, BsmI, FokI and TaqI) and MM disease. Materials and methods In this study, 75 MM and 75 controls subjects were recruited after approved ethical permission and informed consents. VDR gene polymorphism (ApaI, BsmI, FokI and TaqI) was investigated using PCR-RFLP based method. Vitamin D levels were measured in serum samples using ELISA techniques of all recruited study subjects. Results were statistically analyzed using Stata 1.0 software and Graphpad 5.0. Results and conclusion Results demonstrated that there was significant decrease ($p>0.05$) in serum vit D levels in MM patients compared to controls. Additionally, serum levels of Vit D decreases with disease severity in MM patients. Upon division of vitamin D levels among different genotypes of each VDR gene variant, significant concentration difference could be observed between patient and controls. Further, SNP analyses showed that there was significantly higher risk of MM in Ff + ff, Aa + aa; Bb + bb genotypes. Additionally, FokI f, ApaI a and BsmI b alleles are significantly associated with MM disease development. Lastly multiple clinico-pathological parameters showed significant association with various genotypes of VDR gene. In conclusion, this study provides a brief insight about role of VDR gene polymorphisms and increased susceptibility of MM occurrence in Indian population. Additionally, vitamin D supplementation might be given along with conventional chemotherapeutic agents for myeloma treatment, in future.

Keywords:
Multiple myeloma

single nucleotide polymorphism

Vitamin D

Tracks:
Multiple Myeloma Genomics

FP-025

A Maturation Index defines Newly Diagnosed Multiple Myeloma Patients with advanced immunophenotypic and Molecular Differentiation profiles associated with poor prognosis

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Abstract:
The differentiation status plasticity of Multiple Myeloma (MM) plasma cells (PC) is an adaptive strategy that might confer a specific fitness to tumour cells, enabling their interaction to an evolving microenvironment. Therefore, MM clones are not constantly "fit", and the immunophenotypic profile of the fittest MM PCs might be the expression of specific genetic and genomic programs, emerging under therapeutic pressure and promoting tumour development. However, the genomic background that supports any diverse plasma cell differentiation phenotypes has not yet been inferred. To correlate the genetic and genomic background with the immunophenotypic profile of MM clones at diagnosis, in order to stratify patients (pts) according to a Maturation Index. 114 newly diagnosed MM pts were included in the study. For each pts, both the neoplastic PCs and CD19+ B cells compartments were characterized by 8-color multi-parameter flow cytometry analysis. Both whole-genome copy number alterations (CNAs) and a 25-genes targeted mutational panel were assessed in CD138+ PCs. A custom ddPCR assay was employed to evaluate the self-renewal status of PCs. In order to define a Maturation Index, pts were evaluated for: a) differential expression of CD19/CD81 markers; b) level of chromosomal instability (CIN); c) self-renewal status. According to the CD19 and CD81 markers co-expression, we were able to stratify pts in 3 different subgroups, recapitulating a progressive PC maturation process: the most immature, which included pts with PCs CD19+/CD81+ (20/114 = 17%); an intermediate CD19-/CD81+ phenotype subgroup (40/114 = 35%); and the CD19-/CD81- PC subgroup (54/114 = 48%), whose clone was mainly composed by most mature plasma cells. Pts with an advanced differentiation status (CD19-/CD81-) were more frequently associated to a high CIN (medium tot. CNAs = 550, % GC ≥ 25%), including a higher prevalence of high-risk features. Indeed, 1p deletion (FAF1), 16q deletion (WWOX, FANCA) and 17p deletion (TP53) were the most recurrent abnormalities. Genomic instability was also confirmed by a higher incidence of clonal pathogenic mutations in critical genes (e.g. NRAS, KRAS, TP53). Interestingly, the application of a 10 Hh-genes signature, resuming the Hedgehog pathway, demonstrated that PCs with more advanced differentiation status displayed a substantial overexpression of all the genes, indicating a more proliferative, aggressive and, possibly, persistent phenotype. Finally, the presence of a more mature PCs characterized pts carrying baseline clinical features associated to bad prognosis (e.g. n. PET lesions, k/l ratio, ISS III, β2-microglobulin; $p<.05$). In addition, these pts tended to obtain high quality response rates (≥VGPR) to PI induction therapy. A Maturation index defined pts with an advanced differentiation status both at immunophenotypic as well as at molecular level, and this is lastly associated with a prevalence of bad prognosis features.

Keywords:
Differentiation

GENOME STABILITY

immunophenotype

Tracks:
Multiple Myeloma Genomics

FP-026

Loss of TRIM33 in Multiple Myeloma correlates with increased genomic instability

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Abstract:
Introduction Genomic instability is a hallmark of Multiple Myeloma (MM), with almost all patients displaying cytogenetic abnormalities including ploidy changes, deletions, amplifications and translocations. A common recurrent genetic event in MM with prognostic significance is the deletion of chromosome 1p. TRIM33, an E3 ligase, is located within this deleted region at 1p13. Recent studies demonstrate a role for TRIM33 in the PARP-dependent DNA Damage Response (DDR) and showed that loss of TRIM33 results in the accumulation of chromosomal abnormalities. TRIM33 functions as a tumour suppressor in a number of cancer types, including chronic myelomonocytic leukaemia and hepatocellular carcinoma. Low TRIM33 expression has previously been associated with poor overall survival in MM (GSE2658), however, little is known about its molecular function in MM. Methods The CoMMpass dataset (IA13 release) was screened to identify patients with a TRIM33 deletion and correlate this data with structural events and survival. ALC-1, TRIM33 and γH2AX expression was analysed by co-immunoprecipitation and Western blotting. Results To explore the impact of loss of TRIM33 on genomic stability, we analysed chromosomal abnormalities in the CoMMpass dataset. Structural variants, including deletions, inversions, duplications and translocations, were analysed in all MM patients in the dataset (875); of these 47 patients had a deletion of the region containing TRIM33. This analysis identified a median of 29 structural variants per patient in total. However, patients with a TRIM33 deletion had a significantly higher median of 50 structural variants ($P<0.0001$), suggesting that the loss of TRIM33 may contribute to genomic instability of MM cells. Survival data was available for 119 of these patients; Kaplan Meier survival analysis showed that patients with a deletion of TRIM33 ($n = 5$) have a poorer overall survival ($P<0.05$). TRIM33 has been reported to participate in the DNA damage response by limiting the activity of ALC1 at sites of DNA damage. Consistent with this, using co-immunoprecipitation we demonstrate a rapid, but transient, interaction between TRIM33 and ALC1 15 minutes after doxorubicin-induced DNA damage, which is lost after 30 minutes. Furthermore, we show that cell lines with low TRIM33 exhibit higher expression of γH2AX, indicative of higher baseline DNA damage. Conclusion Deficiencies in DDR can lead to genomic instability, resulting in the accumulation of chromosome abnormalities. Here we show that the loss of TRIM33 can lead to DDR deficiencies in MM and is correlated with increased genomic instability. Further understanding of the role of TRIM33 in DDR may open up opportunities to therapeutically exploit DNA repair defects in patients with loss of TRIM33.

Keywords:
DNA REPAIR

GENOME STABILITY

TRIM33

Tracks:
Multiple Myeloma Genomics

FP-027

Dysregulation of HUWE1 is associated with an increased mutational burden in Multiple Myeloma

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Abstract:
Introduction Genomic instability is a prominent feature in the development and progression of Multiple Myeloma (MM). The E3 ligase HUWE1 contributes to the regulation of genomic stability by promoting DNA damage tolerance during replicative stress. Previous studies, by our lab and others, have shown dysregulation of HUWE1 in MM. We have demonstrated an increase in expression of HUWE1 across plasma cell dyscrasias and HUWE1 has been reported as a mutational driver in t(11;14) myeloma. The aim of this study was to investigate the role of HUWE1 in DNA replication and explore whether dysregulation of HUWE1 contributes to genomic instability in MM. Methods Cell cycle analysis was performed using Click-iT Alexa Fluor 488 flow cytometry assay kit (Thermo Fisher). HUWE1 mutational status was analysed using the CoMMpass dataset (IA13 release). Genomic instability was assessed using the PIG-A mutation assay and micronucleus analysis (Litron Labs) in a panel of HUWE1 mutant (U266, XG-1, XG-2, KMS-27, H1112) and HUWE1 wild-type (JJN3, MM.1S, MOLP8, KMS-18, OPM-2) MM cell lines. Results Consistent with previous reports, we found that knockdown or inhibition of HUWE1 in MM cell lines leads to an S-phase cell cycle arrest, indicating that HUWE1 is required for effective replication. Additionally, using proteomic profiling coupled with co-immunoprecipitation we identified novel putative substrates of HUWE1 that are involved in replication. We examined the effects of HUWE1 dysregulation on genomic stability in MM. The CoMMpass dataset (IA13 release), which includes 31 patients with a nonsynonymous HUWE1 mutation, was analysed for markers of genomic instability (structural variants and mutations). Whilst there was no difference observed in large structural variants between HUWE1 wild-type and mutant patients, there was, however, a significant increase in mutational burden. Patients with a HUWE1 mutation exhibited an increase in the average number of both total (519 vs 1013; $p < 0.001$) and nonsynonymous mutations (65 vs 225; $p < 0.0001$). Furthermore, analysis of genomic instability, using the PIG-A assay, in HUWE1 wild-type and mutant MM cell lines demonstrated that the HUWE1 mutant cells exhibit a significantly increased mutation rate ($p=0.0023$) with an associated ≥ 2-fold increase in micronuclei frequency. Conclusion HUWE1 dysregulation has been implicated in promoting genomic instability. Here we show, in silico and in vitro, that MM patients and cell lines with HUWE1 mutations exhibit genomic instability characterised by an increased mutational burden. Understanding of the mechanisms driving genomic instability in MM may highlight novel opportunities for therapeutic targeting.

Keywords:
GENOME STABILITY

HUWE1

replication stress

Tracks:
Multiple Myeloma Genomics

FP-028

Aminopeptidase gene expression in myeloma

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Abstract:
Introduction: A hallmark of myeloma is high level production of immunoglobulins leading to a heavy load on protein folding and homeostasis in tumor cells. The aminopeptidase gene family catalyze the hydrolysis of amino acid residues from proteins or

peptides and are last in line for protein degradation. They are thus an important group of metalloenzymes implicated in cellular functions such as differentiation, cell cycle, DNA repair, and apoptosis. Since aminopeptidases operate downstream of the ubiquitin-proteasome pathway, enzymatic activity of these proteases can be utilized by peptide conjugated drugs. However, there is limited information about the expression of aminopeptidases in myeloma. Methods: 103 bone marrow aspirates from myeloma patients and 2 healthy donors were obtained after written informed consent and following approved protocols in compliance with the Declaration of Helsinki. CD138+ cells were enriched and used for RNA or protein preparation. Illumina compatible RNA sequencing libraries were prepared and sequenced. Proteomic analysis was performed using Q-Exactive MS/Dionex Ultimate 3000 instruments. Contribution of aminopeptidase gene expression on survival outcome was estimated by Kaplan-Meier analysis. Significance for survival curves between two groups (high vs. normal expression) were deduced using a log rank test (Mantel-Cox). Results: We investigated aminopeptidase expression in 103 myeloma samples. Expression levels were ranked based on abundance levels in all samples, then focused on aminopeptidases differentially expressed compared to heathy plasma cells. The majority of the genes in patient samples showed related expression patterns or were modestly overexpressed (DPP7, DPP3, METAP2 and LAP3) compared to healthy plasma cells. Decreased expression was detected for several aminopeptidases including MMP14, MMP15, ANPEP, ENPEP, and CTSH. LAP3 mRNA and protein expression also correlated to each other. Furthermore, we investigated whether any aminopeptidase could be linked to disease progression and found no significant differences. Expression levels of LAP3, ERAP1, METAP2 and DPP7 ($P > 0.005$) appeared higher in relapsed than in NDMM samples. However, comparison of expression levels in six paired NDMM and RRMM samples showed a trend for increased LAP3 at relapse. To assess whether prior exposure to treatments may associate with LAP3 expression, we compared expression between samples exposed and naïve to mel, btz or IMIDs. Elevated expression of LAP3 was detected in all treated groups (mel $P=0.01$, btz $P=0.04$ and IMIDs $P=0.04$). Survival analysis revealed that patients with samples exhibiting 2x or higher LAP3 expression had poorer prognosis with a median survival of six months from the sampling date ($P=0.0001$, HR 4.5; 95% CI 1.45-14.05). Conclusions: Differential aminopeptidase expression was assessed in both normal and malignant human plasma cells with LAP3 identified as a potential poor prognostic marker for myeloma.

Keywords:
Aminopeptidases

gene expression

myeloma

Tracks:
Multiple Myeloma Genomics

FP-029

Whole-genome bisulfite sequencing identifies HDAC3-mediated DNA methylation in multiple myeloma

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Abstract:
Epigenetic regulation of signaling pathways plays a crucial role in tumorigenesis. Histone deacetylases (HDACs) therefore represent novel therapeutic targets for various types of cancers, including multiple myeloma (MM). Non-selective HDAC inhibitor panobinostat has been approved to treat MM; however, unfavorable adverse events limit its clinical application. We have demonstrated that selective HDAC3-inhibition induces significant MM cell growth inhibition, associated with downregulated expression of DNA methyltransferase (DNMT1). The methylation of

genomic DNA is catalyzed by DNMT1/3, and DNA methylation is shown to be abnormal in all forms of malignant cells. In this study, we analyzed the mechanisms and sequelae of HDAC3-mediated modulation of DNA methylation in MM. We first performed whole-genome bisulfite sequencing in MM.1S cells transduced with shHDAC3, shDNMT1 or shLuc (as control). We then examined distribution of differentially methylated positions (DMPs) and regions (DMRs). We identified DMPs and DMRs which were altered in both HDAC3 and DNMT1 knockdown (KD) cells. For example, there were more hypomethylated DMPs than hypermethylated DMPs in HDAC3-KD or DNMT-KD cells (vs shLuc), consistent with the functional significance of our previous study showing HDA3 inhibitor-induced DNMT1 downregulation in MM cells. Importantly, the number of hypomethylated DMPs in HDAC3-KD cells was greater than in DNMT1-KD cells (22,749 and 3,823 in the setting of $p<0.01$ and 3,680 and 324 in the setting of $p<0.001$), respectively. As expected, Venn diagrams for hypomethylated and hypermethylated DMRs showed significant overlap of DMRs between HDAC3-KD and DNMT1-KD cells. These results suggest that HDAC3 inhibition modulates DNA methylation status, at least in part, through DNMT1 inhibition. We next studied hypomethylated DMRs in promoter regions in both HDAC3-KD and DNMT1-KD cells. We identified hypomethylated promoters of 18 genes including ABCA5 and SH3BP2. Since methylation alters gene expression and is therefore a potential therapeutic target, we also analyzed downregulated genes with hypomethylated DMPs and DMRs in gene bodies in both HDAC3-KD and DNMT1-KD cells. Importantly, we identified common DMPs and DMRs in 6 genes (ANK3, RABGAP1L, ROBO1, RUNX2, TCF4 and UNC13C). We further investigated DMPs and DMRs in regulatory regions defined by H3K27 acetylation peak shown in Encyclopedia of DNA Elements (ENCODE), which confirmed upregulated genes with hypomethylated DMPs or DMRs. In summary, our analyses indicate that HDAC3 modulates DNA methylation at a broad range of genomic sites via both DNMT1-dependent and -independent mechanisms mediating MM cell growth inhibition, providing the basis for novel targeted therapeutics in MM.

Keywords:
DNA methylation

DNMT1

HDAC3

Tracks:
Multiple Myeloma Genomic

FP-030

VarianThinker: a classification method to confidently approach the mutation heterogeneity in Multiple Myeloma

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Abstract:
INTRODUCTION: Multiple Myeloma (MM) is a genomically heterogeneous malignancy, characterized by a relevant mutational burden, as compared to other types of cancer. By employing a frequentist approach to define MM driver mutation, a landscape of few variants in a limited number of genes, mostly associated to survival and/or proliferative pathways (eg. KRAS, NRAS, TP53, BRAF), have been reported so far. Nevertheless, given the high genomic heterogeneity of MM plasma cells, new possible driver mutations, being rare and/or scattered across the genome, might be diluted within the genomic complexity and therefore missed. In fact, the frequentist approach applied to a very heterogeneous state, naturally includes false

negative within its classification. This bring into question the canonical frequentist approach ability to correctly determine the true driver status of MM mutations. AIM: To develop a variants classification method able to both harness and harmonize all possible evidences of variants' pathogenicity (i.e. clinical, biological, and in-silico), in order to integrate prior knowledge about driver events and, ultimately, to generate a comprehensive list of candidate driver mutations from sequencing data of each single tumor. PATIENT-METHODS: A targeted ultra-deep Next Generation Sequencing approach was employed to explore a panel of 25 genes (frequently mutated in MM) in 109 newly diagnosed patients. We set up an algorithm, "VarianThinker", designed to obtain the best separation between uncertain significance (VUS) and characterized variants. To this aim, VarianThinker employs, and appropriately combines, each available information derived from Annovar, a commonly used variant annotation tool, consisting of annotations from clinical databases (CLINVAR, COSMIC), population databases (dbSNP, GnomAD) and in-silico biological predictions methods (LJB, VEST, PROVEAN, etc.). The output consists in a bivariate classification system, composed of a 4-class pathogenicity label (PG), spanning from A (pathogenic) to D (benign), combined to a 5-class confidence label (CO), spanning from 1 (confident) to 5 (uncertain). RESULTS: A total of 1214 calls have been obtained; of these, 903 (74,4%) were assigned to a high confidence state (CO≤2), 287 (23,6%) to a medium confidence state (CO≤4) and only a very low number (24, 1,9%) to a VUS state (CO=5). TP53, KRAS and NRAS lesions were confirmed driver variant, being called as stringently pathogenic (PG=A) and confident (CO≤2). Of interest, both CO3 and CO4 are able to efficiently discriminate candidate driver variants among different PA classes, as shown on TP53, DIS3, MYC, LRRK2 and SP140 genes. CONCLUSION: VariantThinker is a new algorithm for variant calling analysis, able to recapitulate canonical driver mutations and to resolve false negative results. It might help to define novel MM driver variants within the complexity of MM genomic landscape.

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Keywords:
Bioinformatics

Mutation

sequencing

Tracks:
Multiple Myeloma Genomics

FP-031

The three-dimensional (3D) spatial distribution of lamin A/C in the nuclei of Myeloma Cells

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Abstract:
Introduction: Myeloma (MM) is an incurable cancer. Effective predictive & prognostic markers are needed to optimize care. Irregular nuclei are common in cancer and may correlate with malignancy. Lamin proteins, type V intermediate filaments classified into A (lamin A & C) and B (B1 & B2), are major components of the nuclear lamina. It determines nuclear shape, architecture, and other structural changes observed in cells. Altered nuclear lamina can interfere with cell functions, increase nuclear fragility, gene expression and proliferation. Changes in the expression of lamin A/C (protein and mRNA) correlated with progression in some cancers. We describe the first report on the 3D spatial distribution of lamin A/C in Myeloma cell line, in Myeloma cells isolated from newly diagnosed patients and compare it with B-lymphocytes from healthy donors. Methods: Commercially available cell line MM.1R CRL-2975 was used (ATCC, Manassas, VA, USA). After REB

approvals, the peripheral blood of ten newly diagnosed MM patients and ten healthy volunteers was obtained. The cells were isolated using Ficoll-gradient centrifugation (Ficoll-PaqueTM Plus, 17-1440-02, GE Healthcare, Little Chalfont, UK). Staining with anti-CD 138 & anti-CD56 antibodies were used to identify MM cells, and anti-CD 20 identified B-lymphocytes. B-lymphocytes were treated with Lipopolysaccharides (LPS) (SIGMA, L2630, St. Louis, MO, USA) prior to imaging to enhance Lamin A/C expression. The cells were incubated at 37 °C with anti-Lamin A (1:200 dilution, 45 minutes, rabbit polyclonal, ab26300, Abcam Ltd., Cambridge, UK) then with goat anti-rabbit antibody (1:500 dilution, 30 minutes, Invitrogen, Carlsbad, CA, USA). All cells were analyzed by 3D imaging with a series of 80 z-stacks, each with a thickness of 0.2 μm. The images were deconvolved using the constrained iterative restoration algorithm with Theoretical point-spread function, and rendered using the Transparency Module. ZEN Blue 2.6 (Carl Zeiss, Toronto, ON, Canada) computer software was used to perform lamin A/C measurements in the identified patterns. Each pattern has different intensity of pixels and the Two-tailed t-test was used to compare lamin A/C pattern ratios. Results: B-lymphocytes displayed regular spherical 3D lamin A/C expression with no lamin A/C internal structures. The MM cell line and patient derived MM cells had irregular 3D distribution of lamin A/C. This was classified according to the complexity of internal lamin structures into statistically distinct patterns 0, A, B, or C. The patterns in cell line were of less complexity compared to patient MM cells. While the cell line results were consistent, there was low variability between patients. Conclusions: This is the first report on the aberrant organization of lamin A/C in MM nuclei. Further studies of lamin A/C internal structures in MM are needed to explore its potential as predictive and prognostic marker.

Keywords:
lamin A/C

Multiple myeloma

Nuclear organization

Tracks:
Multiple Myeloma Genomics

FP-032

Epigenetic regulation of gene expression in progression of multiple myeloma

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Abstract:
Background. Multiple myeloma (MM) is a complex and heterogeneous malignancy of plasma cells that has two precursor states: monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM). Although Ig translocations, copy number alterations and somatic mutations are known genomic events involved in MM progression; precursor patients with similar genomic profiles often display differences in their progression rates to MM. Variations in disease progression rate and response to the treatments highlight the potential contribution of epigenetic events in onset, progression and heterogeneity of MM. This study aimed to define epigenetic pathways that lead to the dynamic regulation of gene expression in MM pathogenesis. Methods. We performed ATAC-seq, RNA-seq and whole genome sequencing on CD138+ plasma cells isolated from bone marrow aspirates of 3 healthy donors, 13 SMM, 9 newly diagnosed MM (NDMM) and 9

relapsed (RRMM) patients. ATAC-seq libraries were normalized using a novel analytical method BREN. The accessibility was calculated for peaks within 100Kb of genes that showed differential expression between normal and SMM or SMM and NDMM samples. The peaks showing the greatest (top 1%) variability was used to cluster the samples in an unbiased manner. Results. To characterize the epigenetic regulation of gene expression in MM progression, we first identified enhancers and promoters around known transcription start sites in normal plasma cells (NPC), SMM, NDMM and RRMM patients. To investigate the dynamic regulation of gene expression in progression to SMM and MM, we looked at 714 differentially expressed genes in SMM vs NPC and NDMM vs SMM comparisons, and integrated them with most variable non-coding regions defined for each gene from matched ATAC-seq patients and H3K27Ac ChIP-seq data from MM cell lines. This analysis led to identification of enhancers for 21 genes differentially expressed in SMM and NDMM such as KIAA0907, PRDM5, TERT, CNTN5 and CD79A. Of note, unbiased clustering of samples on novel enhancers displayed distinct accessibility patterns for SMM, NDMM and RRMM patients indicating that those regulatory elements actively regulate expression levels of their target genes in progression from SMM to NDMM. Conclusion. We have generated a global epigenetic map of primary tumors from patients at the smoldering, newly diagnosed and relapsed/refractory stage of multiple myeloma. Integrative analysis of ATAC-seq data with transcriptome and whole-genome map of active histone marks in our study led to the identification of novel enhancers that gain accessibility upon disease progression and regulate expression of genes that are involved in pathogenesis of multiple myeloma. Those enhancer elements and their target genes thus might represent as novel epigenetic biomarkers and potential vulnerabilities in MM.

Keywords:
epigenetic

Expression pattern

Tracks:

Multiple Myeloma Genomics

FP-033

Effect of t(11;14) on Outcomes of Patients With Newly Diagnosed Multiple Myeloma in the Connect® MM Registry

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Abstract:
Background: t(11;14) is found in 16%–24% of multiple myeloma [MM] patients and is generally classified as standard risk (Sonneveld et al. Blood. 2016). Its effect on MM prognosis is not fully understood. Consensus is lacking on the effects of induction treatment on outcomes with t(11;14). The Connect® MM Registry (NCT01081028) is a large, US, multicenter, prospective observational cohort study of patients with newly diagnosed MM designed to examine real-world diagnostic patterns, treatment patterns, clinical outcomes, and health-

related quality of life patient-reported outcomes in patients with newly diagnosed MM. The association of t(11;14) with treatment outcomes are reported. Methods: Analysis included data from patients from 250 community, academic, and government sites in cohort 1 (9/2009–12/2011) and cohort 2 (12/2012–4/2016), who completed first-line induction treatment (IMiD agent [lenalidomide or pomalidomide] + proteasome inhibitor [PI], PI only, or IMiD agent only) and were tested for t(11;14) by fluorescence in situ hybridization or cytogenetics. Primary end points (progression-free survival and overall survival) were measured from start of first-line treatment to earliest event (progression-free survival, death or progression; overall survival, death), loss to follow-up, or data cutoff, adjusted for baseline risk factors. A sensitivity analysis excluding patients with concomitant cytogenetic abnormalities [del 17p, t(4;14), t(14;16), 1q+] was also performed. Results: As of 1/2018, 3011 patients were enrolled; 2938 were treated. Of 1574 enrolled patients tested for t(11;14), 378 were t(11;14)+ and 1196 were t(11;14)−. More patients in cohort 2 than cohort 1 were t(11;14)+ (60% vs 40%). Baseline characteristics were similar between groups. t(11;14) status did not significantly affect progression-free survival (for all treated patients [34.8 vs 35.7 mo] and each treatment group [IMiD agent + PI, 42.6 vs 45.2 mo; PI only, 32.9 vs 29.5; IMiD agent only, 30.3 vs 32.3 mo]) or overall survival (for all treated patients [74.0 vs 77.3 mo] and each treatment group [IMiD agent + PI, not reached (NR) vs NR; PI only, NR vs 70.0 mo; IMiD agent only, 62.7 vs 73.4 mo]). Patients in cohorts 1 and 2 received similar first-line treatments (IMiD agent + PI, 30% vs 42%; PI only, 42% vs 43%; IMiD agent only, 17% vs 11%). Results were similar when patients with concomitant abnormalities were excluded. Conclusion: Results of this analysis of real-world data from the Connect MM Registry, a large, US-based MM registry, suggest that t(11;14) does not affect progression-free survival and overall survival outcomes in newly diagnosed MM patients with currently utilized treatment regimens.

Keywords:
induction

survival

t(11;14)

Tracks:
Multiple Myeloma Genomics

FP-034

Frequency of and Associations Amongst Baseline Cytogenetics in Patients With Newly Diagnosed Multiple Myeloma in the Connect® MM Registry

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Abstract:
Background:It has been reported that cytogenetic abnormalities, as detected by FISH, occur in ≈60% of patients (pts) with newly diagnosed multiple myeloma (NDMM; Al-Maeen Int J Lab Heme 2016). The Connect® MM Registry (NCT01081028) is a large, US, multicenter, prospective observational study of pts with NDMM

designed to examine real-world diagnostic and treatment patterns, clinical outcomes, and health-related quality of life. We report the incidence of baseline cytogenetic abnormalities in pts from Connect MM and we identify associations between common abnormalities that are currently not well understood for pts with MM. Methods:Data from pts from 250 community, academic, and government sites in cohort 1 (9/2009–12/2011) and cohort 2 (12/2012–4/2016), who had cytogenetic analysis performed via FISH of bone marrow (BM) aspirate or biopsy were included. Cytogenetic abnormalities probed for included hyperdiploidy (trisomies of chromosomes 3, 5, 7, 9, 11, 15, 19, and 21; defined per IMWG; Sonneveld Blood 2016), hypodiploidy (≤44 chromosomes; defined per Van Wier Haematologica 2013), 1q+, del(13), del(17p)/p53, t(4;14), t(11;14), other Ig heavy chain gene abnormalities, other abnormalities (complex results of ≤2 abnormalities not previously listed), and complex (complex results of ≥3 abnormalities). Associations between common cytogenetic abnormalities were classified as isolated (no association; 1 cytogenetic abnormality), single (2 cytogenetic abnormalities), or multiple (>2 abnormalities). Using Circos plots, frequency of abnormalities (segments, proportion along circumference) and associations with other abnormalities (ribbons with relative sizes connecting abnormalities) will be visualized. Results:Of 3011 enrolled pts (84% from community sites), BM aspiration or biopsy was performed in 2943, and baseline cytogenetic abnormalities were assessed by FISH in 2058 (68%). Of the 2058 pts, 538 (26%) had normal cytogenetics, 1423 (69%) had cytogenetic abnormalities, and 97 (5%) were missing/not specified. Among pts with cytogenetic abnormalities, 2986 abnormalities were identified (numbers not mutually exclusive); the most frequent were del(13) (n=655; 22%), t(11;14) (n=372; 12%), and hyperdiploidy (n=371; 12%). Of 1423 pts with cytogenetic abnormalities, 512 (36%) had no association, 436 (31%) had 1 association, and 475 (33%) had multiple associations between abnormalities (numbers mutually exclusive). Del(13) (n=143; 28%), hyperdiploidy (n=106; 21%), and t(11;14) (n=82; 16%) were the most frequent isolated abnormalities. The most common single associations were hyperdiploidy with 1q+ (n=46; 11%) or other (n=37; 8%), and del(17p)/p53 with del(13) (n=36; 8%). Data for karyotyping was similar. Conclusion:Using real-world data from the Connect MM Registry we described the heterogeneity of cytogenetic abnormalities and their associations in pts with NDMM. Characterizing associations amongst abnormalities may help better understand clinical behavior.

Keywords:
cytogenetics

FISH

registry

Tracks:
Multiple Myeloma Genomics

FP-035

Evaluating the efficacy of multiple myeloma cell lines as models for patient tumors via transcriptomic correlation analysis

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Abstract:
Background: Multiple myeloma (MM) cell lines are routinely used in laboratories around the world to model the disease. However, a long-standing question is how well these cell lines truly represent tumor cells in patients. Recently, a novel transcriptional correlation profiling approach used data from >9,000 patient tumors from TCGA and >600 cell lines from CCLE to identify lines that best represent patient disease and encourage their more widespread use in biological studies (Yu et al, Biorxiv, 2018). Here, we applied the same approach to RNA-seq data from 779 newly-diagnosed MM tumor samples and 66 MM cell lines. Our goal is to inform the MM community of cell lines that may be

most reliable for modeling in vivo disease and those which should perhaps be avoided. Methods: Transcriptomic data for patients and cell lines were acquired from the CoMMpass database (IA13 release) and the Keats Lab repository (www.keatslab.org). Counts were normalized via variance stabilizing transformation. The 5,000 most variable genes across patients were used for Spearman's rank correlation to prioritize cell lines. Patient subset identification was performed per SNV calls in CoMMpass and translocation determination as in Barwick et al (Nat Comm (2019) 10:1911). Results: Initial analysis of global transcriptional profiles based on Principal Component Analysis of MM cell lines and patient tumors showed two distinct clusters. The range of Spearman's rank correlations comparing the transcriptome of all MM cell lines to all patient tumors was ~0.4 to ~0.6, similar to values seen in prior TCGA-wide anlysis. For 25 overlapping cell lines also in the CCLE, we found that correlate rank order was robust to RNA-seq performed by different groups. ANBL-6 was the "best" cell line with a mean correlate of 0.58, significantly exceeding that of all other lines ($p<2.2e-16$ by Wilcoxon test). MMM-1 and FR4 cell lines were significantly "worse" than all other lines (mean R = 0.39 and 0.40, respectively, both $p<2.2e-16$). Notably, lines cultured with IL-6 were significantly enriched in the upper half of cell line-patient correlations ($p = 2.3e-4$), indicating that microenvironment factors drive the tumor transcriptome signature. MM.1S and MM.1R were among the best-correlated cell lines grown without IL-6. Gene Set Enrichment and Gene Ontology analyses identified signatures of cell cycle genes and MYC signaling enriched in cell line transcriptomes, whereas immune regulatory pathways were upregulated in patients. Subsetting on genomic features, we found that t(4;14), t(14;16), and t(14;20) tumors were better modelled by cell lines harboring the same translocations, but not t(11;14), KRAS, or NRAS mutations. Conclusion: Our genome-wide analysis systematically quantifies differences between MM cell lines and patient tumors, and provides a metric for choosing cell lines for in vitro studies. In particular, our work suggests that ANBL-6 should be utilized more broadly in MM research.

Keywords:
Bioinformatics

Cell Lines

RNA-Seq

Tracks:
Multiple Myeloma Genomics

FP-036

Gain of Chromosome 1q is Associated with Early Progression in Multiple Myeloma Patients Treated with Lenalidomide, Bortezomib, and Dexamethasone

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Abstract:
Introduction: Gain of chromosome 1q (+1q) in multiple myeloma is associated with inferior outcomes including survival. However, the prognostic impact of +1q has yet to be determined in the setting of current standard-of-care triplet induction regimens. Methods: We retrospectively analyzed all consecutive patients with multiple myeloma who were seen at Emory University between November 1, 2010 and December 31, 2014 and were treated with lenalidomide, bortezomib, and dexamethasone (RVD) induction. Patients were excluded if it was unknown whether +1q was present by fluorescent in situ hybridization (FISH) at the time of initial diagnosis. Clinical characteristics at diagnosis were determined, including age, sex,

and race, laboratory values for hemoglobin, creatinine, calcium, albumin, lactate dehydrogenase, beta-2-microglobulin, isotype, paraprotein, serum free light chain ratio, FISH for +1q, t(11;14), t(4;14), t(14;16), del(17p), del(13q), and hyperdiploidy. Patients were also categorized by their ISS stage, R-ISS stage, treatment with autologous stem cell transplantation (ASCT), and whether maintenance therapy was prescribed. The primary outcomes were response to RVD induction by IMWG criteria, progression free survival (PFS), and overall survival (OS) of patients with +1q compared to patients without +1q. Subgroup analyses were performed to evaluate the impact of 1q copy number (2, 3, or ≥4 copies indicating gain of 0, 1, or ≥2 copies of 1q) and the presence or absence of other high risk cytogenetic abnormalities (t(4;14), t(14;16), or del(17p)) in patients with or without +1q. Results: Our search identified 201 patients who met criteria for inclusion in this study. Patients with +1q (n=94, 46.7%), compared to those without +1q (n=107), had shorter median progression-free survival (PFS) (41.9 months vs 65.1 months, p=0.002, HR=1.90) and overall survival (median not reached for either arm, p=0.003) despite having a higher probability of achieving a very good partial response or better after RVD induction (75.0% vs 59.8%, p=0.02). This hazardous effect on PFS remained significant on multivariate analysis (p=0.018, HR 1.89). Increasing copy number of 1q was associated with progressively shorter PFS (65.1 months, 55.9 months, and 34.6 months for patients with 2, 3, or ≥ 4 copies, respectively; p=0.0063). Patients with co-occurrence of +1q and t(4;14), t(14;16) or del(17p) had a median PFS of 25.1 months, which is significantly worse compared to patients with only one or neither of these cytogenetic abnormalities (p<0.001). Conclusion: Despite excellent responses to RVD induction, patients with +1q myeloma are at high risk for early progression and death. Increasing copy number of 1q was associated with worse PFS. Co-occurrence of +1q with t(4;14), t(14;16), and/or del(17p) may represent a "double hit" myeloma that should be further investigated and prompt consideration of novel treatment approaches.

Keywords:
cytogenetics

High risk

myeloma

Tracks:
Multiple Myeloma Genomics

FP-037

The contribution of proteasome subunits to Myeloma cell viability and proteasome inhibitor sensitivity

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Abstract:
We generated eight multiple myeloma (MM) cell lines resistant to bortezomib (BTZ) by exposure to increasing drug concentration: five of them acquired novel PSMB5 mutations. Given the rarity of similar mutations in over 1,500 analyzed MM patients, we explored in depth the role of the proteasome on MM cell viability and BTZ sensitivity by systematically deleting the major proteasome targets of BTZ. We demonstrated that MM cell lines without PSMB5 were surprisingly viable. PSMB5 mutated, BTZ resistant, MM cell lines were re-sensitized to BTZ when PSMB5 was experimentally deleted, implying that this mutation is activating in its drug resistance function. In contrast PSMB6 knockout was lethal to MM cell lines, which were efficiently rescued by re-introduction of wild type PSMB6. Interestingly, reduction in PSMB6 levels also prevented the splicing of the major catalytic subunits PSMB5, PSMB7, PSMB8 and PSMB10. PSMB6 engineered with no splicing function or catalytic activity, also restored viability, inferring that the contribution of PSMB6 to proteasome structure is more important than functional activity. Supporting this observation, BTZ sensitivity was restored in resistant MM cells line by introducing low level expression of mutated PSMB6 lacking splicing function. As with PSMB6, PSMB7 knockout was lethal to MM cell lines. In

contrast, loss of immunoproteasome subunits PSMB8 and PSMB9 was neither lethal nor restored sensitivity to BTZ. Significant co-dependency was observed between the different constitutive PSMB subunits –for example expression of PSMB6 and PSMB7 was significantly reduced in MM cell lines without PSMB5, and expression of PSMB5 and PSMB7 was significantly reduced in MM cell lines expressing low levels of mutated PSMB6. Therefore: 1) PSMB5 depletion which is lethal to yeast, is surprisingly non-lethal to human MM cell lines; 2) In contrast deletion of PSMB6 or PSMB7 is lethal to human MM cell lines; 3) Expression of PSMB5, PSMB6 and PSMB7 proteins is highly co-dependent. 4) Loss of PSMB6 resulted in a loss of splicing of PSMB5, PSMB7, PSMB8 and PSMB10; 5) Expression of PSMB6 lacking either catalytic or splicing function restored viability and normalized splicing of PSMB5 and PSMB7; 6) With respect to BTZ sensitivity, PSMB5 mutation (Met104Val) found in cell lines confer resistance in MM cell lines which can be reversed by knockout of PSMB5. MM cells exhibiting either low level expression PSMB6 or PSMB6 lacking splicing function also restored sensitivity to BTZ. Together these findings demonstrate that reduction in cellular levels (as opposed to preventing catalytic activity) of PSMB5, PSMB6 or PSMB7 may be a new strategy in MM therapeutics including sensitizing MM cells to proteasome.

Keywords:
myeloma

proteasome

Proteasome Inhibitor

Tracks:
Multiple Myeloma Genomics

FP-038

CRISPR-based functional genomics landscape of genes recurrently mutated in MM

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Abstract:
Next generation sequencing studies have characterized the mutational landscape in multiple myeloma (MM) patients, but the functional relevance of most of these mutations has not been formally studied. We thus examined how genes recurrently mutated in MM patients perform in different CRISPR/Cas9-based functional studies (in the absence of any treatment) for gene editing (loss-of function [LOF]; 20 MM lines) or gene activation (gain-of-function [GOF]; 4 MM lines); genome-scale studies for resistance to different pharmacological or immune-based (e.g. NK cells) treatments; and focused studies on specific genes (sgRNA libraries or individual sgRNAs). In our CRISPR LOF studies, it was reassuring that, among the top 50 most recurrently mutated genes, several known or proposed oncogenic dependencies (e.g. KRAS, NRAS, PTPN11, PIK3CA, IRF4 or MAF) or tumor suppressors (TSGs, e.g. PTEN, TP53, and FAM46C) exhibited depletion or enrichment, respectively, of their sgRNAs. We identified though other genes, which were previously inferred computationally (based on their mutational patterns) to represent TSGs in MM or other neoplasias, but appear to be essential for MM cells (e.g. EP300, ARID1A, CREBBP) or have no major impact on survival/proliferation (e.g. SP140). We extended our evaluation to ~150 genes recurrently mutated in patients from MMRF CoMMpass study and 31 other publicly available studies (mostly in newly diagnosed MM): our CRISPR LOF studies identified genes with patterns of sgRNA depletion consistent

with core essential genes (e.g. SF3B1, ATR, POLE, and SETD2); broad-spectrum dependencies across MM and other cancers (e.g. KRAS, PTPN11 and USP7); and genes with preferentially essential role for MM compared to other neoplasias (e.g. IRF4, PRDM1, ARID1A, CREBBP, XBP1). CRISPR LOF of known/presumed TSGs (e.g. PTEN, TP53, FAM46C, CDKN2C, RASA2 or TRAF3) led to increased proliferation/survival in variable numbers of MM lines. Notably, though the large majority of recurrently, even if infrequently, mutated genes (e.g. FAT1, SP140 or EGR1, ATM, IDH1, IDH2, IKBKE) had CRISPR LOF results indicative of limited or no impact on in vitro survival/proliferation of all or nearly all MM lines tested. For these latter genes, we typically observed no significant change in MM cell survival/proliferation in genome-scale CRISPR activation studies in the absence of treatment; or NK cell sensitivity in vitro (genome-scale LOF or GOF studies). Our results provide insights into the functional role of genes recurrently mutated in MM and indicate that LOF or GOF for many, if not most, of these genes does not alter MM cell survival/proliferation or NK cell recognition in cell-autonomous conditions/ The roles, if any, of these genes and their mutations in MM pathophysiology merit studies in more complex systems e.g. addressing tumor-microenvironment interactions or combinational gene interactions.

Keywords:
CRISPR

Mutation

Tracks:
Multiple Myeloma Genomics

FP-039

Long-term Follow-up of Clonal Evolutions of Myeloma Cells in the Bone Marrow

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Abstract:
Introduction: Gene mutations in multiple myeloma (MM) are strongly predictive of clinical outcomes, and clonal evolutions occur during the course of treatment. In this study, we followed changes in mutations and acquisition of clonal evolution in myeloma cells. Methods: We followed 7 cases of newly diagnosed MM for an average of 8.4 years (range 2-17 years). Bone marrow samples were analyzed at initial diagnosis and at each disease progression. DNA was extracted using QIAGEN DNAeasy Blood and Tissue Kit from myeloma cells in bone marrow, sequenced for targeted genes, and the genomic data was analyzed. We will present changes in gene mutations along with their clinical course for each patient. Results: There were two cases related to TP53 mutation. One acquired TP53 mutation during a long treatment course, while it was present at diagnosis in the other. They were both resistant to various treatments including proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs) or a CD34 antibody, and had short clinical courses. Another 2 cases had multiple gene mutations such as DIS3, FAM46C, KDM6B and EGR1. These mutations, along with some gene translocations and deletions detected by FISH, could not be eliminated by multiple courses of treatment, and they had poor response to each treatment. One case showed a loss of mutation pattern. RB1 mutation was acquired after first treatment, which significantly decreased after the following treatment, however the patient was deceased within 3 months after losing RB1 mutation. We suspect the decrease in RB mutation might reflect the overall loss of RB genes. In the remaining 2 cases, no gene mutations associated with poor prognosis were detected, and both had good response to each treatment. They are currently still in good status, with one in partial remission

(PR) after 10 years, and the other in very good PR after 13 years of clinical courses. Conclusion: To our knowledge, this is the longest follow-up to date of the transition of gene mutations in myeloma patients. After acquiring mutations related to poor prognosis, such as TP53, even a combination regimen of PIs and IMiDs, or a daratumumab-containing regimen seemed unable to eliminate the mutations and prevent disease progression. Therefore, achieving as deep response as possible at an early stage, including Minimal Residual Disease (MRD)-negativity, is crucial for long-term survival.

Keywords:
clonal evolution

Mutation

TP53

Tracks:
Multiple Myeloma Genomics

FP-040

Rare, but complex chromosomal rearrangements, defined "Chromoanagenesis", caused by single-step or stepwise catastrophic genomic events, significantly impact on Multiple Myeloma patients

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Abstract:
BACKGROUND: Multiple Myeloma (MM) is a genetically complex disease, characterized by the recurrence of several chromosomal aberrations, which impair the disease prognosis. Besides these, the use of genome wide technologies has recently highlighted the existence of heterogeneous chaotic genomic events, generically defined "chromoanagenesis", including chromothripsis (caused by single-step genomic events) and stepwise events (consequence of multiple, small and sequential genomic events, occurring throughout subsequent cell cycles). The prognostic impact of chromoanagenesis has not been yet fully elucidated. AIMS of the present study were (1) to set up a reliable bioinformatic method, able to distinguish, characterize and dynamically define the different chromoanagenesis events (CEs), as observed in the genomic landscape of MM patients(pts) and (2) to correlate their presence to the disease prognosis. PATIENTS AND METHODS: 512 newly diagnosed MM pts have been included in the present study. Genomic data have been obtained by SNPs arrays as performed on BM CD138+ enriched cell fractions; data were analysed with Affymetrix's programs and R-scripts. RESULTS: An algorithm, able to characterize CEs, was set up and tested on genomic data of all pts. Criteria able to discriminate among the 2 different CEs were defined, by taking into account both previously reported guidelines for CEs identification and the MM-specific, highly heterogeneous genomic context. Overall, 77 pts (15%) were shown to carry at least one CEs: 49/77 (64%) and 28/77 (36%) carried either chromothripsis or stepwise events, respectively; both events were scattered across the whole genome, with any locus-specific bias. Pts with chromothripsis were more likely to carry both IgH translocations and TP53 deletion, whereas pts with progressive catastrophic events were mostly hyperdyploid and carried chr1q amp. The onset of CEs has been shown to impact on pts' progression-free and overall survival (PFS, OS), with HR of 1.322 (p=0.05) and 1.731 (p=0.002), respectively. In particular, the stepwise events had a greater impact on PFS (HR 1.61, p=0.034) and on OS (HR 2.063, p=0.006). Stepwise events maintain a significant predictive value, both in PFS and OS, in

a multivariate model including TP53 deletion, t(4;14) and ASCT. CONCLUSION: The occurrence of genomic catastrophic events significantly impact on both OS and PFS of MM pts. Despite the co-segregation with low/intermediate-risk genomic aberrations, stepwise events seem to have a more adverse prognostic impact on survival, as compared to chromothripsis. The use of genomic-wide technologies, coupled with specific bio-informatics tools, might help to more deeply dissect the role of these genomic events in myelomagenesis, as well as in the disease progression. Acknowledgements: AIRC IG 2018_22059, BolognAIL, RF-2016-02362532

Keywords:
Bioinformatics

Chromoanagenesis

prognostic factors

Tracks:
Multiple Myeloma Genomics

FP-041

DNA-repair gene mutations are prevalent in circulating tumour DNA from advanced multiple myeloma patients

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Abstract:
Background: Mutational characterisation is described in newly diagnosed (ND) multiple myeloma (MM) but remains largely elusive for relapsed/refractory (RR) patients. Current practice for mutational characterisation is via analysis of DNA from single-site bone marrow (BM) biopsies, which is confounded by the known inter and intra-clonal spatial heterogeneity of the tumour(s). An alternative and more comprehensive approach is through the analysis of circulating cell-free (cf) tumour DNA (ctDNA) derived from the plasma (PL). In this study, MM mutational characterisation was performed on BM MM cell DNA and PL-derived ctDNA from both ND and RR patients to investigate if predominant mutations in the advanced tumour genome can be identified through PL ctDNA analysis. Methods: Paired BM and peripheral blood PL from 76 patients (ND = 24; RR = 52) was processed to extract BM MM cell DNA (CD138 selected) and cfDNA containing ctDNA and evaluated for mutations in KRAS, NRAS, BRAF and TP53 using the 96-mutation OnTargetTM Mutation Detection (OMD) platform. Correlations between progression-free (PFS) and overall survival (OS) and the number and type of mutations and the tumour burden (expressed as the fractional abundance [FA] - defined as the relative frequency of a mutant allele at a particular locus and expressed as a percentage) were evaluated. Results from this platform were then validated utilizing customized targeted amplicon sequencing (TAS) of 36 paired BM and PL samples (ND = 5; RR = 31) for RAS-RAF (KRAS, NRAS and BRAF) and DNA damage-repair genes (DDR) (TP53, ATM and ATR). All statistical analyses were performed with GraphPad Prism V7. Results: OMD analysis revealed that RRMM patients had significantly more mutations in the PL than NDMM patients (mean 0.94 vs 0.19, respectively, p=0.0002) with 36.5% of RRMM patients harbouring PL-specific (not detected in BM) mutations compared to only 8.3% of NDMM patients. Patients with >2 mutations or a >1% FA in the PL had significantly shorter OS (p=0.04 and p=0.0006, respectively). Patients with PL-specific TP53 mutations had significantly shorter OS compared to patients with no PL-TP53 mutations (p=0.003), with no difference in patients with or without PL-specific KRAS mutations. Comprehensive TAS confirmed the presence of PL-exclusive variants in 33/36 (91.7%) of patients, recapitulating the findings of the OMD platform. DDR mutations were present at significantly higher levels in the PL when compared to RAS-RAF

mutations (p=0.0095) with 16% of the patients demonstrating PL-specific DDR mutations but only 2.5% of patients with PL-specific RAS-RAF mutations Conclusion: ctDNA analysis captures the spatial heterogeneity and provides important prognostic information in advanced MM, and identifies more potentially actionable DDR mutated sub-clones compared to BM analysis. This confirms the potential of ctDNA analysis for the genetic characteristation of MM patients at both presentation and relapse.

Keywords:
circulating cell-free DNA

DNA REPAIR

prognostic impact

Tracks:
Multiple Myeloma Genomics

FP-042

A COMPREHENSIVE SERUM MICRORNA PROFILING IN INDIAN MULTIPLE MYELOMA PATIENTS UNIFORMLY TREATED WITH VCD-PROTOCOL

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Abstract:

Background & Introduction: Inadequate clinical response is a major cause of the poor clinical outcome in multiple myeloma (MM). Although many biomarkers are available for risk-stratification of MM, no markers are available that can reliably predict therapeutic response. Many studies have reported selective miRNA dysregulation at different stages of plasma-cell-neoplasms (MGUS to MM), and their association with high-risk MM. We have studied a comprehensive serum miRNA profiling in Indian MM patients treated with VCD-protocol to explore their clinical relevance in the prediction of initial response. Methods: Serum microRNA-profiling was performed in a discovery cohort of newly diagnosed MM patients and four age-matched healthy controls. Affymetrix® miRNA 4.1 24-Array platform was used for expression profiling and data was analyzed using GeneSpring. Results: Our study included 20 newly diagnosed MM patients (10 males and ten females) with age-range 35-75 years. A comprehensive miRNA-profiling revealed 13 miRNAs were differentially expressed between MM patients and healthy controls. Among these, ten miRNAs were significantly down-regulated, and three were up-regulated, with p-values<0.05. Down-regulated miRNAs include let-7a-5p, miR-23a-3p, miR-150-5p, miR-320a, miR-342-3p, miR-320b, miR-320c, miR-320d, miR-4467 and miR-4485. Up-regulated miRNAs are miR-1281, miR-4440, miR-4801. Expression pattern of these 13 miRNAs divided MM patients into two clusters. However, the cohort of 20 was too small for any statistical correlation with the initial response. Hence, miRNA profiling is being performed in an additional 65 newly diagnosed MM patients. Conclusion: Our results revealed dysregulation of a new set of microRNAs as compared to reports published in western studies. It may be due to the ethnic variation of Indian patients from the western population. To validate our finding, we are studying the expression of these in an additional 65 MM patient serum samples, and the results of the same will be presented in the meeting.

Keywords:
Biomarker

Expression pattern

microRNA

Tracks:
Multiple Myeloma Genomics

FP-043

ABL kinase inhibitor increases cytotoxicity of chemotherapeutic agents while reducing/inhibiting genomic instability in multiple myeloma

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Abstract:
One of the major problems in Multiple myeloma (MM) treatment is the genomic instability or adaptability of the tumor cells which contributes to their continual survival and progression to advanced stages of the disease including development of drug resistance. A number of factors such as inherent or acquired genomic and epigenomic changes, microenvironment and treatment itself could contribute to genomic instability and clonal evolution. Importantly, most chemotherapeutics are DNA damaging agents which may increase genomic instability in surviving myeloma cells making them evolve at even a greater rate. Data from our laboratory show that homologous recombination (HR) is dysregulated in myeloma and contributes to genomic instability and development of drug resistance. We now report that ABL kinase plays an important role in HR and an ABL kinase inhibitor such as nilotinib can reduce HR activity in myeloma. Moreover, treatment of MM cells with nilotinib inhibited spontaneous DNA breaks and genomic instability, whereas increased their sensitivity to melphalan. We have further confirmed this in additional MM cell lines and show that treatment with nilotinib sensitizes MM cells to melphalan treatment with a high combination index. Flow cytometry based annexin/PI staining demonstrated that treatment of MM.1S cells with nilotinib, melphalan and combination of both drugs was associated with apoptosis in ~ 12%, 25% and 40% of cells, respectively, indicating that nilotinib increases melphalan-induced apoptosis in MM cells. A notable increase in melphalan-induced apoptosis in MM cells was detected by Western blotting and also confirmed by increase in PARP cleavage (> 3-fold). Importantly, the treatment with nilotinib could also significantly resensitize primary patient MM cells from relapsed MM patients to melphalan treatment. To confirm these observations in an animal model, we have now evaluated the impact of nilotinib, melphalan and their combination in a murine xenograft model of human MM. Two weeks after treatment, both nilotinib and melphalan had similar effects as single agent while combination had synergistic activity; (tumor volumes increased in vehicle control, nilotinib, melphalan and combination group by 6-fold, 3-fold, 2.8-fold and 1.2-fold, respectively; $P \leq 0.02$). The combination treatment demonstrated ability of nilotinib to increase cytotoxicity of melphalan in vivo. The tumors were removed and evaluated for HR activity in the lysates using a functional assay. Consistent with in vitro data, melphalan treatment was associated with a significant increase in HR activity, whereas nilotinib significantly inhibited both the endogenous and melphalan-induced HR activities in vivo. These data suggest that nilotinib has potential to increase cytotoxicity of chemotherapeutic agents such as melphalan while reducing/inhibiting genomic instability in multiple myeloma in vivo.

Keywords:
Chemotherapy

Genomic instability

Tracks:
Multiple Myeloma Genomics

FP-044

Large deletions (>10.9 MB) in 17p and bi-allelic TP53 inactivation events in newly-diagnosed multiple myeloma are associated

with higher clonal cell fraction and poor prognosis

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Abstract:
Deletions in Chromosome 17p (del17p) are associated with poor outcome in Multiple Myeloma (MM). We compiled a cohort of 139 whole-exome and whole-genome sequenced del17p newly diagnosed patient tumors and correlated the size of the deletion, as calculated by controlFreec, against progression-free and overall survival. Large (> 10.9MB) deletions in chromosome 17p that included TP53 region were significantly associated with poorer overall survival (mOS = 28.8 months vs. mOS = 45.0 months, pval= 0.047). Further, patients with large del17p deletions were more likely to be bi-allelic TP53 with high clonal cell fraction (CCF) for deletion of TP53 ($p < 0.05$). We identified a gene expression signature composed of genes in the 17p region that were associated with high CCF and large TP53 deletions. Compared to low CCF tumors, gene expression pathways uniquely downregulated to large-deletion 17p tumors included mitotic checkpoint ($p < 0.05$) and spindle formation ($p < 0.05$) pathways. This analysis suggests that biallelic inactivation or large TP53 deletion are involved in early events associated with myelomagenesis and in-part drive high-risk phenotype. Further clinical data validation in relapsed setting and experimental validation of TP53-driven pathways and targets in isogenic CRISPR and KD models are ongoing and results from these analyses will be presented.

Keywords:
Genetic profiling

genomic architecture

Overall survival

Tracks:
Multiple Myeloma Genomics

FP-045

Enrichment for copy number alterations and a unique pattern of gene mutations characterize multiple myeloma in elderly patients

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Abstract:
An ever improving understanding of the heterogeneity of multiple myeloma (MM) in older populations supports frailty-adapted therapy as an evolving treatment approach. A deeper understanding of the mutations and sub-chromosomal alterations that underlie MM in elderly patients has the potential to generate more precise management strategies. To this end, we analyzed data collected as part of the Myeloma Genome Project (MGP) (n = 1273, mean age = 65) utilizing next generation sequencing to evaluate single nucleotide variants (SNV), copy number alterations (CNAs), and mutational signatures. The incidence of specific alterations in the population diagnosed older than age 75 (elderly patients, n = 232, mean age = 80 yrs) was compared with those diagnosed at age ≤ 74 (n = 1041, mean age = 62 yrs) as well as a younger

subgroup of patients diagnosed at age ≤ 65 (n = 632, mean age = 57 yrs). When compared to all patients presenting at age ≤ 74 yrs, a significantly greater proportion of elderly patients harbored SNVs or indels in DIS3 (14.2% vs 8.7%, p = 0.005), HIST1H1E (5.6% vs 3.3%, p = 0.044), and IRF4 (5.6% vs 2.4%, p = 0.005). Elderly patients exhibited fewer SNVs and indels in CDKN1B (0% vs 1.3%, p = 0.038), FAM46C (6.5% vs 9.7%, p = 0.043), HUWE1 (1.7% vs 6.1%, p = 0.004) and SP140 (0.4% vs 2.9%, p = 0.014). The elderly patient population was found to have proportionally more copy number gains in 1q21: CKS1B (47.4% vs 40.7%, p = 0.031), 5q23: TNFAIP8 (58.2% vs 50.0%, p = 0.012), 5p15: ADCY2 (58.2% vs 50.4%, p =0.016), 6p21: TNXB (39.2% vs 31.4%, p= 0.011), and 17q22: AKAP1 (30.2% vs 23.9%, p = 0.035) along with copy number losses in 16q: CYLD (38.8% vs 32.6%, p = 0.035), 6q25: PARK2 (40.5% vs 33.9% p = 0.028) and 2p23: DNMT3A (28.4% vs 23.0% p = 0.038). At the sub-chromosomal level, a greater proportion of elderly patients exhibited MYC tandem duplications (9.0% vs 5.6%, p = 0.032) while fewer elderly patients harbored MYC translocations (26.2% vs 19.3%, p = 0.015). Finally, when compared to patients presenting before the age of 65, elderly patients exhibited relatively fewer t(4;14) translocations (9.1% vs 14.4%, p = 0.019). There was no difference in homologous DNA repair gene alterations, amplification 1q21, t(11;14), t(6;14), del(17p) or the presence of the APOBEC mutational signature between any of the age-based subgroups in this cohort. These results serve to provide an initial description of the genetic alterations that characterize multiple myeloma clones and potentially determine disease phenotype in the elderly. The findings of this study suggest that, in this population, these aberrant clones may be driven relatively more frequently by acquired copy number alterations occurring over a period of long disease latency. These results may open avenues of investigation into the integration of genetic data and frailty-adaptive risk models to aid in treatment and prognostication of multiple myeloma that presents late in life.

Keywords:
Elderly patients

gene mutation

Next Generation Sequencing

Tracks:
Multiple Myeloma Genomics

FP-046

IgH translocations with undefined partners are associated with superior outcome in multiple myeloma patients

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Abstract:
Background: Multiple myeloma (MM) is a genetically complex and heterogeneous disease with multiple genomic events associated with tumor development and progression.Chromosomal translocations into the immunoglobulin heavy-chain

(IgH) locus on 14q32 are the main primary events, occurring in about 50% of total MM cases.Currently, there are five main chromosomal translocation partners involving with immunoglobulin heavy-chain (IgH), including t(4;14), t(6;14), t(11;14), t(14;16) and t(14;20). However, IgH translocation with undefined partner genes can still be found in 15% of all newly-diagnosed MM (NDMM) patient, and little is known about their survival. Methods: A prospective non-randomized clinical study (BDH 2008/02) was conducted at a single center, with a total of 715 NDMM patients included. The median follow-up time was 45.3 (42.13-48.47) months. Sorted plasma cells(by anti-CD138-coated magnetic beads) were analyzed for del(13q14), del(17p), gains of 1q21, IgH split, t(11;14), t(4;14), t(14;16), t(14;20) and t(6;14). K-M curves for PFS and OS were plotted; univariate analysis and cox proportional hazards model were conducted. Results: There was about 13.6% patients translocation t(14; undefined) positive. Translocations t(4;14) and t(14;16) were classified into one high-risk group according to IMWG risk stratification. Translocation t(14;20)(0.9%, 3/322) and t(6;14)(0.8%, 2/228) were assigned to the t(14; undefined) group due to their low incidence. Therefore, the whole cohort (n=715) was divided into four groups: no IgH group (47.7%, 341/715); t(14; undefined) group (13.6%, 97/715); t(11;14) group (17.6%, 126/715); and t(4;14) or t(14;16) group (21.1%, 151/715). The median overall survival (OS) for the four groups was 84.2 [95% confidence interval (CI), 69.7-98.7] months, not reached (NR), 58.7 (95% CI, 41.9-75.5) months, and 44.2 (95% CI, 34.1-54.3) months, respectively, with p values for the t(14; undefined) group compared with no IgH, t(11;14), and t(4;14)/t(14;16) groups of 0.197, 0.022 and 0.001, respectively. In patients receiving bortezomib-based therapies, the survival prolongation in the no IgH and t(14;undefined) groups was more significant compared with the t(11;14) and t(4;14)/t(14;16) groups. Importantly, in multivariate analysis, translocation t(14;undefined) was an independent predictive factor for OS of MM patients (HR=0.51, 95% CI 0.30-0.85, p=0.01). Collectively, our findings indicated the favorable outcome of NDMM in the t(14; undefined) and no IgH groups compared to the t(11;14) and t(4;14)/t(14;16) groups. Conclusion: In summary, our data confirmed the favorable prognosis of the t(14; undefined) and no IgH groups, especially in the era of novel agents. Most importantly, translocation t(14; undefined) was identified as an independent protective factor for prolonged OS in multivariate analysis.

Keywords:
cytogenetic abnormality

myeloma

survival

Tracks:
Multiple Myeloma Genomics

FP-047

Multiple high-risk cytogenetic aberrations confer a progressively negative impact on survivals of newly diagnosed myeloma patients

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Abstract:
Background:Cytogenetic aberration detected by fluorescence in situ hybridization is one of the most important prognostic factors for multiple myeloma (MM). Identifying patients with high risk aberrations (HRA) is critical for initial risk stratification as well as follow-up treatment. Although specific HRA has been well discussed, cumulative impact of multiple HRA is still unclear. Methods:In our prospective non-randomized clinical study (BDH 2008/02) study, 573 cases of NDMM with a comprehensive FISH panel were evaluated. Results:In multivariate analysis, we found that, of all these parameters, age≥65 years old (HR=1.64, 95% CI 1.19-2.28, p=0.003), LDH level ≥220 U/L (HR=1.58, 95% CI 1.07-2.32, p=0.02), ISS 3 stage (HR=1.59, 95% CI 1.13-2.26, p=0.009), del(17p) (HR=1.68, 95% CI 1.03-2.73, p=0.036), amp(1q21) (HR=1.72, 95% CI 1.26-2.34, p=0.001), and adverse IgH translocation (t(4;14) or t(14;16)) (HR=1.65, 95% CI 1.17-2.34, p=0.005) were statistically independent prognostic factors for shortened OS; while taking autologous stem cell transplant (ASCT) (HR=0.37, 95% CI 0.22-0.63, p=0.000) profoundly prolonged OS for patients.Accordingly, HRA was defined by the presence of t(4;14), t(14;16), 1q21 gain or del(17p). For all 573 cases, number of patients harboring 0-3 HRA were 236(41.2%), 236(41.2%), 94(16.4%) and 7(1.2%), respectively. When occurred in isolation, every HRA conferred a similar and modulate impact on OS [for del(17p), amp(1q21), and t(4;14)/ t(14;16), overall survival (OS) was 50.1, 63.9 and 64.3 months, respectively, with p value across three subgroup of 0.33]. OS of patients with 0-3 HRA was NR (Not Reached), 62.1, 38.8, and 22.9 months, respectively (with p value across three subgroup of 0.000). A clear progressive association between the accumulation of HRA and impairment of survival was observed. In risk stratification analysis by age, serum LDH level, DS stage, ISS stage, induction therapy and transplantation, the cumulative cytogenetic model remained its prognostic value in differentiating patients into three risk group: low-risk group was defined as patients with 0 HRA; intermediate-risk group was defined as patients with 1 HRA; and patients with ≥2 HRA was assigned to the high-risk group. Specifically, ASCT remarkably improved survival of patients across different groups, especially those with one or more HRA. Conclusion:Taken together, our study showed that while isolated adverse IgH (t(4;14) or t(14;16)), del(17p) and 1q21 gain carried similar negative impact on survival, concurrent multiple HRA progressively impaired overall survival of MM patients. Patients with two or more HRA were considered as high-risk group, and transplantation may attenuate their negative prognosis

Keywords:
cytogenetic abnormality

myeloma

survival

Tracks:
Multiple Myeloma Genomics

FP-048

The mutational landscape underlying carfilzomib and pomalidomide resistance in relapsed /refractory multiple myeloma

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Abstract:
Introduction: The 2nd-generation proteasome inhibitor carfilzomib (CFZ) and the 3rd-generation immunomodulatory drug pomalidomide (POM) are potent, yet not curative treatment options in relapsed/refractory multiple myeloma (rrMM). In order to better understand mechanisms underlying drug resistance in rrMM, we have compared the clonal structure before exposure of rrMM patients to

one of these drugs and at disease progression. Methods: We studied 16 pairs of bone marrow samples collected before treatment (T1) and at disease progression (T2). The median number of prior therapy lines was 4 (range: 2-9). 7 rrMM patients were treated with CFZ, and 9 with POM containing regimens. CD138-purified plasma cells were studied by whole genome sequencing (WGS, median coverage of 80X). To identify sub-clones, we calculated the cancer clonal fraction for each variant, taking both sample purity and local CNV into account. Results: The median time to progression was 4 months. Stable disease was seen in 2 patients, while 5 and 8 patients achieved minimal and partial response, respectively. 11 of 16 patients had at least one established high-risk copy number aberration or structural variant (t(4;14), gain1q, del17p) at T1. 2 patients acquired a del17p and one presented with a new gain1q21 at T2. Stable clonal evolution was seen in 2 patients, new minor sub-clones emerged in 10 patients, and 4 patients presented with a new dominant clone at T2. Of note, 2 of the latter patients had stable disease or minimal response, indicating that major changes in the clonal architecture can occur despite poor responses. In general, we observed a higher average number of somatic variants and somatic functional variants at T2 (10734 vs. 9855, and 100 vs. 83, respectively). In the CFZ group, 14 genes were recurrently mutated at T2 only, including KRAS, SMC5 and genes involved in ion/calcium transport, such as NF2, RYR3, and TCHH. Furthermore, we saw expansion of clones with mutations in the driver genes NRAS, KRAS, FGFR3, or ARID2 during CFZ treatment. In the POM group, newly acquired mutations included FAM46C and TP53, MKNK2 (interacting with ubiquitin ligase E3 complex), as well as XIRP2, DMXL1, KIF5C, LRRN4 and PDXDC1 with unknown roles in MM. Selection was seen for clones with mutations in NRAS and TP53, the epigenetic modifiers KAT6A, and BAP1, and NOTCH3. Recent studies have shown the strong negative clinical impact of biallelic inactivation events affecting tumor suppressor genes. At T1, we found 5 biallelic events in 4 patients, with RB1 being the most frequently affected gene (n=3). At T2 the number increased to 9 events in 7 patients. Newly acquired events included RB1, TP53, FAM46C and CYLD (n=1, each). Conclusion: Using WGS on paired samples, we illustrate the importance of biallelic events in CFZ/POM-treated patients, the expansion of RAS driven subpopulations, and identified novel candidate mutations for resistance that represent potential new drug targets in MM.

Keywords:
carfilzomib

Pomalidomide

Whole genome sequencing

Tracks:
Multiple Myeloma Genomics

FP-049

Feasibility study to establish diagnostic biomarkers for relapsed refractory multiple myeloma

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Abstract:
While the advent of novel agents has improved the outcome for patients with multiple myeloma (MM), MM remains an incurable disease. Patients with high-risk features still have poor outcomes and management of relapsed/refractory (RR) cases remains challenging. RRMM cases require prompt diagnosis and suitable treatment depending on disease characteristics. However, diagnosis is not

easy and requires multidisciplinary approach, which may result in delayed treatment. To address this issue, we carried out a multicentre study to identify diagnostic biomarkers for relapsed refractory multiple myeloma (RRMM) in patients treated with lenalidomide-based regimens. We designed a RRMM specific custom panel of 22 genes (ATM, BIRC2, BRAF, CARD11, CCND1, CRBN, CUL4B, CYLD, DIS3, EGFR, FAM46C, FGFR3, IL6ST, IRF4, KRAS, NFKB2, NRAS, RASA2, SP140, STAT3, TP53, and TRAF3) and performed next-generation sequencing (NGS) analysis in 4 patients. MM cells were purified from the patient's bone marrow cells by sorting CD138 positive fraction, and DNA was extracted from the collected MM cells. Tumor DNA was subjected to NGS analysis with matched control DNA from the buccal mucosa. To date, 17 patients (DRd (N=16), VRd (N=1)) are enrolled. Bone marrow and buccal mucosa was obtained from the patients. As a result, 4 possible driver mutations including NRAS-Q61K, a known oncogenic mutation was found in 2 cases. We are planning to analyze 20 cases in total, and determine whether the circulating cell-free DNA (cfDNA) in the patient's peripheral blood plasma carries the same mutations. Moreover, we will validate the potential of cfDNA as a diagnostic biomarker in RRMM using digital droplet PCR.

Keywords:
Lenalidomide

NGS

RRMM

Tracks:
Multiple Myeloma Genomics

FP-050

CD24 Is a Phenotypic Marker and a Potential Therapeutic Target for Multiple Myeloma Tumor-Initiating Cells

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Abstract:
Background Treatment failure in cancers, including multiple myeloma (MM) are mostly likely due to the persistence of a minor population of tumor initiating cells (TICs), which are non-cycling or low-cycling and very drug-resistant tumor cells. In this study, we have identified that the cell surface antigen CD24 as a TIC biomarker in MM. Methods We examined self-renewal potential by clonogenicity and drug resistance of CD138+ CD24+ sorted cells. To confirm the presence of MM CD24+ subpopulation we analyzed 60 patients' samples by flow cytometry using the panel of plasma cell markers (CD138, CD38, k+ or λ+ light chain, and CD56), and B cell markers (CD45, CD19), as well as the CD24 antibody. We analyzed CD24 expression in 84 newly diagnosed MM patients using immunohistochemistry with CD138 and CD24 antibodies. Transcriptional factor activation assay and gene expression profiles were performed on CD24+ and CD24– MM cells. Results We have identified that the cell surface protein CD24 is a TIC biomarker in MM. CD24+ MM cells show increased clonogenicity, drug resistance, and tumorigenicity as few as 10 CD24+ MM cells were required to develop plasmacytomas in mice. In complete remission (CR) MM patients with minimal residual disease (MRD), CD24+ MM cells were enriched after chemotherapy thus exhibiting increased drug resistance. The induced pluripotent or embryonic stem cell genes, such as NANOG, OCT4, KLF4, and SOX2, were significantly upregulated in CD24+ MM cells. We also discovered that nucleosomal remodeling by pioneer transcription factors facilitates STAT3 to mediate TIC features in MM. Targeting of CD24+ MM cells prevented tumor progression in vivo. Conclusion The studies presented here demonstrate that CD24 maintains the feature of self-renewal and drug resistance in MM. Improved understanding of myeloma tumor-initiating cell biology will lead to the development of novel therapeutic targets and drugs that will be tested pre-clinically and in the clinic. The evidence from clinical trials and correlative studies should also provide valuable information about how

inhibition of TIC cells leads to improvement in long-term clinical outcome.

Keywords:
Biomarker

therapy-related

Tumor-Initiating

Tracks:
Multiple Myeloma Genomics

MULTIPLE MYELOMA MICROENVIRONMENT

FP-051

Modeling tumor microenvironment interactions of IMID sensitive and resistant cells in 3D organotypic culture models

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Abstract:
Organotypic culture models developed using 3D conditions recapitulate tissue-specific structural features and cell-cell interactions more accurately than conventional 2D cultures. Our goal is to optimize culture conditions which promote the survival and proliferation of multiple myeloma (MM) cells and could serve as a platform for molecular mechanistic, clinical biomarker and pharmacodynamic marker studies using immune-modulatory compounds (IMIDs) and other myeloma drugs alone and in combination. Using gas permeable microfluidic devices (MFDs), we cultured and compared growth/morphologic properties of six multiple myeloma cell lines, MM1.S, MM1.SPR, H929, H929PR, H929-220R and RPMI-8226 in 2D and 3D conditions. Pomalidomide and CC-220 resistant cell lines were originally developed in our group by culturing them with increasing concentrations of these drugs. Morphologically, cells grown in 3D conditions appeared to have higher tendency of forming spheroids. Cell lines grown in 3D conditions demonstrated higher proliferation index compared to 2D conditions. To further study the effects of other components of MM tumor micro-environment on Pomalidomide response, we optimized the culture conditions to co-culture MM cell lines with bone marrow stromal cells. The co-culture of bone marrow stromal cells, HS5 with MM cell line H929 protected Ikaros degradation induced by Pomalidomide. Interestingly, CD44 expression in H929 cells was upregulated in co-culture conditions with stromal cells. We then utilized these optimized 3D and 3D-stromal-media culture conditions to culture primary bone marrow bone nuclear cells (BMMCs) from MM patients. Our initial experiments demonstrate higher survival and proliferation of BMMCs cultured under 3D conditions in the MFD with maintained expression of oncogenic receptors, CD138 and CD38. These culture conditions are currently being optimized to study the (1) drug effects in MM and immune cells alone and in combination and (2) long term growth of primary Myeloma cells in these conditions for ex vivo manipulation and downstream molecular and biological effects.

Keywords:
immunomodulatory drugs

organotypic models

proliferation

Tracks:
Multiple Myeloma Microenvironment

FP-052

A Hematopoietic Score Predicts Survival in Newly Diagnosed Multiple Myeloma Patients.

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Institutions:
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Abstract:
Introduction: Risk stratification of multiple myeloma (MM) at diagnosis allows prognostication and drives therapeutic decisions and currently the International staging system (ISS) and the Revised International staging system (RISS) are routinely utilized. Increased red blood cell distribution width (RDW), anemia, and thrombocytopenia have been shown to predict worse progression-free (PFS) and overall survival (OS). We hypothesized that the hematopoietic indices including mean corpuscular volume (MCV), hemoglobin (Hgb), and platelet (Plt) count may reflect the impact of the tumor cells on the marrow microenvironment and examined its ability to predict outcomes of patients with MM. Methods: This was a retrospective study of patients with newly diagnosed MM seen at Mayo Clinic between January 2004 and April 2018. We evaluated the prognostic impact of the hematopoietic indices of Hgb, Plt count and MCV. Based on multivariate analysis, we incorporated three commonly available variables using cutoffs that have been previously explored (Hgb<10, Plt<150), and MCV>96, assigning a score of 1 to each. Patients were categorized into four groups based on the total score. Results: We identified 1633 newly diagnosed MM patients, of whom 462 (28%) had an MCV >96 fl, 521 (32%) had Hgb<10, and 286 (18%) had Plt<150. Overall, 707 (46%) had a score of 0, 513 (33%) had a score of 1, 260 (17%) had a score of 2, and 60 (4%) had a score of 3. Anemia with a Hgb<10 was predictive for PFS and OS (median PFS 22.5 months for Hb<10 vs 30.4 months for Hgb≥10, P<0.0001; median OS 50 months for Hgb<10 vs 76.4 months for Hgb ≥10, P<0.0001). Thrombocytopenia (plt<150) predicted PFS and OS (median PFS 20.1 months for Plt<150 vs 29.9 months for Plt ≥150, P<0.0001; median OS 42.4 months for Plt<150 vs. 70.5 for Plt ≥150, P<0.0001). Macrocytosis (MCV>96) was predictive for OS (55.9 months for MCV >96 vs 71.3 months for MCV≤96, P=0.0003). The overall score risk stratified patients into four groups with differing survival (median PFS was 32.3 months for score 0, 24.8 months for score 1, 21.7 months for score 2, and 18.3 months for score 3, P<0.0001; median OS was 80.7 months for score 0, 59.9 months for score 1, 51.7 months for score 2, and 31.3 months for score 3, P<0.0001). On the multivariable analysis, predictors for PFS were age ≥65 (RR,1.31; P=0.0012), RISS stage (1-2 vs 3) (RR, 0.48; P<0.0001), and >50% plasma cells in the bone marrow (RR,1.23;P=0.01). Predictors of OS on the multivariable analysis were age ≥65 (RR,1.93; P<0.0001), RISS stage (1-2 vs 3) (RR, 0.48; P<0.0001), and hematopoietic score (0-2 vs 3)(RR,0.51; P=0.0028). Conclusion: Hematopoietic parameters available on a complete blood count can be incorporated in to a scoring system that predicts survival in patients with newly diagnosed myeloma. This is likely to reflect alterations in the bone marrow microenvironment of patients with myeloma that reflects the aggressiveness of the disease.

Keywords:
Bone marrow microenvironment

Hematopoiesis

Multiple myeloma prognosis

Tracks:
Multiple Myeloma Microenvironment

FP-053

Bone marrow Ki67 staining is prognostic for survival in newly diagnosed multiple myeloma

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Institutions:
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Abstract:
Background: Revised International Staging System combines beta-2 microglobulin, albumin, LDH, and high-risk FISH/cytogenetic features to provide prognostic information useful for stratification in multiple myeloma (MM). Ki-67 is a nuclear protein expressed by proliferating cells. The Ki-67 index has shown to impact the outcome in some types of lymphomas, but its prognostic value in MM is unclear. The aim of this study was to investigate the association of Ki-67 expression with survival outcomes in MM patients treated with novel therapies. Methods: We interrogated our plasma cell disorder database between 6/ 2012- 6/ 2018, for newly diagnosed MM patients with available information on Ki-67 expression (by IHC) on bone marrow biopsies. Clinical features and outcomes were compared between the two cohorts: Ki-67hi (Ki-67 expression >5%) and Ki-67lo (Ki-67 expression ≤5%). Continuous variables were compared using the median of two-sample tests, while incidences and proportions were compared using Fisher's exact tests. Survival distributions were estimated with Kaplan Meier techniques and compared between Ki-67 categories using the log-rank test. Differences in overall survival (OS) and progression-free survival (PFS) between the two cohorts were quantified with hazard ratios (HR) from Cox regression. Model selection was performed to determine adjusted hazard ratios. Results: We identified a total of 155 patients (42 Ki-67hi, 113 Ki-67lo). There were no significant differences in age, gender, beta-2 microglobulin, or LDH levels between the cohorts (p=0.165 and 0.175, respectively). Standard-risk and high-risk cytogenetics were similarly distributed except for enrichment of 1q gain/amplification in the Ki-67hi cohort (10.8% in Ki-67lo vs. 31.7% in Ki-67hi, p=0.005). Ki-67 expression was associated with both PFS and OS. At a median follow-up of 38.1 months, median PFS was 19.8 months in Ki-67hi cohort compared with 35.7 months in Ki-67lo, with an HR of 2.020 (95% CI: 1.261 – 3.237, p=0.003). Median OS was 42 months for Ki-67hi vs. not reached for Ki-67lo, with HR of 2.681 (95% CI: 1.432 – 5.019) and p=0.001. Additionally, after adjusting for age, the risk of death in the Ki67-hi cohort was 2.7 times that of the Ki67-lo cohort (95% CI: 1.379, 5.106; p = 0.004). Conclusions: Our results demonstrate that elevated Ki-67 expression (cutoff value of 5%) is an independent prognostic factor associated with worse PFS and OS in newly diagnosed MM. IHC staining for Ki67 can potentially be utilized in economically constrained healthcare settings globally.

Keywords:
prognostic factors

proliferation

survival

Tracks:
Multiple Myeloma Microenvironment

FP-054

Excessive abdominal fat content indicates poor prognosis in patients with newly diagnosed multiple myeloma

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Abstract:
Purpose: Obesity has been identified as a risk factor for developing multiple myeloma (MM). The various indexes of body fat composition make it difficult to assess the value of body fat composition in predicting disease activity, adverse events and treatment responses in MM patients. Methods: A total of 36 newly diagnosed MM (NDMM) patients, who underwent abdominal and pelvic computed

tomography (CT) before induction therapy, and 72 matched healthy people sorted from a database were included in this study. Total fat area (TFA), visceral fat area (VFA) and subcutaneous fat area (SFA) were measured from the last thoracic vertebrae (T12) to the sacrum (S1) and analyzed as six slices of vertebral interfaces, namely, T12/L1, L1/L2, L2/L3, L3/L4, L4/L5 and L5/S1, on CT images (cm2). We also examined the levels of adiponectin in 25 NDMM patients and 17 healthy people. Results: NDMM patients had larger TFA (L4/L5 and L5/S1), VFA (L4/L5 and L5/S1) and SFA (T12/L1, L1/L2, L2/L3, L4/L5 and L5/S1) than healthy people. Moreover, plasma adiponectin (1147.40 pg/ml vs. 2077.10 pg/ml, p=0.037) was significantly lower in NDMM patients than in healthy people. The percentage of bone marrow (BM) plasma cells was significantly inversely correlated with SAT at L2/L3 (p=0.018) but positively correlated with VFA/SFA (T12/L1, p=0.047; L2/L3, p=0.039). A significant inverse correlation was observed between the high-risk cytogenetic abnormality gain 1q21 (p=0.044) and VFA at L4/L5. SFA at L4/L5 (p=0.025) and VFA/SFA (L4/L5) (p=0.002) had a significant effect on treatment responses. Conclusions: NDMM patients had higher abdominal fat content but lower adipokine levels than healthy people. Excessive subcutaneous fat might be a predictive factor for high tumor burden and poor treatment response. Visceral fat content may be correlated with high-risk cytogenetic abnormalities. However, further investigation in larger samples is necessary to verify this association.

Keywords:
subcutaneous fat

treatment response

visceral fat

Tracks:
Multiple Myeloma Microenvironment

FP-055

IMMUNE PROFILING OF PLASMA CELL DYSCRASIAS REVEALS A THERAPY RELATED T-CELL MODULATION IN MULTIPLE MYELOMA PATIENTS.

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Abstract:
Multiple Myeloma (MM) is a hematological malignancy always preceded by a not malignant precursor state defined monoclonal gammopathy of undetermined significance (MGUS) and by a asymptomatic MM (smouldering MM, sMM). Immune dysfunction plays a key role in the pathogenesis of the disease, as demonstrated by the prognostic role of immunoparesis in the progression of MGUS and sMM into active MM (aMM). The aim of this study is to analyze the immune subsets distribution into plasma cells dyscrasias. A total amount of 895 bone marrow samples (170 MGUS, 188 sMM, 586 aMM) of 714 patients affected by plasma cells dyscrasias were studies at the different time point by flow cytometry for CD3, CD4, CD8, CD16, CD19, CD56, CD57, HLA-DR and Tgd antigens. In aMM cases, no differences were found in total T and NK cells percentages towards sMM (73.2±12.5 vs 72.4±10.3, p=0.6717 and 14.8±8.9 vs 14.1±7.9, p=0.5676) and MGUS cases (73.2±12.5 vs 71.9±9.0 p=0.3336 and 14.8±8.9 vs 13.3±7.3, p=0.1205) while CD19+ B cells were usually lower in aMM, even if statistically significant only towards MGUS (9.8±9.1 vs 10.7±5.9, p=0.2955 and 9.8±9.1 vs 12.3±7.1, p=0.001). A more detailed analysis of T cell subsets showed that aMM patients were also characterized by lower percentages of CD4+ T cells (32.9±12.9 vs 39.9±9.5, p=0.0001 and 32.91±12.9 vs 38.4±8.6, p=0.0001) and higher percentages of CD8+ cells (45.1±14.1 vs 38.8±10.0, p=0.0001 and 45.1±14.1 vs 38.7±9.9, p=0.0001), CD8+/DR+ cells

(9.7±13.1 vs 4.1±4.7, p=0.0001 and 9.7±13.1 vs 3.8±4.5, p=0.0001) and CD3+/CD57+ cells (18.9±12.7 vs 14.5±9.2, p=0.0001 and 18.9±12.7 vs 13.6±8.8, p=0.0001) while no differences were found in Tgd cells in the different groups (3.6±4.0 vs 4.2±3.6, p=0.2872 and 3.6±4.0 vs 4.2±3.2, p=0.2638). Interestingly, all these differences were mostly attributed to treated patients towards newly diagnosed MM (CD4+ cells= 27.0±12.1 vs 39.5±10.3, p<0.0001, CD8+ cells=50.5±14.6 vs 39.0±10.5, p<0.0001, CD8+/DR+ cells =14.1±15.8 vs 4.5±4.7, p<0.0001 and CD3+/CD57+ cells =21.7±13.5 vs 15.8±10.9, p<0.0001). In 60 treated patients, a bone marrow evaluation was performed within 3 months from autologous stem cell transplantation (ASCT). These cases displayed towards other treated patients higher percentage of CD8+ cells (59.3±13.8 vs 48.2±13.9, p<0.0001), CD8/DR+ cells (24.2±19.1 vs 10.8±13.1, p<0.0001) and CD3+/CD57+ cells (33.2±12.2 vs 18.6±12.1, p<0.0001) and lower percentages of CD4+ cells (16.6 ±7.7 vs 29.8±11.4, p<0.0001), NK cells (11.3±6.2 vs 16.4±10.0, p=0.0006) and Tgd cells (2.0±3.2 vs 4.4±5.6, p=0.0016). Our results demonstrated a profound T cell immune-modulation in aMM patients towards MGUS and sMM precursor states. Moreover, most of these changes are therapy-related and are the result of ASCT, indicating that myeloma treatment can shape the T cell compartment.

Keywords:
Multiple myeloma

T-Lymphocytes

treatment

Tracks:
Multiple Myeloma Microenvironment

FP-056

Macrophages promote DNA repair of double strand break in multiple myeloma cells by non-homologous end joining(NHEJ), nevertheless sacrifice the accuracy of NHEJ

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Abstract:
Multiple myeloma (MM) is a hematological malignancy of B cells, characterized by clonal proliferation of malignant plasma cells. DNA damage and genomic instability play an important role in the pathogenesis of MM. Based on the characteristics of high heterogeneity and genomic instability of MM, and the protective effect of MΦs on MM cells (MMCs), our study intended to further clarify whether MΦs affect MMCs DNA damage response and DNA repair, and the relationship between MΦs and genomic instability of MMCs. We found that the content of MΦs in bone marrow biopsy of MM patients is related to the results of cytogenetics. The higher the content of MΦs, the more complicated the cytogenetic abnormalities of patients. In our study, MΦs were harvested from peripheral blood monocytes, which were incubated for 7 days with M-CSF. The results showed that MΦs reduces the baseline γH2AX of MMCs, contributing to MMCs survive in the case of genomic instability. In the case of severe injury of MMCs' DNA, MΦs promote the DDR and DNA damage repair. We examined the effects of macrophages on HR and NHEJ using U2OS cells with HR/NHEJ reporter, and found that macrophages increased NHEJ but have no sense on total HR. Furthermore, we adopt paired gRNA-CRISPR/Cas9 system to detect NHEJ level in endogenous genes. The results showed that MΦs significantly promoted the NHEJ in MMCs both in vitro and in vivo, however reduced accuracy of NHEJ repair, and increased the length of base loss in NHEJ meanwhile promoted genomic instability of MMCs.

Keywords:
Genomic instability

Macrophage

Multiple myeloma

Tracks:
Multiple Myeloma Microenvironment

FP-057

Investigation of the relationship between obesity, weight cycling, and tumor progression in a myeloma xenograft model

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Obesity and obesogenic behaviors are positively associated with both monoclonal gammopathy of unknown significance and multiple myeloma (MM). As one of the only modifiable risk factors, this association has emerged as an optimal target for MM prevention, but little is known about the mechanistic relationship of weight patterns with MM disease progression. Preliminary data from epidemiologic studies suggest that repeated episodes of weight cycling (WC), resulting from intentional weight loss followed by unintentional weight gain, leads to increased risk of MM compared to weight-stable individuals. The SCID-Beige MM.1S xenograft model was used to investigate the physiologic effects of different body weight regulation patterns in vivo. We hypothesized that repeated episodes of diet-induced WC would increase MM proliferation. Male SCID-Beige mice (6 weeks of age) were fed control diet (CD; 10% kcal from fat), high fat diet (HFD; 60% kcal from fat), or weight cycling regimen (WC; CD for 4 weeks followed by HFD for 4 weeks) for 16 weeks. At this time mice were injected intravenously with 2 million MM.1S cells and the initial dietary regimen continued, with the exception that mice on the WC regimen transitioned between the CD and HFD every 2 weeks. Tumor burden was imaged and quantified weekly using in vivo bioluminescence imaging. Mouse weights and signs of hind-limb paralysis were monitored daily upon tumor engraftment and used to determine IACUC-approved survival endpoints. Maximal differences in body composition between mice on CD, HFD, and WC were observed at approximately 8 weeks of diet administration, whereas bone parameters exhibited the largest differences by the end of the 16-week regimen, as measured by PIXIMUS-DEXA. Modest weight cycling was observed as early as the first switch from HFD to LFD and was pronounced by the second cycle in the cycling cohort. A significant increase in tumor burden was observed in the HFD group compared to CD mice two weeks after MM-inoculation ($p<0.001$), suggesting a role for HFD in MM homing, engraftment and early expansion. No significant differences were observed in either HFD or WC in terms of survival when compared to mice on CD. A general trend for earlier MM-induced paralysis was observed in the HFD and WC cohorts, although these results were not significantly different from control mice. This trend in a small sample supports the conduct of future, more detailed studies to fully elucidate any potentially deleterious effects of HFD and WC on MM progression. Combined, these results suggest that HFD and WC may contribute to MM risk through changes in the bone marrow microenvironment (BMM) that affect MM cell homing, engraftment and early expansion. This study provides the first investigation of WC and MM in mice and lays the groundwork for the future characterization of the relationship between weight patterns, the BMM, and MM pathogenesis, which will help inform MM prevention messages.

Abstract:
Keywords:
Bone marrow microenvironment

myeloma

Obesity

Tracks:
Multiple Myeloma Microenvironment

FP-058

A New 'Vicious Cycle': Bidirectional Interactions Between Myeloma Cells and Adipocytes

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Abstract:
The bone marrow (BM) microenvironment allows for migration, growth, proliferation, and drug-resistant clonal evolution of multiple myeloma (MM) cells. BM adipocytes (BMAs) expand with aging and obesity, two key MM risk factors. BMAs are important contributors to systemic adipokine levels, bone health and hematopoiesis, and have also recently been implicated in acute myeloid leukemia. We investigated the interactions between MM cells and BMAs and found that adipocyte gene expression and cytokine secretion profiles are altered, creating a "MM-associated" adipocyte (MM-adipocyte) phenotype that is supportive of MM cell survival. We investigated interactions between MM cells and BMAs in vitro using microarrays and RNA-Sequencing (RNA-Seq), and in vivo with the SCID-Beige MM.1Sgfp+luc+ xenograft and C57/KaLwRij 5TGM1 models. Proximal femurs from naïve SCID-Beige mice contained significantly more BMAs than tumor-bearing mice, and similar results were observed in the 5TGM1 model ($p<0.001$). These findings mimic results observed in patients with MM or other types of BM-homing tumors, and suggest that tumor cells may induce delipidation, lipolysis, or dedifferentiation of BMAs. In vitro, murine adipocytes (3T3-L1, BMAs, and ear-derived MSC) showed significant reductions in lipid content ($p<0.0001$) and adipogenic gene expression (Adipoq, Fabp4, $p<0.001$) when co-cultured with MM cells via transwell. Pathway analysis of MM-3T3-L1 adipocyte microarray data indicated dysfunction of metabolic pathways. Increased basal ($p<0.05$) and non-mitochondrial respiration ($p<0.05$) coupled with increased levels of proton leak further suggested defects in bioenergetic function. In human patient-derived BMAs, MM-adipocytes exhibited decreased expression of adipogenic genes and elevated expression of genes encoding senescence associated secretory proteins (SASPs), including: SERPINB2 (204x), IL6 (175x), ICAM1 (33x), CXCL1 (58x), CXCL2 (39x) and VEGFA (5x), compared to normal BMAs as evidenced by RNA-Seq. The "senescent-like" phenotype was confirmed via cytokine arrays of conditioned media and increased β-galactosidase staining in adipocytes exposed to MM.1S cells via transwell ($p<0.001$). In co-cultures, 3 MM cell lines exhibited different gene expression profiles in response to BMAs. However, 6 genes were commonly upregulated (>2 fold change) in MM cells in the presence of BMAs, 3 of which have been implicated in glucocorticoid receptor signaling. These findings may partially explain increased dexamethasone resistance, which we observed in MM.1S cells co-cultured with BMAs, as measured via flow cytometry and bioluminescence quantification. In summary, we provide evidence that BMAs change in response to MM-BM infiltration and expansion in vivo. Interestingly, MM-adipocytes exhibit a "senescent-like" phenotype in vitro that may explain their support of MM cells. Interactions between BMAs and MM cells may have important implications in the understanding and treatment of myeloma.

Keywords:
Bone marrow adipocytes

Bone marrow microenvironment

Senescence

Tracks:
Multiple Myeloma Microenvironment

FP-059

PD-1 blockade reinvigorates bone marrow CD8+ T cells from patients with multiple myeloma in the presence of TGF-β inhibitors.

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Abstract:
Background: Immune checkpoint inhibitors have shown therapeutic efficacy in various malignant diseases. However, anti-programmed death (PD)-1 therapy has not shown clinical efficacy in multiple myeloma (MM). To enhance the clinical efficacy of immune checkpoint blockade in MM, elaborate characterization of tumor (myeloma) antigen-specific T cells is an essential prerequisite. In addition, the role of immunosuppressive factors abundant in the bone marrow (BM) of MM patients need to be considered. Patients and Methods: BM mononuclear cells were obtained from 77 newly diagnosed MM patients. We examined the expression of immune checkpoint receptors in BM CD8+ T cells and their functional restoration by ex vivo treatment with anti-PD-1 and TGF-β inhibitors. Results: We confirmed the upregulation of PD-1 and PD-L1 expression in CD8+ T cells and myeloma cells, respectively, from the BM of MM patients. PD-1-expressing CD8+ T cells from the BM of MM patients co-expressed other checkpoint inhibitory receptors and exhibited a terminally differentiated phenotype. These results were also observed in BM CD8+ T cells specific to myeloma antigens NY-ESO-1 and HM1.24. BM CD8+ T cells from MM patients exhibited reduced proliferation and cytokine production upon T-cell receptor stimulation. However, anti-PD-1 did not increase the proliferation of BM CD8+ T cells from MM patients, indicating that T-cell exhaustion in MM is hardly reversed by PD-1 blockade alone. Intriguingly, anti-PD-1 significantly increased the proliferation of BM CD8+ T cells from MM patients in the presence of inhibitors of TGF-β, which was overexpressed by malignant plasma cells. Conclusion: Our findings indicate that combined blockade of PD-1 and TGF-β may be useful for the treatment of MM.

Keywords:
Multiple myeloma

PD-1

TGF-β

Tracks:
Multiple Myeloma Microenvironment

FP-060

Targeting bone marrow adipose tissue and the FABP family increases efficacy of dexamethasone in MM

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Abstract:
It is well known that multiple myeloma (MM) cells have a dependency on the bone marrow (BM) microenvironment for survival and proliferation. Targeting stromal cells of the BM, rather than just the tumor cells themselves, can be useful for reducing tumor burden in mice and humans. Our lab has recently explored targeting the bone marrow adipocyte (BMA) due to correlations between obesity to increased risk of MM and increased BM adiposity. To test the effects of BMAs on MM1S in vivo, 5-week old SCID-beige female mice were treated with saline or an anti-sclerostin antibody (Scl-Ab, 100 mg/kg once per week IP) for 5 weeks (a treatment shown to increase bone volume and decrease BMAs). Then, 5x10^6 human

GFP+luc+MM1S cells were injected i.v. followed by 5 additional weeks of Scl-Ab or saline treatments. Mice were treated with or without dexamethasone (dex) (9mg/kg IP) during weeks 4-6 after MM1S injection. Mice were assessed with biweekly whole body bioluminescent imaging (BLI) and survival. Dex treatments led to a significantly lower total flux BLI signal ($p<0.05$ vs MM1S alone), and Scl-Ab+dex combination treatments had the least total flux BLI signal ($p<0.01$ vs MM1S alone) at day 33. Interestingly, Scl-Ab+dex combination treatments increased mouse survival significantly versus dex alone, Scl-Ab treatment alone, or no treatment. Thus, our in vivo data suggested that decreasing bone marrow adiposity enhanced anti-myeloma effects of dex. Next, to specifically examine the effects of BMAs on myeloma cells, we generated human BMAs from BM mesenchymal stem cells with adipogenic media. MM1S cells were cultured in conditioned media from BMAs (BMA-CM); BMA-CM from many, but not all donors, supported MM1S proliferation, migration, or drug resistance. Specifically, some BMAs protected MM1S cells against dex-induced apoptosis, assessed by Annexin V/DAPI flow cytometry and bioluminescence cell counting. Gene expression and protein data from MM1S cells treated with BMA-CM revealed a significant increase in fatty acid binding protein 4 (FABP4), a fatty acid shuttling molecule with broad signaling effects (pcr: $p<.01$, ELISA: $p<0.0001$). While unknown in MM, the FABP family has demonstrated pro-tumorigenic effects in other cancers. We used inhibitors of FABP4 (iFABP4), and its compensatory FABP5 family member, to study their effects on basal and dex-induced apoptosis, cell number, cell cycle and proliferation in MM1S cells. After 72 hours, FABP4i and FABP5i alone, and in combination, significantly decreased cell number and proliferation. In combination, FABP4i/FABP5i improved efficacy of dex. Decreases in MM1S cell number and proliferation, (assessed by BLI, Ki67 and cell cycle flow cytometry analyses) from FABP4i, FABP5i, or the FABP4i/FABP5i combination were attributed to increased sub G1/G0 population. Overall, targeting BMAT and FABPs may be novel approaches to inhibiting progression and decreasing the drug resistance properties of MM cells in the BM.

Keywords:
Adipocyte

Drug resistance

Fatty acid binding proteins

Tracks:
Multiple Myeloma Microenvironment

FP-061

Dynamic CD138 surface expression regulates switch between myeloma growth and dissemination in the bone marrow

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Abstract:
The canonical plasma cell marker CD138 (syndecan-1) is highly expressed on the myeloma cell surface, but its functional role in vivo is unclear, as well as the ontogeny of CD138-high and CD138-negative (neg) myeloma cells Using the murine Vk*MYC myeloma model we find CD138 expression is heterogeneous and varies with tumor burden. We find CD138-high subset of myeloma cells in the bone marrow is highly proliferative, less apoptotic, and enhanced IL-6R signaling, as compared to CD138-neg subset. Additionally, CD138-high myeloma engrafts better than its CD138-neg counterpart. In contrast we find that CD138-neg cells are more motile both in vitro and in vivo, and more readily disseminate and spread to other bones in vivo than CD138-high subset. Treating mice with anti-CD138 rapidly triggers migration of myeloma cells in vivo by intravital imaging, and leads to intravasation into the blood, which results in increased dissemination to other bones. Both murine and human myeloma cells can rapidly recycle CD138 surface expression through endocytic

trafficking, in response to serum levels. Blocking CD138 enhances myeloma sensitivity to bortezomib chemotherapy and significantly reduces tumor size compared to bortezomib treatment alone. Thus, our data show that CD138 surface expression dynamically regulates a switch between growth versus dissemination for myeloma, in response to nutrient conditions.

Keywords:
Bone marrow microenvironment

Imaging

immunotherapy

Tracks:
Multiple Myeloma Microenvironment

FP-062

TLR4 signaling drives mesenchymal stromal cells (MSC) commitment to promote tumor microenvironment transformation in multiple myeloma

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Abstract:

Background On the contrary of MGUS-MSC, MM-MSC promote cancer immune evasion through the activation of myeloid derived suppressor cells. Since it has been demonstrated that specific Toll-like receptors (TLR) can drive MSC activation status, including two distinct phenotypes defined MSC1 (TLR4-dependent) or MSC2 (TLR3-dependent), we evaluated the effect of TLR activation on MM-MSC Methods Healthy Peripheral blood mononucleated cells (PBMC) were cultured with MSC for 6 days; neutrophils were isolated and studied for their immunosuppressive activity. Immunocompetent adult Zebrafish was used as in vivo model for myeloma cells engraftment. Results We pre-treated HC-MSC with MM cell lines for 24h before co-culturing with PBMC. PC pre-treatment drove HC-MSC to activate neutrophils in immunosuppressive cells. We further analyzed the two downstream of TLR4 and TLR3 pathways, NFκB and IRF3 in HC-MSC after co-culture with PC. An early NFκB and a late IRF3 nuclear translocation were observed. To better examine which TLR may be involved, specific agonists for TLR4 (LPS) or TLR3 (poly(I:C)) were used. Only LPS pre-treated HC-MSC induced neutrophils to become immunosuppressive. Wester blotting analysis confirmed the activation of TLR4/MyD88 pathway in MM-MSC. To investigate if the polarization status of MM-MSC could promote tumor-growth in vivo, a mixtures of fluorescently labeled MM cells plus HC- or MM-MSC were implanted in zebrafish. Compared with zebrafish injected with plasma cells (PC) and HC-MSC, the animals co-injected with PC and MM-MSC showed enhanced tumor growth, more hCD138+ cells and up-regulated gata3, IL-4 and IL-13, revealing a Th2 response. Pre-treating MM-MSC with TAK-242, a TLR4 inhibitor, before injection in zebrafish, a reduction of 41% of tumor area was observed ($p<0.001$) with a Th1 response. Injecting zebrafish with MM cells and HC-MSC co-cultured or not for 24h with PC, we observed that animals injected with HC-MSC pre-treated with PC showed more tumor engraftment and more hCD138. Inhibition of TLR4 signaling during co-culture in vitro of HC-MSC with MM cells led to a reduction of tumor growth and hCD138 infiltrate. Conclusion TLR4 signaling plays a key role in MSC transformation by inducing a pro-

tumor phenotype associated with a permissive microenvironment that circumvents the immune response and allows a better tumor engraftment.

Keywords:
Immunosuppression

MSC

TLR4

Tracks:
Multiple Myeloma Microenvironment

FP-063

Utilization of Microscopy to Inform and Generate a Patient-Specific, 3D Model of Multiple Myeloma

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Abstract:
Despite the introduction of new targeted treatments, multiple myeloma (MM) remains an incurable hematological malignancy. The challenging aspects of the disease include the high clonal heterogeneity of myeloma cells and its clinical repercussions. Malignant plasma cells (PCs) reside within the bone marrow microenvironment (BMME) of myeloma patients and provide sites of PC production, differentiation, and malignant transformation. The BMME plays a critical role in mediating interactions between myeloma cells contributing to pathogenesis, mediating resistance to cell death, sustained proliferation, and immunosuppression. Given the complexity and function of the BMME, characterizing the efficacy of novel agents should not only assess the impact on myeloma cells, but also define effects on the tumor microenvironment. The purpose of this project was to investigate the BMME of PCs as they transition from premalignant to malignant myeloma cells in order to provide valuable insight, which could be exploited to investigate current and novel treatments. By utilizing confocal and transmission electron microscopy techniques, we have been able to better characterize PC dysfunction in MM as well as a related PC disorder, monoclonal gammopathy of undetermined significance (MGUS). As it relates to disease progression from MGUS to MM, our data demonstrate significant changes in the expression of fibronectin (FN), an adhesion molecule responsible for mediating homotypic and heterotypic interactions in the BMME. FN is thought to be essential for the development of chemotherapeutic resistance. Furthermore, electron micrographs (EMs) of PCs from bone marrow (BM) biopsies exhibited morphological changes characteristic of the transition of MGUS to active MM. EMs identified eccentric nuclei, typical of PC morphology, along with extensive endoplasmic reticulum within in cytoplasm. Interestingly, EMs from MM patients identified densely packed vesicles within the cytoplasm, which was not seen in MGUS core samples. This phenotype is indicative of a cell undergoing autophagy, which was confirmed by the presence of autophagosomes in MM cores. Thus, our data indicates that autophagy is a potential survival mechanism for sustainable immunoglobulin production during malignant transformation of PCs. Finally, this project sought generate a 3D in vitro myeloma marrow culturing system using a high-throughput hydrogel platform. By using patient cells isolated from BM aspirates within a type I collagen matrix, our BM cultures were capable of reproducing key features of PC malignant progression, including abnormal immunoglobulin production and PC survival. These 3D 'marrow-cultures' maintained their abnormal phenotypes for at least five days of culture. This extended timeframe allows for the better characterization of the mechanisms of action of current therapies, testing of emerging treatments, and the development of novel, patient-specific interventions for this disease.

Keywords:
3D patient modeling

Bone marrow microenvironment

collagen hydrogel

Tracks:
Multiple Myeloma Microenvironment

FP-064

A prospective study of circulating chemokines and angiogenesis markers and risk of multiple myeloma and its precursor

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Abstract:
Background: Experimental and clinical studies have implicated certain chemokines and angiogenic cytokines in multiple myeloma (MM) pathogenesis. To investigate whether systemic concentrations of these markers are associated with future MM risk and progression from its precursor, monoclonal gammopathy of undetermined significance (MGUS), we conducted a prospective study within the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Methods: We measured concentrations of 45 immunologic and pro-angiogenic markers in sera from 241 MM cases, 441 subjects with non-progressing MGUS, and 258 MGUS-free controls using Luminex-based multiplex assays and ELISA. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using multivariable logistic regression. We also evaluated absolute risk of progression using weighted Kaplan-Meier estimates. Results: Pre-diagnostic levels of six markers were significantly elevated among MM cases compared with MGUS-free controls using a false discovery rate of 10% (EGF, HGF, Ang-2, SDF-1/CXCL12, MCP-2/CCL8, and BMP-9). Of these, three angiogenesis markers were associated with future progression from MGUS to MM: EGF (fourth vs. first quartile: OR=3.01, 95% CI 1.61 to 5.63; Ptrend=0.00028), HGF (2.59, 1.33 to 5.03; Ptrend=0.015) and Ang-2 (2.14, 1.15 to 3.98; Ptrend=0.07). A composite angiogenesis biomarker score substantially stratified risk of MGUS progression to MM beyond established risk factors for progression, particularly during the first 5 years of follow-up (AUCs of 0.71 and 0.64 with and without the angiogenesis marker score, respectively). Conclusions: Our prospective findings provide new insights into mechanisms involved in MM development and suggest that systemic angiogenesis markers could potentially improve risk stratification models for MGUS patients.

Keywords:
angiogenic cytokines

chemokine

MGUS

Tracks:
Multiple Myeloma Microenvironment

FP-065

The bone marrow microenvironment of multiple myeloma promotes myeloma related anemia by suppressing the differentiation of hematopoietic stem cells

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Abstract:
Background and aims: Multiple myeloma (MM) is a hematologic malignancy characterized by monoclonal plasma cells infiltrating the bone marrow thereby causing anemia and lytic bone lesions. MM patients always accompanied with severe anemia, which may significantly contribute to patient mortality. However, the mechanisms underlying myeloma related anemia have not been fully elucidated. We hypothesized that the MM microenvironment plays a pivotal role on their hematopoiesis differentiation. In the present study, the number and the function of HSPCs in the MM microenvironment were analyzed by MM patient primary samples and myeloma mouse model. Methods & Results: The clinical analysis showed that there was 80% (620/776) MM patients with anemia at diagnosed and more than 60% patients had moderate or severe anemia. The flow cytometry was utilized to detect the CD138+ cells and CD34+ HSPCs in the same patient. We found that the degree of anemia was positively correlated with their number of CD138+ cells. The number of CD34+ HSPCs in bone marrow was negatively correlated with their number of CD138+ cells ($r=-0.526$, $p=0.0082$). The data indicated that the percentage of HSPCs in NDMM patients was significantly lower than that of normal controls ($P<0.001$). We did not find variation of HSC (Lin-CD34+CD38-) in MM microenvironment compared with healthy bone marrow. However, the ratio of HPC (Lin-CD34+CD38+) significantly decreased ($P<0.001$). And the proportion of megakaryocyte-erythrocyte progenitors (MEP) downstream of the HSPCs was decreased significantly ($p<0.0001$) in MM patients. The proportion of granulocyte-macrophage progenitors (GMP) was increased in MM patients compared to healthy donors ($p<0.01$). The ability of colony forming of CD34+ cells from MM patients was significantly suppressed than that of normal controls, especially in the forming of BFU-E ($p<0.01$). To explore the extrinsic factors for the suppression of erythropoiesis differentiation, we performed a CFC assay by co-culture CD34+ cells from healthy donors with BM plasma of MM patients. It is as expected that the patient's bone marrow plasma severely inhibited the formation of BFU-Es. The further detect with ELISA showed that the expression of TGFβ, IL-1β, CCL3 in bone marrow plasma of MM patients were increased. Our RNA-seq data indicated that the expression of transcription factors, GATA1 and KLF1 were significantly decreased in MM CD34+ cells. Conclusion: Bone marrow microenvironment of multiple myeloma suppressed hematopoietic stem cells differentiation and promote the myeloma associated anemia. High level of tumor burden positively correlated with the degree of hemoglobin reduction. The bone marrow microenvironment with high level of TGFβ, IL-1β and CCL3, which might be one of the important reasons for anemia in MM patients. The transcription factors of erythrogenesis in myeloma CD34+ cells were down regulated by MM microenvironment.

Keywords:
hematopoietic stem/progenitor cells

microenvironment

Multiple myeloma

Tracks:
Multiple Myeloma Microenvironment

FP-066

The impact of lactate dehydrogenase (LDH) in association with the International Staging System (ISS) on patients with multiple myeloma.

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Abstract:
Introduction: Multiple Myeloma (MM) is a heterogenous disease, with different clinical outcomes, even though the patients undergo the same treatments. As such, the identification of high-risk patients is fundamental. The Revised International Staging System (R-ISS) is a prognostic score, which combines the ISS, serum lactate dehydrogenase (LDH) and chromosome abnormalities (CA), evaluated by in situ hybridization by fluorescence (FISH). However, access to the evaluation of chromosome abnormalities is not readily available on a global scale. Objective: To evaluate the impact of the LDH rate in combination with the ISS in the median overall survival in newly diagnosed multiple myeloma (NDMM) patients. Patients and Methods: This was a retrospective cohort with 252 NDMM patients, diagnosed between January 2008 and December 2016, who received treatment and follow-up at a single center and who had sufficient data to fill out the necessary scores. Results: The 252 patients analyzed had a median age of 62.9 years, 55.6% were male and 44.4%, female. The most common immunoglobulin subtype was IgG (62.2%), followed by IgA (22.9%) and light chain (12.5%). As for the ISS, 28.6% were ISS I, 34.9%, ISS II and 36.5%, ISS III. The median follow-up was 62.5 months, with a total of 109 deaths during this period. The median overall survival was 70.2 months and at 5 years, 57.8%. Upon combining LDH and ISS, it was possible to identify 6 groups with the following results: ISS I and normal LDH, with a median overall survival not reached and at 5 years, 70%; ISS I and high LDH, with a median overall survival of 69.8 months; ISS II and normal LDH, with a median overall survival of 78.8 months; ISS II and high LDH, with a median overall survival of 73.9 months; ISS III and normal LDH, with a median overall survival of 46.7 months, and; ISS III and high LDH, with a median overall survival of 45.5 months ($p < 0.0001$). Conclusion: The combination of ISS and LDH is a simple tool to stratify the MM patients, especially at centers which do not have access to chromosome abnormalities evaluation.

Keywords:
ISS

lactate dehydrogenase

Multiple myeloma

Tracks:
Multiple Myeloma Microenvironment

FP-067

Mesenchymal Stromal Cell Sialylation Modulates Antitumor Immune Responses In Multiple Myeloma

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Abstract:
Background: Multiple myeloma (MM) is a haematological malignancy characterised by a clonal proliferation of plasma cells in the bone marrow (BM) and the detection of monoclonal immunoglobulin in the blood and/or urine. The interactions between MM cells and the stromal microenvironment contribute heavily to MM cell survival. Little information to date is known about the mechanisms of immune modulation mediated by BM-mesenchymal stromal cells (BM-MSCs) in MM. Glycosylation modulates the hallmarks of

cancer playing important roles in tumour progression. In this study we investigate if regulation of BM-MSC sialylation alters their ability to inhibit effector T-cell function in an inflammatory microenvironment. We investigate if BM-MSCs isolated from MM mice (MM-MSCs) have elevated levels of sialic acid and if this correlates with T-cell modulation. Methods: MM-MSCs and BM-MSC were isolated from mice and extensively characterized in vitro. BM-MSC were treated with both tumour necrosis factor alpha (TNF-α) and interleukin 1 beta (IL-1β) (i-MSC) or MM-MSCs were treated with tumour conditioned media (TCM) generated from 5T3MM cell lines for 72 hours and the sialic acid levels were analysed by flow cytometry. MM-MSCs, BM-MSC and i-MSC were co-cultured T lymphocyte assays for 96 hours. T-cell proliferation and activation were determined by flow cytometry. To assess the role of increased sialylation in lymphocyte suppression, both BM-MSC and i-MSC were pre-treated with the sialyltransferase inhibitor (SI) 3Fax-Neu5Ac for 72 hours prior to TNF-α and IL-1β stimulation. Results: MSCs treated with either TNF-α and IL-1β or TCM from mouse MM cell lines displayed significant phenotypical changes with CD73, CD44 and PD-L1 changing significantly. MM-MSCs and i-MSCs have significantly increased levels of both α2-3 and α2-6 linked sialic acid when compared to BM-MSC. In vitro, both MM-MSCs and i-MSCs displayed an enhanced ability to inhibit the proliferation of lymphocytes when compared to BM-MSC alone. Both MM-MSCs and i-MSC inhibited the proliferation of stimulated CD3+CD4+ and CD3+CD8+ lymphocytes significantly. SI BM-MSC and iMSC displayed no significant changes in phenotype, viability, proliferation and cell size. However, following SI treatment, i-MSC lost the ability to suppress both CD3+CD4+ and CD3+CD8+ lymphocytes resulting in significant restoration of lymphocyte proliferation. Sialic acid expression on the cell surface correlated with both CD3+CD4+ and CD3+CD8+ lymphocyte suppression. Conclusion: Our findings report that inflammation induces BM-MSC sialylation and enhances their ability to suppress activated adaptive and innate immune effectors. Understanding the potential utility of targeting BM-MSC sialylation and consequently their immunomodulatory potential, may enhance immune cell activation in the MM microenvironment, providing further rationale to targeting BM-MSC sialylation in the context of MM.

Keywords:
Immunomodulatory

Multiple myeloma

tumor immunology

Tracks:
Multiple Myeloma Microenvironment

FP-068

FlowCT: A semi-automated workflow for deconvolution of immunophenotypic data and objective reporting on large datasets

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Abstract:
Background: The advent of immunotherapy renewed the interest in immune monitoring to identify determinants of treatment response. Flow cytometry is widely adopted in immunotherapy-based clinical trials, but manual analysis of multiparameter files poses a challenge to capture full cellular diversity and to provide unbiased reporting in large datasets. Methods: Here, we developed a semi-automated pipeline named "FlowCT" which, starting from compensated data obtained with standardized protocols, allows simultaneous analyses of multiple files and automated cell clustering. FlowCT starts with quality control and data normalization followed by an analytical stage with clustering algorithms, dimensional reduction techniques and cluster identification based on antigen expression. Statistical tools are included for immediate analysis of results. Results: As proof-of-concept, we used FlowCT in three different datasets. First, we applied FlowCT to bone marrow (BM) samples from three multiple myeloma (MM) patients stained with 17-color flow cytometry, to determine the increment in the complexity of analyzing 8 and 17 markers, chosen to characterize T cells. Of note, a single combination of CD3, CD4, CD8, CD45RA, CD56, CCR7, PD1 and TIGIT, allowed the identification of 31 lymphocyte subsets using FlowCT, which increased to 39 different clusters with 17 markers and unveiled a novel population of CD3- CD56- CD8+ CD16+ lymphoid cells in the MM immune microenvironment. Secondly, we applied FlowCT to matched peripheral blood (PB) and BM samples from 10 patients with smoldering MM, to objectively assess if PB represents a good surrogate of T-cell distribution in the BM. Using an 8-color combination to characterize CD4 T cells, up to 26 different subsets were identified, including several CD4 T helper (Th) type subsets. Of note, their distribution within PB CD4 T cells was similar to that found in BM, except for CD4 T CXCR3+CCR4+ effector memory and Th17 central memory subsets that decreased in the BM tumor immune microenvironment. Thirdly, we analyzed 30 BM samples from 10 MM patients studied every year during maintenance therapy, monitored with CD4, CD8, CD25, CD45RA, CD127, CCR7, PD1, and TCRγδ to characterize T cells. FlowCT identified 29 different T-cell populations, including 9 CD4 subsets, 14 CD8 subsets, 4 Tγδ cell subsets and 2 distinct Treg subsets. Longitudinal, semi-automated and unbiased analysis unveiled a significant fluctuation of CD4 naïve and transitional memory cells during maintenance, as well as a significant decrease of CD8 CD127- effector memory and transitional effectors cells after 2 years of maintenance. Conclusions: Here, we presented FlowCT, a pipeline optimized for the analysis of large flow cytometry datasets that could be easily implemented by research laboratories to unveil full cellular diversity, singular patterns of antigen expression, and to provide unbiased reporting in large studies.

Keywords:
Automated Analysis

Flow Cytometry

Multiple myeloma

Tracks:
Multiple Myeloma Microenvironment

FP-069

Endothelial Progenitor Cells as Drug Delivery Trojan Horses for Theranostic Use in Multiple Myeloma

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Abstract:

Background: Endothelial progenitor cells (EPCs) are a subtype of stem cells capable of differentiating into mature endothelial cells. Tumor-derived paracrine signals activate the bone marrow residing EPCs to home to the tumor, including multiple myeloma (MM), and to promote angiogenesis. The aim of this study was to utilize the EPCs and their specific patho-physiological homing to tumors as a biologically-targeted drug delivery system as a "Trojan horse"-cellular immunotherapy and imaging in MM. Methods: To test the specificity of EPCs' homing to myeloma, chemotaxis of EPCs towards conditioned media derived from MM cell lines (MM.1S, OPM2, RPMI8226, H929 and U266) was performed in vitro using Boyden Chamber. EPCs chemotaxis towards different MM cell numbers, kinetics, and after "priming" EPCs in vitro by exposing them to conditioned media from hypoxic (1% O2) MM cells was also tested, both in vitro and in vivo. In vivo biodistribution of EPCs was studied in MM xenograft mouse model after injecting EPCs intravenously, by analysis of the EPCs accumulation in the tumors and other organs. Next, EPCs were loaded with LS-542 (NIR imaging dye), with Titanocene (Tc) (a non-toxic compound used in phototherapy that can be activated by positrons to become toxic), and with bortezomib (BTZ), and tested for the effect of the loading on viability and functionality of EPCs, using MTT and chemotaxis assays, respectively. In addition, the effect of BTZ-loaded EPCs and Tc-loaded EPCs followed by activation with 18FDG, was studied on MM.1S-GFP killing in vitro. Results: We found that EPCs specifically homed to myeloma in vitro and in vivo, in a tumor-size-dependent and a time-dependent manner, and that EPCs selectively accumulated in tumor tissues with significantly negligible amounts in other organs. Hypoxia-"priming" of EPCs significantly improved their homing to cancer in vitro and in vivo. Loading EPCs with LS-542, Tc or BTZ did not affect their viability or functionality. Additionally, Tc-loaded EPCs (and activated by 18FDG) and BTZ-loaded EPCs induced a dose-dependent killing of MM.1S cells. Conclusions: EPCs have a highly specific and efficient biological machinery to target MM, especially when "primed" with hypoxic tumor media. Loading EPCs with LS-542, Tc, or BTZ did not change their viability and functionality, thus are promising molecules for imaging and therapy of MM, respectively. These results provide a proof-of-concept that EPCs can be used as a novel cellular immunotherapy for specific and efficacious delivery of theranostic agents in MM. Unlike engineered/targeted immunotherapies such as cellular (CAR-T cells), bispecific T cell engagers, or monoclonal antibodies that target specific molecules on a specific tumor type, EPCs can be used as a pan-cancer "Trojan-horses" drug delivery platform due to the universality of EPC-dependent angiogenesis in all cancer types.

Keywords:
Endothelial Progenitor Cells

Imaging

immunotherapy

Tracks:
Multiple Myeloma Microenvironment

FP-070

Cell surface glucose-regulated protein 78 (GRP78) is upregulated in plasma cells of patients with multiple myeloma compared to monoclonal gammopathy of uncertain significance

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Abstract:
Background: Multiple myeloma (MM) is characterised by paraprotein (PP) and/or serum free light chain (SFLC) production, a hypoxic tumour microenvironment (TME) and increased cellular

stress. Glucose-regulated protein 78 (GRP78), an endoplasmic reticulum stress-inducible molecular chaperone, is upregulated at times of cellular stress and acts to limit proteotoxicity and promote cell survival. Translocation of GRP78 to the cell surface (csGRP78) and interaction with cell signalling and survival pathways is emerging as a critical step providing tumour cells with a survival advantage. csGRP78 is of interest as both a prognostic marker and a potential therapeutic target in MM. We aim to objectively quantify the cell surface expression of GRP78 in plasma cells (PC) and cells of the TME in patients (pts) with monoclonal gammopathy of undetermined significance (MGUS), newly diagnosed (NDMM) and relapsed/refractory MM (RRMM). Method: Formalin-fixed, paraffin-embedded bone marrow trephine sections from pts with MGUS (n=14), NDMM (n=21) and RRMM (n=21) were stained for CD138 and GRP78 by multiplex immunofluorescence histochemistry using the OpalTM workflow. Data were extracted using inForm® software with multispectral images scored based on membrane expression of CD138 and GRP78. Patient demographics, disease characteristics, and treatment outcomes were extracted from medical records. Descriptive statistics, ordinary one-way ANOVA, Pearson's or Spearman's correlation were applied as appropriate. Results: There was no difference in the total number of nucleated cells (NCs) assessed across the 3 cohorts; p=0.459. CD138+ve PCs (% of all NCs; mean+/-SD) in the MGUS, NDMM and RRMM cohort were 7.5+/-5.0 vs 32.2+/-22.6 vs 22.6+/-25.1 respectively (p=0.0052). Overall csGRP78 expression (% of all NCs; mean+/-SD) was highest in NDMM pts (30.6+/-23.8, 49.6+/-25.3, 23.7+/-21.7; p=0.0027). PC csGRP78 expression (CD138+, GRP78+) was highest in NDMM pts [60.3+/-29.3 vs 36.6+/-29.2 (MGUS; p=0.0341), vs 34.9+/-21.9 (RRMM; p=0.0090)]. csGRP78 expression in non-plasma cells (GRP78+ CD138-) was increased in MGUS pts [91.4+/-6.3 vs 62.3+/-24.6 vs 63.7+/-30.5; p=0.0017]. Globally, there was no correlation between PC csGRP78 expression and PP level (r=0.102; p=0.489) and a significant, though weak trend with SFLC ratio (r=0.338; p=0.012). In the NDMM cohort, there was an insignificant trend between PC csGRP78 expression and depth of response to treatment (r=0.188; p=0.441). Conclusion: This study is the first to demonstrate upregulation of csGRP78 expression in plasma cells of pts with NDMM compared to MGUS, associated with a downregulation of csGRP78 in the cells of the TME, suggesting a potential role for csGRP78 in the tumorigenesis and progression from MGUS to MM. There is a weak trend between PC csGRP78 expression and depth of response which is intriguing and warrants further larger-scale exploration.

Keywords:
Biomarker

Glucose-regulated protein 78, GRP78

microenvironment

Tracks:
Multiple Myeloma Microenvironment

FP-071

Macrophages as a potential therapeutic target: Clodronate-liposome treatment inhibits multiple myeloma tumour establishment in vivo

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Abstract:
Multiple myeloma (MM) is a fatal malignancy characterised by the clonal proliferation of malignant plasma cells (PC) within the bone marrow (BM). Numerous cells within the BM microenvironment have been shown to influence myeloma pathogenesis. Specifically, phagocytic macrophages have been implicated in MM disease progression, angiogenesis and drug resistance; however, the role

of this cell type in the initial establishment of MM disease has not been investigated. In this study, the role of macrophages in MM disease establishment was investigated in the 5TGM1/C57BL.KaLwRijHsd (KaLwRij) murine model of MM. Clodronate-liposomes (clo-lip) were used to globally and transiently deplete macrophages in these mice. We found that within 24 hours of clo-lip treatment, 90% of CD169+ macrophages were depleted from the BM ($p<0.01$). Notably, a single injection of clo-lip 24 hours prior to tumour cell inoculation resulted in greater than 95% reduction in MM tumour burden at week 4, compared with that observed following control PBS-lip injections ($p<0.0001$). Moreover, MM PC homing and retention were impaired in clo-lip treated mice compared with PBS-lip, as evidenced by a 2.7-fold reduction in GFP+ 5TGM1 cells within the BM ($p<0.001$) and a concomitant 5.4-fold increase in circulating tumour cells ($p<0.01$), 24 hours post-tumour cell inoculation. Taken together, these data suggested the involvement of CD169+ BM-resident macrophages in MM establishment. Next, we investigated whether macrophages play a role in MM PC migration. We determined that BM-macrophage conditioned medium enhances 5TGM1 MM PC migration in a dose-dependent manner in vitro ($p<0.01$). Moreover, BM-derived macrophages expressed abundant mRNA transcripts encoding the pro-proliferative and migratory factor, insulin-like growth factor 1 (Igf1) ($p<0.0001$). Consistent with this finding, clo-lip treated mice exhibited significantly reduced Igf1 mRNA levels within the BM compared with PBS-lip treated mice ($p<0.001$). Western blot analysis revealed that BM-macrophage conditioned medium stimulated IGFR1 phosphorylation in 5TGM1 cells, suggesting that macrophage secreted IGF-1 may stimulate 5TGM1 MM PC homing. Lastly, a single injection of clo-lip in the established disease setting (i.e. 2 weeks after 5TGM1 tumour inoculation) resulted in a 64% reduction in MM tumour burden, compared with PBS-lip controls ($p<0.05$), thereby demonstrating the potential therapeutic efficacy of targeting macrophages in MM. Collectively, our studies suggest that CD169+ BM-resident macrophages are an important component of the MM niche and are required for disease establishment and progression in vivo. Furthermore, we have demonstrated that macrophage-secreted factors, including IGF-1, play an important role in MM PC migration and homing to the BM. These findings highlight the potential of targeting BM-resident macrophages as a novel therapy for MM.

Keywords:
Bone marrow microenvironment

Clodronate-liposome

Macrophage

Tracks:
Multiple Myeloma Microenvironment

FP-072

Syndecan-1 and stromal HSPGs: key moderators of communication between myeloma plasma cells and the bone marrow niche

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Abstract:
Upon antigen recognition by the B-cell antigen receptor (BCR), B-cells differentiate into plasma cells, which represent the effector cells of the humoral immune system. However, in contrast to their B-cell precursors, plasma no longer express a cell-surface BCR and, hence, are deprived of the BCR-derived signals, which are crucial for survival throughout B-cell development. Instead, for their survival, long-lived plasma cells heavily rely on communication with the bone-marrow (BM) microenvironment, which provides adhesion-mediated as well as multiple soluble signals. Plasma cells acquire strong expression of the cell-surface

heparan sulfate proteoglycan (HSPG) syndecan-1, a phenotypic hallmark of plasma cells and their malignant multiple myeloma (MM) counterparts. Our research addresses how syndecan-1, in concert with HSPGs in the bone marrow microenvironment, mediates homing and survival of normal plasma cells, and promotes MM growth, by co-opting growth an survival factors from the BM niche and targeting them to their cognate receptors. The crucial function of syndecan-1 and of stromal HSPGs in the communication of MM with the bone marrow niche, designates these molecules and their synthesis machinery as potential treatment targets. Various venues to target syndecan-1/HSPGs in MM are currently being explored in preclinical and clinical studies. van Andel et al. PNAS 114:376-381 (2017). Ren et al. Blood 131:982-994 (2018).

Keywords:
hspg

microenvironment

syndecan-1(CD138)

Tracks:
Multiple Myeloma Microenvironment

FP-073

A Highly Reproducible 3D Culture Approach for Functional Drug Testing on Primary Multiple Myeloma Cells.

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Abstract:
Introduction: One of the main challenges in multiple myeloma (MM) management is the emergence of multi-drug resistance, which eventually leads to disease relapse. Clonal evolution of malignant plasma cells over the course of treatment leads to outgrowth of clones whose drug sensitivity is difficult to predict, as the factors conditioning this evolution are poorly understood and may greatly differ between patients. Until recently, studies on primary MM cells have been limited due to the short lifespan of malignant plasma cells outside their niche. Therefore, development of novel culture systems able to preserve primary MM cell viability is needed as a tool to better understand the survival requirements for malignant plasma cells and to test drug sensitivity in a patient-specific manner. Methods and results: We have tested cell viability and drug sensitivity of primary MM cells in different 2D and 3D culture setups and identified a 3D culture system in which viability of primary MM cells is preserved significantly better than in conventional 2D cultures. This 3D setting, based on a self-assembling peptide hydrogel in the presence of pro-survival cytokines IL-6 and APRIL, was able to keep primary MM cells alive up to multiple weeks even in the absence of supportive cell subsets, such as mesenchymal stromal cells (MSC). In contrast to matrigel, the nature of this specific peptide hydrogel allows easy isolation of the primary cells after culture for further analysis. In this setup primary MM cells, as well as human myeloma cell lines, were significantly more resistant to apoptosis induced by conventional or novel MM drugs, including bortezomib, dexamethasone, melphalan, venetoclax, or MCL-1-specific inhibitors, in 3D- than in 2D-culture. In addition, we found that both T cells and/or NK cells can be co-cultured in this 3D setup. Conclusions: We have established a fully controllable 3D culture approach able to preserve primary MM cell survival in the absence of additional bone marrow-derived cell subsets. This method allows testing of (novel) MM drugs and, when co-cultured with immune cells, can be used to test immunomodulatory drugs (IMiDs) and immunotherapeutic approaches. Combined, this experimental setup will lead to a better understanding of MM cell-intrinsic and -extrinsic mechanisms to escape apoptosis, and may be a useful tool to predict, in a patient-specific manner, the most effective drug combinations to prevent disease relapse.

Keywords:
3D

Drug Screen

Primary patient cells

Tracks:
Multiple Myeloma Microenvironment

FP-074

Detailed Phenotypic, Molecular and Functional Profiling of Myeloid Derived Suppressor Cells (MDSCs) in the Tumor Immune Micro-Environment (TIME) of Multiple Myeloma (MM)

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Abstract:
Background: Deep understanding of the TIME and its influence on response to therapy is needed to improve the ability to predict and monitor immunotherapeutic responsiveness. Among cells composing the MM-TIME, granulocytic-MDSCs (G-MDSCs) have a prominent role in promoting tumor growth and inducing immunosuppression; however, their phenotype in MM is not well-established. Aim: To define the phenotype of G-MDSCs based on the immunosuppressive potential, gene regulatory networks and clinical significance of granulocytic subsets in the MM-TIME. Methods: We used multidimensional flow cytometry (MFC) to evaluate the pre-established phenotype of G-MDSCs in bone marrow (BM) samples from healthy donors (HD) (n=4) and MM patients (n=5); principal component analysis (PCA) to unbiasedly identify granulocyte subsets in the MM-TIME, and FACSorting for in vitro experiments (n=9) and RNAseq in MM (n=5) vs HD (n=5). The clinical significance of these subsets was determined comparing their numbers at diagnosis within the BM TIME of MM patients (n=71) included in the GEM2012MENOS65 trial. Results: Human G-MDSCs have been defined as a cell population with a CD11b-CD14-CD15+CD33+HLADR- phenotype, representing 1% of total BM nucleated cells in HD and 25% in MM patients. However, we found no differences in the percentage of these cells in HD and MM patients (median of 8% in both, P>.99). Using MFC and according to PCA, 3 granulocyte subsets were identified in the BM of HD and MM, based on homogeneous CD14-CD15+CD33+HLADR- expression but differential CD11b, CD13 and CD16: CD11b-CD13lo/-CD16-, CD11b+CD13lo/-CD16- and CD11b+CD13+CD16+. The percentage of all 3 subsets was similar (P>.5) between HD and MM. We used FACSorting to isolate (1) or deplete (2) each subset from MM-BM and determine its immunosuppressive potential. In (1), T cell proliferation significantly decreased when these were stimulated with CD3/CD28 and in presence of CD11b+CD13+CD16+ neutrophils (0.5-fold, P=.01) but not of the other subsets. In (2), we noted that the cytotoxic potential of T cells significantly increased in presence of the BCMAxCD3 bispecific antibody (P=.04) reaching its maximum with the depletion of the CD11b+CD13+CD16+ subset (4-fold, P=.007). RNAseq of the 3 subsets in HD and MM patients revealed that genes commonly associated with G-MDSCs (e.g. PTGS2, TGFβ1) were specifically upregulated in the CD11b+CD13+CD16+ granulocytic subset. Finally, we analyzed the distribution of the 3 subsets in MM patients. We observed that patients with high number of CD11b+CD13+CD16+ neutrophils at baseline had lower count of T cells and patients with low

CD11b+CD13+CD16+/T cells ratio had inferior 3-year rates of progression-free survival as compared to the remaining patients (100% vs 75%, P=.03). Conclusion: Using a comprehensive panel of assays we have provided, for the first time, a set of optimal markers (CD11b/CD13/CD16) for monitoring G-MDSCs in MM.

Keywords:
Granulocyte

MDSC

Multiple myeloma

Tracks:
Multiple Myeloma Microenvironment

FP-075

Inhibitor of DNA binding 2 (ID2) regulates key transcriptional programs in multiple myeloma

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Abstract:
Dysregulation of transcriptional control is a common mechanism driving oncogenesis. Microenvironment is a critical factor promoting myelomagenesis, tumor growth and drug resistance by impacting myeloma transcriptome. Here, we used RNA-sequencing of multiple myeloma (MM) cells cultured with stromal cell line HS-5 to identify transcriptional changes enhancing MM cell proliferation. We identified a reproducible and significant downregulation of inhibitor of DNA binding 2 (ID2), a known regulator of transcription through heterodimerization with basic HLH (bHLH) proteins and inhibition of their binding to DNA, across various MM cell lines in presence of stroma. RNA sequencing data from a cohort of 360 newly diagnosed MM patients and 16 normal plasma cells confirmed significant downregulation of ID2 in primary patient MM cells in comparison to normal plasma cells (p 0.013). To study ID2 function in MM cells, we next overexpressed ID2 in 2 MM cell lines (MM1S and NCIH929) and observed a significant decrease in proliferation rate and G0/G1 phase cell cycle arrest. Importantly, ID2 overexpression abrogated the impact of BMSC on MM cell proliferation. RNA-sequencing following ID2 overexpression in MM cells showed broad transcriptomic changes, and gene set enrichment analysis (GSEA) revealed significant downregulation of genes involved in E2F pathway, a known important transcriptionnal axis in MM. Conversely, stable ID2 knockdown in 4 MM cell lines (MM1S, NCIH929, RPMI8226 and KMS11) expressing intermediate levels of ID2, led to increased proliferation rate and upregulation of pathways involved in inflammatory response and epithelial-to-mesenchymal transition. Next, we sought to investigate the mechanisms involved in ID2 downregulation in MM. We observed that both cell-cell interactions and soluble factors secreted by BMSC or HS5 cells were able to significantly downregulate ID2 expression, both at RNA and protein level, suggesting an epigenomic control of its expression. We performed sequenom massarray to evaluate the methylation profile of ID2 promoter CpG islands and did not observe any significant change after co-culture. Next, we used the assay for transposase-accessible chromatin sequencing (ATAC-seq) to identify binding motifs and related transcription factors in open chromatin regions corresponding to ID2 promoter and enhancers in 3 MM cell lines. We focused on SP1 and confirmed its binding to ID2 promoter by ChIP-sequencing in MM1S, NCIH929 and U266 cell lines, and showed that SP1 inhibition increased ID2 expression. Our data demonstrate that ID2 is downregulated in MM cells and promotes major transcriptomic changes and cell cycle dysregulation. Bone marrow stromal cells induce significant downregulation of ID2 in MM

cells suggesting that bHLH axis and other ID2 related pathways represent an important functional node with potential for therapeutic application in myeloma.

Keywords:
epigenetic

microenvironment

Transcription factor

Tracks:
Multiple Myeloma Microenvironment

FP-076

Enhanced lipid accumulation and metabolism are required for the differentiation and activity of tumor-associated macrophages in multiple myeloma

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Abstract:
Introduction: Heterogeneity of macrophages (MΦs) has long been recognized as the result of the plasticity and versatility of these cells to different microenvironmental stimuli. In multiple myeloma, tumor-associate macrophages (TAMs) have been shown to regulate many critical processes associated with malignancy including promotion of tumor cell growth, drug resistance, metastasis, induction of angiogenesis, and immune suppression. Activated MΦs show changes in their metabolism, which are associated with cellular function. For example, pro-inflammatory M1 MΦs switch their metabolism toward an enhanced anaerobic glycolysis, while M2 MΦs are associated with enhanced fatty acid oxidation and oxidative phosphorylation. Protumor TAMs have a phenotype that more closely resembles the features of IL-4-induced M2 MΦs. However, the mechanism underlying how multiple myeloma and its microenvironment reprogram these cells remains elusive. Here we report that TAMs from both human and murine multiple myeloma are enriched with lipids as a result of increased lipid uptake by macrophages and elucidated the mechanisms underlying TAM accumulation of lipid and their function on myeloma progression in vitro and in vivo. Methods: Human and mouse MΦs were generated from human PBMCs and BM cells in vitro. MΦs were cultured with myeloma cells in vitro to generate TAMs. Lipids accumulation in control MΦs and TAMs was measured with flow cytometry and confocal. The proliferation and cell cycle progression of human and mouse myeloma cells were measured with Ki-67 and BrdU assay. The relative expression of genes involved in M1 MΦs, M2 MΦs, fatty acid oxidation, and glucose metabolism in control MΦs and TAMs was measured with microarray assay. The oxygen consumption rates and extracellular acidification rates were determined using seahorse assay. Results: Lipids accumulation was observed in TAMs compared to control MΦs in vitro and in vivo, indicate that lipid accumulation may be important and required for TAM function. Gene expression analysis revealed that elevated expression of SRs, including MSR1, CD68, CD36 and MARCO, in TAMs compared to control MΦs. Using neutralized antibodies, enzyme inhibitors, gene knockdown and CD36 KO mice, we confirmed that lipid uptake and accumulation in TAMs were mainly mediated via the SR CD36. Interestingly, we also found that high level of lipids uptaken by CD36 in TAMs promotes TAM fatty acid oxidation and their protumoral function in vitro and in vivo. High levels of FAO promoted mitochondrial oxidative phosphorylation, production of reactive oxygen species, phosphorylation of JAK1 and dephosphorylation of SHP1, leading to STAT6 activation and transcription of M2-related genes. These processes were critical for TAM polarization and protumor activity in vitro and in vivo. Inhibition of FAO in TAMs could significantly inhibit the progression of human and mouse myeloma progression in vivo. Conclusion: we describe a novel mechanism

Keywords:
Fatty acid metabolism

Macrophage

Tumor-associated macrophages

Tracks:
Multiple Myeloma Microenvironment

FP-077

Mass cytometry reveals increase in marrow resident monocytes associated with response to daratumumab and pomalidomide

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Abstract:
The CD38-targeting monoclonal antibody daratumumab (DARA) has been approved in combination with the immunomodulatory drug pomalidomide (POM) for the treatment of multiple myeloma (MM) (Chari et al. Blood 2017). Understanding the impact of both therapies on immune cell populations in the bone marrow environment is a key component in leveraging immune composition and therapeutic-driven enhancements to help treat MM and potentially stratify patients likely to benefit from treatment. In this study, we investigate changes in the immune composition of bone marrow samples before/after treatment with either DARA or DARA+POM in a cohort of 9 patients using high-dimensional mass cytometry (CyTOF®). Data was analyzed in R using the CATALYST and diffcyt package. Results show notable changes in monocyte, NK and T cell populations in the tumor microenvironment as a consequence of therapy. Trends are observed highlighting increases in monocytes for sensitive patients (as defined by IMWG criteria for disease progression) (mean 29.5% before to 47.4% after treatment), but not in resistant patients (30.2% to 25.4%). This is particularly relevant given the putative role of monocytes in ADCP (antibody-dependent cellular phagocytosis). Phenotypically, in monocytes of resistant patients, we note an overall higher expression of CD33, a transmembrane receptor implicated in inhibition of cellular activity and phagocytosis. NK cells are diminished in both sensitive (12.9% to 1.85%) and resistant (7.5% to 1.4%) patients, consistent with prior results (Krejcik et al. Blood 2016). In terms of marker expression, we observe a shift toward a more immature phenotype with increased median expression of CD56, HLA-DR, NKG2A, CD27 and a decrease of CD57. Furthermore, the proportion of CD8+ T cells is increased in resistant patients (19.9% to 39.6%), but not in sensitive patients (19.6% to 20.3%). The high-dimensional panel allows us to distinguish T cell subsets and demonstrates that the increase is concentrated to an expansion of a senescent phenotype (with higher CD57, CD45RA, GZMB, HLA-DR and lower CD27 and CD28 in resistant patients). Lastly, in resistant patients, we note an increase of PD-1+ T cells, both CD4+ and CD8+, as well as an increase in the proportion of regulatory T cells. In conclusion, we report novel changes in the bone marrow microenvironment in both frequency and phenotype of multiple major immune cell types in a small cohort of patients after treatment with DARA ± POM. These findings complement earlier reported scRNA-seq data on the same group of patients (Neri et al. Blood 2017), although we acknowledge the importance of confirming these trends in future cohorts.

Keywords:
daratumumab

Immune Tumor Microenvironment

Pomalidomide

Tracks:
Multiple Myeloma Microenvironment

FP-078

Activated and Bone-marrow Resident Treg Alterations Underlie Malignant Transformation from MGUS to Multiple Myeloma

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Abstract:
Multiple Myeloma (MM) is preceded by the pre-malignant, clonal plasma cell disorder monoclonal gammopathy of undetermined significance (MGUS). Altered immune surveillance during malignant transformation from MGUS to myeloma may involve changes in the regulatory T cell (Treg) compartment which are permissive to myeloma immune escape. To address this hypothesis, we used mass cytometry and unsupervised clustering algorithm Flow Self-organizing Map (FlowSOM) to interrogate at high resolution the heterogeneity within the Treg (CD25+CD27low/neg cells) compartment, in matched bone marrow (BM) and peripheral blood (PB) of MGUS and newly diagnosed NDMM patients. Both mass cytometry and flow cytometry confirmed a trend toward prevalence of CD39-Treg within the Treg compartment in BM and PB of NDMM patients compared to CD39-Treg in MGUS patients. FlowSOM clustering which displayed Treg in 25 metaclusters suggested Treg heterogeneity in both MGUS and NDMM patients, and discovered two subsets which emerged within CD39-Treg of NDMM patients but were negligible or absent in CD39-Treg of MGUS patients. One subset resembled activated Treg based on CD45RO, CD49d and CD62L expression and was found in both BM and PB; another subset resembled BM-resident Treg based on its tissue-resident CD69+CD62L-CD49d- phenotype and restricted location within the BM. Both subsets co-expressed PD-1 and TIGIT, but PD-1 was expressed at higher levels on BM-resident Treg then on activated Treg. Within BM, both subsets had limited Perforin and Granzyme B production, whilst activated Treg in PB acquired high Perforin and Granzyme B production. In conclusion, the use of mass cytometry revealed two discrete subsets of CD39-Treg which are discordant in MGUS and NDMM patients. These subsets may be permissive of plasma cell growth and thus play a role in malignant transformation from MGUS to myeloma, which warrants further study. Understanding the regulatory properties of these Treg subsets may have diagnostic and prognostic significance in MGUS and MM, including the definition of risk in smoldering MM, as well as therapeutic implications.

Keywords:
MGUS

Multiple myeloma

Treg

Tracks:
Multiple Myeloma Microenvironment

FP-079

The combination of complement 1q and its receptor gC1qR could promote the proliferation of plasma cells through IGF2BP3 in multiple myeloma patients with 1q21 amplification

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Abstract:
Background: Specific cytogenetic abnormalities such as 1q21 amplification indicate poor prognosis in patients with multiple myeloma (MM). There are relatively few studies focusing on the immunomodulatory effects of the complement system on MM. Methods: Plasma samples were obtained from 5 healthy donors (HD), 33 patients with monoclonal gammopathy of undetermined significance (MGUS) or smoldering MM (SMM) and 65 new diagnosed MM (NDMM). Bone marrow (BM) biopsies were obtained from 13 patients and BM aspirates from 6 patients of the 65 NDMM. The main research methods included immunofluorescence, collection of mononuclear cells, CD138+/CD138- cell sorting, flow cytometry (FC), transfection by siRNA, fluorescence in situ hybridization (FISH), RNA preparation and quantitative real time-polymerase chain reaction (qRT-PCR), Western Blot (WB), EDU cell proliferation assay, CCK8, Co-Immunoprecipitation-Mass Spectrum (CoIP-MS) and RNA Immunoprecipitation (RIP)-Seq. Results: Firstly, comparing to the HD and MGUS/SMM group, Complement 1q (C1q) significantly reduced and had clinical prognostic role for overall survival (OS) in patients with NDMM. In NDMM patients older than 60, with 1q21 gain or with t (4;14) had most significantly lower levels of plasma free C1q. Secondly, the amount of C1q deposited around the CD138+ plasma cells in the BM biopsy section was significantly more in the MM patients with 1q21 gain. Thirdly, CD138+ plasma cells expressed higher level of cC1qR and gC1qR than CD138- cells. Moreover, comparing to the 1q21- group, the 1q21+ group expressed higher levels of C1qRs on CD138+ plasma cells. Therefore, we selected 3 MM cell lines with 1q21 gain confirmed by FISH, which were H929, U266 and MM1S. Then we determined that the 3 cell lines all expressed C1qRs and the protein expression level of gC1qR on H929 was the highest. Through CCK8 and EDU cell proliferation assay, we found that C1q could stimulate the proliferation of wild-type U266, H929, MM1S. However, when gC1qR was down regulated, the role of C1q turned into the inhibitor of cell proliferation. Through CoIP-MS and WB validation, the results showed that gC1qR may interact with a protein called insulin like growth factor 2 mRNA binding protein 3 (IGF2BP3) in these 3 cell lines. By repeating CCK8 and EDU assays, we found that knockdown of IGF2BP3 could also reverse the effect of C1q on cell proliferation. Moreover, by qRT-PCR, down-regulation of gC1qR or IGF2BP3, respectively, significantly reduced the CKS1B mRNA level. Based on the above results, RIP-Seq on IGF2BP3 was performed using U266 and the data showed that this protein could interact with CKS1B mRNA. Therefore, we hypothesized that IGF2BP3 may stabilize CKS1B mRNA by binding to them, thus influencing the cell cycle. Finally, Pomalidomide reduced the gC1qR and IGF2BP3 of U266 and H929 most significantly among five drugs, which suggested that regimens containing Pomalidomide could be more suitable for MM patients with 1q21 gain.

Keywords:
cytogenetic abnormality

Multiple myeloma

Tracks:
Multiple Myeloma Microenvironment

FP-080

Hypoxia-induced long non-coding RNA DARS-AS1 regulates RBM39 stability to promote myeloma malignancy

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Abstract:

Multiple myeloma is a malignant plasma-cell disease, which is highly dependent on the hypoxic bone marrow microenvironment. However, the underlying mechanisms of hypoxia contributing to myeloma genesis are not fully understood. Here, we show that long non-coding RNA DARS-AS1 in myeloma is directly upregulated by HIF-1. Importantly, DARS-AS1 is required for the survival and tumorigenesis of myeloma cells both in vitro and in vivo. DARS-AS1 exerts its function by binding RBM39, which impedes the interaction between RBM39 and its E3 ubiquitin ligase RNF147, and prevents RBM39 from degradation. The overexpression of RBM39 observed in myeloma cells is associated with poor prognosis. Furthermore, the knockdown of DARS-AS1 inhibits the mTOR signaling pathways, which is reversed by RBM39 overexpression. We reveals a novel HIF-1α/DARS-AS1/RBM39 pathway for the pathogenesis of myeloma. Therefore, targeting DARS-AS1/RBM39 may represent a novel strategy to combat myeloma.

Keywords:
LncRNA

Multiple myeloma

RBM39

Tracks:
Multiple Myeloma Microenvironment

MULTIPLE MYELOMA SIGNALING

FP-081

CD27 antigen negative expression indicates poor prognosis in newly diagnosed multiple myeloma

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Abstract:

To investigate the role of CD27 in multiple myeloma (MM), bone marrow samples from 130 newly diagnosed MM cases were analysed by 8-colour flow cytometry. CD27- group (n=52) had higher level of β2-MG (5.68 vs 3.20 mg/L, $p< 0.05$), calcium (2.48 vs 2.20 mmol/L, $p< 0.05$) as well as higher percentage of ISS stage III (48.72% vs 28.85%, $p< 0.05$) and high-risk cytogenetics (51.28% vs 40.38%, $p < 0.05$) than CD27+ group (n=78). After 4 cycles of chemotherapy, the overall response rate and complete remission rate in the CD27- group were both lower than those in the CD27+ group (62.50% vs 76.19%, 7.81% vs 16.67%, respectively; $p<0.05$). After a median follow-up of 17 months, progression-free survival and overall survival (OS) were both shorter in CD27- group than in CD27+ group (15 months vs 27 months and 31 months vs not reached, respectively; $p < 0.05$). Multivariate analysis showed CD27-negative expression was an independent risk factor for OS. Gene sequencing from 22 cases showed more adverse mutations were detected in CD27-group than CD27+ group. CD27-negative expression is often accompanied by high-risk genetics and adverse gene mutations and indicates poor outcome.

Keywords:
CD27

gene mutation

Overall survival

Tracks:
Multiple Myeloma Signaling

FP-082

Next Generation Proteomics and Drug Sensitivity Resistance Testing Allow for the Identification of Distinct Sub-clones of Multiple Myeloma Patients

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Abstract:
Introduction: A hallmark of Multiple Myeloma (MM) is the sequel development of drug resistant phenotypes. These drug resistant phenotypes reflect the intra-tumor and inter-patient heterogeneity of MM. Although several novel drugs have recently been approved or are in development for MM, there are few molecular indicators to guide treatment selection. To address this limitation we have combined mass spectrometry-based proteomics analysis together with ex vivo drug response profiles and clinical outcome to elucidate a best possible accurate phenotype of the resistant sub-clones, thus yielding a theranostic profile that will inform therapeutic and drug development strategies. Methods: We performed mass spectrometry-based proteomics analysis on plasma cells isolated from 38 adult MM patient bone marrow aspirates (CD138+). Samples were obtained at diagnosis or prior to commencing therapy. The participating subjects gave written informed consent in accordance with the Declaration of Helsinki that was approved by local ethics committees. For the proteomics analysis, peptides were subjected to label-free liquid chromatography mass spectrometry (LC-MS/MS) using a Thermo Scientific Q-Exactive MS mass spectrometer and analysed using the MaxQuant and Perseus softwares, UniProtKB-Swiss Prot and KEGG Pathway databases. In parallel, we undertook a comprehensive functional strategy to directly determine the drug dependency of myeloma plasma cells based on ex vivo drug sensitivity and resistance testing (DSRT) as previously described (1). Results: Our DSRT analysis stratified the MM patients into four distinct subgroups: highly sensitive (Group I), sensitive (Group II), resistant (Group III) or highly resistant (Group IV) to the panel of drugs tested. We then performed blinded analysis on the 4 groups of CD138+ plasma cells divided based on the ex vivo sensitivity profile, identifying a highly significant differential proteomic signature between the 4-chemosensitivity profiles, with Cell Adhesion Mediated-Drug Resistance (CAM-DR) related proteins (e.g. integrins αIIb and β3) significantly elevated in the highly resistant phenotype (Group IV). In addition our results showed that Group I patients displayed significant upregulation of cell proliferation proteins (e.g. MCM2, FEN1, PCNA). Furthermore, Group I patients have shorter Overall Survival (OS) compared to the other subgroups. Conclusions: We show that the disease driving mechanisms in the patient subgroups are distinct, with highly resistant patients exhibiting cell adhesion mediated cytoprotection, while highly sensitive patients show an increased cell proliferation protein profile with shorter OS. Our study aims to guide treatment decisions for individual cancer patients coupled with monitoring of subsequent responses in patients to measure and understand the efficacy and mechanism of action of the drugs. References: (1) M. M. Majumder et al., Oncotarget 8(34), 56338 (2017)

Keywords:
Drug Screen

Personalized Medicine

Proteomics

Tracks:
Multiple Myeloma Signaling

FP-083

Blocking of WIP1 Phosphatase Overcomes Bortezomib Resistance and Promotes Cell Death via ER Stress-induced Apoptotic JNK/c-Jun Signaling: Novel Therapeutic Target in Multiple Myeloma

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Abstract:
Wild-type p53-induced phosphatase 1 (WIP1) is an oncogenic serine/threonine phosphatase implicated in silencing of cellular responses to genotoxic stress. WIP1 overexpression was documented in various solid cancers in correlation with aggressive features and poor prognosis. Thus, we studied WIP1 in MM addressing its potential role in mediating resistance and aggressive phenotype. Increased WIP1 was detected in MM cell lines and primary samples at both mRNA and protein level as compared with normal PBMCs ($p<0.01$). WIP1 levels were significantly upregulated following bortezomib (Bort) exposure and in Bort-resistant MM cell lines suggesting a possible role for WIP1 in the acquisition of drug resistance to proteasome inhibitors. WIP1 was also upregulated in MM cells cultured on human BMSC known to protect the tumor cells from Bort-induced apoptosis, further supporting its function in mediating resistance. GSK2830371 (GSK), a novel inhibitor of WIP1, significantly suppressed MM cells proliferation ($p<0.01$) and induced apoptosis, as demonstrated by phosphatidylserine externalization, mitochondrial depolarization, caspase 3 and activation, and DNA fragmentation. Moreover, combined treatment with GSK and Bort synergistically potentiated cell death in both Bort-sensitive and resistant MM cells and overcame BMSC protection ($CI<0.5$). The robust apoptosis induced by Bort/GSK was accompanied by increased mitochondrial ROS, mitochondrial destabilization and extensive DNA damage. To determine the molecular mechanism of Bort/GSK synergism we performed gene and protein expression analysis. Combination of both agents significantly reduced expression of anti-apoptotic proteins cIAP1, cIAP2, XIAP and Survivin. IAPs expression maintenance is part of an adaptive UPR that promotes MM survival upon Bort-induced endoplasmic reticulum (ER) stress. Therefore, it is conceivable that targeting IAPs upon WIP1 inhibition may overcome protective responses, inducing unresolved ER stress and MM cell death. Indeed, combination of Bort and GSK significantly enhanced ER stress, as indicated by increase in the pro-apoptotic factors ATF4, CHOP and GADD34. Furthermore, we assessed the signaling pathways that may be involved in WIP1 mediated cessation of stress response. GSK profoundly augmented Bort-induced phosphorylation of JNK and c-Jun. Accordingly, JNK inhibition successfully reverted both the apoptosis and the downregulation of IAPs induced by Bort/GSK treatment. These results identify pro-apoptotic JNK/c-Jun signaling being preferential target of WIP1 in the process of dampening Bort-induced stress response. Finally, in xenograft murine model of systemic MM with BM involvement, the Bort/GSK combination effectively reduced tumor burden, decreasing the number of MM cells in BM. To conclude, we disclose the role of WIP1 in blunting stress response and promoting resistance to bortezomib. Collectively, WIP1 suppression prevents MM cell recovery upon ER stress.

Keywords:
Drug resistance

ER stress

Tracks:
Multiple Myeloma Signaling

FP-084

Blocking of Transient Receptor Potential Vanilloid1 (TRPV1) Promotes Lysosomal Destabilization and Enhances Bortezomib-induced ER Stress and Cell Death via HSP70 and LAMP3 Down-regulation: Novel Therapeutic Target for Multiple Myeloma

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Abstract:
Recent data have highlighted the contribution of Ca2+channels in the regulation of cell proliferation, chemo-resistance, migration and invasion. Transient Receptor Potential Vanilloid type-1 (TRPV1) is a calcium-permeable ion channel that has been demonstrated to be expressed in solid tumors. As no data is available evaluating TRPV1 in MM, the aim of the current study was to evaluate its possible role in MM. Elevated levels of TRPV1 transcript was detected in MM cell lines and BM aspirates from MM patients in comparison to normal BM. AMG9810 (AMG) a specific antagonist of TRPV1, significantly reduced the viability of MM cell lines and primary CD138+ cells ($p<0.01$) and induced DNA fragmentation and apoptosis. AMG-triggered apoptosis could be partially blocked by inhibition of calpains and cathepsins, indicating the role of lysosomal rapture in AMG-mediated cell death. Indeed, treatment with TRPV1 antagonist induced rapid lysosomal acidification and increased the number of acidic vesicles, that appeared as early as 1 hour post exposure to AMG preceding the mitochondrial destabilization and apoptosis. Combining AMG with the proteasome inhibitor bortezomib (Bort) induced synergistic cell death in both native and Bort-resistant cells ($CI<0.4$). Moreover, TRPV1 inhibition successfully overcame the CXCR4-mediated protection from Bort provided by BM stromal cells. This finding suggests that the TRPV1 channel may regulate the activity of CXCR4 chemokine receptor in MM cells affecting the MM-microenvironment interactions. In accordance, the TRPV1 antagonist AMG prevented the responsiveness of CXCR4-expressing MM cells to CXCL12 stimulation, decreased the phosphorylation of signaling mediators like Erk1/2 and AKT and suppressed cell migration, while TRPV1 activator capsaicin promoted the CXCR4-mediated signaling and migration. Gene and protein expression analysis were next performed to delineate the molecular mechanisms underlying the observed synergism between Bort and AMG. Bort treatment resulted in robust induction of ER stress genes including ATF4, CHOP and GADD34. Compensatory unfolded protein response (UPR) was activated as well, with increase in chaperons HSP27, HSP70, HSP90, and lysosomal chaperon LAMP3 known to stabilize lysosome, protecting cells against lysosomal membrane permeabilization (LMP) and cell death. AMG further increased ER stress, elevating CHOP and GADD34 expression, while significantly reducing both basal and Bort-increased levels of HSP70 and LAMP3, thus overcoming the protective response to Bort treatment and prompting lethal LMP. Finally, AMG/Bort combination demonstrated profound antimyeloma activity in xenograft MM model with BM involvement. Altogether, our data indicate that TRPV1 is implicated in MM cell proliferation, migration, microenvironment interactions and stress response. These results unravel the mechanism mediating the synergistic anti-MM activity of Bort in combination with TRPV1 inhibition.

Keywords:
Ca++ channels

CXCR4

ER stress

Tracks:
Multiple Myeloma Signaling

FP-085

Roundabout 1 (ROBO1) Mediates Multiple Myeloma Survival and Interaction with the Bone Marrow Microenvironment

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Abstract:
Introduction Molecular mechanisms of multiple myeloma (MM) pathogenesis are largely unknown. A role for the bone marrow (BM) in supporting MM growth is well established. The transmembrane receptor Roundabout1 (ROBO1) portends poor survival in MM, however its function is unknown. Material and Methods We used western blotting and immunohistochemistry to assess ROBO1 expression in human MM cell lines, primary MM, normal BM plasma cells and a panel of human cancer cell lines. The IFM/DFCI 2009 data set was used to assess ROBO1 expression and overall survival in a cohort of newly diagnosed MM patients. We used short hairpin RNA and CRISPR-Cas9 for ROBO1 knock down (KD) and knock out (KO), respectively. For addback studies, ROBO1 KO cells were transduced with lentivirus constructs expressing ROBO1 full-length (FL) or truncations devoid of extracellular (Cyt) or intracellular domain (DeltaCyt). We used a hydrogel 3D system to assess proliferation in vitro, while murine SCID and plasmacytoma models were used to study intramedullary and extramedullary engraftment/proliferation of ROBO1 wild type (WT) and KO tumors in vivo. To study dissemination and homing, KO and FL MM cells were injected intravenously (IV) in SCID mice. ROBO1 immunoprecipitation, western blotting and immunofluorescence were used to study ROBO1 interacting partners and signaling. Results ROBO1 is highly expressed in MM cell lines and primary MM, being enriched in t(4;14) patients, in contrast to low/absent expression in normal BM plasma cells and non-MM hematologic cancer cell lines. ROBO1 KD was specifically cytotoxic against MM cell lines and ROBO1 KO MM cells showed a significant proliferative defect that can be fully rescued by FL or Cyt ROBO1 expression. Viceversa, DeltaCyt ROBO1 acts as a dominant negative. In vivo, ROBO1 KO MM cells have impaired engraftment to BM and significantly reduced growth within and outside the BM. Furthermore, ROBO1 KO MM cells have a significant defect in adhesion to BM endothelial and stromal cells that can be fully rescued by FL ROBO1. Mice injected IV with ROBO1 KO cells show a modest prolongation in overall survival compared to ROBO1 FL mice (90 versus 75 days, respectively), however the pattern of disease is strikingly different. ROBO1 FL mice develop hindlimb paralysis with extensive BM infiltration of femurs/pelvis while ROBO1 KO mice present with osseous plasmacytoma with no/minimal BM infiltration. These data suggest that ROBO1 is necessary and sufficient for BM homing and dissemination in MM. Mechanistically, we showed that ROBO1 interacts with ABL and discovered that ROBO1 cytoplasmic domain localizes to the nucleus. Conclusions We propose a dual model for ROBO1 function in MM: the full transmembrane receptor regulates MM adhesion, dissemination and homing to the BM; the intracellular domain is cleaved and translocates to the nucleus where it participates in transcriptional regulation via unknown mechanisms, promoting MM survival.

Keywords:
microenvironment

proliferation

signaling

Tracks:
Multiple Myeloma Signaling

FP-086

ILF2 antisense oligonucleotide therapy and CRISPR/Cas9-based screening for DNA repair effectors identify synthetic lethal approaches to enhancing myeloma cells' sensitivity to DNA damage

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Abstract:
In previous studies of recurrently amplified 1q21 genes in multiple myeloma (MM), we identified ILF2 (Interleukin Enhancer Binding Factor 2) as a key modulator of the DNA repair pathway, which promotes adaptive responses to genotoxic stress in a dose-dependent manner, explaining why 1q21 patients benefit less from high-dose chemotherapy than non-1q21 patients do (Cancer Cell 2017). These findings prompted us to develop strategies for blocking ILF2 signaling to enhance the effectiveness of available DNA-damaging agent-based treatments. We collaborated with IONIS Pharmaceuticals to develop antisense nucleotides (ASOs) targeting ILF2 (ILF2 ASOs). ILF2 ASOs that elicited the best dose response in A451 cells and had no off-target toxicities in Balb/c mice were used for functional validation studies in MM cells. Consistent with our previous work using ILF2-targeting shRNAs, ILF2 ASO-induced ILF2 depletion was associated with significantly inhibited cell proliferation, increased ATM/Chk2 pathway activation, γH2AX accumulation, and caspase 3-mediated apoptosis in KMS11 and JJN3 cells and sensitized these cells to melphalan and bortezomib treatment. However, whereas KMS11 cells had a high level of DNA damage activation and a significantly higher apoptosis rate after more than 2 weeks of ILF2 ASO treatment, JJN3 cells overcame ILF2 ASO-induced DNA damage activation and apoptosis and became resistant to ILF2 ASO treatment. To gain insights into the molecular mechanisms by which MM cells can overcome ILF2 ASO-induced DNA damage activation, we subjected ILF2 ASO-treated KMS11 and JJN3 cells to RNA sequencing analysis at early and late treatment times. We found that the genes that were significantly downregulated in JJN3 but not KMS11 cells treated with ILF2 ASOs for more than 2 weeks as compared with those treated for 1 week were mostly involved in the regulation of the DNA damage response. These findings suggest that MM cells can activate compensatory mechanisms to overcome the deleterious effects of DNA damage and survive. To identify DNA repair effectors whose loss of function suppresses 1q21 MM cells' capability to overcome ILF2 ASO-induced DNA damage, we performed a CRISPR/Cas9 screening using a pool of single-guide RNAs (sgRNAs) targeting 196 genes involved in the DNA damage response. Using the drugZ algorithm to assess differences in the representation of all sgRNAs between cells treated with non-targeting (NT) or ILF2 ASOs for 3 weeks, we found that sgRNAs targeting the DNA replication helicase/nuclease 2 (DNA2) were among the most significantly depleted sgRNAs in ILF2 ASO-treated JJN3 cells. Using the DNA2 inhibitor C5, we further validated that targeting DNA2 significantly enhances ILF2 ASO-induced apoptosis in JJN3 cells. Functional validation experiments are ongoing to evaluate whether DNA2 inhibition is a synthetic lethal approach to targeting 1q21 MM cells in the setting of therapies with DNA-damaging agents.

Keywords:
DNA damage

replication stress

Synthetic lethality

Tracks:
Multiple Myeloma Signaling

FP-087

Downregulation of the unfolded protein response is a potential mechanism for therapeutic resistance in multiple myeloma

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Abstract:
Introduction: Normal and malignant plasma cells rely on an adapted unfolded protein response (UPR) in order to withstand the endoplasmic reticulum stress associated with high immunoglobulin production. Proteasome inhibitors (PIs) overwhelm the UPR machinery, shifting from a pro-survival response to a pro-apoptotic one. Leung-Hagesteijn et al. (2013) demonstrated in multiple myeloma (MM) cell lines that downregulation of IRE1 (a principal stress sensor in the UPR and the enzyme responsible for splicing the transcription factor XBP1) leads to PI resistance. Furthermore, they demonstrated in patient samples that immature progenitors exist which have lower basal UPR activity, are resistant to PIs, and repopulate as a treatment-refractory subset following treatment with PIs. We sought to determine whether the association of UPR gene expression and treatment response was specific to PIs. Methods: We performed a secondary analysis of data from the MMRF CoMMpass study (IA14). In the CoMMpass study, RNAseq on CD138-enriched bone marrow cells was performed using Illumina TruSeq RNA library kits. We identified patients who had pre- and post-treatment RNAseq data, and segregated them based on whether they had relapsed disease, relapse following completion of therapy, or refractory disease, progression on or within 60 days of completing therapy. We analyzed expression of UPR genes from the pre- and post-treatment specimens using paired T-tests. Results: Forty-six patients met inclusion criteria. Twenty-two had relapsed disease while off of treatment and 24 had developed refractory disease while on treatment. Patients who had refractory disease had a significant decrease in the expression of IRE1 ($p = 0.008$) and a trend toward decreased expression of PERK ($p = 0.079$) and XBP1 ($p = 0.191$). In the subset of patients refractory to PI-based treatments ($n = 8$), both IRE1 and PERK were significantly decreased (both $p = 0.044$) but not XBP1 ($p = 0.229$). Unexpectedly, patients with IMiD-refractory MM ($n = 13$) also had a significant decrease in PERK expression ($p = 0.009$) and a trend towards decreased expression of IRE1 ($p = 0.054$) but not XBP1 ($p = 0.330$). In contrast, there was not a significant difference between pre-treatment and post-treatment IRE1, PERK, or XBP1 expression in relapsed disease ($p = 0.312$, 0.415, and 0.716, respectively). Discussion: As hypothesized, refractoriness to PIs was associated with downregulation of IRE1 and PERK expression, key regulators of the UPR. Surprisingly, downregulation was also seen in IMiD-refractory MM. While in vitro studies have demonstrated that PIs select for immature MM cells with lower basal UPR activity and inherent PI-refractoriness, the same has not been investigated for IMiDs. The UPR may be a mechanism for IMiD resistance or a marker of general resistance, not specific to PIs. Further basic research and clinical correlatives will help illuminate the relationship between UPR dynamics and myeloma drug resistance.

Keywords:
ER stress

resistance

Unfolded Protein Response

Tracks:
Multiple Myeloma Signaling

FP-088

Targeting myeloma metabolisms regulated by HDAC1-IRF4 axis can be a novel therapeutic strategy

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Abstract:
Histone deacetylases (HDACs) mediate epigenetic regulation of gene expression and post-transcriptional protein modification. HDACs consist of 4 classes and 18 isoforms, which are aberrantly upregulated in malignant cells. We have already reported that inhibition of HDAC1 or HDAC3 is able to induce significant MM cell death (Leukemia 2014, 2017). A non-selective HDAC inhibitor panobinostat in combination with bortezomib and DEX shows anti-tumor effects in relapsed/refractory MM patients; however, there are notable adverse events such as fatigue and muscle weakness to cause discontinuation of the treatment. To improve tolerability and clinical efficacy of this class of agents without unfavorable events, isoform-selective biologic impact and their clinical significance in MM need to be elucidated. In this study, we aim to delineate the role of HDAC1 in MM tumor metabolisms and its therapeutic implication in MM cells. In order to clarify downstream targets of HDAC1 in MM cells, we first carried out RNA-Seq in HDAC1-knockdown RPMI 8226 cells using lentiviral shRNA and found that IRF4 and PIM2 were significantly downregulated. IRF4 has been demonstrated to be associated with MM cell metabolisms through regulating oncometabolism-related gene expression (Nature 2008), while PIM2 is associated with glycogenesis and mitochondrial generation and function. We hypothesized that HDAC1 specifically maintains IRF4 and PIM2 expression and associated transcription/metabolisms through modification of histone deacetylation in MM cells. We therefore treated MM cells in the presence of a HDAC1/3 selective inhibitor MS-275 (Entinostat) or a histone acetyltransferase (HAT) inhibitor C646. Importantly, both MS-275 and C646 were able to downregulate IRF4 and PIM2 expression, suggesting that IRF4 and PIM2 expression is regulated by the balance of acetylation status of histones. Since IRF4 is a master regulator of various transcription signaling pathways in MM cells, we next investigated the impact of inhibition of HDAC1-IRF4 axis on MM cell survival. IRF4-overexpression by retroviral cDNA attenuated HDAC1 knockdown-induced MM cell growth inhibition. Moreover, IRF4 bound to PIM2 promoter region as determined by ChIP-Q-PCR assay; conversely, IRF4 knockdown reduced PIM2 and c-Myc at mRNA and protein levels, indicating the HDAC1-IRF4-PIM2 and/or HDAC1-IRF4-c-Myc axes plays a crucial role in MM cell proliferation/survival. We have previously demonstrated that PIM2 is upregulated through major growth/survival signaling pathways in MM cells in the context of the bone marrow (BM) microenvironment (Leukemia 2011, 2015). Importantly, addition of a PIM inhibitor SMI-16a further enhanced the cytotoxic effects on MM cells of MS-275 at suboptimal concentrations. Taken together, our study provides the framework for novel rationale combinatory treatment of class-I HDAC inhibitors with PIM inhibitors in MM cells in the BM microenvironment.

Keywords:
histone deacetylase

IRF4

PIM2

Tracks:
Multiple Myeloma Signaling

FP-089

Combined targeting of distinct c-Myc and JunB transcriptional programs for multiple myeloma therapy

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Abstract:
INTRODUCTION c-Myc plays a pivotal role in multiple myeloma (MM) pathogenesis; and the BET protein BRD4 is a key regulator of c-Myc transcription. Recently, a pathophysiologic role in MM has also been attributed to the AP-1 family member JunB. Approaches to target transcription factors (TFs), such as c-Myc and JunB, currently emerge among the most promising novel anti-MM strategies, with a potentially high therapeutic index. However, redundancy phenomena present a challenge for targeting c-Myc- or JunB-mediated tumor proliferation programs. METHODS BRD4, c-Myc and JunB expression was measured by qPCR and WB analysis. The functional relevance of BRD4/c-Myc- and JunB-induced transcriptional programs was investigated using knockdown approaches followed by 3H-thymidine incorporation, survival assays, PI/annexin staining, flow cytometry, RNAseq, luciferase reporter assays and a MM xenograft mouse model. RESULTS MZ-1 is a novel proteolysis-targeting chimera combining the recognition sequence for the E3-ligase Von-Hippel-Lindau with JQ1, a moiety that targets BRD4. Indeed, beyond direct inhibition by JQ1, MZ-1 significantly decreased BRD4 as well as c-Myc protein levels in MM cell lines and primary cells. Consequently, MZ-1 inhibited MM cell growth through G0/G1 arrest; and induced tumor cell death. Of note, patient-derived BMSCs or exogenous IL-6 induced BRD4/c-Myc upregulation in MM cells, which was inhibited by MZ-1 treatment, indicating that targeting BRD4, at least in part, overcomes the protective effect of the microenvironment. Likewise, BMSCs/IL-6 upregulate JunB expression. Despite BMSCs/IL-6 upregulated the expression of BRD4/c-Myc and JunB, neither MZ-1 nor siBRD4 or siMyc had an impact on JunB RNA or protein levels. Conversely, dox-induced knockdown of BMSC/IL-6-triggered JunB upregulation in TetshJunB/MM.1S cells did not decrease BRD4/c-Myc RNA or protein levels. Similar data were obtained in other MM cell lines. RNAseq, unbiased GSEA, and luciferase reporter assays of representative target genes confirmed these findings, and thereby excluded a molecular interrelation of c-Myc- and JunB-mediated proliferative programs, which are initiated by the same stimuli. However, our in vitro results demonstrate that dox-induced knockdown of BMSC/IL-6-triggered JunB upregulation in TetshJunB/MM.1S cells in combination with MZ-1 treatment significantly decreased both JunB as well as BRD4/c-Myc protein levels; synergistically inhibited tumor cell proliferation; and induced cell death. These data indicate that that combined TF-inhibition overcomes redundancy phenomena. Ongoing experiments investigate the in vivo activity of MZ-1 in BMSC:TetshJunB/MM.1S versus BMSC:TetshSCR/MM.1S-carrying dox-treated NSG mice. CONCLUSION Our data demonstrate for the first time the existence of non-overlapping c-Myc- and JunB-regulated transcriptional programs; and strongly support the therapeutic benefit of combined targeting of these two TFs in MM.

Keywords:
BET/BRD4

JunB

Multiple myeloma

Tracks:
Multiple Myeloma Signaling

FP-090

RNF6 promotes myeloma cell proliferation and survival by stabilizing and activating glucocorticoid receptor

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Abstract:
Dexamethasone as one of the major anti-myeloma drugs induces myeloma (MM) cell apoptosis via its receptor glucocorticoid receptor (GR). GR expression levels and post-translational modifications are critic for MM resistance to dexamethasone, but the mechanisms are largely unknown. In the present study, the RING type ubiquitin ligase RNF6 was found highly expressed in association with GR expression levels in MM cells and promotes cell proliferation. Subsequent studies showed that RNF6 induces GR with K63-linked polyubiquitination, and then increases its stability. Moreover, RNF6 binds to the ligand binding domain of GR, which results in upregulated GR transcriptional activity. This hypothesis is confirmed by the expression of pro-survival genes including BCL-2 and Mcl-1, all are upregulated by GR. Consistent with these findings, inhibition of RNF6 leads to MM cell apoptosis, and decreased MM cell proliferation. In summary, we revealed that RNF6 promotes MM cell proliferation and survival and it could be a promising therapeutic target for the treatment of MM.

Keywords:
dexamethasone

ubiquitination

Tracks:
Multiple Myeloma Signaling

FP-091

Discovery, Functional Characterization and Therapeutic Targeting of Lnc-17-92 Metabolic Signaling in Multiple Myeloma

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Abstract:
Long noncoding RNAs (lncRNAs) play key roles in regulating chromatin dynamics and gene expression. We have recently described the lncRNA landscape in multiple myeloma (MM) and reported their role as independent risk predictors for clinical outcome, providing a strong rationale to evaluate their molecular and biological impact in the disease. From this lncRNA profile, we have identified lnc-17-92 as an independent risk predictor highly correlating with EFS and OS in newly-diagnosed MM providing rationale for its further evaluation in MM. This lncRNA is involved in the biogenesis of miR-17-92 cluster of microRNAs, however, here we are for the first time establishing its microRNA-independent role in MM pathobiology. Suppression of lnc-17-92 by antisense oligonucleotides (n=3) led to apoptosis in 12 genotypically distinct human MM cell lines (HMCLs) as well as in 13 primary patient MM cells. Importantly, ectopic expression of miR-17-92 microRNAs does not fully rescue the inhibitory effect on MM cell growth confirming its independent activity. To identify transcriptional targets of lnc-17-92, we performed an integrative analysis of gene expression changes after lnc-17-92 suppression and RNA-seq data from 2 large independent cohorts of MM patients. The identified lnc-17-92 target genes are significantly enriched within metabolic pathways, suggesting an unexplored role for lnc-17-92 in MM cell metabolism. We have further confirmed the microRNA-independent role of lnc-17-92 in the transcriptional control of these genes using DROSHA knock-out cells. The impact of lnc-17-92 target genes on MM cell growth was evaluated using loss-of -function screen with an RNAi-based approach in 2 HMCLs revealing a specific vulnerability to modulation of lcn-17-92 transcriptional program. One of the most significant

genes in the screen, ACC1, encodes the limiting enzyme in the de novo lipogenesis (DNL) pathway. Analysis of incorporation of C14-radiolabeled glucose into lipids revealed that inhibition of ACC1 or lnc-17-92 strongly inhibits DNL in HMCLs and in primary MM cells. Moreover, supplementation of palmitate, the main downstream product of ACC1 activity, significantly reverses the growth inhibitory effect of either ACC1 or lnc-17-92 suppression in MM cells. These data suggest an important role for DNL pathway on lnc-17-92-promoted MM cell growth. Mechanistically, our preliminary data suggest that lnc-17-92 may function as a scaffold between MYC and the E-box motifs present on ACC1 intronic sequences, facilitating MYC binding and its transcriptional activity on ACC1. Finally, small molecule inhibitors of ACC1 are available in pre-clinical or clinical setting and we are currently evaluating their impact against a large panel of HMCLs and primary patient MM cells. In conclusion, we highlight a transcriptional regulatory activity of a lncRNA in MM with significant functional impact on lipogenesis via ACC1 that can be therapeutically translated.

Keywords:
lipogenesis

LncRNA

Metabolism

Tracks:
Multiple Myeloma Signaling

FP-092

Aberrant Wnt signaling in multiple myeloma: molecular mechanisms and targeting options

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Abstract:
Aberrant activation of Wnt/β-catenin signaling plays a central role in the pathogenesis of a wide variety of malignancies and is typically caused by mutations in core Wnt pathway components, driving constitutive, ligand-independent signaling. In multiple myelomas (MMs), however, these pathway intrinsic mutations are rare despite the fact that most tumors display aberrant Wnt pathway activity. Recent studies indicate that this activation is caused by genetic and epigenetic lesions of Wnt regulatory components, sensitizing MM cells to autocrine Wnt ligands as well as to paracrine Wnts emanating from the bone marrow niche. These include deletion of the tumor suppressor CYLD, methylation of the promotors of Wnt antagonists WIF1, DKK1,-3, and sFRP1,-2,-4,-5, as well as overexpression of the co-transcriptional activator BCL9 and co-receptor LGR4. Furthermore, Wnt activity in MM is strongly promoted by interaction of both Wnts and R-spondins with syndecan-1 on the MM cell-surface. Functionally, aberrant canonical Wnt signaling plays a dual role in the pathogenesis of MM: i) It mediates proliferation, migration, and drug resistance of MM cells; ii) MM cells secrete Wnt antagonists that contribute to the development of osteolytic lesions by impairing osteoblast differentiation. As will be discussed, these insights into the causes and consequences of aberrant Wnt signaling in MM, will help to guide the development of targeting strategies. Importantly, since Wnt signaling in MM cells is largely ligand dependent, it can be targeted by drugs/antibodies that act upstream in the pathway, interfering with Wnt secretion, sequestering Wnts, or blocking Wnt (co)receptors. Derksen et al. PNAS, 101:6122-27, (2004). van Andel et al. Oncogene, 36:2105-15, (2017). van Andel et al. PNAS, 114:376-81, (2017). Ren et al. Blood,131:982-94, (2018). van Andel et al. Leukemia, 33:1063–75 (2019)

Keywords:
signaling

therapy

Wnt

Tracks:
Multiple Myeloma Signaling

FP-093

CD28 Mediates Pro-Survival Autophagy In Multiple Myeloma

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Abstract:
Multiple myeloma (MM) is incurable by current therapies, primarily due to acquired chemotherapy resistance and subsequent relapse. Defining the pro-survival responses in MM is critical to discover novel targets and develop new therapies. Our lab previously reported that CD28, the prototypic T cell costimulatory molecule, is also expressed on myeloma cells and is essential to support MM stress adaptation, survival and chemotherapy resistance. However, how CD28 mediates pro-survival responses has been largely undetermined. Here, we report that CD28 mediates a pro-survival response in MM through autophagy. Direct CD28 activation on MM cells by anti-CD28 mAb or co-culture with dendritic cells expressing CD28 ligands CD80 and CD86 protected MM cells from chemotherapy (melphalan) or serum starvation induced death, improving MM viability more than 2 folds. Inhibition of autophagy by the pharmacologic reagents bafilomycin A1 (Baf) or 3-methyladenine (3MA), or knockdown ATG5, a critical autophagy regulator, abrogated CD28's pro-survival effects. CD28 activation resulted in a 2-fold increase in the autophagy marker LC3II as well as elevated autophagosome numbers assessed by CytoID. Conversely, knockdown of CD28 decreased these effects. By using the MM cell lines that expressed tandem mCherry-GFP tagged LC3, which GFP is quenched by autophagic degradation, we confirmed that CD28 engagement induced autophagic flux. Additionally, we found CD28 activation upregulated ATG5 protein expression 2 folds, which has not been previously reported in any cell type. Inhibition of autophagy by Baf or 3MA failed to inhibit upregulation of ATG5 by CD28 signaling, which indicates CD28 signaling upregulates ATG5. Activation of CD28 did not robustly increase the expression of the ATG5 gene as measured by mRNA expression. Analysis of gene expression databases of CD138+ cells from healthy donors, MGUS, smoldering myeloma and MM patients (GSE5900, GSE4581) demonstrated that CD28 expression did not correlate ATG5 mRNA expression. Blocking translation with cycloheximide failed to inhibit upregulation of ATG5 by CD28 activation. However, blocking protein degradation using the proteasome inhibitor MG132 completely abolished ATG5 upregulation, suggesting CD28 signaling induces ATG5 protein expression by preventing ATG5 degradation through a novel mechanism. To answer how CD28-mediated autophagy improves MM survival, we found inhibition of autophagy by 3MA or shATG5 or shATG7 minimizes CD28-mediated induction of oxidative phosphorylation in MM. Active mitochondrial respiration requires fatty acids fueled and released by breakdown of lipid droplet. We found lipid droplets in MM decreased upon CD28 activation. Blocking lysosomal lipase activity by lalistat1&2 decreased CD28-mediated pro-survival effects. These findings suggest a novel mechanism where CD28-mediated autophagy is fueling fatty acid oxidation and mitochondrial respiration to maintain metabolic fitness and improve survival.

Keywords:
ATG5

Autophagy

CD28

Tracks:
Multiple Myeloma Signaling

FP-094

INCREASED EXPRESSION OF PD-1 CHECKPOINT MOLECULE ON BONE MARROW T-CELLS FROM PATIENTS WITH MULTIPLE MYELOMA: POTENTIAL IMPACT ON CLINICAL OUTCOME ?.

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Abstract:
Background: Multiple myeloma (MM) is associated with complex immune deregulation that includes loss of myeloma-reactive effector T-cell populations. PD-1 cell surface expression is a characteristic marker of T cell exhaustion. Therefore, the role of the PD-1/PD-L1 pathway in mediating immune escape in MM could have an influence in response to therapy. Although some investigators have analyzed the presence of PD1 in cell suspension samples from myeloma patients, little is known about their potential impact on clinical outcome. Aims: In the present study, we hypothesized that the presence of PD1+ T-cells in the bone marrow from patients with MM, could be related to the pattern of marrow infiltration and might have an impact on survival. Materials and methods: Bone marrow tissue samples from MM patients were obtained at initial diagnosis. Both PD1 expression on T cells , and CD138+ plasma cells were measured by immunohistochemical methods. Plasma cell infiltration pattern was considered diffuse when the percentage of CD138+cells exceeded 40%. Correlation between number of PD1+ cells, and pattern of infiltration, or the presence of ostheolytic lesions, was evaluated by logistic regression. Kaplan-Meier estimates and Cox regression were used to analyze the impact of PD1 expression on, either progression free survival (PFS), or overall survival (OS). Results: Thirty-one MM patients, diagnosed and treated at a single institution, were included. Median age at diagnosis was 66y (38-89). 59.4% of the patients were on ISS-R clinical stage 2. Poor risk cytogenetic abnormalities were present in 14.3% of the cases. Median percentage of CD138+ plasma cells in the bone marrow was 45% (range 8-100), showing a diffuse pattern in 58.6% of the cases. Maximum PD-1+ T-cell count was highly variable, ranging from 0 to 42 cells per field, with a median of 8 c/f. PD-1+ cells were distributed heterogeneously , either in focal aggregates or in a widespread fashion. There was no correlation between a diffuse CD138+ plasma cell infiltration pattern, and the number of PD-1+ cells (p=0.216) There was also no correlation between PD1+ count and the presence of ostheolytic lesions . Kaplan-Meier estimates showed median PFS and OS of 42 and 90 months, respectively. The presence of a high PD1+ cell count (>10/field) showed no impact on PFS (Log-rank p=0.75) or OS (log-rank p=0.95. Conclusion: Taken together, our results showed upregulation of PD1 in bone marrow T-cells from MM patients. Nevertheless this finding had no apparent impact on clinical outcome, in terms of PFS or OS. Larger studies are needed to address this issue.

Keywords:
myeloma

PD-1 blockade

prognostic impact

Tracks:
Multiple Myeloma Signaling

FP-095

The study on the expression of long noncoding RNA in multiple myeloma with extramedullary disease

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Abstract:
Objective: To explore the different expression of lncRNAs and mRNAs between medullary plasma

cells and extramedullary plasma cells in multiple myeloma (MM) patients. Methods: We collected the medullary plasma cells of newly diagnosed MM patients and extramedullary plasma cells when these patients relapsed with extramedullary involvement. Human lncRNA and mRNA microarrays were used to determine the different expression of lncRNAs and mRNAs between medullary plasma cells and extramedullary plasma cells. Results: Human lncRNA and mRNA microarrays were used to determine the different expression of lncRNAs and mRNAs between medullary plasma cells and extramedullary plasma cells in three patients. The results showed that there were 2490 dysregulated lncRNAs (Fold Change≥5, $p<0.05$), including 1559 upregulated lncRNAs and 931 downregulated lncRNAs in extramedullary plasma cells compared with medullary plasma cells. There were 1647 dysregulated mRNAs (Fold Change≥5, $p<0.05$), including 687 upregulated mRNAs and 960 downregulated mRNAs in extramedullary plasma cells compared with medullary plasma cells. We present gene-coexpression networks to identify interactions among genes. We found that gp130 expression increased in extramedullary plasma cells. Next, we found potential deregulated lncRNA lncAMM associated with gp130. This result indicated that lncAMM/gp130 might be associated with extramedullary migration. Conclusion: Our researches detect the role of lncRNA regulation as a new perspective of mechanism in the pathogenesis of extramedullary disease.

Keywords:
extramedullary disease

Tracks:
Multiple Myeloma Signaling

FP-096

In vivo modeling of clonal competition using CRISPR-based gene editing reveals novel fitness variables in multiple myeloma

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Abstract:
Multiple Myeloma (MM) is an incurable malignancy characterized by the proliferation of clonal plasma cells in the bone marrow (BM). MM almost always progresses from the precursor states, which indicates the presence of a gradual clonal evolution underlying progression from the original stages of tumor development to the time of clinical presentation. Clonal heterogeneity adds another layer of complexity to that, by introducing interclonal competition in the context of disease progression or therapeutic bottlenecks. Here we developed a mouse model to investigate the impact of multiple clonal mutations on tumor development, as well as the competitive expansion of individual clones. Methods: Primary mouse MM Vk*Myc cells stably expressing Cas9 were infected with validated sgRNAs to knockout (KO) genes of interest (P53, Cyld, Rb1, Dis3, Prdm1, Traf3 and Fam46c) that are significantly mutated in human MM. KO cells were mixed at a 1:1 ratio with control cells and injected intravenously into 8-week-old RAG2 KO mice. Vk*Myc cells were then isolated from BM and spleen, followed by genomic DNA extraction and NGS sequencing to understand the dynamic changes in abundance of mutants from injection to late timepoints. Results: In vitro, most KO Vk*Myc cells had a similar proliferation rate to control cells except P53 and Rb1 KO cells, which grew fasteras both P53 and RB1 are known cell cycle regulators. However, when co-injected into RAG2 KO mice, although P53 and Rb1 KO cells remained the strongest competitors, occupying the majority of the tumor, most KO cells exhibited significantly enhanced proliferation over control cells. These results indicate that certain mutations only become advantageous in the context of tumor

microenvironment, while mutations that directly affect proliferation rate give rise to more flexible, potent clones. When looking at clonal abundancy rates within each KO population separately, we also found mutants with certain insertions/deletions grew faster than others and were overrepresented at the late stage of disease. Conclusion: We established a mouse model to study clonal competition in vivo, utilizing the CRISPR-Cas9 genome editing toolset. We observed a range of competitive potential among genes that are significantly mutated in multiple myeloma, with P53- and RB1-mutants as the strongest competitors. Furthermore, competitive potential can be conditional, with certain mutants conferring fitness advantage only in the context of tumor microenvironment. In this study, we thus demonstrate that mutational candidates can be prioritized based on competitive potential, a process of the utmost importance given multiple myeloma's marked genetic heterogeneity.

Keywords:
clonal competition

tumor microenvironment

Tracks:
Multiple Myeloma Signaling

FP-097

Dexamethasone synergizes with MCL-1 inhibition in multiple myeloma through suppression of S6 phosphorylation

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Abstract:
The number of anti-cancer drugs that are approved for clinical use or in late-stage clinical trials for treatment of multiple myeloma is extensive and rapidly increasing. However, drug resistance and relapse after treatment are still very common problems. There is an unmet need for a strategy to identify logical combinations of (partially) successful drugs to reach synergistic effects. Testing all possible drug combinations and redefining pharmacodynamics for combination treatments is practically challenging. Therefore, we performed a lethality screen in three human multiple myeloma cell lines (HMCLs) in which we combined two drugs representing different drugs classes, including classical chemotherapeutics, proteasome inhibitors, pro-survival BCL-2 protein family inhibitors, HDAC inhibitors and corticosteroids to test for synergy. Of the twenty-eight combinations tested, seven showed synergistic effects in all three HMCLs. The combination of dexamethasone with the specific MCL-1 inhibitor S63845 was found to be the most potent, resulting in strong synergistic killing with average combination indexes of 0.3-0.5. In accordance with literature we observed a minor increase in dexamethasone-induced BIM mRNA and protein expression. Additional kinome analysis of HMCLs revealed a reduction in Akt kinase activity upon dexamethasone treatment. We did not observe downstream effects on nuclear FOXO1/3a levels or localization but did detect a great reduction in phosphorylation of ribosomal protein S6 on both serine 235/236 and 240/244 positions. Inhibition of S6 phosphorylation by a S6K1 inhibitor also had synergistic effects on cell death in combination with MCL-1 inhibition. This suggests that a S6K1 inhibitor might be used as a substitute of dexamethasone in the combinatorial treatment with MCL-1 inhibitors. In conclusion, we reveal a novel molecular mechanism mediated by Akt and S6 phosphorylation that is underlying synergy between dexamethasone and MCL-1 inhibition in multiple myeloma.

Keywords:
dexamethasone

Mcl-1 inhibitor

S6

Tracks:
Multiple Myeloma Signaling

FP-098

A progressive auto-amplification loop in TAK1 expression and activation in myeloma cells

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Abstract:
We have reported that TGF-beta-activated kinase-1 (TAK1) is constitutively over-expressed and phosphorylated in myeloma (MM) cells to mediate their growth and survival signaling. TAK1 expression and phosphorylation levels appear to be much higher in MM cells compared to their surrounding cells in bone marrow. In the present study, we therefore explored whether MM cells have a unique mechanism to augment the TAK1-mediated signaling. Okadaic acid, an inhibitor of protein phosphatase 2A (PP2A), a major serine and threonine protein phosphatase, further enhanced the phosphorylation levels of TAK1 in MM cells, whereas SMAP, an activator of PP2A, dose-dependently suppressed phosphorylation of TAK1 along with TAK1 protein levels to induce MM cell death, indicating the critical role of the suppression of PP2A activity in TAK1 phosphorylation and thereby MM cell growth and survival. Although PP2A but not PP2C is constitutively expressed in MM cells, MM cells also expressed endogenous PP2A inhibitors, including cancerous inhibitor of PP2A (CIP2A), SET and PME-1. Interestingly, normal quiescent cells expressed SET and PME-1 but not CIP2A. Furthermore, CIP2A gene silencing by its shRNA suppressed TAK1 phosphorylation and activation of their corresponding downstream signaling molecules including NF-κB, p38 and ERK to induce apoptosis in MM cells. Taken together, these results suggest that CIP2A plays an important role in the constitutive phosphorylation of TAK1 in MM cells but not in normal cells. The TAK1 inhibitor LLZ1640-2 or TAK1 gene silencing reduced the expression of Sp1, a critical transcription factor for MM growth and survival; the Sp1 inhibitor terameprocol reduced TAK1 levels in MM cells. Intriguingly, LLZ1640-2 markedly suppressed CIP2A but not SET and PME-1 at protein as well as mRNA levels in MM cells. These results suggest a progressive auto-amplification loop in TAK1 expression and activation in MM cells, which can be effectively disrupted by TAK1 inhibition. Because PP2A inhibition by CIP2A not only activates TAK1 but also other serine and threonine kinases such as PIM2 and Akt, TAK1 appears to be a bottleneck of simultaneous activation of multiple signaling pathways in MM cells. Indeed, TAK1 inhibition was able to suppress VEGF production by MM cells and their expression of BCMA and TACI, receptors for BAFF and APRIL, and integrin beta1. Besides, TAK1 inhibition reduced VCAM-1 expression in BMSCs in cocultures with MM cells, and impaired MM cell adhesion onto BMSCs to suppress RANKL expression and IL-6 production by BMSCs. Therefore, TAK1 plays a pivotal role in tumor progression and bone destruction in MM, and is regarded as an important therapeutic target for MM.

Keywords:
CIP2A

PP2A

TAK1

Tracks:
Multiple Myeloma Signaling

FP-099

YWHAE/14-3-3ε expression impacts the proteasome load contributing to proteasome inhibitor sensitivity in multiple myeloma

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Abstract:
Background: High protein load is a feature of multiple myeloma (MM), which makes this disease exquisitely sensitive to proteasome inhibition (PI). 14-3-3 are chaperone and scaffold proteins that exert a widespread influence on cellular processes through binding to serine/threonine-phosphorylated residues on target proteins. Here we report that loss of YWHAE, the coding gene for the 14-3-3ε protein, causes an imbalance in the protein load in MM cells potently impacting their sensitivity to PI. Methods and Results: We evaluated the expression of 14-3-3ε in MM cells and found it to be constitutively expressed at both RNA and protein level in primary patient MM cells and in a large panel of MM cell lines, with lower expression in healthy donor B cells. However, lower expression of 14-3-3ε was associated with poor outcome in MM patients receiving a bortezomib (Btz)-based therapy. To evaluate its potential role in MM, we evaluated 14-3-3ε protein interactome by mass spectrometry (MS) analysis and identified binding proteins enriched in mTORC1, PI3K-AKT-mTOR, and unfolded protein response (UPR) related pathways. Cell signaling studies showed that 14-3-3ε impacts mTORC1 signaling in MM cells by binding to serine-phosphorylated residues on mTOR and its upstream negative regulator TSC2, resulting in mTORC1 activation. Conversely, depletion of 14-3-3ε inhibits TSC2 phosphorylation, causing a subsequent inhibition of mTORC1 signaling. As a result, we observed modulation of the eukaryotic initiation factor 4E (eIF4E) binding protein (4E-BP) and eIF2α, leading to inhibition of the translation initiation complex formation, with consequent decreased protein synthesis in MM cells and increased resistance to both carfilzomib (CFZ) and Btz. These observations were corroborated by gain-of-function studies where ectopic overexpression of 14-3-3ε in MM cells was associated with increased protein load and an enhanced sensitivity to PIs. In a large panel of MM cell lines the expression levels of YWHAE showed a significant negative correlation with both BTZ and CFZ response. Importantly, we confirmed a significant correlation between 14-3-3ε expression, PIs sensitivity and protein load (evaluated as M protein production) in primary MM cells from 2 independent datasets. Moreover, MM patients with del17p, where YWHAE is located, have lower 14-3-3ε expression providing an explanation for inability of Btz to overcome high-risk feature associated with del17p. Conclusion: Our results suggest that 14-3-3ε is a predictor of clinical outcome in MM and may serve as a potential target to modulate PI sensitivity in MM.

Keywords:
Multiple myeloma

Proteasome Inhibitor

YWHAE/14-3-3ε

Tracks:
Multiple Myeloma Signaling

FP-100

Functional proteogenomic screens in multiple myeloma

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Abstract:
Multiple myeloma is the second most common hematological malignancy and remains incurable despite recent advances in treatments. A comprehensive understanding of survival signaling pathways that sustain myeloma cells is lacking, partly due to the substantial heterogeneity found within this disease. Among the host of mutations identified in myeloma, oncogenic mutations of KRAS and NRAS are the most common and are associated with inferior patient outcomes. To understand how oncogenic RAS mutations function in the context of myeloma biology, we have employed quantitative mass spectrometry in tandem with genome-wide CRISPR-Cas9 screens in several myeloma lines to discover novel and essential RAS interaction partners. These initial experiments have identified new interactions between RAS and therapeutically actionable signaling pathways. Our data provide an initial roadmap for the rational deployment of signaling inhibitors in multiple myeloma tumors expressing oncogenic KRAS and NRAS.

Keywords:
screening

signaling

Tracks:
Multiple Myeloma Signaling

FP-101

Comprehensive profiling of circular RNA expressions reveals potential diagnostic and prognostic biomarkers in multiple myeloma

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Abstract:
Objective: This study aimed to explore the heterogeneity of circRNA expression pattern via microarray, and further evaluate the potential of 10 specific circRNAs as diagnostic and prognostic biomarkers in MM. Method: In exploration stage (stage I), circRNA expression profiles were detected by the microarray in bone marrow plasma cells from 4 MM patients and 4 healthy controls (HCs), and bioinformatic analyses were performed. In validation stage (stage II), top 5 upregulated and top 5 downregulated circRNAs identified in stage I were detected in 60 MM patients and 30 HCs for further validation; the diagnostic and prognostic values of these circRNAs in MM patients were analyzed. Results: In stage I, 122 upregulated and 260 downregulated circRNAs were identified in MM patients compared with HCs. GO, KEGG and pathway enrichment analyses revealed that these circRNAs were implicated in neoplastic pathways such as MAPK and VEGF signaling pathways. In stage II, circ-PTK2 and circ-RERE independently predicted higher, while circ-AFF2 and circ-WWC3 independently predicted lower MM risk; combination of these 4 circRNAs was of great diagnostic value for MM susceptibility (AUC=0.939). Besides, circ-PTK2, circ-RNF217 and circ-SETD5 predicted lower, while circ-AFF2 predicted higher treatment response; circ-PTK2 and circ-RNF217 correlated with worse while circ-AFF2 associated with better survival profiles in MM patients. Conclusion: This study provides valuable reference for profound understanding about circRNA expression patterns in MM, and validates that circ-PTK2, circ-RERE, circ-AFF2 and circ-WWC3 could serve as novel diagnostic biomarkers, while circ-PTK2, circ-RNF217, circ-SETD5 and circ-AFF2 might serve as potential prognostic biomarkers in MM.

Keywords:
circular RNA

diagnostic and prognostic

Multiple myeloma

Tracks:
Multiple Myeloma Signaling

MULTIPLE MYELOMA NOVEL AGENTS

FP-102

A Phase I study of PNK-007, allogeneic, off the shelf NK cell, post autologous transplant in multiple myeloma (NCT02955550)

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Abstract:
Background: PNK-007 is an allogeneic, off the shelf cell therapy enriched for CD56+/CD3- NK cells expanded from placental CD34+ cells. PNK-007 exhibit cytotoxicity against various cancer cell types, including multiple myeloma (MM), and secrete cytokines during co-culture with cancer cells. This is a Phase I study of single infusion PNK-007 after autologous stem cell transplant (ASCT) in MM. Methods: Placental CD34+ cells were cultivated in the presence of cytokines for 35 days to generate PNK-007 under cGMP standards followed by release testing. HLA matching and KIR mismatching were not used. Four treatment arms were evaluated on eligible patients (pts) following ASCT: 10 million (M) cells/kg Day (D) 14 with or without recombinant human IL-2 (rhIL-2), 30M cells/kg D14 with rhIL-2 or 30M cells/kg D7 with rhIL-2. rhIL-2 was administered subcutaneously at 6M units every other day for up to 6 doses to facilitate PNK 007 expansion. Pts received variable pre-ASCT induction therapy. Maintenance therapy was permitted after the Day 90-100 visit (D90). Enrollment is complete, and all pts have completed the D90 visit as of the cutoff date Oct 26, 2018. Results: 15 pts who received PNK-007 (12 of whom received rhIL-2) were evaluated for clinical response at D90. Pts aged 44-69 yrs included 12 newly diagnosed (ND)MM and 3 relapsed/refractory (RR)MM. The 3 RRMM received 1, 2 or 5 prior lines of therapy, with 2 pts having previous ASCT. All pts had been exposed to immunomodulatory drug (IMiDs) and proteasome inhibitors (PIs). No serious adverse events (AEs) were attributable to PNK 007 and the reported AEs were consistent with AEs related to ASCT treatment plan. No dose-limiting toxicity, GvHD, graft failure or graft rejection were observed. Based on physician assessed responses by International Myeloma Working Group pre-ASCT, 10/15 pts achieved VGPR or better (1 CR and 9 VGPR), and by D90, 12/15 pts achieved VGPR or better (5 CR or sCR and 7 VGPR). Using a validated Euro-flow minimal residual disease (MRD) assay by bone marrow aspirate (BMA), pre-ASCT, 4/15 pts were MRD negative (MRD-), and by D90, 10/15 pts were MRD-. PNK-007 did not interfere with immune reconstitution kinetics. Administration of rhIL-2 coincided with a transient increase in circulating regulatory T cell levels. Host NK cells reached a maximum level between 21-28 days post-ASCT followed by contraction independent of rhIL-2 administration. Conclusion: PNK-007 is the first fully allogeneic, off the shelf CD34+ derived NK cell product in MM clinical trials. A single infusion of PNK-007 up to 30M cells/kg with and without rhIL-2 was well tolerated in the post-ASCT setting. We established the feasibility of infusing PNK-007 as early as 7 days post-ASCT without negative impact on blood count recovery or successful engraftment. BMA MRD- status was observed in 10/15 pts at D90 post ASCT. These clinical data are encouraging and warrant further evaluation.

Keywords:
immunotherapy

NK cells

transplant

Tracks:
Multiple Myeloma Novel Agents

FP-103

The first-in-class BMI-1 modulators PTC-028 and PTC596 display potent activity in pre-clinical models of multiple myeloma

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Abstract:
Future progress in the treatment of multiple myeloma (MM) requires both the characterization of key drivers of the disease and novel, innovative approaches to tackle these vulnerabilities. Initially linked to the pathogenesis of MM more than a decade ago, with close associations to high-risk genes such as MYC and FOXM1, the polycomb group protein BMI-1 is a prominent example of oncogenic factors without a suitable clinical grade inhibitor. Here, we analyzed the pre-clinical activity of the first in class BMI-1 modulators PTC-028 and PTC596 using a comprehensive set of in vitro and in vivo models. BMI-1 modulators decreased BMI-1 protein levels within 24h of treatment and demonstrated potent activity in parental and PI-resistant HMCLs (n=16) (median IC50 40/57 nM for PTC-028/PTC596, respectively). IC50s are >10-fold reduced compared to the previously reported BMI-1 repressor PTC-209 (median IC50 680 nM, $P<0.05$). Similar potency was observed in co-culture and colony formation assays. Importantly, the reduction of BMI-1 protein levels significantly correlated with IC50s ($R>0.8$, $P<0.01$). Surprisingly, neither BMI-1 overexpression nor silencing affected MM cell growth or BMI-1 modulator activity. The non-essential role of BMI-1 in MM was further confirmed in a publically available CRISPR dataset of 18 MM cell lines suggesting that alternate mechanisms mediate the anti-survival effects of this drug class. Time course experiments demonstrated a potent mitotic arrest 6-24h post treatment associated with elevated expression of Cyclin B1, AURKA and BIRC5 as well as downregulation of MCL1. Prolonged mitosis was followed by the induction of apoptosis verified by the presence of Annexin V positive cells, cleaved caspases 8 and 9, cleaved PARP, loss of MCL1 protein and depolarization of the mitochondrial membrane potential. Furthermore, we noted a significant reduction of key MM signaling cascades, including MYC, FOXM1 and AKT activity. Drug combination studies with established agents (IMiDs/Dex/PIs/MEL) showed cell line specific effects. However, additional combination studies with four BH3 mimetics and four epigenetic compounds revealed A1331852 and GSK343 as the most promising partners, suggesting that mitotic arrest as well as impaired polycomb repressive complex 1 activity due to loss of BMI-1 might sensitize MM cells to BCLxL and EZH2 inhibition, respectively. Finally, in vivo experiments with PTC596 in the 5TGM1 murine model demonstrated a dose dependent reduction of BM infiltration and complete eradication of MM cells at 30 mg/kg/weekly. This remarkable activity was confirmed in an independent experiment demonstrating similar potency (i.e. no detectable MM cells post PTC596 treatment). Taken together, these results bring into question the postulated role of BMI-1 as an essential MM gene and reveal BMI-1 modulators as potent anti-mitotic agents with encouraging pre-clinical activity that supports their rapid translation into clinical trials.

Keywords:
BMI-1

PTC-028

PTC596

Tracks:
Multiple Myeloma Novel Agents

FP-104

Ex vivo sensitivity to venetoclax is predictive of clinical activity

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Abstract:
A drug screening platform including 76 multiple myeloma (MM) relevant therapeutics was evaluated in 113 primary MM samples. The panel included venetoclax, a selective BCL-2 inhibitor that has shown exceptional antitumor activity in hematological malignancies. Here we explored the ex vivo venetoclax response and its association to clinical features and BCL-2 family RNA expression levels. Venetoclax was screened in a 7-point, 10-fold dilution starting at 10 µM, incubated for 24 hours, and response was evaluated through cellular viability. The majority of the 113 primary patient samples (93%) exhibited a dose response to the drug; broad mid-point EC50 ranges were observed (<0.1 to >10000 nM) and AUCs varied from 0.03584 to 0.9327. A mid-point EC50 lower than 100nM was measured in 49% of samples, demonstrating the overall potency of venetoclax in MM. As expected, samples from patients harboring t(11;14) had an increased ex vivo sensitivity to the drug (n=28; median AUC 0.1491) when compared to patients lacking the translocation (n=82; median AUC 0.3644) (p=0.0013). Additionally, increased sensitivity was demonstrated in samples from patients with newly diagnosed MM (n=35; median AUC 0.1977) when compared to relapsed MM (n=64; median AUC 0.4025) (p=0.0041); and standard risk (n=36; median AUC 0.2324) when compared to high risk (n=60; median AUC 0.4025) (p=0.0199). Other cytogenetic characteristics associated to venetoclax sensitivity was low plasma cell S-Phase (n=65; median AUC 0.2697) when compared to high S-Phase (n=31; median AUC 0.4353) (p=0.0035); samples lacking Gain(1q) (n=63; median AUC 0.2788) when compared to samples with Gain(1q) (n=47; median AUC 0.4047) (p=0.0383); and in samples lacking t(4;14) (n=99; median AUC 0.307) when compared to samples harboring the translocation (n=11; median AUC 0.5514) (p=0.01). Then, anti-apoptotic BCL-2 family member transcriptomic ratios were evaluated in the nine most (responders; median AUC 0.09409) and least (non-responders; median AUC 0.7195) sensitive primary patient samples. Overall BCL-2 RNA expression (p=0.0036), BCL-2/MCL-1 ratio (p=0.0019), and BCL-2/BCL-2L1 ratio (p=0.0106) were significantly increased in the responders when compared to the non-responders. Finally, two relapsed t(11;14) MM patients were treated with venetoclax, after the ex vivo drug screen results pointed to moderate sensitivity to the drug, with AUCs of 0.3380 and 0.3575. Both patients were treated with venetoclax in combination with dexamethasone or dexamethasone and carfilzomib and achieved partial responses. Collectively, our data obtained through a drug screening assay in ex vivo primary patient samples corroborates the strong preclinical and clinical associations of venetoclax response, including t(11;14) and favorable BCL-2 family profiles. The assessment of ex vivo sensitivity to venetoclax was shown to be an applicable tool to enrich for likely responders.

Keywords:
Drug Screen

Ex-Vivo

Venetoclax

Tracks:
Multiple Myeloma Novel Agents

FP-105

Risk of Renal Toxicities with Carfilzomib in Patients with Multiple Myeloma: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Abstract:
BACKGROUND: Carfilzomib, a second-generation proteasome inhibitor, is widely used in patients with multiple myeloma [MM]. Renal toxicities have been described with carfilzomib-based regimens in clinical trials and observational studies, however, the overall risk has been incompletely characterized. OBJECTIVE : To determine whether carfilzomib-based regimens are associated with an increased risk of renal toxicity compared with control regimens in MM. DESIGN: A systematic search of EMBASE, MEDLINE, Web of Science, Cochrane Central Register of Controlled Trials, and ClinicalTrials.Gov was conducted through 03/20/19, to find all randomized controlled trials [RCTs] comparing carfilzomib with other agents in MM. We pooled point estimates using random effects model by DerSimonian and Laird. Heterogeneity of effect size across studies was quantified using I2 statistic and Cochran's Q. Analyses were performed with Review Manager [RevMan.v 5.3. Copenhagen]. STUDY POPULATION: Patients with MM in RCTs comparing carfilzomib-based with non-carfilzomib-based regimens and reporting renal toxicities as adverse events. MAIN OUTCOMES MEASURE: Pooled risk ratio [RR] for renal toxicities associated with carfilzomib. ADDITIONAL OUTCOME MEASURE: Pooled incidence rate ratio [IRR] adjusted for duration of treatment in study arms. RESULTS: Four phase III studies randomizing 2954 patients [1486 in carfilzomib arm and 1468 in control arm] were included in the analysis. All but one study [CLARION] were conducted in relapsed/refractory MM. Carfilzomib was administered twice weekly in all trials, with dose ranging from 20/27 to 20/56 mg/m2. Cumulative incidence of all-grade and grade 3-5 renal toxicities with carfilzomib was 21.3% and 8.3%, respectively, at median treatment durations ranging from 16 to 88 weeks. Carfilzomib was associated with a significantly higher risk of renal toxicities compared to control, with pooled RR of 1.79 [95% CI: 1.43-2.23, p<0.00001] and 2.29 [95% CI: 1.59-3.30; p<0.00001], for all grade and grade 3-5 toxicities, respectively. After adjusting for the duration of therapy in experimental and control arms, pooled IRR for all-grade and grade 3-5 renal toxicities was 1.28 [95% CI, 1.06-1.54; P=0.01] and 1.66 [95% CI, 1.19-2.30; P=0.003] respectively for carfilzomib compared to control arm. Moderate heterogeneity was noted across trials. Subgroup analysis based on carfilzomib dose [≤ 27 vs. >27 mg/m2], duration of infusion [10 vs. 30 mins], and treatment setting [relapsed/refractory vs. newly diagnosed] did not reveal any significant subgroup effect. CONCLUSIONS: Carfilzomib is associated with a significantly increased risk of renal toxicities in MM. Our study will guide clinicians in counselling patients and assessing risk-benefit ratio prior to initiating carfilzomib-based regimens. Further studies are needed to identify patient and disease-specific risk factors for predicting serious renal toxicities with carfilzomib.

Keywords:
Adverse effects

carfilzomib

Multiple myeloma

Tracks:
Multiple Myeloma Novel Agents

FP-106

Real world vs. clinical trial outcomes of triple class refractory penta-exposed multiple myeloma (MM)

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Abstract:
Introduction: Despite dramatic successes in drug development almost all MM patients (pts) eventually progress to relapsed and/or refractory MM (RRMM). Disease which becomes triple class refractory (TCR, i.e. refractory to an IMiDs, PIs and CD38 MoABs) has survival measured in months (mos). Selinexor is a selective inhibitor of nuclear export compound targeting exportin 1 (XPO1) which is overexpressed in MM cells and essential for MM cell survival. In the STORM study (JCO, 2018), selinexor was in combination with low-dose dexamethasone (Sd) and demonstrated promising efficacy in TCR, penta-exposed (TCR-PE, i.e. exposed to lenalidomide, pomalidomide, bortezomib, carfilzomib and daratumumab) MM. However, the lack of benchmark for outcomes in the TCR-PE population has been a concern. In the retrospective MAMMOTH study (Leukemia, 2019), we reported the outcomes of pts with RRMM after they become refractory to CD38 MoABs, including a subset of pts who were TCR. We therefore further analyzed the MAMMOTH dataset to generate a cohort of pts comparable to pts in STORM in order to report the "real world" outcomes of TCR-PE pts who received subsequent therapy. Methods: All pts in STORM with Sd as the first line therapy after they achieved TCR-PE status were included (n=64). All patients in MAMMOTH who had TCR-PE MM and received subsequent therapy but were not exposed to Sd in a subsequent line of therapy were identified (n=128). Overall response rate (ORR) was evaluated per IMWG criteria and OS was assessed by Kaplan Meier. In both cohorts, OS was assessed from the initiation of next line of therapy after TCR-PE criteria was met. Direct comparison between the two cohorts, including multivariate model with adjustment for possible imbalances between cohorts will be presented at the meeting. Results: The two cohorts were similar in terms of pts age, number of prior lines of therapy (median 6 prior lines for both cohorts) and presence of high-risk cytogenetic abnormalities (50% in STORM and 53.7% in MAMMOTH; defined as del(17p)/p53, t(14;16), t(4;14), or 1q21). STORM pts had longer time between MM diagnosis and post TCR-PE therapy (6.4 years vs 5 years in MAMMOTH) and were

more likely to be refractory to carfilzomib (96.9% vs. 82% in MAMMOTH). Pts in STORM receiving Sd as first line of therapy after reaching TCR-PE had an ORR of 32.8% and median OS of 10.4 mos (95% CI 7.9 mos - NE). In contrast, pts in the MAMMOTH cohort received single (n=6, 4.7%) or a combination of two or more anti-MM agents (N=122, 95.3%) and obtained an ORR of 25% with median OS of 6.9 mos (95% CI 5.3-8.6 mos). Conclusions: Despite inherent limitations in comparison of trial eligible vs. real world pts, this matched cohort analysis suggests improved survival outcomes with Sd compared with other standard of care treatment options for RRMM. Prognosis for pts with TCR-PE MM remains poor and underscores the need for therapeutic advancements to improve patient outcomes.

Keywords:
Real-World Data

Relapsed Refractory MM

selinexor

Tracks:
Multiple Myeloma Novel Agents

FP-107

TAK-573, an anti-CD38-targeted attenuated interferon alpha (IFNα) fusion protein, showed anti-myeloma tumor responses in combination with standard of care (SOC) agents in multiple myeloma (MM) xenograft tumor models in vivo

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Abstract:

Background: Even with transformative therapies, multiple myeloma is a relapsing and ultimately fatal disease. We previously reported that targeting an attenuated form of IFNα, or Attenukine™, to MM tumor cells via direct fusion to an anti-CD38 antibody (TAK-573) has direct anti-proliferative activity on MM cancer cells in vitro and induces robust and durable responses in MM xenograft tumor models. Here we demonstrate the anti-tumor impact of TAK-573, alone and in combination with SOC agents in MM xenograft tumor models in vivo. Methods: Several MM cell line-derived tumor models were established in xenograft mice, and anti-tumor activity of TAK-573 was evaluated alone or in combination with approved SOC agents for MM including melphalan, cyclophosphamide and proteasome inhibitors. Results: The anti-tumor impact of single agent TAK-573 varied across different MM cell line-derived xenograft tumors. Treatment with TAK-573 in combination with SOC agents induced anti-tumor responses, including complete tumor responses, compared to single agent SOC treatment alone. All treatments and combinations were well tolerated in mice. Conclusion: The anti-tumor responses observed following administration of TAK-573 and SOC agents warrant further investigation in the ongoing clinical evaluation of TAK-573 in a Phase 1 trial in patients with relapsed refractory MM (NCT03215030).

Keywords:
CD38

Immunomodulatory

interferon alpha

Tracks:
Multiple Myeloma Novel Agents

FP-108

A murine reactive version of TAK-573 (anti-CD38-targeted attenuated IFNα fusion protein) shows immunomodulatory and

Authors:

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Abstract:
Background: Despite recent improvements in survival outcome for multiple myeloma (MM) patients, most will eventually relapse and require additional treatment. We previously reported that targeting an attenuated form of IFNα, or Attenukine™, to MM tumor cells via direct fusion to an anti-CD38 antibody (TAK-573) has direct anti-proliferative activity on MM cancer cells in vitro and induces robust and durable responses in MM xenograft tumor models. Additional mechanism of action (MOA)-based analyses in MM xenograft tumor models pointed to a role for M1 macrophage and NK cells in propagating this anti-tumor response. Here we demonstrate the anti-tumor and broad immunomodulatory impact of a murine reactive version of TAK-573 in an immunocompetent murine lymphoma tumor model. Methods: Anti-tumor activity of anti-human CD38-attenuated murine IFNα (hCD38-mATT) treatment was evaluated in a syngeneic murine tumor lymphoma model engineered to express human CD38 (hCD38). Pharmacodynamic changes in the tumor immune microenvironment post-treatment were determined using multi-color flow cytometry and immunohistochemistry (IHC). The impact of targeted immune cell depletion on tumor growth post-treatment with hCD38-mATT was determined in vivo. Results: Treatment with hCD38-mATT induced complete tumor regressions in hCD38-38C13 tumor-bearing mice. Immune-profiling and IHC analyses indicated significant infiltration of different immune cell subtypes within the tumor microenvironment post-treatment with hCD38-mATT compared to a non-targeted mATT control reagent. Targeted depletion of specific immune cell subsets pointed to CD8+ T cells as a key component of long-term anti-tumor activity mediated by hCD38-mATT. Conclusion: The anti-tumor response observed in hCD38-mATT treated mice is driven by direct (anti-proliferative) and indirect (immune-mediated) mechanisms. These data support the ongoing clinical evaluation of TAK-573, a CD38-targeted Attenukine™ immunotherapy being evaluated in a Phase 1 trial in patients with relapsed refractory MM (NCT03215030).

Keywords:
CD38

immunotherapy

interferon alpha

Tracks:
Multiple Myeloma Novel Agents

FP-109

Prognostic value and clinical correlations of serum cereblon (CRBN) levels in multiple myeloma patients treated with Lenalidomide/Dexamethasone (RD).

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Abstract:
Background: Cereblon (CRBN) was identified as a key protein in Immunomodulatory Drugs (ImiDs) action. Although, resistance to ImiDs has been linked to decrease expression of CRBN protein and recent research suggest CRBN as a new target of treatment, limited data exist about the importance of serum CRBN concentrations. Aims: To investigate the prognostic impact of serum CRBN levels and to study eventual correlations with clinical characteristics in MM patients treated with RD (lenalidomide-dexamethasone). Methods: We studied 91 MM patients from RD initiation until last follow up or death; Medical records were reviewed after patients' informed consent was obtained, while clinical and laboratory characteristics were collected. Frozen patients' sera, drawn at the time of RD treatment (68 patients), best response (59 patients) and at relapse/refractoriness to Rd (54 patients) were retrospectively analyzed. CRBN was measured by commercially available ELISA kit (cloud clone), according to the manufacturer's instructions. Twenty healthy individuals (HI) were also analyzed. Statistical analysis was performed using the SPSS v24.0. software. Results: The median age of patients was 70 years (56% men, 44% women). Ig type was IgG in 64%, IgA in 22%, light-chain in 11% and IgD or biclonal in 3%. Thirty percent of patients were staged ISS 1, 20% ISS 2 and 51% ISS 3. RD was administered in 1st line in 8% of patients, second in 37%, third in 26%, forth in 16% and in 5th to 9th line in 13%. Median serum CRBN levels at RD initiation were 247 pg/ml (0-9760), 148,8 pg/ml (0 -9940) at best response and 294 pg/ml (0-9840) at relapse/resistance to RD. In HI CRBN ranged from 0 to 580 pg/ml. CRBN values at RD initiation were negatively correlated with paraprotein levels (τ= -0,204, p=0,05). At best response they marginally correlated with quality of response (τ=-0,250, p=0,055). Median serum CRBN level was used as a cut-off point in survival analysis. Median overall survival was 70 months (range, 7-345) and time until next treatment was 14 months (range, 1-110). Five-year survival was improved in patients with CRBN levels below median at the time of RD initiation (p=0,03), during best response (p=0,035), and in relapse/refractory patients to Rd (p=0,05) while time to next treatment was significantly shorter in patients with CRBN levels above median at best response (p=0,026). Conclusions: A better 5-year survival was observed in patients with serum CRBN levels below median after RD treatment. To our knowledge, this is the first study to describe the serum CRBN levels impact in multiple myeloma. Mechanisms leading to protein release in the serum possibly explain this apparent discrepancy with the reported effect of low CRBN expression.

Keywords:
immunomodulatory drugs

prognostic factors

survival

Tracks:
Multiple Myeloma Novel Agents

FP-110

Effect of Age on the Safety and Efficacy of Selinexor in Patients with Relapsed Refractory Multiple Myeloma: A Post-hoc Analysis of the STORM Study

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Abstract:
Introduction: The advent of newer therapies has significantly improved the outcomes in patients (pts) with refractory multiple myeloma (MM). However, the treatment of elderly pts remains challenging. Selinexor (SEL) is a novel, oral selective inhibitor of nuclear export (SINE) which forces nuclear retention and activation of tumor suppressor proteins. SEL plus low dose dexamethasone (SEL-DEX) induced an overall response rate (ORR) of 26.2% in pts with penta-exposed, triple-class refractory MM. Side effects were generally reversible without evidence of major organ toxicities. We performed post-hoc analyses to determine the effect of age on the safety and efficacy of SEL-DEX in this population. Methods: STORM was a phase 2b, open-label study which enrolled pts previously treated with bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab, glucocorticoids, and an alkylating agent, and had disease refractory to ≥1 proteasome inhibitor, ≥1 immunomodulatory agent, daratumumab, a glucocorticoid, and their last therapy. Oral SEL 80 mg+DEX 20 mg were administered twice weekly in 4-week cycles. The primary endpoint was ORR. For this analysis, pts were categorized into 3 age groups to compare outcomes. Results: Of 122 pts, 46 (38%) were ≤60, 49 (40%) were >60-70 and 27 (22%) were >70 years. Baseline characteristics were generally well balanced across groups. The proportion of pts with creatinine clearance <30 mL/min was higher in pts >70 (≤60: 2%; >60-70: 0%; >70: 19%). Dose reductions (≤60: 52%, >60-70: 53%, >70: 68%) and discontinuations due to adverse events (AEs) [≤60: 22%, >60-70: 33%, >70: 50%] occurred at a higher incidence in pts >70. AEs were similar across groups: grade ≥ 3 AEs in the ≤60, >60-70 and >70 groups were thrombocytopenia (54%, 65%, 54%), anemia (46%, 47%, 36%), neutropenia (24%, 18%, 21%), and hyponatremia (20%, 25%, 21%); serious AEs occurred in 61%, 65% and 64% of pts. Pneumonia and sepsis occurred in 13%, 4%, 21% and 7%, 14%, 4% in the ≤60, >60-70 and >70 groups respectively. Treatment related deaths occurred in 1 pt each in the >60-70 (sepsis) and >70 (pneumonia) groups. ORRs were 21.7%, 28.6% and 29.6% (P=0.68) in the ≤60, >60-70 and >70 groups respectively. Two (4.1%) stringent complete responses occurred in the >60-70, with very good partial responses in 4 (14.8%) pts in the >70 group compared with 1 pt each in the ≤60 and >60-70 groups. Median progression-free survival was 4.1, 3.0 and 4.3 months (P=0.56) and median overall survival was 10.4, 6.4 and 7.9 months (P=0.42) in the ≤60, >60-70 and >70 groups respectively. Conclusions: Regardless of age, pts have similar clinical benefit with comparable ORR, PFS and OS. There were no increased AEs in pts in the >70 group with a similar AE profile as the younger groups. As expected, more discontinuations due to AEs and increased pneumonia was observed in pts in the >70 group. Overall, SEL-DEX demonstrated durable responses and similar AEs across all age groups.

Keywords:
Elderly patients

novel agents

relapsed/refractory multiple myeloma

Tracks:
Multiple Myeloma Novel Agents

FP-111

Improvements in Renal Function with Selinexor in Relapsed/Refractory Multiple Myeloma: Post-hoc Analyses from the STORM Study

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Abstract:
Introduction: There is an unmet need for effective therapies in patients (pts) with adverse prognostic factors such as renal impairment, a common complication of multiple myeloma (MM). Selinexor (SEL), a novel, oral selective inhibitor of nuclear export (SINE) blocks XPO1, forcing nuclear activation of tumor suppressor proteins. In the STORM study, SEL plus low dose dexamethasone (SEL-DEX) induced an overall response rate (ORR) of 26.2% in pts with penta-exposed, triple-class refractory MM. Side effects were generally reversible without evidence of major organ toxicities. We performed post-hoc analyses to compare the safety and efficacy of SEL-DEX in pts across different levels of baseline renal function. Methods: STORM was a phase 2b, multicenter, open-label study which enrolled pts previously treated with bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab, glucocorticoids, and an alkylating agent, had disease refractory to ≥1 PI, ≥1 IMiD, daratumumab, a glucocorticoid, and their last therapy and had creatinine clearance (CrCl) ≥20 mL/min. Oral SEL 80 mg + DEX 20 mg were administered twice weekly in 4-week cycles. The primary endpoint was ORR. Pts were separated into 3 groups based on CrCl (measured by the Cockroft-Gault formula) to compare outcomes. Results: 121 pts with baseline CrCl were included; 14 (12%) had CrCl <40, 25 (21%) had CrCl 40-<60 and 82 (68%) had CrCl ≥60 mL/min. In pts with CrCl <40, a higher proportion of pts were >70 years and chronic kidney disease, acute kidney injury, anemia, fatigue, peripheral neuropathy, thrombocytopenia, diabetes, and hyperlipidemia were more prevalent. Most common grade ≥3 adverse events (AEs) in the <40, 40-<60 and ≥60 groups were thrombocytopenia (73%, 44%, 61%), anemia (47%, 60%, 39%), neutropenia (20%, 20%, 22%), leukopenia (20%, 4%, 16%), lymphopenia (33%, 0%, 11%), fatigue (7%, 32%, 18%), asthenia (20%, 8%, 4%), and hyponatremia (20%, 32%, 20%); serious AEs occurred in 73%, 68% and 61% of pts. Treatment related deaths occurred in 1 pt each in the <40 (pneumonia) and ≥60 (sepsis) groups. There was no clinically significant increase in dose reduction (67%, 56%, 54%) or discontinuation (40%, 28%, 33%) due to AEs with lower CrCl. ORR was similar across groups: 35.7%, 16.0% and 28.0% (P=0.35) in the <40, 40-<60 and ≥60 groups respectively. Median progression-free survival was not reached, 4.7, and 3.4 months (P=0.37) and median overall survival was 6.1, 5.8, and 10.4 months (P=0.16) in the <40, 40-<60 and ≥60 groups respectively. Improvement in renal function (increase in CrCl by at least one category level from baseline) was observed in 4 of 6 (67%), 2 of 8 (25%), and 9 of 24 (38%) of pts with CrCl <30, 30-<40 and 40-<60 respectively. Conclusions: SEL-DEX is an option for RRMM pts with moderate to severe renal

impairment. Renal function has no impact on the efficacy and safety of SEL-DEX with improvement in renal function observed in 25 to 67% of pts during treatment.

Keywords:
relapsed/refractory multiple myeloma

Renal impairment

Tracks:
Multiple Myeloma Novel Agents

FP-112

Proteasome inhibition by Carfilzomib, but not by Bortezomib, induces a specific, proteasome subunit-dependent impairment in cardiac contractility.

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Abstract:
INTRODUCTION. All approved proteasome inhibitors (PI), Bortezomib (BTZ), Ixazomib (IXA) and Carfilzomib (CFZ), by design target the rate-limiting B5 proteasome subunit. Only CFZ at higher doses shows co-inhibition of B5/B2. The CFZ-type B5/B2 co-inhibition induces increased proteotoxic stress and higher cytotoxicity in MM than the BTZ-type, B5/B1 inhibition, consistent with increased survival of relapsed/refractory MM patients. However, higher doses of CFZ produce acute heart failure not commonly seen with the first-generation PI, which is mechanistically poorly understood. We hypothesised that the acute cardiotoxicity of CFZ is related to its unique proteasome-subunit inhibition pattern. METHODS. We used an in vitro model of murine primary cardiomyocytes, which show spontaneous, rhythmic contractions in vitro. cardiomyocytes were treated with either PI drugs or the mono-specific proteasome inhibitors. After incubation with PI for 1h, contractility was assessed using motion vector image analysis. To evaluate PI effect in calcium transients, cardiomyocytes were transduced with the GCaMP vector and assessed by confocal microscopy imaging. To gain a deeper understanding of the acute molecular changes after PI treatment, mass spectrometry analysis of cardiomyocytes was performed after 1h incubation treated with either the CFZ-type or the BTZ-type PI. Finally, mice were monitored with an in vivo electrocardiogram (ECG) to assess heart frequency rate and electrical changes. Calcium transients and ECG signal analysis was performed with an in-house script developed for R software version 3.5.1 (2018-07-02). RESULTS. Co-inhibition of B5/B2 proteasome subunits using CFZ, or the combination of respective monospecific proteasome inhibitors, induced acute (within 1h) arrhythmia and impairment of contractility in vitro, in contrast to inhibition of B5/B1 proteasome subunits by BTZ or the respective monospecific inhibitors. In vivo, the combined CFZ-induced inhibition of B5/B2 proteasome activity triggered acute bradycardia. The disruption of cardiomyocyte contractile activity by CFZ was associated with a shift of intracellular calcium pools from the endoplasmatic reticulum to the cytosol. Quantitative mass-spectrometry showed an accumulation of proteins in the Retinoic Acid pathway and co-treatment with all-trans-retinoic acid (ATRA) prevented CFZ-induced acute cardiotoxicity in vitro. CONCLUSION. Our data suggests that CFZ specifically impairs cardiac contractility in a dose-dependent manner that is related to its unique B5/B2 subunit co-inhibition.The calcium shift in cardiomyocytes upon CFZ treatment is consistent with the known ER-to-cytosol translocation of calcium stores upon induction of ER stress and links the induction of proteotoxic stress to the induction of cardiac arrhythmia and contraction failure. The disturbances found in the retinoid pathway may provide means to interfere with CFZ cardiac toxicity.

Keywords:
Cardiotoxicity

Proteasome Inhibitor

Proteomics

Tracks:
Multiple Myeloma Novel Agents

FP-113

Synergistic Drug Combinations to Overcome Venetoclax Resistance in Multiple Myeloma

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Abstract:
We have established a functional precision medicine platform to evaluate the chemosensitivity of 76 FDA-approved and clinical therapeutics relevant to multiple myeloma (MM), alone or in combinations, in human myeloma cell lines (HMCLs) and in primary MM samples. The panel includes the Bcl-2 inhibitor venetoclax, currently in clinical development. There is a pressing need to identify rational drug combinations that select for synergistic activity with venetoclax, overcome its resistance, and provide patients with less toxic treatment options. Here we report the results of a drug screen combining venetoclax with our MM drug panel (MMDP), and examine how venetoclax sensitivity modulates drug synergy profiles. The MMPD was first screened in dose-response format in 25 HMCLs and in 113 primary MM samples using a cellular viability assay (CellTiter Glo, Promega). Single drug response data were used to calibrate concentration ranges for MMDP drugs combined with venetoclax, acoustically dispensed on assay-ready plates in matrix format. Cellular viability was assayed after 72h incubation and synergism quantified using Bliss, HSA, and Loewe scores (Combenefit). Two independent combination screens evaluated synergism of MMDP with venetoclax in a cell line of intermediate (OPM2, EC50 = 690 nM) and low (AMO1, EC50 = 5185 nM) venetoclax sensitivity. Maximum synergism was observed for the HDAC inhibitor panobinostat at 0.80 nM combined to 5.86 nM venetoclax in OPM2, corresponding to a 3.6 and 4.4 fold dose decrease respectively, as compared to single agent response. The most synergistic drug combinations were then confirmed in 3 additional cell lines per class (Intermediate: XG2, NCI-H929, JJN3; Resistant: RPMI-8226, KMS11, KMS26). Five drugs presented concordant synergism in the intermediate class while 10 drugs were found to synergize with venetoclax in the resistant class. The AKT1 inhibitor afuresertib and crenolanib, a PDGFRalpha/beta inhibitor, presented similar patterns of synergism in both groups. Panobinostat, the DNMT inhibitor azacitidine, and dexamethasone had the highest venetoclax synergism in intermediate HMCLs, but had moderate synergism in resistant HMCLs. Eight drugs synergized with venetoclax in resistant HMCLs only. These included carfilzomib, lenalidomide, paclitaxel, and kinase inhibitors cobimetinib, ceritinib, quizartinib, nilotinib, and dovitinib. These results corroborate our ex vivo single agent screen results where high sensitivity of signal transduction inhibitors concomitant with low venetoclax sensitivity was observed in primary MM samples. In summary, our screen identified 13 drugs synergizing with venetoclax in HMCLs of intermediate to low venetoclax sensitivity, concordant with single drug contextual sensitivities identified in MM primary samples. These results validate "direct to drug" screening as a promising tool to identify the most appropriate combinations of FDA approved drugs for each patient.

Keywords:
Drug Screen

Drug synergism

Venetoclax

Tracks:
Multiple Myeloma Novel Agents

FP-114

Targeting both BET and CBP/EP300 proteins with the novel dual inhibitors NEO2734 and NEO1132 leads to anti-tumor activity in Multiple Myeloma

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Abstract:
Introduction / Background: Multiple myeloma (MM) is a malignancy that is characterized by clonal proliferation of neoplastic plasma cells. Epigenomic abnormalities contribute to the pathogenesis of MM. Bromodomain 4 (BRD4), a member of the bromodomain and extra terminal (BET) family, binds to acetylated histones during M/G1 transition in the cell cycle promoting progression to S phase. Other histone modifiers include the acetyltransferases cyclic AMP response element binding protein-binding protein (CBP) and the E1A interacting protein of 300 kDa (EP300). Disruption of these epigenetic processes leads to altered gene function and tumorigenesis, and contributes to the pathogenesis of MM. A number of studies have shown that targeting these individual classes of proteins has anti-tumor activity in MM cell lines (MMCLs), as well as other cancers. Here we present the first data exploring the anti-tumor activity of the novel dual inhibitors of BET and CBP/EP300 in MM. Methods: 16 MMCLs were exposed to increasing concentrations of dual BET/CBP inhibitors NEO2734 and NEO1132, single BETis JQ1, OTX015, iBET-762 and iBET-151, and a single CBP/EP300 inhibitor CPI-637 for 72 hrs. Cell viability, cell cycle and protein levels were analysed in MMCLs following exposure to compounds. Results: 16 MMCLs were exposed to NEO2734 and NEO1132. The compounds showed anti-tumor activity with a median IC50 of 140 nM (95% C.I., 62-284 nM) and 402 nM (95% C.I., 153-817 nM) respectively, with NEO2734 being significantly more potent that NEO1132 ($P<0.001$). As a comparison, all MMCLs were exposed to the BETis JQ1, OTX015, iBET-762 and iBET-151, and to a CBP/EP300 inhibitor CPI-637, the median IC50 values of these compounds were 83 nM (95% C.I., 40-155 nM), 250 nM (95% C.I., 110-497 nM), 360 nM (95% C.I., 178-912 nM), 687 nM (95% C.I., 313-1316 nM) and 1970 mM (95% C.I., 606-5250 nM) respectively. The novel dual inhibitor NEO2734 was more potent than the single BET inhibitors iBET-762 ($P = 0.0084$), iBET-151 ($P = <0.0001$) and the CBP/EP300 inhibitor CPI-637 ($P = <0.0001$), and showed no significant difference from the highly potent JQ1 and OTX015 inhibitors ($P = 0.067$ and $P = 0.056$ respectively). When comparing the IC50 across the different MMCLs JQ1 ranks as consistently the most potent followed by NEO2734 for each of the MMCLs tested. Sensitivity to compounds differs for each MMCL with some being more sensitive than others. Like the single BET and CBP/EP300 inhibitors, NEO2734 and NEO1132 induce a G1 cell cycle arrest in sensitive MMCLs at 24 hrs. We also observed a marked decreased in the levels of proteins regulated by BET and CBP/EP300, including c-Myc and IRF4, following compound exposure indicating an effect on the regulatory domains. Conclusion: The dual BET and CBP/EP300 inhibitor NEO2734 shows a strong anti-tumor activity and is consistently highly active against all MMCLs, being as potent as JQ1 and more so than other single BET and CBP/EP300 inhibitors.

Keywords:
BET/BRD4

CBP/EP300

Dual inhibitor

Tracks:
Multiple Myeloma Novel Agents

FP-115

Efficacy and Safety of Selinexor for Heavily Pretreated Multiple Myeloma Treatment – A Systematic Review

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Abstract:
Introduction Exportin-1 (XPO-1) is responsible for nuclear export of tumor suppressor proteins, glucocorticoid receptors and mRNAs of oncoproteins. Selinexor (S) induces apoptosis of multiple myeloma (MM) cells by inhibition of overexpressed XPO-1 receptors and has shown synergism with dexamethasone, daratumumab, lenalidomide and pomalidomide. The aim of this study is to review the efficacy and adverse events of selinexor in patients with MM. Methods A comprehensive literature search for studies of selinexor in MM patients on the following databases was completed on 06/13/2019: PubMed, Embase, Clinicaltrials.gov and AdisInsight. Results Out of 82 studies found on initial search, we finalized 8 studies after screening by two reviewers. Chen et al. (2018) studied selinexor alone (S) and in combination with 20 mg dexamethasone (Sd) in 84 patients with 6 median prior therapies. The complete response (CR) was seen in 1% and partial response (PR) in 8% patients giving an overall response rate (ORR) of 10% (95% CI: 0.05-0.18). Sd at 45 mg/m2 led to ORR of 50% in 6 out of 12 patients. The best response with Sd 60 mg/m2 was minimal response (MR) in 2 out of 15 patients. Adverse events (AE) of Grade ≥ 3 were thrombocytopenia in 38 (45%), anemia in 19 (23%), neutropenia in 19 (23%), fatigue in 11 (13%) and hyponatremia in 22 (26%) patients. In phase II trial using Sd regimen, Vogl et al. (2018) observed ORR of 21% in 16 out of 21 evaluable MM patients. Among 48 quad-refractory patients, clinical benefit rate (CBR= ≥MR) was 29% while in 30 penta-refractory patients, CBR was observed in 12 (40%) patients. The most significant AEs of G≥3 included hyponatremia in 17 (22%), thrombocytopenia in 47 (59%), anemia in 22 (28%) and neutropenia in 18 (23%) patients. Using Sd in a phase II trial by Chari et al. (2018) showed ORR of 26.2% in 122 patients with 7 prior lines of therapies (sCR 1.6% + VGPR 4.9% + PR 19.7%). G4 AEs included sepsis in 1, thrombocytopenia in 38, anemia in 1, neutropenia in 4 and lymphopenia in 3 patients. Selinexor and backbone Treatments of Multiple Myeloma Patients (STOMP) trial (NCT02343042) has published results of combination of Sd with pomalidomide (SPd), bortezomib (SVd) and daratumumab (SDd). The best response noted with SPd was VGPR in 5 and PR in 12 patients. Three patients using SVd had CR and 7 had stable disease while 19/26 patients had response ≥PR on SDd. A phase I/II study (n=27) with S+Doxorubicin+d resulted in ORR of 15% with VGPR of 7.4 % (n=2) and PR of 7.4 % (n=2), (Raz et al., 2017). S-Carfilzomib-d regimen when administered in 21 relapsed MM patients has achieved VGPR in 3 and PR in 7 patients. The CBR was seen in 15 (71%) patients and the most common G≥3 AE was thrombocytopenia in 71% of the study population, Jakubowiak et al., 2016. Conclusion Selinexor based regimens are showing promising results in heavily pretreated myeloma patients. The adverse events profile is also significant but manageable.

Keywords:
Multiple myeloma

novel agents

Systematic Literature Review

Tracks:
Multiple Myeloma Novel Agents

FP-116

Synergistic Effect of Carfilzomib and Metformin in Vascular Plasticity

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Abstract:
Background: Carfilzomib (Cfz), a clinically used proteasome inhibitor against Multiple Myeloma, induces reversible cardiotoxicity in patients. We have recently showed that metformin (Met) acts as a prophylactic therapy against the induced cardiotoxicity, through activation of AMPKα axis. While the cardiac effects of Cfz are described, the impact on vascular function is not clarified. Therefore, we sought to investigate the i) the acute, ii) the sub-chronic effect on Cfz on the vasculature iii) the effect of metformin co-administration on the phenotype and iv) Cfz and Met effect on primary young Vascular Smooth Muscle Cells (prVSMCs) and senescent Human Aortic Smooth Muscle Cells (HAoSMCs). Methods: Male C57Bl/6 mice were randomized as follows: Acute Protocol i. Normal Saline (N/S 0.9%) ii. Cfz (8mg/kg ip) iii. Met (140mg/kg po) iv. Cfz+Met (8mg/kg ip; 140mg/kg po, respectively). Administrations were performed for 2 days (n=5 per group). : Sub-chronic Protocol i. N/S 0.9% ii. Cfz (8mg/kg ip) iii. Met (140mg/kg po) iv. Cfz+Met (8mg/kg ip; 140mg/kg po, respectively) for 6 days. Administrations were performed on alternate days (n=5 per group). Whole blood (WB) samples were used to determine ROS production (oxidative burst) and aorta sections (1mm) underwent ex vivo vascular relaxation and contraction studies. For the in vitro experiments prVSMCs passage (P) 2 and HAoSMCs P7 were subjected to Cfz (0.1, 0.3μM), Met (10μM, 10mM) treatment and to the combination of the two compounds. Subsequently, both cell lines were treated the optimal concentrations of the compounds 24h after treatment with Angiotensin II (AngII, 100nM), CoCL2 (150μM) and 48h after Glucose (25μM) to simulate the hypertensive, hypoxic and diabetic stimuli respectively. Proliferation was assessed by MTT and p53 expression was analyzed by immunofluorescence (IF). Results: In the acute setting, Met did not inhibit the oxidative burst induced by Cfz, while no effect of Cfz on vascular function was evident. In the sub-chronic setting, Met confined WB macrophage-derived oxidative burst and, while Cfz did not affect vascular function, the co-administration of Cfz and Met increased PDGF2α aortic contraction, deducing an increased plasticity of the vessel. In the prVSMCs, both Cfz and Met (10mM) led to a decreased proliferation and when co-administered, an additive effect in presence of high glucose, in a p53 dependent manner was observed. In the senescent HAoSMCs, only Met exhibited anti-proliferative capacity, while Cfz failed to exhibit any cytotoxicity. The co-treatment of Cfz and Met led to an additive effect in presence of CoCL2 and AngII, which was independent of p53 expression. Conclusions: Sub-chronic co-administration of Cfz and Met increases vascular plasticity in vivo. In vitro Cfz alone does not present any effect on senescent cells, probably due to the decreased proteasome activity, while Met synergizes with Cfz to decrease proliferation in a p53 independent mechanism.

Keywords:
carfilzomib

metformin

vascular function

Tracks:
Multiple Myeloma Novel Agents

FP-117

Preclinical evaluation of the new GPRC5DxCD3 (JNJ-7564) bispecific antibody for the treatment of multiple myeloma

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Abstract:
Background: The prognosis of multiple myeloma (MM) patients who are refractory to all currently available therapies, including anti-CD38 monoclonal antibodies, remains poor, indicating that there is an unmet need for novel treatment strategies. Although data on G protein-coupled receptor 5D (GPRC5D) protein expression is scarce, RNA levels are selectively elevated in MM cell lines and primary MM cells. This makes GPRC5D an attractive target for the novel anti-myeloma JNJ-7564 bispecific antibody. Methods: We determined GPRC5D protein expression levels on MM cell lines and bone marrow (BM) mononuclear cells (MNCs) derived from healthy donors (HD) and MM patients by flow cytometry. We also analyzed the impact of differential GPRC5D gene expression in purified CD138+ MM cells derived from patients who participated in 5 large randomized clinical trials (HOVON65, MRC-IX, TT2, TT3 and APEX), on overall survival (OS) and progression free survival (PFS). Furthermore, the activity of a new GPRC5DxCD3 bispecific antibody (JNJ-7564) was evaluated in MM cell lines and patient-derived whole BM samples after 48 hours of incubation (concentrations 0.00064-4µg/ml), as well as biomarkers for in vitro JNJ-7564 response. At baseline, MNCs were characterized for the composition of T-cell subsets. Results: GPRC5D protein expression was significantly higher on MM cells compared to HD plasma cells and immune cells. Gene expression levels of GPRC5D were highly variable in MM, but were significantly higher in patients with t(4;14) or gain 1q. There was no association with OS or PFS in the clinical trials (n=1421). JNJ-7564 effectively killed GPRC5D+ MM cell lines (MM1.S, UM9 and RPMI-8226) in a dose-dependent manner, using HD or patient-derived blood MNCs as effector cells. Co-incubation with patient-derived BM stromal cells resulted in a modest impairment of killing capacity in 2 out of 3 cell lines. In MM patient samples (n=29), the mean lysis of MM cells with 4.0µg/mL JNJ-7564 was 57% (range: -8-97%), while NK-cell and T-cell frequencies were not affected. JNJ-7564 was also active in samples from extensively pretreated and daratumumab (DARA)-refractory patients (n=8; mean lysis with 4.0µg/mL: 59%; range: 22-97%). JNJ-7564-mediated MM cell lysis was associated with activation (CD25+) and degranulation (CD107a+) of CD4+ and CD8+ T-cells. Maximum kill was correlated with GPRC5D expression on MM cells (Spearman r=0.40, p=0.029), % of regulatory T-cells (r=-0.41, p=0.023) and % of PD-1+ T-cells (r=-0.43, p=0.033). Conclusion: GPRC5D is highly and selectively expressed on MM cells, which makes it an attractive therapeutic target. The GPRC5DxCD3 bispecific antibody, JNJ-7564, effectively lysed MM cell lines and primary MM cells in samples derived from both newly diagnosed and heavily pretreated patients, including DARA-refractory patients. Altogether, this strengthens the preclinical rationale for an ongoing phase 1 study with JNJ-7564 in relapsed/refractory MM.

Keywords:
bispecific antibody

immunotherapy

Multiple myeloma

Tracks:
Multiple Myeloma Novel Agents

FP-118

Chidamide, a novel histone deacetylase inhibitor, suppresses myeloma proliferation via inhibiting proteasome activity and ASH2L gene expression

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Abstract:
The impact of epigenetic regulations on myeloma cells is attracting more and more attention. Chidamide, a novel histone deacetylase inhibitor (HDACi) independently developed in China, has been approved for the treatment of T cell lymphoma. Yet its action on myeloma is not elucidated. We previously found that ASH2L gene, which enhanced the activity of oncogene methyltransferase, was highly expressed in some patients with multiple myeloma (MM). The main purpose of this study is to investigate the anti-myeloma effects of Chidamide and ASH2L involvement. Four human MM cell lines RPMI8226, U266, NCI-H929, MM.1s were treated with Chidamide. Half inhibitory concentration (IC50) at 24 hours was calculated. RNA-seq technology was applied to analyze the changes of gene expression profile before and after Chidamide treatment. BGI interactive reporting system platform was used to analyze the signal pathway mechanism. Western blot and Real time Quantitative PCR were used to verify the relevant pathways. Bortezomib or lenalidomide were combined with Chidamide for synergy evaluation. The mRNA levels of ASH2L in 36 newly diagnosed MM patients were tested. Meanwhile, The mRNA and protein expression of ASH2L gene in myeloma cell lines were determined with treatment of chidamide, bortezomib or lenalidomide. The IC50s of Chidamide at 24h were 2.4, 2.8, 9.3, and 3.5umol/L, respectively, with a dose-dependent inhibitory effect. Chidamide also had a cell inhibitory effect on human primary myeloma cells. A variety of signaling pathways after Chidamide treatment were involved, including proteasome activity, PI3K-AKT signaling pathway and MAPK signaling pathway etc. The activity of β1 proteasome subunit was strongly inhibited by Chidamide, rather by bortezomib. Synergistic effects of Chidamide with Bortezomib or lenalidomide were positive. Heterogenous mRNA expression of ASH2L gene in bone marrow mononuclear cells was seen in newly diagnosed MM patients. Six over thirty-six patients demonstrated high ASH2L mRNA expression, which was significantly higher than that of the normal controls (p=0.039). All these 6 patients were in ISS III, all with three or more cytogenetic abnormalities including three with TP53 deletion. Among other 30 patients, no TP53 deletion was found and only 2 cases had three or more cytogenetic abnormalities. The mRNA level of ASH2L gene was all elevated in 4 myeloma cell lines. Chidamide treatment significantly inhibited mRNA and protein expressions of ASH2L gene in MM cell lines, while bortezomib or lenalidomide did not make the difference. A novel HDAC inhibitor, Chidamide, suppresses myeloma cell proliferation in vitro mainly via inhibition of proteasome activity and ASH2L expression. The synergistic effect with other anti-myeloma drugs provides the possibility of Chidamide containing regimens in MM patients.

Keywords:
histone deacetylase

Multiple myeloma

proteasome

Tracks:
Multiple Myeloma Novel Agents

MULTIPLE MYELOMA NOVEL DRUG TARGETS

FP-119

Aberrant RHAMM (receptor for hyaluronan-mediated motility) splicing in MM is associated with upregulation of PTBP1/2 (polypyrimidine tract binding protein 1/2): therapeutic implications

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Abstract:
Background: Overexpression and/or unbalanced splicing of the RHAMM is linked to various types of hematological malignancies. High RHAMM-V3 variant expression and RHAMM-V3/FL expression ratio induces mitotic instability in MM and correlates with poor survival in MM patients. Thus, understanding the cause of RHAMM splicing alterations can both provide novel insights into MM pathogenesis and identify innovative RNA-based targeted therapy. Methods/results: Splicing alterations can be caused by single nucleotide variations (SNVs) that affect splicing regulatory elements (SRE), or by deregulated expression of splicing factors (SFs). We here evaluate the incidence of SNVs located in the vicinity of RHAMM, based upon publicly available databases and reported in MM patients. We identified a total of 57 SNVs: 72% SNVs are in the intronic region, and 28% are in the RHAMM coding region. We used the "HEXplorer" tool and predicted that four SNVs have the potential to contribute to aberrant RHAMM splicing in MM either by altering SF binding to SREs or by impacting splice sites selection. Predicted SNVs were evaluated using an in vivo splicing assay. These analyses identified SNV-cluster that caused aberrant RHAMM splicing, thereby leading to increased RHAMM-V3 transcript expression. We have observed progressive overexpression of SF PTBP1/2 in MM patients and associated with disease progression. Since SNVs on the RHAMM modulate canonical SFs binding sites, we tested the effects of PTBPs deregulation on RHAMM splicing. We expressed PTBP1/2 in H929 cells, and then evaluated the RHAMM splicing pattern in transfected cells at a single cell (SC) level. SC analyses showed that overexpression of PTBP1/2 increased (2.5-fold) the RHAMM-V3/FL ratio in MM cells. SC analyses also identified overexpression of RHAMM-V3 splice variant in 18% H929 SCs expressing PTBP1, and in 37% of cells expressing PTBP2. Our findings were confirmed at the SC level in different subpopulations of cells within relapsed MM patient BM samples overexpressing PTBP2. We also evaluated RHAMM splicing patterns and determined RHAMM-V3/ FL ratios. Our SC analyses suggested selective expression of RHAMM-V3 in marrow-infiltrating myeloid cells: 50% myeloid cells express RHAMM-V3 variant alone, and 79% PC express this variant in combination with RHAMM-FL. Moreover, RHAMM-V3/FL ratio in PC is elevated (2.6-fold), further confirming a correlation between the RHAMM variant ratio and clinical outcome. Conclusions: Our study suggests that aberrant RHAMM splicing in MM can result from SNPs/SNV affecting SRE, and due to the upregulation of PTBP1/2. Importantly, our study is the first to show RHAMMV3 variant associated with PTBP2 overexpression and identifies novel targets for RNA-based therapeutics. For example, overexpressed RHAMM-V3 in MM can be selectively targeted using an antisense oligonucleotide (ASO) based approach, thereby decreasing RHAMM-V3 production and improving MM patient outcome.

Keywords:
Multiple myeloma

Mutation

Tracks:
Multiple Myeloma Novel Drug Targets

FP-120

A short term biomarker-based assay predicts apoptotic response to combined BCL-2/MCL-1 BH3 mimetic targeting in Myeloma cells

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Abstract:
Background:Multiple myeloma is an incurable haematological malignancy characterised by molecular complexity and clonal heterogeneity. Although both MCL-1 and BCL-2 are necessary for myeloma survival, most myelomas are dependent on MCL-1 such that BCL-2 inhibition alone only yields significant cytotoxicity in a minority of cases. Cooperative inhibition of both proteins may be beneficial. In the era of novel medicines and targeted molecular therapies, there is a shortfall of rapid and reliable assays that can predict patient response to new agents. This is particularly true in myeloma where primary samples survive poorly in vitro away from the bone marrow niche. We present a novel short-term biomarker-based cytochrome c release assay capable of predicting long term sensitivity to MCL-1 and BCL-2 BH3-mimetics. This short term and reproducible assay can provide a quick response profile and mitigate the difficulty in culturing primary myeloma cells for long periods ex vivo. Method: Myeloma cell lines and CD138 selected primary samples were treated with venetoclax and S63845 alone and in combination. Sub-toxic doses of drugs were determined for each cell line. Samples were fixed after 4 hours drug incubation thus precluding the need to keep cells alive in culture for prolonged periods and then assayed for cytochrome c release using flow cytometry. To verify that our assay can predict long term sensitivity we assessed apoptosis and cytotoxicity using Annexin V and Alamar Blue assays after 48 hours incubation with equivalent doses of the drugs. Protein lysates were prepared at 4 hours and immunoblots performed for anti-apoptotic proteins and D cyclins. Results:The cytochrome C release assay demonstrated that the combination of venetoclax and S63845 was synergistic compared to controls and single agent treatment in all cell lines tested (Combination index values 7.8-80). Cyclin D2 expressing cell lines were particularly sensitive to the combination and synergy was p53 independent. The assay was used on CD138-selected primary myeloma cells also demonstrating effective cooperative targeting in patient samples. 48-hour Annexin V and Alamar Blue data correlated with short term cytochrome c release verifying the assay as a predictor of drug sensitivity. Normal stem cells were not affected by the single agents or the combination hinting at low collateral toxicity to normal haematopoietic cells. Combination therapy resulted in down-regulation of MCL-1, BCL-xl, cyclin D1 and cyclin D2. Conclusion: We have developed a novel assay to predict response to apoptosis induction in myeloma cell lines and primary samples. This rapid assay will allow quick cytotoxicity testing of primary samples to BH3 mimetics, overcoming the challenge of interpreting viability assays after prolonged primary cell culture due to spontaneous cell death. It also provides a proof of concept for live testing of patient samples in the era of individualised medicines and targeted therapies

Keywords:
BCL-2

Cytochrome c

Mcl-1

Tracks:
Multiple Myeloma Novel Drug Targets

FP-121

Infectious complications following Venetoclax-Proteasome Inhibitor based regimens in relapsed myeloma: a single center retrospective analysis

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Abstract:
Introduction: Venetoclax is an oral BCL2 inhibitor undergoing investigation for use in relapsed or refractory multiple myeloma (RRMM), particularly in combination with proteasome inhibitors

(VPI)[1,2]. An interim analysis of a current phase 2 trial of venetoclax with carfilzomib in RRMM demonstrated an overall response rate of 78% with a very good partial response rate of 56%[3,4]. However, a separate ongoing phase 3 trial of venetoclax with bortezomib found a decrease in overall survival due to increased fatal infections in the venetoclax arm compared to placebo. Better describing these infections may give insight into the pathophysiology and prove useful in mitigating strategies for use with VPI therapy in RRMM. Methods: We retrospectively analyzed patients treated with VPI for infectious complications from initiation of treatment until one month after progression. Infections were classified by site, pathogen and severity of infection defined as requiring hospitalization. Additional data collected were regimen, demographics, cell counts, quantitative immunoglobulins, m-spike, cytogenetics, prior lines of therapy, prophylactic antibiotics and IVIG use. Results: 18 patients treated with a VPI combination regimen were identified with 78% males. The median age was 64.5 (range 47-76) and a median of 3 prior regimens. 14 were treated with combination carfilzomib and 4 with bortezomib. 4 patients progressed by the time of data collection. 11 patients experienced 35 discrete infectious episodes resulting in 5 hospitalizations. Respiratory infections predominated (29/35) with 24 upper respiratory infections/sinusitis. 5 were lower respiratory infections and comprised all hospitalizations. Among respiratory infections, viruses were the only pathogens identified, including influenza, rhinovirus, coronavirus and RSV. Other sites of infection were gastrointestinal (including recurrent C. difficile) and urinary tract. No CNS, blood, or intra-abdominal infections were identified. A qualitative analysis of laboratory data revealed that ALC and non-monoclonal IgG levels rapidly declined and remained suppressed after initiation of VPI, while ANC remained nominal. No clear trends between severe infections and degree or hypogammaglobulinemia or lymphopenia were observed. Conclusion: Patients with RRMM treated with VPI experience frequent infectious complications, some severe, and sustained reductions in serum IgG and lymphopenia without neutropenia. Identified infectious pathogens tend toward viral infections for likely multifactorial reasons. These findings warrant continued investigation into mechanisms of immunocompromise and if a differential risk profile exists between proteasome inhibitors in this type of regimen. Additionally, these findings suggest that IVIG infusion may be a more biologically-logical strategy to infection prophylaxis compared to oral antibiotics and requires further research.

Keywords:
hypogammaglobulinemia

Infections

Venetoclax

Tracks:
Multiple Myeloma Novel Drug Targets

FP-122

Nelfinavir interacts with mitochondrial VDACs and disrupts oxidative phosphorylation in proteasome inhibitor resistant myeloma

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Abstract:

Background: Proteasome inhibitor (PI) resistance remains a problem in multiple myeloma (MM) therapy. Metabolic reprogramming towards oxidative phosphorylation (OXPHOS) and high mitochondrial ATP supply provide proteasome inhibitor resistance (Tsvetkov, NatureChemBiol 2019). The anti-HIV drug nelfinavir (NFV) overcomes PI-resistance in combination with bortezomib. We identified the molecular targets of NFV and addressed the effect of NFV on the metabolic reprogramming of PI-resistant MM. Methods: Photo-reactive NFV-mimetics were used to identify proteins interacting with NFV in MM cells, using an affinity purification/mass spectrometry approach. Seahorse was used to assess mitochondrial metabolic properties, ratiometric constructs were used to assess cellular ATP content, radio-labelled glucose tracing and mass spectrometry was used to assess glucose uptake and metabolism. Genome-wide CRISPR-Cas9 screening identified candidate NFV-resistance/sensitivity genes. To model ER-to-Golgi protein translocation, the Retention Using Selective Hooks (RUSH) system was used. Results: Nelfinavir interact specifically with mitochondrial transmembrane proteins VDAC 1, 2, 3 and ANT2. These are involved in forming the mitochondria permeability transition pore (mPTP), mediating the export of ATP from mitochondria. NFV resulted in a shutdown of mitochondria OXPHOS and decreased ATP supply to the endoplasmic reticulum (ER). Glucose tracing suggests that NFV likewise impairs hexokinase II, a key player in glucose metabolism, whose function is linked to mPTP. In addition, NFV interacts with the ER-resident proteins BCAP31, CANX, SRPRB, involved in protein quality control and trafficking. We demonstrate that NFV retains newly-synthesized secretory protein in the ER of PI-resistant MM, in line with the synergistic induction of proteotoxic stress by NFV and bortezomib. CRISPR-Cas9 screening identified candidates involved in adiponectin/ cholesterol/ fatty acid metabolism to be involved in mediating NFV resistance. Treatment of PI-resistant MM with fatty acids reversed the metabolic shut down caused by NFV, while depletion of fatty acids sensitized PI-resistant MM cells towards NFV treatment. Interestingly, modulation of fatty acid metabolism in MM cells using the FDA-approved lipid-lowering drug Ezetimibe sensitized the PI-resistant MM cells to proteasome inhibition in a NFV-like manner. In conclusion, NFV interacts with mitochondrial proteins and depletes ATP supply of PI-resistant MM. In addition, NFV interacts with membrane-anchored, ER-resident proteins, blocking ER protein export. Both targets, disruption of OXPHOS in mitochondria and blockade of protein trafficking from the ER are in line with current concepts for the metabolic reprogramming of PI-resistant MM. Our results support the validity of NFV as a promising drug in PI-refractory MM and they suggest OXPHOS and mitochondrial ATP supply as promising new targets for the treatment in PI-resistant MM.

Keywords:
Drug resistance

Metabolism

Nelfinavir

Tracks:
Multiple Myeloma Novel Drug Targets

FP-123

Biomarker based targeting of the epichaperome as a novel therapeutic approach for Multiple Myeloma (MM)

Authors:
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Abstract:

The management of high-risk and relapsed/refractory (R/R) MM patients remain a therapeutic challenge as outcomes remain poor. To further investigate the resistance mechanisms in myeloma and cancer, we have described a new entity termed "the epichaperome" that consists of tightly integrated chaperome units that facilitate cancer cell survival (Rodina et al Nature 2016). We have developed sensitive methodologies to assess the abundance of the epichaperome at a single cell level or using capillary electrophoresis in purified CD138 populations from bone marrow aspirates from MM patients. We sought first to determine the abundance of the epichaperome in MM using cell lines and primary MM samples at different stages of the MM progression, including MGUS, at diagnosis or relapsed/refractory (R/R) to several therapy lines including IMiDs (lenalidomide & pomalidomide) and proteasome inhibitors (bortezomib and carfilzomib). We found that plasma cells (CD138+) presented higher abundance of the epichaperome when compared to CD138negative cells, regardless of the state of progression. We also evaluated several MM cell lines such as MM1.S, MM1.R, SKO0-007, U266, U266-LR (lenalidomide resistant), AMO1, AMO1-BR (bortezomib resistant) and AMO1-CR (carfilzomib resistant) using three different methodologies (capillary electrophoresis, immunoblots in native gels and flow cytometry), we found different levels of epichaperome abundance across cell lines. Importantly, we observed that the abundance of the epichaperome correlated with the sensitivity of the cells to in vitro treatment with PU-H71 (epichaperome inhibitor). Currently we are evaluating the in vivo response of U266 and U266-RL luciferase labeled xenograft models and results will be discussed. These results indicate the high abundance of the epichaperome in MM plasma cells represents a vulnerability that can be targeted with PU-H71. Thus, taken together, our results suggest that PU-H71 represents a potential therapeutic candidate for MM patients, and together with the assessment of the epichaperome abundance we could implement a biomarker driven clinical trial for MM

Keywords:
Biomarker
epichaperome
Hsp90

Tracks:
Multiple Myeloma Novel Drug Targets

FP-124

CDK4/6 Inhibition Suppresses Myeloma Cell Growth and Viability via Perturbation of E2F Proliferative Program

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Abstract:
Cancer cells are characterized by perturbed transcriptional profiles. These dysregulations depend on transcriptional regulators unpredicted by genetic changes. Multiple myeloma cells also tend to develop striking dependencies on super-enhancer regulatory elements. Also, promoter proximal transcription factors like E2F1 and SP1 play prominent roles in myeloma cell biology by controlling proliferative and survival genes. Importantly, our genome-wide profiling of the MM epigenome revealed that promoter and enhancer-associated factors govern distinct biological functions providing a non-overlapping control of the myeloma transcriptome. The goal of this study is to understand global gene regulation in MM by deploying novel therapeutics to target MM cell proliferation. Genomic analysis using ChIP-seq, ATAC-seq, and RNA-seq and loss of function screening in MM cell lines and primary MM cells revealed two distinct regulatory axes: SP1, DP1, E2F and MYC localized to promoters of growth/proliferation genes and CDK9, BETs and

other factors disproportionately enriched at enhancer regulated tissue-specific genes. This enhancer and promoter axes is also observed in diffuse large B-cell lymphoma, suggesting transcriptome control. Inhibition of promoter and enhancer axes using RNAi shows a superior inhibition of MM cell growth compared to single perturbation, providing an important molecular mechanism for combination therapy. We targeted TF SP1 with Terameprocol, inhibitor of DNA binding activity and a peptide to disrupt the E2F1-DP1 heterodimerization responsible for the E2F transcription for successful inhibition of MM cell growth and viability, and the effect was augmented in presence of inhibitors of enhancers, like BRD4 inhibitor JQ1. We also investigated inhibitors of upstream regulators of the pRB-E2F axis such as CDK4/6 to impact E2F1 activity. CDK4-6 complexes can phosphorylate RB, releasing E2F and modulating the expression of E2F target genes. Thus, we investigated the combination of CDK4/6 inhibitor Palbociclib with low JQ1 doses and saw profound effects on E2F promoter driven transcription, and a highly synergistic effect on growth and survival in cell lines and primary MM cells from newly diagnosed and relapsed patients. Cell cycle studies revealed complete G1 arrest post treatment. The combination regimen had no significant effect on PHA-activated healthy donor PBMCs, implying a favorable therapeutic index. Next, in vivo study in a human xenograft mouse model using MM cells expressing luc-E2F-reporter confirmed significant effect of the combination against MM tumor growth and E2F activity. These implicate the existence of a sequestered cellular function by promoter and enhancer driven processes providing non-overlapping vulnerabilities. Simultaneous targeting of these processes using clinically applicable agents can synergistically impair the myeloma proliferative program, with potential for development of a promising therapeutic strategy.

Keywords:
Multiple myeloma

myeloma

Tracks:

Multiple Myeloma Novel Drug Targets

FP-125

MAGE-A3 mediates survival and proliferation through regulation of BIM and p21Cip1 in multiple myeloma

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Abstract:
The type I Melanoma Antigen Gene (MAGE) A3 is a promising functional target in multiple myeloma (MM) that is associated with proliferation and progression of disease. MAGE-A3 inhibits apoptosis and promotes cell cycle regulation in human myeloma cell lines (HMCL) and primary cells. We investigated the mechanisms of these oncogenic activities in laboratory models and through analysis of gene expression and clinical outcome data. Gene expression profiling (GEP) by RNA sequencing (RNAseq) of p53+/+ HMCL MM.1r and H929 after MAGE-A knockdown identified a set of 201 differentially expressed genes (DEG, $p<0.05$). Of the top DEGs, eight were BH3-only Bcl-2 family members or apoptotic pathway genes. Four of the top DEGs were cell cycle regulation genes and three were DNA binding/damage repair genes. We interrogated protein expression after MAGE knockdown and demonstrated significantly increased levels of pro-apoptotic BIM, but other Bcl-2 proteins were either not altered or not detected, and in this

setting, MAGE appears to mediate post-translational modification and degradation of BIM. We also detected increased levels of the endogenous cyclin-dependent kinase (CDK) inhibitor p21Cip1, which correlated with the GEP results. Depletion of MAGE-A in HMCL increased apoptosis in response to MM chemotherapy agents such as melphalan and panobinostat. To assess the clinical significance of these findings, we analyzed RNAseq data from the iA9 release of the Multiple Myeloma Research Foundation CoMMpass database of more than 650 newly diagnosed MM patients based on high or low MAGEA3 expression, which revealed a set of significantly DEGs ($p<0.05$) that included several MAGE family members and related X-linked genes. Gene set enrichment analysis demonstrated associations with cell cycle and DNA replication pathways, similar to that observed in HMCL. We ranked subjects based on MAGEA3 mRNA expression levels and correlated the highest (219 subjects) and lowest quartiles (212 subjects) with clinical outcome, which showed that the MAGEA3 high group had worse overall survival (Hazard Ratio = 2.5, $p<0.01$, data not shown). This survival difference was even more striking in the subgroup of subjects that had undergone high dose melphalan chemotherapy and autologous stem cell transplantation. MAGEA3 high subjects (39 subs) had worse progression-free ($p<0.1$) and overall survival ($p<0.01$) compared to the lowest (37 subs). These results demonstrate that MAGE-A3 negatively regulates BIM at both the transcriptional and post-translational levels, which favor survival and resistance to chemotherapy. MAGE-A3 inhibits p21Cip1 transcription which promotes passage through the early G1 checkpoint and proliferation. These mechanisms are a biochemical basis for MAGE-A3-mediated resistance to chemotherapy-induced apoptosis and the associations with progression of disease and tumor proliferation.

Keywords:
apoptosis

MAGEA3

proliferation

Tracks:

Multiple Myeloma Novel Drug Targets

FP-126

HDAC8 Mediates Homologous Recombination and Cytoskeleton Integrity in Myeloma with Potential Impact on Cell Growth and Survival

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Abstract:
The chromatin structure and histone modifications have emerged as essential epigenetic layers affecting gene expression changes in cancer. In recent years, both clinical and preclinical studies have confirmed that MM is vulnerable to epigenetic intervention, with histone deacetylases (HDACs) emerging as the most promising epigenetic targets. Although Pan-HDAC inhibitors are effective as therapeutic agents, there is an increasing emphasis on understanding the biological and molecular roles of individual HDACs. Here we evaluated the functional role of HDAC8, a member of Class I HDAC isoenzymes in MM based on our observation of the significant impact of its high expression on overall survival in 3 large independent clinically annotated transcriptomic data. We observed that HDAC8 depletion with RNAi resulted in significant inhibition of myeloma cell proliferation and a decrease in colony formation ($p<.001$). Importantly, HDAC8 knock-down inhibited DNA repair as measured by γH2Ax, via affecting homologous recombination (HR) activity,

measured by plasmid-based assay and by RAD51 foci. This led to increasing in DNA damage, suggesting a novel connection between HDAC8 and DDR pathway in MM cells. To further confirm the impact of HDAC8 on double-strand break repair, we performed single-cell electrophoresis (Comet-assay) after ionizing radiation in OPM2-HDAC8 depleted cells and observed decreased repair of DSBs. Using laser micro-irradiation in myeloma and U2OS cells, we observed HDAC8 recruitment to DSBs sites and its co-localization with Rad51 and Scm3, a member of cohesin complex suggesting a link with the cytoskeleton. Transcriptomic analysis of HDAC8 knock-down cells also shows perturbation of a number of cytoskeleton-related genes. Along with the evaluation of the effects of genetic modulation of HDAC8, we have explored the efficacy of two specific HDAC8 inhibitors, PCI-34051 and OJI-1, and observed myeloma cell killing in a time and dose-dependent manner, with IC50 correlating with HDAC8 expression level. A significant higher IC50 was observed in PBMCs, suggesting a favorable therapeutic index. Moreover, pharmacological inhibition of HDAC8 specifically inhibited HR but not non-homologous end joining. In conclusion, our results demonstrate a novel function of HDAC8 in promoting homologous recombination and DNA repair in MM cells. This study provides insight into the effect of HDAC8 on DNA stability and cell growth and viability that may have therapeutic implications in MM.

Keywords:
DNA damage

HDAC inhibitor

Multiple myeloma

Tracks:
Multiple Myeloma Novel Drug Targets

FP-127

Targeting Aurora-kinase B with the novel Aurora Kinase B inhibitor MK7 in multiple myeloma

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Abstract:
The management of high-risk and relapsed/refractory (R/R) MM patients remain a therapeutic challenge as outcomes remain poor. The most part of these patients ultimately become refractory to treatment, due in part to a lack of a successful mechanism-based therapies and genetic instability with numeric chromosomal abnormalities. Aurora kinase B (AURKB) is a key regulator of mitosis as a component of the chromosomal passenger complex (CPC). The CPC has essential functions at the centromere in ensuring correct chromosome alignment and segregation and is required for chromatin-induced microtubule stabilization and spindle assembly as well as orderly cytokinesis. AURKB is a member of a family of three mammalian Aurora-kinases (Aurora-kinases A, B and C), each with a conserved tyrosine kinase domain but differing in localization and function. The clinical significance of centrosome amplification and centrosome-associated gene expression in MM has been validated. AURKA has been recognized for some time as an important molecule in cancer and this has led to more recent exploration of the role of AURKB (Keen & Taylor, 2004; Girdler et al, 2006). We sought to characterize the potential of MK7, a novel AURKB inhibitor, as a therapeutic approach for MM. MK7 is an orally bioavailable AURKB specific inhibitor with good pharmacokinetic (PK) properties. We first evaluated the mRNA and protein expression levels of AURKB in a panel of MM cell lines (MM1S, MM1R, U266, SKO-007, U266 lenalidomide resistant, AMO-1 bortezomib resistant and AMO-1 carfilzomib resistant) and primary CD138+ BM samples from MM patients (n=14). In addition, we examined the levels of phosphorylated Histone H3 as readout of the activity of AURKB . We found that all the cell

lines evaluated had detectable levels of phospho-H3 suggesting that the cells may be sensitive to inhibition of AURKB using MK7. Next we evaluated the dose response sensitivity of all the MM cell lines to MK7 and found a significant decrease in viability as early as 24 hours post-treatment. Furthermore, we observed changes in size and shape as early as 6 hours post treatment. MK7 is the most potent AURKB inhibitors identified so far. MK7 demonstrated appropiate PK properties in an oral dosing formulation. With this promising orally active chemical platform, we believe that AURKB inhibitors with better drug properties and a lower toxicity profile can be discovered and developed for MM.

Keywords:
Aurora-kinase B

MK7

Multiple myeloma

Tracks:
Multiple Myeloma Novel Drug Targets

FP-128

Protein Synthesis Rates Regulate Tumor-initiating Potential and Chemoresistance in Multiple Myeloma

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Abstract:
Multiple myeloma (MM) plasma cells rely on the proteasome to maintain protein homeostasis and limit proteotoxic stress from immunoglobulin production. Although proteasome inhibition is markedly effective for MM, virtually all patients experience relapse. Low immunoglobulin-secreting tumors are more frequent in relapse, suggesting that modulating protein synthesis might be driving proteasome inhibitor resistance. However, this pattern is also observed at relapse even in those unexposed to proteasome inhibition. Therefore, modulating protein synthesis may generally impact basic properties such as chemoresistance and tumor-initiating potential that are required for relapse. To determine the effect of protein synthesis rates on chemoresistance, we treated MM cells with cycloheximide (CHX), a small molecule inhibitor of ribosomal elongation. At sub-lethal doses, CHX decreased 35S-methionine incorporation by ~30%, but increased the relative IC50 of cells to bortezomib, dexamethasone, and melphalan in cell viability assays (1.5–5-fold, p-value <0.05). Notably, CHX also enhanced clonogenic growth potential as determined in methylcellulose-based colony forming cell assays (2.1–4-fold, p<0.05). We discovered that eIF5, a translation initiation complex subunit, was upregulated in response of cells to bortezomib (30–100-fold) and upon co-culture with chemoresistance-inducing stromal cells. Forced over-expression of eIF5 significantly inhibited protein synthesis (2.5–3-fold, p-value <0.05), and, similar to CHX, also increased the relative IC50 for multiple chemotherapeutic agents (range 1.8–3-fold, p<0.05) and increased clonogenic growth potential (3–4-fold, p<0.05). In limiting dilution assays, eIF5 over-expression enhanced tumor initiating cell (TIC) frequency in xenografted immunodeficient mice (TIC frequency of 1/4358 for control vs. 1/262 for eIF5 over-expressing cells; p<0.05). EIF5 was also enriched in CD138-negative populations of MM cells in cell lines (2.1–2.6-fold, p<0.05) and patient samples (1.5–7.3-fold), which corresponded with decreased protein translation rates in these progenitor-like cells (7.4–13.6-fold, p<0.05). In contrast, supplementing MM cells with leucine increased protein synthesis, particularly in CD138-negative cells (10–20%-increase, p<0.05), which consequently decreased colony formation when used in combination with either bortezomib or dexamethasone (1.5–2-fold, p<0.05). Strikingly, combining leucine supplementation with bortezomib also extended survival in immunodeficient mice harboring MM xenografts when compared to bortezomib alone (log-rank p<0.05). In conclusion, we have shown that protein translation rates are

inversely linked to chemoresistance and stem cell functions in MM, providing novel evidence that protein homeostasis mechanisms may drive relapse in cancer. Augmenting protein synthesis rates may be an innovative strategy to prevent and treat relapsed disease.

Keywords:
malignant stem cells

Multiple myeloma

Proteostasis

Tracks:
Multiple Myeloma Novel Drug Targets

FP-129

Inhibition of the JAK-STAT3-Mcl-1 Axis by Combining Ruxolitinib with S63845 Completely Prevents Plasmacytoma Growth in the Gp130-Regulated INA-6 Xenograft Mouse Model

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Abstract:
Introduction: Growth of malignant plasma cells in multiple myeloma is regulated by the JAK/STAT3 pathway via cytokines such as interleukin(IL)-6 which is produced in the bone marrow microenvironment. IL-6 stimulation leads to upregulation of anti-apoptotic proteins of the Bcl-2 family including Mcl-1 and/or Bcl-xL. Growth of INA-6 plasmacytomas in SCID mice depends on activation of the signal transducer gp130, the common receptor for IL-6 and other cytokines of the IL-6/gp130 family (Burger et al., Haematologica 102, 2017). Materials and Methods: SCID-beige mice xenografted with INA-6.Tu1 cells were treated with the JAK1/2 inhibitor ruxolitinib (60 mg/kg p.o. bid), the Mcl-1 inhibitor S63845 (25 mg/kg i.v. Q3Dx4), or a combination of both. All compounds were provided by Novartis. The control group was treated with vehicle. Treatment started one day after cell inoculation and continued for ten consecutive days. STAT3 and ERK1/2 phosphorylation was evaluated by Western blotting. Cell growth in vitro was measured using an MTS-based colorimetric assay. Results: Treatment of mice was well tolerated in all groups, without significant body weight changes during time of treatment. All mice of the control group (n=8) developed overt plasmacytomas and had to be sacrificed (median survival time 23 days). A significant delay in tumor growth was observed in about half of the mice treated with ruxolitinib (n=7) or the Mcl-1 inhibitor (n=8), median survival times were 56 days and 91 days, respectively. Remarkably, none of the animals treated with the combination (n=6) showed any signs of disease until day 98 when the experiment was terminated. The combination was superior to treatment with ruxolitinib alone (p-value 0.0325). In mice with established plasmacytomas, one oral application of ruxolitinib resulted in inhibition of constitutive and (ex vivo) IL-6 stimulated STAT3 phosphorylation. In contrast, the MAPK pathway remained unaffected. Sensitivity of INA-6 cells to ruxolitinib and S63845, evaluated in freshly explanted tumors, was retained in vivo and similar to the parental cells. Additional effective combination partners for ruxolitinib in vitro are inhibitors of mToR (rapamycin) and PI3K (NVP-BKM120). Conclusion: While both the JAK1/2 inhibitor ruxolitinib and the Mcl-1 inhibitor MIK665 (S64315) are currently in early clinical evaluation for patients with relapsed/refractory myeloma, either in combination with steroids and lenalidomide (ruxolitinib) or as single agent (MIK665), the results from our studies in the INA-6 xenograft model indicate a superior outcome using a combination of the two drugs.

Keywords:
signaling

therapy

Tracks:
Multiple Myeloma Novel Drug Targets

FP-130

TAZ functions as a tumour suppressor in multiple myeloma by downregulating MYC

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Abstract:
TAZ is a transcriptional coactivator downstream of the Hippo signaling pathway that functions as an oncogene in many solid tumours. However, its role in haematological malignancies is largely unexplored. Multiple myeloma (MM) is an incurable blood cancer that is often characterized by amplification and overexpression of the MYC oncogene. Despite efforts, direct targeting of MYC is not yet possible; therefore, alternative strategies to inhibit MYC activity are necessary. In this study, we show that, in contrast to solid tumours, expression of TAZ is lower in MM, with decreasing expression from normal plasma cells to intermediate stages of MM to fully active disease. Furthermore, high expression of TAZ correlates with better patient outcomes. We further show that TAZ is hypermethylated in MM patient samples and in a panel of MM cell lines. Genetic overexpression of TAZ or pharmacological upregulation of TAZ by treatment with the demethylating agent decitabine induces apoptosis. Importantly, TAZ-induced apoptosis is independent of canonical Hippo components LATS1/2 or the TEAD family of transcription factors. Instead, RNA-seq analysis revealed that overexpression of TAZ represses a MYC transcriptional program and we show that increased TAZ expression correlates with decreased MYC expression in both cell line models and patient samples. Finally, promoter de-repression of TAZ expression sensitizes MM cell lines through a reciprocal reduction in MYC expression using both clinically relevant therapeutics such as bortezomib and panobinostat. Our findings uncover an unexpected role for TAZ in MM tumorigenesis and provide compelling rationale for exploring the therapeutic potential of upregulating TAZ expression to restore sensitivity to specific therapeutics in MM.

Keywords:
decitabine

MYC

TAZ

Tracks:
Multiple Myeloma Novel Drug Targets

FP-131

Preclinical evaluation of tropolone and proteasome inhibitor therapy for multiple myeloma

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Abstract:
Introduction: Tropolones are naturally occurring 7-membered non-benzenoid aromatic compounds that have activity as zinc and iron chelators and may inhibit selective metalloenzymes such as histone deacetylase (HDAC) 2 and 8. Recently, our group investigated the activity of a novel alpha-substituted tropolone MO-OH-Nap (2-hydroxy-7-naphthalene-2-yl-cyclohepta-2,4,6-trien-1-one), in multiple myeloma (MM) cells and demonstrated that MO-OH-Nap (MO) induces caspase cleavage in a time frame distinct from that of the pan-HDAC inhibitor vorinostat. MO, but not vorinostat, promotes the expression of markers associated with the unfolded protein response (UPR) in MM cells. The combination of MO and the proteasome inhibitor bortezomib (Bor) induces synergistic cytotoxic effects in a manner that is independent of aggresome

formation. The ability of MO to induce apoptosis and upregulate markers of the UPR is prevented by co-incubation with iron. An initial dose-finding study revealed that MO administered at 9.4 mg/kg IV three-times weekly was well-tolerated in CD-1 mice. Collectively, these findings prompted further investigation into the potential anti-myeloma activity of MO. Methods: The effects of MO in combination with Bor on markers of the UPR in human MM cell lines were evaluated via qRT-PCR. For in vivo study, MO was dissolved in a 5% DMSO, 45% W/V hydroxypropyl-beta-cyclodextrin solution in PBS. NOD/SCID mice were subcutaneously inoculated in the flank with MM.1S cells. Mice were randomly divided into one of four treatment groups (n=8 per group): control (PBS), MO (18.8 mg/kg IV three times-weekly), Bor (0.3 mg/kg SQ twice weekly) and MO/Bor combination. Tumor volume was recorded three times per week. Blood samples were analyzed for blood counts, renal/hepatic function and iron/ferritin. Results: The effect of Bor on augmenting MO-induced upregulation of UPR markers was both cell line- and time-dependent. Studies are ongoing to determine whether this effect is associated with an accelerated time course of UPR activation and induction of apoptosis. MO was well-tolerated with no effects on animal weight, hematological, renal/hepatic function or iron/ferritin levels. Further MO dose escalation was not possible because of drug solubility issues. Mice treated with MO were grossly and histologically normal. The MO/Bor combination did not result in any evidence of toxicity as assessed by body weight, histology and blood parameters. MO treatment was associated with a trend towards smaller tumor volume over time relative to control (p=0.068). Combination treatment did not result in further reduction of tumor growth. Conclusion: These studies suggest that the observed synergy between the novel tropolone MO and Bor may be related to effects on the UPR and are the first to explore the in vivo anti-MM activity of MO. Further optimization of the formulation of MO will allow further dose escalation and confirmation of in vivo anti-MM activity

Keywords:
apoptosis

ER stress

tumor

Tracks:
Multiple Myeloma Novel Drug Targets

FP-132

N-glycan Analysis from Monoclonal IgG in Patients with Multiple Myeloma Enables Differentiation of Disease States

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Abstract:
Background It is well recognized that symptomatic myeloma (MM) is preceded by monoclonal gammopathy of undetermined significance (MGUS) and asymptomatic smouldering myeloma (SMM). The pathological progression from MGUS to SMM and finally to symptomatic MM is poorly understood. The immunological characteristic feature of plasma cell disorders is the presence of a monoclonal immunoglobulin (M-protein), which is post-translationally modified by N-glycosylation affecting structure, stability, and biological function. Using a targeted glycomic platform, we evaluated the N-glycans on IgG M-proteins from patients across the myeloma spectrum to gain insight into the role of N-glycosylation in disease progression and potential therapeutic targets. Methods Polyclonal IgGs were extracted from sera of 70 patients with MGUS, SMM, MM, and age-matched controls. Charge variant analysis enabled the separation of the monoclonal IgG from the polyclonal residual background. N-glycans from IgG M-protein were liberated by enzymatic digestion, fluorescently labelled, purified, and analyzed using hydrophilic interaction ultra-performance liquid chromatography coupled to high-resolution mass spectrometry (LC-

MS/MS). Linkage and positional specificity of glycan structures were further elucidated by utilizing exoglycosidase digestions and DMTMM derivatization. The pattern of differential N-glycans between patient groups were mapped by Progenesis QI using the observed relative abundance of individual glycan obtained from LC-MS/MS. Results N-glycan analysis of IgG M-protein was differentially expressed across the patient groups. Glycosylation profiles from MGUS patients resembled those of normal control. The abundance of sialylated glycans was highest in MM and lowest in MGUS and control groups. Specifically, the fucosylated biantennary tri-galactose mono-sialylated glycan (FA2BG3S1) showed clear separation between MM and SMM with more than 300-fold higher in the symptomatic state. Furthermore, the afucosylated biantennary bi-sialylated glycan (A2BG2S2) was more than 100-fold higher in SMM compared to MGUS. In patients with MM, the observed N-glycans of M-proteins displayed similar profiles to those of polyclonal IgG, consisting of mainly biantennary glycans with low level of core fucosylation and sialylation at the Fc region. However, higher abundance of sialylation was observed in the Fab region. The formation of these larger sialylated glycans is likely the result of less steric hindrance allowing better access by glycosyltransferases during oligosaccharide biosynthesis. Conclusions Glycan analysis of the enriched IgG M-protein from sera of patients across myeloma spectrum were successfully characterised showing differential glycosylation between patient groups with alteration in the levels of fucosylation and sialylation. Specific biantennary sialylated glycans displayed potential as markers for disease progression and therapeutic targets.

Keywords:
glycosylation

Progression

therapeutic targets

Tracks:
Multiple Myeloma Novel Drug Targets

FP-133

Treatment of RAS-Mutated Multiple Myeloma by Targeting MAP4K2

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Abstract:
Introduction: Next-generation sequencing (NSG) is performed often in relapsed /refractory multiple myeloma (MM) with limited consequences based on a missing rationale to target the identified mutation. Nevertheless, NGS revealed NRAS, KRAS, or BRAF mutations in the RAS/mitogen-activated protein kinase (MAPK) pathway in up to 50% of newly diagnosed MM patients. The majority of the NRAS, KRAS, and BRAF mutations occur in hotspots causing constitutive activation of the corresponding pathways. This makes the MAPK pathway an attractive therapeutic target in MM. Therefore, over the last years, we focused our research on the MAPK pathways and discovered the critical role of MAP4K2 in MM cell survival and growth. Methods and Results: Silencing MAP4K2 pathway using shRNA effectively inhibited proliferation and induced MM cell death. Of note, we found that MAP4K2 is significantly stronger expressed in K-RAS and N-RAS mutated MM cells compared to RAS-wild type (WT) MM cells. Accordingly, K-RAS mutated (MM.1S, RPMI-8266) and N-RAS mutated (H929, JJN3) myeloma cell lines exhibited a significantly higher sensitivity to MAP4K2 inhibition than RAS-WT (OPM2, LP-1) MM cell lines. Next, we introduced inducible shRNA to knockdown MAP4K2 (tet-on-sh-MAP4K2) in MM cells upon doxycycline treatment. Cell proliferation assays showed that knockdown of MAP4K2 expression resulted in significant inhibition ($p<0.01$) of MM cell growth. In accordance, cell cycle analysis revealed that the knockdown of MAP4K2 decreased the cell numbers in S-phase with a concomitant increase of cells in G0/G1 growth arrest (55% vs. 67%). Importantly,

MAP4K2 knockdown resulted in a significant increase ($p<0.01$) with 3.2% vs. 60.8% of apoptotic cells. To confirm the critical role of MAP4K2 in MM tumor growth in vivo, we generated subcutaneous MM xenografts in SCID Beige (CB17.Cg-PrkdcscidLystbg-J/Crl) mice using the doxycycline-inducible knockdown MAP4K2 MM cells (tet-on-sh-MAP4K2). Doxycycline or vehicle treatment was started after the tumor was established to induce MAP4K2 silencing in MM cells. In contrast to vehicle-treated MM.1S-tet-on-shMAP4K2 or doxycycline-treated but shRNA-knockdown resistant control tumors (MM.1S-tet-on-shCNTL), MAP4K2 knockdown group showed a significant inhibition ($P<0.01$) of tumor growth by 80% after 30 days. Conclusion: Taken together, we show for the first time, the critical role of MAP4K2 in MM. Our data confirm that the inhibition of MAP4K2 is a potential therapeutic approach in RAS-mutated MM cells and provide the rationale for the clinical development of target treatments based on mutations identified by NGS. Further, our findings could prompt the development of a series of MAP4K2 inhibitors as novel anti-MM therapeutic agents.

Keywords:
Kinase

MAP4K2

ras mutation

Tracks:
Multiple Myeloma Novel Drug Targets

FP-134

Synergistic targeting of Sp1 in myeloma cells with hyperthermia plus proteasome inhibitors

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Abstract:
Multiple myeloma (MM) and extramedullary plasmacytoma still remain incurable despite recent advances in the treatment of MM. MM-initiating cells or MM progenitors are considered to contribute to disease relapse through their drug-resistant nature. We recently developed novel superparamagnetic iron oxide nanoparticles which selectively accumulate in extramedullary plasmacytoma and to kill their progenitors by heat generated with magnetic resonance (Theranostics, 2013). Therefore, superparamagnetic iron oxide nanoparticles potentially achieve what is called "theranostics", a combination of tumor imaging and targeting treatment for extramedullary tumors. We found that hyperthermia accumulated the polyubiquitinated proteins and induced endoplasmic reticulum (ER) stress in MM cells. We also found that hyperthermia induced time- and temperature-dependent MM cell death, besides minimized side population and suppressed colony formation in MM cells (Oncotarget, 2017). In the present study, we aimed to clarify the effects of hyperthermia plus proteasome inhibitors (PIs) on MM cells, focusing on its apoptotic signaling pathway. Hyperthermia and PIs (bortezomib, carfilzomib) induced the phosphorylation of eIF2α, up-regulated ER stress mediators, ATF4 and CHOP, along with death receptor (DR) 5, a CHOP-target gene in MM cells. Hyperthermia up-regulated heat shock proteins and induced caspase-8 activation, reduced specificity protein-1 (Sp1) expressions at protein levels in MM cells. Hyperthermia up-regulated DR5, but down-regulated c-FLIP and DR4, did not affect Sp1 at mRNA levels in MM cells. Hyperthermia and PIs synergistically induced caspase-8 activation and Sp1 reduction, and markedly suppressed Sp1 driven pro-survival factors, IRF4 and c-Myc, in MM cells. Hyperthermia cooperatively induced MM cell death

in combination with PIs. Interestingly, caspase-8 inhibition suppressed heat-induced Sp1 protein degradation; and Sp1 inhibition reduced c-FLIP expression in MM cells, indicating caspase-8-mediated enzymatic Sp1 degradation and thereby suppression of c-FLIP expression. These results suggest that caspase-8-mediated post-translational Sp1 degradation appears to be important mechanisms for synergistic anti-MM effects of hyperthermia and PIs in combination. We are currently developing new versions of smart nanoparticles which generate heat in response to an alternating current magnetic field and that sequentially release an anticancer drug, such as doxorubicin (Theranostics, 2014). Therefore, the above smart nanoparticles carrying PIs warrant further study, especially in the setting of drug-resistant extramedullary plasmacytomas.

Keywords:
hyperthermia

Proteasome Inhibitor

Sp1

Tracks:
Multiple Myeloma Novel Drug Targets

FP-135

KDM5A reinforces MYC transcriptional program and promotes myeloma cell growth

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Abstract:
Deregulation of MYC is deeply implicated in the pathogenesis of multiple myeloma (MM). Recent studies show that MYC selectively activates or represses its target genes, cooperating with other factors such as WDR5 and MIZ1 in a cancer-specific manner. Hence, the factors mediating cancer-specific MYC program could be ideal therapeutic targets in MYC-driven cancers. However, little is currently known about the crucial factors involved in the aberrant MYC transcriptional program in MM. KDM5A (Lysine demethylase 5A; also known as JARID1A/RBP2) is one of the Jumonji C domain-containing demethylases which recognizes and removes histone H3 lysine 4 di- and tri-methylation (H3K4me2 and H3K4me3), epigenetic marks of transcriptional gene activation. KDM5A is not only involved in development and differentiation, but is also engaged in tumorigenesis, metastasis, and drug resistance in various cancers, either dependent or independent of catalytic function; however, the biological roles of KDM5A in MM have not been delineated. In this study, we characterized the biological and molecular functions of KDM5A in MM. KDM5A is highly expressed in MM cell lines and primary MM samples, and higher KDM5A expression is associated with poor prognosis in the IFM/DFCI 2009 MM study dataset. We therefore examined the biological function of KDM5A in MM using both sh-mediated knockdown and a novel KDM5-selective inhibitor pck82, which dramatically improves cell permeability of KDM5-C49. Knockdown of KDM5A or pharmacologic inhibition of KDM5 induced G0/G1 cell cycle arrest and decreased growth of MM cell lines. Pck82 induced only modest apoptosis in MM cell lines after the cell cycle arrest, indicating that KDM5 is primarily required for MM cell proliferation rather than survival. In contrast, pck82 did not affect the growth of normal PBMNCs. To clarify the molecular mechanisms whereby KDM5 mediates MM cell growth, we examined gene expression profile using RNA-seq after the treatment of MM.1S cells with pck82. Importantly, gene set enrichment analysis showed that pck82 decreased expression of MYC target genes. We confirmed that knockdown of KDM5A, but not of KDM5B, similarly

downregulated MYC targets. Of note, ChIP-seq analysis revealed that KDM5A not only colocalized with H3K4me3 mark, but also with MYC across the genome. Treatment with pck82 increased H3K4me3 mark globally, but did not increase this mark at the loci of MYC targets whose expression is downregulated after pck82 treatment. These data suggest that KDM5A may activate MYC targets in an enzymatically-independent manner, and that pck82 may abrogate this transcriptional activation by binding KDM5A and interfering with KDM5A related-transcriptional complex. Our results both delineate KDM5A function that reinforces MYC transcriptional program promoting MM cell growth, and identify KDM5A as a potential therapeutic target in MM.

Keywords:
epigenetic

histone modifications

Transcription factor

Tracks:
Multiple Myeloma Novel Drug Targets

FP-136

Targeting Ubiquitin Receptor Rpn13/ADRM1 in Plasmacytoid Dendritic Cells Enhances Anti-Myeloma Immunity

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Abstract:
Introduction The proteasome inhibitor (PIs)-therapies are often associated with the emergence of drug-resistance in multiple myeloma (MM). Additionally, tumor-extrinsic MM bone marrow (BM) accessory and immune effector cells interactions, also contribute to drug-resistance and immune suppression. For example, interactions of plasmacytoid dendritic cells (pDCs) with MM cells and T/NK effector cells in BM milieu confer immune suppression and induce MM cell growth. A novel therapeutic strategy is hence needed to overcome both tumor-intrinsic and -extrinsic PI-resistance and restore anti-MM immunity. We recently reported that targeting proteasome-associated ubiquitin receptor Rpn13 can trigger cytotoxicity and overcome tumor-intrinsic PI-resistance in MM (Song et al, Leukemia 2016;30;p1877). However, it is unsettled whether targeting Rpn13 overcomes immune suppression in the MM BM milieu. Here, we utilized our coculture models of pDCs-T-NK-MM cells to show that pharmacologic or genetic inhibition of Rpn13 activates pDCs to induce MM-specific cytotoxic T cell lymphocytes(CTL) and NK-cells cytolytic activities. Mechanistic studies show involvement of calnexin, an endoplasmic reticulum chaperone, in RA190-mediated pDC-activation and generation of anti-MM immunity. Methods Patient-pDCs (N=7) were treated with Rpn13 inhibitor RA190 (0.05 μM) for 24h, to evaluate CD80/CD83/CD86 markers on pDCs by FACS. CTL/NK activity: MM-BM CD8+ T- or NK-cells were cocultured with autologous BM-pDCs (N=8; pDC:T/NK;1:10 ratio) in the presence or absence of RA190 (100 nM) for 3 days; cells were washed to remove RA190; resuspended in complete medium; followed by addition of pre-stained MM cells for 24h (E/T;10:1; T/NK:MM), and quantification of viable MM cells by FACS. Results 1) RA190 triggers significant upregulation of maturation markers CD80, CD83, and CD86 on MM-pDCs (Fold change vs untreated: CD80:1.2; p=0.007; CD83:2.15;p=0.006; CD86:1.4;p=0.003). In contrast, bortezomib-treated pDCs showed no significant upregulation of these markers. 2) Rpn13-siRNA also increased CD80 (1.76-fold), CD83 (3.12-fold), and CD86 (2.28-fold) expression in pDCs ($p<0.01$). Importantly, both RA190 and bortezomib block proteasome-mediated protein degradation, but only RA190 activates pDCs. 3) RA190 treatment significantly increases pDC-induced MM-specific CD8+ CTL activity (67%viability:treated vs control;p=0.0015) as well

as NK cell-mediated cytolytic activity against autologous tumor cells (3.5-fold MM lysis:treated vs control; p=0.001). 4) The treatment of MM-BM pDCs with RA190 increases calnexin expression (1.21-fold vs control;p=0.0215). These findings were confirmed using pDC cell line CAL1 (p=0.0032). Conclusions Rpn13 blockade overcomes PI-resistance in MM, and as shown here, restores both innate and adaptive immune responses. Together, these findings provide basis for a novel therapeutic strategy targeting Rpn13 to both restore immunity and overcome PI-resistance in MM.

Keywords:
immunotherapy

Plasmacytoid Dendritic Cells

Ubiquitin Receptor Rpn13/ADRM1

Tracks:
Multiple Myeloma Novel Drug Targets

FP-137

Molecular markers of myeloma cell sensitivity vs. resistance to heterobifunctional degraders of oncoproteins: therapeutic implications.

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Abstract:
Heterobifunctional proteolysis-targeting chimeric (PROTAC) compounds exhibit potent preclinical activity against multiple myeloma (MM) and other neoplasias by "reprogramming" E3 ligases to ubiquitinate and cause degradation of target oncoproteins. The mechanisms regulating MM cell sensitivity to different classes of these PROTACs are incompletely understood. To address this topic, we performed CRISPR studies (at genome-scale and with individual sgRNAs) to define genes whose editing (loss-of-function, LOF) or activation (gain-of-function, GOF) confer MM cell resistance to PROTACs that target oncoproteins (e.g., BET bromodomain, CDK9) through different E3 ligases (e.g. CRBN, VHL, MDM2). We also examined the patterns of cross-resistance between these PROTACs, in experiments whereby cell populations surviving from a genome-scale CRISPR study with one class of PROTACs were sequentially exposed to other PROTACs that engaged the same or different E3 ligases and/or oncoproteins. Through these studies, we observed that MM cell resistance to CRBN- or VHL-based PROTACs does not involve genes whose LOF confers high-risk in MM patients (e.g. TP53, PTEN, negative regulators of cell cycle, et.c.), suggesting that PROTACs may be active in the context of MM with adverse genomic features. Resistance to all PROTACs studied so far primarily involves prevention of, rather than adaptation to, breakdown of the target

oncoprotein and involves e.g. LOF for the cognate E3 ligase or regulators of the respective cullin-RING ligase (CRL) complex. MM cells resistant to CRBN-based PROTACs were enriched for LOF of CRBN and, to a lesser extent, regulators of its CRL-CUL4A, including COP9 signalosome genes, DDB1 or the E2 enzyme UBE2G1. MM cells resistant to VHL-based PROTACs were enriched for LOF of CUL2, VHL itself, and other CUL2-VHL interactors (e.g. RBX1, TCEB1, TCEB2, UBE2R2) and LOF of COP9 signalosome genes is less protective against VHL- (vs. CRBN-) based PROTACs: these differences reflect different composition/regulation of CUL4A-CRBN vs. CUL2-VHL. MDR1 transporter (ABCB1) is the sole gene so far whose GOF is associated with resistance to any PROTAC we tested. PROTACs engaging the same E3 ligase but different oncoproteins can exhibit synergy with simultaneous, but cross-resistance with sequential, administration. PROTACs engaging different E3 ligases/CRLs but the same oncoprotein can exhibit antagonism with simultaneous, but overcome cross-resistance with sequential, administration. Our observations have major implications for the development of new PROTACs and the clinical testing of different classes of PROTACs, as single-agents or in combination with established anti-MM agents, including CRBN-binding thalidomide derivatives, or other PROTACs.

Keywords:
E3 ligase

High-risk cytogenetics

PROTACs

Tracks:
Multiple Myeloma Novel Drug Targets

FP-138

Downregulation of methylation and demethylation enzymes in unsorted cell population of multiple myeloma patients

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Abstract:
Objective: DNA methyltransferases (DNMTs) including DNMT1, DNMT3A and DNMT3B, catalyze the transfer of methyl groups to cytosine position 5, and play an important role in epigenetic regulation, which could be involved in pathogenesis of multiple myeloma (MM). Active DNA demethylation occurs during 5-methylcytosine through TET (Ten Eleven Translocation) enzyme-mediated oxidation removal, and this process is necessary for the epigenetic reprograming of genes and is directly involved in tumor progression. Methods: Expression profiles of demethylation enzymes of TET protein family and DNA methyltransferases were determined from three independent repeats in untreated myeloma cell lines: NCI-H929, MM1S, OPM2, U266 and lymphoma cell lines JURKAT, C7H2. In addition, unsorted cells from bone marrow aspirates of 13 and 18 MM patients were also analyzed. Results: Multiple myeloma cells from tested myeloma cell lines, and in comparison to used lymphoma cell lines show decreased expressions of all DNMTs, especially in de novo DNMT3A and DNMT3B is very low. In tested myeloma cell lines, the TET1 expression is undetectable, TET2 and TET3 expressions are also very low. Similar expression profiles of methylatin and demethylation genes we obtained from samples

of multiple myeloma patients. Although the TET3 expression is higher compared to TET1 and TET2, their expressions in multiple myeloma are also very low. In addition to three analyzed DNMTs, the DNMT3B expression is the lowest in multiple myeloma patients. Conclusion: We present the first data on DNMT and TET expressions on myeloma cells. MM cell lines show decreased expressions of de novo DNMT3A and DNMT3B in comparison to DNMT1, and the DNMT1 expression in lymphoma cell lines is lower in comparison to myeloma cell lines. In tested myeloma and lymphoma cell lines, the TET1 expression is undetectable, TET2 and TET3 expressions are lower in myeloma cell lines compared to lymphoma cell lines. Samples of MM patients showed similar expression profiles of methylation and demethylation enzymes to their expression profiles determined in myeloma cell lines. This study was supported in part by NV18-03-0050 from the Ministry of Health of the Czech Republic, LF_2018_001 from Palacky University Olomouc, and MH CZ – DRO (FNOL, 00098892).

Keywords:
DNA methylation

epigenetic

Multiple myeloma

TET enzymes

Tracks:
Multiple Myeloma Novel Drug Targets

FP-139

Salsalate is An Active Agent in Multiple Myeloma

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Abstract:
Background: Multiple Myeloma (MM) is an incurable plasma cell neoplasm for which novel therapeutic options are required. Constitutive activity of the nuclear factor kappa B (NF-κB) pathway is critical to the pathogenesis of MM. NF-κB activation is mediated by inducible phosphorylation and degradation of the IkB members by IkB kinase (IKK). Inhibiting NF-kB by interfering with IKK activity induces apoptosis in MM. However, there is as yet no IKK inhibitor in clinical development. Salsalate is an IKK inhibitor used historically as an anti-inflammatory drug. It is a non-acetylated form of salicylate, which strongly inhibits the NF-kB pathway, but weakly inhibits the cyclooxygenase pathway, resulting in a favorable toxicity profile. Salicylic acid derivatives have been shown to inhibit NF-kB and induce apoptosis in chronic lymphocytic leukemia. To the best of our knowledge, there have been no studies evaluating the effect of Salsalate in MM. The aim of our study is to evaluate the anti-tumor efficacy of Salsalate in MM cell lines. Methods: MM cell lines with different translocations, including t(4;14), t(14;16) and t(11;14): KMS28PE, KMS18, KMS11, H929, U266, and KMS12BM were cultured in RPMI 1640 supplemented with 10% fetal bovine serum (FBS). We assessed the cell viability by seeding a panel of MM cell lines in a 96 well plate at 25,000 cells/well and treating them with Salsalate over a range of 0-5mM for 24, 48 and 72 hours. At the indicated time points, cell viability was assayed with Cell-TiterGlo (Promega) according to the manufacturer's protocol. Dose-response curves were plotted to determine the IC50 values using the GraphPad Prism software (La Jolla, CA). Results: Salsalate effectively inhibits tumor cell viability and achieves IC50 at a concentration range of between 1.1-1.8mM at 72h in a panel of 6 MM cell lines. This is promising as it is comparable to the therapeutic plasma drug level clinically. Interestingly, our studies demonstrate that Salsalate is efficacious across the different translocations, namely t(4;14) (MMSET), t(14;16) (MAF) and t(11:14) (cyclin D) translocation subtypes. It is also similarly cytotoxic regardless of

whether the MM cell lines exhibit a constitutively activated classical or alternative NF-κB pathway phenotype. Conclusion: Salsalate inhibits MM cell lines at therapeutically relevant concentrations irrespective of translocation subtypes. This is a promising result and we intend to further evaluate the apoptotic induction in MM and probe the effects of Salsalate on the signaling partners of the NF-kB pathway. We plan to eventually expand this study by using patient samples with the eventual aim for translation into clinical application.

Keywords:
Multiple myeloma

NFkB-pathway

Salsalate

Tracks:
Multiple Myeloma Novel Drug Targets

FP-140

Inhibition of Ubiquitin Receptor PSMD4/Rpn10 as Therapeutic Strategy to Overcomes Bortezomib-Resistance in Multiple Myeloma cells

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Abstract:
Background and Rationale Proteasome inhibitors (PIs) represent major advance in the treatment of relapsed/refractory and newly diagnosed multiple myeloma (MM); however, PI-therapy is associated with adverse effects and the development of drug-resistance. Strategies to overcome PI-resistance include targeting ubiquitin proteasome system (UPS) upstream of 20S proteasome subunit. One such exemplary target is ubiquitin receptor PSMD4/Rpn10, which is localized on 19S regulatory lid of proteasome, and play a key role in recognizing ubiquitylated substrate proteins for degradation via downstream 20S proteasome. Here, we utilized both biochemical and genetic studies to show the therapeutic potential of targeting Rpn10 in MM. Materials and Methods Rpn10 knockout cell line was generated using CRISPR/Cas9 in 293 cells. Rpn10-inducible knockdown (KD) MM.1S cell line was generated using shRNA. Cell viability was assessed using WST-1 assays. Signal transduction pathways were evaluated using western blotting. Human MM xenograft model was utilized to characterize the role of Rpn10 on tumor progression. Statistical significance of data was determined using a Student's t test. Results 1) Bioinformatic analysis of publicaly available gene expression profiling database show that Rpn10 expression inversely correlate with overall patient survival (n=175; p = 0.00064). 2) Using real-time PCR, immunoblot analysis, and IHC analysis of MM patient bone marrow biopsies, we found higher Rpn10 levels in primary patient tumor cells and MM cell lines versus normal cells. 3) Transient transfection of siRNA against Rpn10 significantly decreased MM cell viability (p = 0.002); conversely, co-transfection of WT-Rpn10 prevented siRNA-Rpn10-induced decrease in viability. 4) Rpn10-siRNA decreased viability in both tumor cells obtained from bortezomib-refractory MM patients and in bortezomib-resistant MM cell lines. 5) CRSPR/Cas9-mediated knockout (KO) of Rpn10 led to decreased cell growth. 6) A significant accumulation of polyubiquitylated proteins was noted in both Rpn10-KO and Rpn10-KD cells. 7) Mechanistic studies showed that Rpn10-KD triggers apoptosis, cell-cycle arrest, activation of caspases, and endoplasmic reticulum (ER) stress response signaling pathways. 8) Animal model studies showed a significantly reduced tumor growth in mice xenografted with Rpn10-KD MM.1S cells versus mice engrafted with WT-MM.1S cells (p = 0.02). Conclusion Collectively, Our data demonstrate the therapeutic potential of targeting ubiquitin receptor Rpn10, and support the development of Rpn10 inhibitors to overcome PI-resistance in MM.

Keywords:
Ubiquitin Receptor PSMD4/Rpn10

Tracks:
Multiple Myeloma Novel Drug Targets

FP-141

A Small Molecule-induced Targeted Degradation of Ubiquitin Receptor Rpn13 as a Novel Therapeutic Strategy in Multiple Myeloma

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Abstract:
Background and Rationale Proteasome inhibitors (PIs) represent major advance in the treatment of multiple myeloma (MM); however, PI-therapy is associated with adverse effects and the development of drug-resistance. Strategies to overcome PI-resistance include targeting ubiquitin proteasome system (UPS) upstream of 20S proteasome. Our earlier studies identified one such target ubiquitin Receptor (UbR) Rpn13 as a mediator of MM cell growth and survival. Rpn13 is associated with 19S regulatory lid of proteasome and play a key role in recognizing ubiquitylated proteins and directing their degradation via downstream 20S proteasome. Here, we synthesized a novel covalent degrader of Rpn13, WL40, using a small molecule-induced targeted protein degradation strategy (PROTAC/Degronimid). Moreover, WL40 showed potent anti-MM activity both in vitro and in vivo models. Methods WL40 was synthesized by linking the covalent inhibitor of Rpn13 RA190 with cereblon (CRBN) binding ligand thalidomide. Cell viability was assessed by WST-1 assays. Apoptosis was quantified with Annexin V/PI staining. Cell signaling were determined by western blotting. In vivo efficacy of WL40 was assessed using human MM xenograft model. Statistical significance of data was obtained with Student's t test. Results We utilized three distinct strategies to confirm the functionality of WL40: (1) Biochemical binding assays showed that WL40 binds to both Rpn13 and CRBN; (2) WL40-treated MM.1S cells had markedly reduced Rpn13 expression; in contrast, WL40-treated CRBN-Knockout (KO) MM.1S cells had no decrease in Rpn13 levels; and (3) Treatment of HCT116-CRISPR-Rpn13KO cells with WL40 showed no significant cytotoxic activity versus WT-HCT116 cells. These findings confirm the requirement of both CRBN and Rpn13 for degradative activity of WL40. To ascertain if WL40 blocks proteasome-mediated protein degradation, we utilized a GFPu-1 reporter cell line expressing Ub-tagged GFP, which is marked for constitutive degradation by the proteasome. Treatment of GFPu-1 cells with WL40 led to accumulation of GFP, indicating blockade of protein degradation via proteasome. Moreover, WL40 blocks 20S function without affecting 20S proteasomal activities. Importantly, WL40 degrades Rpn13 in both bortezomib-sensitive and -resistant cells and decreases their viability. We confirmed the anti-MM activity of WL40 in a panel of genetically distinct and drug-resistant MM cell lines as well as primary patient tumor cells. Mechanistic studies showed that WL40 triggers MM cell apoptosis via activation of caspase cascade and induction of endoplasmic reticulum stress response signaling. In animal model studies, WL40 inhibits xenografted human MM cell growth and prolongs survival. Conclusions Overall, we show the development of the first heterobifunctional degrader of UbR Rpn13 with potent anti-MM activity and provide proof of principle for the development of degraders targeting components of the UPS for therapeutic applica

Keywords:
Ubiquitin Receptor Rpn13/ADRM1

Tracks:
Multiple Myeloma Novel Drug Targets

FP-142

Panobinostat (LBH589) in combination with the β-catenin inhibitor Tegavivint (BC2059) exerts significant anti-myeloma activity both in vitro and in vivo

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Abstract:
Introduction: Panobinostat (LBH589) is approved for the treatment of relapsed myeloma (MM). The Wnt canonical pathway and its key player, β-catenin are dysregulated in advanced MM supporting the evaluation of β-catenin inhibition as a potential therapy. We evaluated the anti-MM effect of Tegavivint (BC2059) in combination with LBH589 in vitro and in vivo. Results and Methods: In vitro combination of low doses (BC2059≤100nM; LBH589≤10nM) for 48h was synergistic against both OCI-My1 and U266 MM cells, with combination indices (CI) ranging from 0.569 to 0.883 (CI<1: synergism). Similarly, the combination demonstrated synergistic killing of primary MM tumour cells in a validated autologous co-culture assay with synergism quotients (SQ) ranging from 1.2 to 2 (SQ>1: synergism). The combination rapidly (<24h) decreased the expression of downstream β-catenin targets c-myc, pan-myc, cyclinD1 and cyclinD2 as shown by immunoblotting. Furthermore, by 20h, the combination decreased both oxidative phosphorylation and aerobic glycolysis as measured by oxygen consumption rate (OCR) and extracellular acidification rate (ECAR), respectively (Seahorse XFe96 analyser). Basal, maximal and ATP coupled OCR was also significantly reduced by the combination when compared to vehicle (for OCI-My1 from 203.93 to 56.20, from 105.81 to 33.29 and from 156.29 to 34.67 pmol/min/50K cells OCR respectively). Similarly, glycolytic activity was also inhibited by the combination reducing both basal glycolysis and glycolytic capacity (from 48.88 to 9.77 and from 61.68 to 8.58 mpH/min/50K cells ECAR, respectively for OCI-My1). In vivo, BC2059 combined with LBH589 was superior to either single drug treatment in a murine xenograft of U266-luciferase cells. Disease burden was reduced in the combination arm compared to single drug and vehicle arms as early as day 14 after inoculation ($p=0.02$), the difference increasing through until the last day of bioluminescence imaging (day 49, $p<0.001$) and translated into significantly prolonged OS for the combination ($p=0.006$, Mantel-Cox test). Potential on-target toxicities with BC2059 are a concern as the Wnt canonical pathway is essential for stem cell maintenance in several organs and has a role in bone homeostasis, but the combination did not result in cytopenias nor body weight loss, implying maintenance of normal haematological and gastrointestinal function. After euthanasia, μCT demonstrated that neither BC2059 nor the combination negatively affected bone morphometric indices (bone volume fraction, trabecular thickness, connectivity density). Likewise, osteoblastic activity as measured by serum osteocalcin was unaffected, whereas osteoclastic activity (as indicated by serum CTX1) was reduced when compared to healthy mice ($p=0.008$ and $p=0.013$, respectively). Conclusion Panobinostat combined with Tegavivint may be an effective therapeutic modality for MM patients with advanced/refractory disease and warrants further evaluation.

Keywords:
Metabolism

Panobinostat

Wnt

Tracks:
Multiple Myeloma Novel Drug Targets

FP-143

Immunosuppressive adenosine - a novel treatment target for multiple myeloma

Authors:

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Abstract:
Anti-PD1/PDL1 checkpoint therapy has been unsuccessful in myeloma patients. Adenosine is a new therapeutic target for cancer therapy. Two ectoenzymes, CD39 and CD73, catalyse adenosine from extracellular ATP. CD39 converts ATP to AMP and CD73 AMP to adenosine. When investigating the role of adenosine in the immune response patients, we found increased concentration of adenosine in bone marrow plasma from myeloma patients compared with healthy controls. CD39 was expressed on myeloma cells and immune cells whereas CD73 was found on leukocytes and stromal cells in the bone marrow. Adenosine generated from co-cultures of CD39+ myeloma cells and CD73+ stromal cells reduced the proliferation of T cells stimulated with anti-CD3/CD28 beads which was reversed by inhibitors of the A2ARA adenosine receptor. A CD39 inhibitor, POM-1, and an anti-CD73 antibody inhibited adenosine generation and blockade of T cell proliferation in vitro. Blocking of the adenosine pathway in vivo with a combination of POM-1, anti-CD73, and the A2AR antagonist AZD4635 activated immune cells, increased IFNγ production and reduced the tumor load in a murine model of multiple myeloma. This suggests that the adenosine pathway is involved in immune suppression in multiple myeloma and that this pathway is a potential novel therapeutic target.

Keywords:
immune modulation

immunotherapy

tumor immunology

Tracks:
Multiple Myeloma Novel Drug Targets

FP-144

CD200 expressing multiple myeloma cells show increased resistance against T cell-mediated cytotoxicity

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Abstract:
Introduction Checkpoint inhibitors have improved patients' outcome in a variety of hematologic and solid cancers, although in multiple myeloma (MM), PD-1 inhibitors have yielded only limited rates of tumor regression in early clinical trials. We therefore set out to analyze the role of CD200 which may constitute an alternative yet less well-characterized immune checkpoint. CD200 is expressed on distinct immune effector cells and can also be found in various hematologic malignancies including MM, although its physiological role remains elusive. Here, we investigated the functional role of CD200 for T cell-mediated cytotoxicity against MM cells in vitro. Methods CD200 expression on primary MM samples from routine bone marrow aspirates of MM patients was analyzed with flow cytometry. Stable expression of CD200 in constitutively non-expressing MM cell lines MM.1S, L363, and U266 was achieved by transfection with a Sleeping Beauty transposon vector system. The newly established CD200+ cell lines were co-cultured in different ratios with CD3+ T cells from healthy donors which were obtained by negative selection and activated with CD3/CD28 beads. Alamar blue assays were

used to analyze possible changes in proliferation. MM and T cell counts were measured by flow cytometry comparing CD200+ MM cell line survival to that of the respective CD200– cell lines. Furthermore, the impact of CD200 expression on anti-MM activity of MM-specific CD4+ and/or CD8+ CAR T cells directed against the MM-specific target SLAMF7 was analyzed. Results Three fourth of primary MM cases (n=43) displayed strong CD200 expression, whereas constitutive CD200 expression could not be detected in any of the tested MM cell lines (n=9). By transfection of a Sleeping Beauty transposon vector system, stable expression of CD200 in MM cell lines MM.1S, L363, and U266 was achieved for further functional analysis. Co-culture of activated primary CD3+ T cells with CD200– MM cell lines resulted in reduced MM cell survival and/or proliferation compared to co-culture with non-activated controls. In contrast, CD200+ MM cell lines displayed increased resistance against T cell-mediated cytotoxicity resulting in up to 2-fold higher MM cell counts. However, when co-cultured with SLAMF7-directed MM-specific CAR T cells, CD200 expression in MM cell lines did not attenuate the cytotoxic effects of the CAR T cells. Conclusion CD200 expression on MM cell lines increased resistance against cytotoxic effects mediated by primary T cells, but did not overcome the anti-MM activity of SLAMF7-directed CAR T cells.

Keywords:
immune checkpoint

therapeutic targets

tumor immunology

Tracks:
Multiple Myeloma Novel Drug Targets

FP-145

Functional characterization of the RAL-dependent survival pathway in multiple myeloma

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Abstract:
Introduction The small GTPase Ras-like protein (RAL) is considered to mediate RAS-dependent oncogenic signaling, malignant transformation and tumor cell survival. Whereas to date, oncogenic RAS itself is still not druggable, RAL may represent a therapeutic target in RAS-driven multiple myeloma (MM). Here, we functionally characterized its role in MM and investigated the RAL interactome to identify possible downstream effectors. Methods Expression of the isoforms RALA and RALB was analyzed in bone marrow biopsies (n=24) and in CD138+ selected primary MM cell samples (n=10) by immunohistochemistry and Western blotting. Knockdown studies were performed using isoform-specific shRNA expression vectors against the two isoforms RALA and RALB. Combination experiments with clinical anti-myeloma drugs were also included. MM cells were treated with the recently developed pharmacological RAL inhibitor RBC8. MM cell survival and apoptotic cells were measured by flow cytometry with annexin V/propidium iodide staining. RAF/MAPK, PI3K/AKT or RAL activation status was detected by Western analysis. To investigate the functional link between RAL activation and oncogenic RAS signaling, GTP-bound RAL was pulled down after RAS abrogation by shRNA-mediated knockdown. In addition, RAS- and RAL-mediated gene expression profiles were compared with RNA sequencing. Last, we performed mass spectrometry to identify potential RAL effectors and interaction partners. Results RALA protein was strongly present in all MM cells, whereas RALB yielded heterogeneous stainings. In contrast, RAL expression was at most weakly expressed in MGUS or normal plasma cells. MM cell survival was strongly reduced by shRNA-mediated RALA or RALB knockdown (cell survival rates of 25% or 40

% in L-363 cells and 32% or 52% in MM.1S cells, respectively), yet RAL activation did not exert any influence on PI3K/AKT or RAF/MAPK pathway signaling. The pharmacological RAL inhibitor RBC8 displayed effectivity most pronouncedly in the MM cell line INA-6. RAL abrogation and treatment with carfilzomib, pomalidomide, or ixazomib in combination led to enhanced cell death. Of note, constitutive RAL activation as detected by the pulldown assay was not altered by knockdown of oncogenic RAS. Additionally, RNA sequencing after RAS or RAL knockdown yielded differential gene expression profiles (1473 KRAS-regulated genes versus 771 RALA-regulated genes, with an overlap of 235 genes), underlining that both targets represent distinct signaling pathways. Mass spectrometry identified the exocyst complex as RAL interaction partner, which is currently evaluated for its role as potential downstream RAL effector. Conclusion Our data identified RAL as a promising therapeutic target in MM, as RAL mediates MM cell survival and apoptosis independently of oncogenic RAS. Pharmacological RAL inhibition may therefore be a therapeutic strategy against MM and development of second-generation RAL inhibitors appears to be warranted.

Keywords:
RAS

signaling

therapeutic targets

Tracks:
Multiple Myeloma Novel Drug Targets

FP-146

E2 ubiquitin conjugase UBE2T contributes to genome maintenance through homologous recombination in multiple myeloma

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Abstract:
Multiple myeloma (MM) cells are hypersensitive to proteasome inhibitors, indicating that aberrant ubiquitin signaling may have an important role in its pathogenesis. Here, we investigated translational role of ubiquitin signaling in MM and show that the E2 ubiquitin conjugase, UBE2T, is frequently amplified and highly expressed in MM cells, and its elevated expression as well as copy number correlate with poor patient survival. UBE2T is involved in genome maintenance via the Fanconi Anemia pathway. We show that knockdown of UBE2T significantly impairs DNA repair by homologous recombination in MM cells. UBE2T-knockdown and evaluation of HR activity by two different methods resulted in ~ 60% ($P<0.05$) inhibition of HR activity in MM cells. Similar reduction in HR activity following UBE2T-knockdown was also observed in U2OS (osteosarcoma cell line), which has been widely used for studying DNA repair. MM cells depleted of UBE2T were also unable to efficiently form RAD51 foci at DSB sites. Furthermore, DNA damage-induced phosphorylation of RPA32 on serine 4/8, a prerequisite modification during double-strand DNA break end resection prior to RAD51 focus formation and HR repair, was diminished in UBE2T-knockdown MM cells. Consistent with these data, UBE2T-depleted MM cells were sensitized to agents that induce DNA damage requiring HR for repair. Overall, the IC50 values of cytotoxicity for all three DNA breaking agents (melphalan, camptothecin, and mitomycin C) in UBE2T-knockdown myeloma cell lines were 2.7- to 11-fold lower, relative to those for control cells, indicating increased sensitivity of the UBE2T-silenced cells towards chemotherapy. Our studies identify a direct role for UBE2T in genome maintenance through HR in MM, and suggest UBE2T as a potential therapeutic target to increase chemosensitivity in MM.

Keywords:
GENOME STABILITY

homologous recombination

Tracks:
Multiple Myeloma Novel Drug Targets

FP-147

ATR addiction in Multiple Myeloma: synthetic lethal approaches exploiting established therapies

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Abstract:
Therapeutic strategies designed to tinker with cancer cell DNA damage response have led to the widespread use of PARP inhibitors for BRCA1/2-mutated cancers. In the hematological cancer multiple myeloma, we sought to identify analogous synthetic lethality mechanisms that could be leveraged upon established cancer treatments. The combination of ATR inhibition with a drug eliciting interstrand cross-links, melphalan, was tested in in vitro, ex vivo, and most notably in vivo models. Cell proliferation, induction of apoptosis, tumor growth and animal survival were assessed. The combination of ATM inhibition with a drug triggering double strand breaks, doxorucibin, was also probed. We found that ATR inhibition is strongly synergistic with melphalan, even in resistant cells. The combination was dramatically effective in targeting myeloma primary patient cells and cell lines reducing cell proliferation and inducing apoptosis. The combination therapy significantly reduced tumor burden and prolonged survival in animal models. Conversely, ATM inhibition only marginally impacted on myeloma cell survival, even in combination with doxorucibin at high doses. These results indicate that myeloma cells extensively rely on ATR, but not on ATM, for DNA repair. Our findings posit that adding ATR inhibitors to established therapeutic regimens provides a remarkably broad benefit to myeloma patients.

Keywords:

DNA damage

DNA REPAIR

melphalan

Tracks:
Multiple Myeloma Novel Drug Targets

FP-148

MIF acting as a chaperone of SOD1 mediates MM cell intrinsic resistance to carfilzomib by modulating ROS-induced mitochondrial dysfunction

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Abstract:
We previously discovered that high levels of macrophage migration inhibitory factor (MIF) were detected in multiple myeloma (MM) and associated with poor survival of patients. Knocking down MIF impaired MM cell adhesion to bone marrow stromal cells in vitro and led to the formation of extramedullary tumors more susceptible to chemotherapeutic treatment. Whether MIF directly regulates MM cell intrinsic resistance to chemotherapy has yet to be explored. We recently identified that MIF-knockout (KO) MM cell lines displayed greater apoptosis than control (CTR)-KO MM cells when treated with proteasome inhibitors, especially carfilzomib (CFZ). CFZ-resistant KMS-11/Cfz cells had higher MIF expressions than their CFZ-sensitive parental cells. Knocking out MIF re-sensitized KMS-11/Cfz cells to CFZ treatment. Further CFZ treatment induced greater apoptosis in human primary MM cells with low levels of MIF compared to high MIF expression. Ingenuity Pathway Analysis of microarray data of CTR-KO and MIF-KO MM cells treated with CFZ identified a significant enrichment of genes involved in

mitochondrial dysfunction in MIF-KO MM cells. Thus, we examined the mitochondrial membrane potential (Δψm) with fluorescent TMRE and the oxygen consumption rate via Seahorse assay for mitochondrial respiration, a key function for ATP production, in CTR-KO or MIF-KO MM cells treated with CFZ and found that CFZ-treated MM cells exhibited decreased Δψm and mitochondrial respiration. These observations were significantly enhanced by knocking out MIF in MM cells. Further, we examined mitochondrial morphology in CTR-KO and MIF-KO MM cells treated with CFZ. In CTR-KO MM cells treated with CFZ, mitochondrial functional damage was readily visualized as a loss of the mitochondrial filamentous network and induction of swelling, whereas in CFZ-treated MIF-KO cells the morphological change was primarily swelling. Mechanistically, CFZ-treated MIF-KO MM cells showed significantly elevated ROS levels, a well-known contributor to mitochondrial damage. Array data of MM cells treated with DMSO or CFZ identified that the superoxide dismutase 1 (SOD1) gene, a scavenger for ROS, is highly expressed in CFZ-treated MM cells. CFZ treatment upregulated SOD1 expression in both CTR-KO and MIF-KO MM cells but only caused SOD1 misfolding in MIF-KO MM cells. MIF-KO cells showed lower SOD1 activity than CTR-KO MM cells when treated with CFZ. Re-expressing MIF in CFZ-treated MIF-KO MM rescued SOD1 misfolding and activity, while re-expressing mutated MIF's lack of forming homotrimer did not. Further, MIF inhibitor 4-IPP and MIF homotrimer disrupter ebselen caused SOD1 misfolding, and thus, SOD1 loss of function in CFZ-treated MM cells. The SOD1 inhibitor disulfiram and MIF inhibitors 4-IPP and ebselen largely promoted CFZ killing, not only in MM cell lines, but also in primary MM cells. These data suggest that targeting MIF is a promising strategy to improve the efficacy of proteasome inhibitors in MM.

Keywords:
Carfilzomib sensitivity

MIF

Mitochondrial dysfunction

Tracks:
Multiple Myeloma Novel Drug Targets

FP-149

DNp73 promotes the proliferation and drug resistance of multiple myeloma

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Abstract:
Introduction Genomic instability and chromosomal abnormalities induced by DNA damage are important biological characteristics of multiple myeloma (MM). DNp73 is one of the main isomers of TP73, a member of the TP53 protein family. We found that DNp73 was highly expressed in MM which could resist the apoptosis induced by DNA damage in MM cells, leading to clinical drug resistance. Aim(s) In order to further explore the mechanism of DNp73 mediating drug resistance to DNA damage in MM, this study verified and explored from multiple levels including cell phenotype changes in vivo and in vitro. Methods MM cell lines OCI-MY5 and ARP1 were used to construct DNp73 overexpression (OE) cell lines respectively. Cell proliferation activity of DNp73 OE/EV cell lines was compared by absolute cell count method and CCK8 method, and cell proliferation was determined under the action of doxorubicin (5nM &50 nM) or epirubicin (5nM & 10nM) at different concentrations. The cloning formation and drug sensitivity of ARP1 DNp73

OE/EV cells were determined by soft agar cloning formation assay. Flow cytometry was used to detect the apoptosis and cell cycle arrest of cells in DNp73 OE/EV cells under UV and at different concentrations of reagents treatment. Xenografted model and 5TGM1 spontaneous mouse MM model were used to detect the effect of DNp73 on the proliferation of MM cells and the treatment of DNA damage reagents in vivo. RNA-seq and gene enrichment analysis (GSEA) were performed to explore the potential signaling pathway of DNp73 against apoptosis. Further western blotting and quantity-real time PCR were performed for validation. ChIP and CoIP were used to search for the potential downstream key target genes and target proteins of DNp73. Results DNp73-OE ARP1 & OCI-MY5 cell lines showed stronger proliferation activity than EV MM cell lines, and showed significant resistance to DNA damage reagents, doxorubicin and epirubicin treatment. The cloning formation experiment of soft agar confirmed that DNp73 induced the resistance of MM cells to those drugs. Flow cytometry analysis showed that DNp73 OE suppressed the MM cells apoptosis and suppressed G1 phase arrest induced by those drugs treatment ($P<0.05$). In vivo experiments showed that the tumor burden of mice was significantly more severe compared with the mice of control group. The tumor-bearing mice in DNp73 OE group were resistant to the treatment of DNA damage reagents.RNA-seq, GSEA analysis and western blot assay revealed that DNp73 overexpression induce drug resistance and proliferation through the activation of c-myc and AKT-related pathways and inhibition of p21/p27 signal pathway which caused cell cycle arrested in MM. Conclusion DNp73 promote MM cell proliferation, anti-apoptosis and inhibit cell cycle arrest through activating c-myc and Akt-related pathways. DNp73 overexpression is related to the occurrence of drug resistance in MM.

Keywords:
myeloma

proliferation

Resistant

Tracks:

Multiple Myeloma Novel Drug Targets

ANTIBODY BASED APPROACHES TO MULTIPLE MYELOMA

FP-150

Safety of rapid daratumumab infusion in relapsed and refractory multiple myeloma

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Abstract:
Daratumumab is a CD38 monoclonal antibody approved in monotherapy or in combination with bortezomib and dexamethasone (Dara-VD) or lenalidomide and dexamethasone (Dara-RD) for the treatment of relapsed and refractory multiple myeloma (RRMM). Daratumumab displays an excellent safety profile, with moderate-grade infusion-related reactions (IRRs) occurring mostly during the first infusion. The recommended administration rates provide a timing of 6.5, 4.5 and 3.5 hours for the first, second, and following infusions respectively. A single centre experience of rapid daratumumab infusion (90 minutes) is reported (Barr, Leukemia 2018). In our practice, moving from the observation of a low rate of adverse reactions even in patients with advanced disease, since February 2019 we adopted an analogue infusion protocol. Herein we report the results of the single-center safety study of the rapid daratumumab infusion. The only inclusion criterion was the previous delivery of six doses of daratumumab, according to standard practice. Previous IRR was not an exclusion criterion. From February 2019 to June 2019, we evaluated 24 consecutive patients affected by RRMM. Median age was 65 years (range 42-78 yrs), M/F=12/12. MM IgGK was 46%, IgG λ 17%,

IgAK 12%, IgAλ 9%, micromolecular K 8% and micromolecular λ 8%. Six patients (30%) were on treatment with daratumumab single agent, 7 patients (29%) with Dara-VD and 11 (46%) with Dara-RD. Median previous lines of treatment were two (range 2-5). Median number of daratumumab infusions prior starting protocol was 12 (range 6-24). Seventeen patients (71%) referred IRRs, grade 1, according to CTCAE, occurring only during first infusion. These were mainly conjunctivitis, rhinorrhoea, cough, wheezing or hypertension treated with hydrocortisone 500 mg and promptly reverted. Twenty-two percent of patients suffered from cardiovascular disease (hypertension, arrhythmia or valvulopathy) and one patient presented cardiac amyloidosis at diagnosis. Premedication regimens does not differ from standard: chlorphenamine 10 mg, paracetamol 1000 mg and intravenous dexamethasone 20 mg or 40 mg depending on Dara-VD or Dara-RD. Short time infusion was carried out administering daratumumab at an infusion rate of 200 ml/h for the first 30 minutes, increasing to 400 ml/h for the next 60 minutes. No adverse events were observed during infusion, neither 30 min after completion. Rapid infusion turned out to be safe even in patients who experienced grade I (40%) and II (10%) anaemia or in those with a history of immediate hypersensitivity reactions (20%) to drugs or aeroallergens and in the only patient concomitant COPD. All patients maintained accelerated infusion regimen for subsequent administrations. Daratumumab infusion time of 90 minutes was well tolerated, thus allowing a considerable saving of time for RRMM patients and potentially ameliorating their adherence to treatment.

Keywords:
daratumumab

infusion

Tracks:
Antibody Based Approaches to MM

FP-151

Prospective monitoring of immune signatures in newly diagnosed high risk multiple myeloma patients under treatment with Isatuximab, Carfilzomib, Lenalidomide and Dexamethasone (I-KRd): First results of the GMMG-CONCEPT trial

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Abstract:
Minimal residual disease (MRD) negativity is correlated with improvement in progression-free (PFS) and overall survival (OS) for standard and high-risk multiple myeloma (MM). Reconstitution of the immune system might play a crucial role in long-term disease control. The GMMG-CONCEPT trial investigates combination treatment of isatuximab, carfilzomib, lenalidomide and dexamethasone in induction, consolidation and maintenance for first-line treatment of high risk MM. The primary endpoint is MRD negativity after consolidation. In a prospective scientific program, prospective immune monitoring is performed in order to correlate response outcomes with distinct immune signatures. Here, we report on results of the first 12 patients of the ongoing trial. Immune

monitoring consists of 4 different 13-colour flow cytometry panels defining different T cell, natural killer (NK) cell and myeloid cell subsets in peripheral blood (PB) and bone marrow (BM). The response is determined by IMWG criteria. Analysis was performed at baseline (bs), during induction, prior consolidation and prior maintenance (pm). Longitudinal analysis from baseline until start of maintenance treatment showed a marked decrease of absolute numbers of mature CD57+CD56+ NK cells in PB (bs: median 7.77x10*4/ml, range 0.0 – 78.7 x 10*4/ml; pm 0.416 x 10*4, 0.0- 2.13 x10*4) and BM (bs: 19x10*4/ml, 4.42 – 393 x 10*4/ml; pm 0.695 x 10*4, 0.00-2.85x10*4) with a subtotal loss of the CD57+CD56dim population. NK cells in PB and BM showed baseline expression of PD-1, which significantly decreased under treatment resulting in a loss of PD-L1 expression (median MFI at bs 130, median MFI pm 36). Furthermore, we detected a decrease of CD4+CD25+CD127-FOXP3+ regulatory T cells (bs 0.3x10*5/ml, 0.07 – 7.942 x 10*5/ml; pm 0.1 x 10*5, 0.08-0.413x10*4) in PB and BM with a markedly reduced number of proliferating Ki67+ regulatory T cells. Prior maintenance a substantial increase of γδ T-cells (bs 4.22x10*3/ml, 1.316 – 59.67 x 10*3/ml; pm 10.69 x 10*3, 2.89 – 187.56 x10*3) was observed in BM. All patients analyzed showed response under treatment achieving at least very good partial remission (VGPR). Prospective immune monitoring under optimized first-line MM treatment shows distinct quantitative and phenotypically changes in NK-cell and T-cell populations over time. Continuous analysis is aimed to prospectively identify distinct immune signatures correlating with durable, MRD negative responses in high-risk MM patients.

Keywords:
High risk

immunophenotype

isatuximab

Tracks:
Antibody Based Approaches to MM

FP-152

Practice Patterns with Focal Progression on Daratumumab Therapy

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Abstract:
Background The introduction of monoclonal antibody therapy has significantly improved the outcomes for patients (pts) with relapsed Multiple Myeloma (MM). Recent studies suggest that the outcomes of patients progressing on CD38 antibody-based therapy are dismal. Development of focal progression with daratumumab (dara) escape lesions is encountered in clinical practice, although the incidence is unknown. We questioned if radiation (RT) to the involved site(s) with the continuation of the antibody-based regimen is feasible. To address this, we evaluated the practice patterns among patients who developed focal progression while on dara-based regimens at our center. Methods We identified all pts who were treated with dara within the period November 1, 2015, to July 4, 2018. 306 pts received at least one dose of dara. 45 pts received RT for bone lesions during the queried period. 32 pts received RT, which did not overlap with dara therapy. 13 pts received RT overlapping with the initiation of first dara therapy, and 8 pts received RT for focal progression events while on dara and continued dara-based therapy. Here we describe the clinical course of these latter 8 pts. Results The median age at diagnosis was 60.5 years (32-76), 62.5% females, males 37.5%. Only 1 patient had high-risk cytogenetics per RISS (del 17p). 68% patients had the gain of chromosome 1q. Pts had received a median 3 prior lines of therapy (range 1-

11), the median time to initiation of dara from diagnosis was 66 months (1998 days;1085-2799). Pts received a median 20 months of dara-based treatment (617 days; 91-1234). The median time to development of the first dara escape lesion was 6 months (196 days; 37-504). 2 pts (25%) received a modification in therapy in addition to RT with dara escape lesion, len was added in one pt on single agent dara and changed from len to pom in the other. 75% pts were continued on same regimen. 4 pts were able to continue dara-based therapy for median 6 months (185 days; 76-313) before developing a second lesion, and regimen was not changed in these pts at time of development of additional lesion(s), but palliative RT to the new sites of dara escape lesion(s) was administered. Pts were able to continue the dara-based regimen for a median of 12 months (380 days; 54-848) beyond the initial escape lesion and a median of 3 months (82 days; 41-127) if a second escape lesion was treated with RT. 3 pts remain on dara-based therapy with 31 months follow-up. Conclusion Local palliative RT followed by the continuation of dara-based therapy is feasible and can delay time to next treatment. This option should be explored in the appropriate clinical scenario. Also, these pts may reflect an ideal population to investigate other synergistic immuno-modulatory approaches. Patterns of disease progression and characteristics of pts that are appropriate for focal RT with the continuation of dara-based treatment programs require further investigation.

Keywords:
daratumumab

Progression

radiation

Tracks:
Antibody Based Approaches to MM

FP-153

The impact of neonatal FcRn receptor-mediated recycling on the kinetics of daratumumab in multiple myeloma

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Abstract:
Introduction. Daratumumab (Dara) is a therapeutic human IgG1 monoclonal antibody indicated for multiple myeloma (MM). The pharmacokinetics of Dara demonstrate large differences in linear clearance between IgG patients and those with other M-protein isotypes. This could be explained by competition between Dara and endogenous IgG for binding neonatal Fc receptors (FcRn), effectively impacting IgG catabolic rates and half-life. We propose a model of coupled Dara and IgG kinetics accounting for recycling by FcRn and assess the impact on Dara usage in MM patients. Methods. We developed an in-silico model of endogenous IgG production that replicates time-course measurements of plasma IgG from refractory MM patients. Dara input was based on the recommended dosing regimen for Dara as monotherapy for MM: 16 mg/kg weekly for 8 weeks; then every 2 weeks for 16 weeks; then every 4 weeks. FcRn-mediated recycling of Dara and endogenous IgG was approximated using Michaelis-Menten kinetics; target-mediated elimination of Dara (i.e. due to binding to CD38) was modelled using a time-varying Michaelis-Menten approximation. Results. In model simulations comparing the kinetics of Dara and endogenous IgG, the clearance of the drug was greater during the initial treatment cycles due to FcRn saturation; but approached normal rates as the endogenous IgG load fell towards normal levels and receptors become less saturated. These results suggest that competition for recycling receptors could impact circulating Dara concentrations; consequently, we compared the kinetics of Dara for high (approx. 100 g/L) and low (near normal levels) endogenous IgG loads. Pre- and post-infusion plasma Dara concentrations were lower for the high-IgG loads during the initial treatment cycles,

consistent with faster IgG clearance rates; subsequently these differences reduced as the endogenous IgG load approached normal levels and clearance rates normalised. Maximum trough Dara concentrations (maximal quantity of drug before an infusion) was observed immediately prior to the ninth Dara infusion in both models (1.0 and 1.5 g for high- and low-IgG loads, respectively). We assessed whether the increased drug clearance caused by high IgG loads could be compensated with a more intensive dosing regimen consisting of eleven Dara infusions every five days. In simulations Dara kinetics show a similar profile for high- and low-IgG loads, despite the former having an increased drug clearance rate. Notably, the maximum trough quantity of drug was now 1.5 g for both models. Conclusion. Our results suggest that FcRn-mediated recycling has an important impact on Dara kinetics in MM. We found evidence to suggest that Dara clearance correlated with the patient's IgG load. Our model shows theoretical potential for personalised dosing to improve drug exposure (i.e. maximum trough concentration), which has been strongly associated with response to treatment.

Keywords:
daratumumab

monoclonal antibody

Multiple myeloma

Tracks:
Antibody Based Approaches to MM

FP-154

QIP-MS: An alternative to electrophoresis to distinguish endogenous M-proteins from therapeutic monoclonal antibodies in multiple myeloma

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Institutions:
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Abstract:
Background: The introduction of more effective therapies over the last two decades has led to improved survival outcomes in myeloma patients. The last generation of myeloma drugs include therapeutic monoclonal antibodies (t-mAb) that have demonstrated exceptional efficacy but can interfere with historic electrophoretic methods for measuring the patient's monoclonal immunoglobulin (M-Ig), making monitoring of these patients challenging. Alternative laboratory methods that overcome the limitations of traditional approaches are necessary. Mass spectrometry is a highly sensitive technique that has shown potential for the identification of individual M-Igs based on their unique mass-to-charge (m/z) protein characteristics. Here we assess the performance of Quantitative ImmunoPrecipitation Mass Spectrometry (QIP-MS), a polyclonal antibody-based assay, for identifying the presence of M-Ig in myeloma patients and to distinguish them from t-mAb. Methods: Polyclonal antibodies (anti-IgG, -IgA, -IgM, -total κ and -total λ) covalently attached to paramagnetic microparticles were incubated with serum, washed and treated to simultaneously elute and reduce patient immunoglobulins. Light chain mass spectra were generated on a MALDI-TOF-MS system, and specificity was assessed using normal human serum (NHS) and patient sera containing M-Ig. t-mAbs daratumumab or elotuzumab were spiked at 0.2 g/L into NHS or myeloma patient sera. In a blind study, sensitivity was compared to capillary zone electrophoresis (CZE) and serum immunofixation (IFE). Results: The limit of detection of QIP-MS for monoclonal proteins diluted into sheep serum were: 0.7 mg/L for IgG, 1.4 mg/L for IgA, IgM and total κ, and 0.17 mg/L for total λ. QIP-MS had a greater sensitivity for the detection of the M-Ig than either CZE (100x) or IFE (10x). QIP-MS was able to distinguish the monoclonal light chains originating from the M Ig from those of daratumumab and elotuzumab at therapeutically relevant concentrations (0.2 g/L) in all samples analysed. Conclusion: QIP-MS provides a highly reproducible and sensitive alternative to conventional

electrophoresis. The ability to determine a unique molecular mass for any myeloma paraprotein offers an innovative addition for the identification and quantification of monoclonal immunoglobulins. t-mAbs daratumumab and elotuzumab were easily distinguishable from the endogenous M-protein, even in the presence of a high polyclonal background and at levels below the detection limit of IFE.

Keywords:
MALDI Mass Spectrometry

monoclonal antibody

Multiple myeloma

Tracks:
Antibody Based Approaches to MM

FP-155

Subcutaneous Daratumumab Plus Carfilzomib and Dexamethasone (D-Kd) in Relapsed/Refractory Multiple Myeloma: An Open-label, Multicenter, Phase 2 Study (PLEIADES)

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Abstract:
Trials in Progress Background: Daratumumab, a human CD38-targeting monoclonal antibody, is approved in many countries for use as monotherapy in relapsed/refractory multiple myeloma (RRMM), and in combination with standard-of-care (SOC) regimens in RRMM and newly diagnosed multiple myeloma. A subcutaneous formulation of daratumumab (DARA SC; co-formulated with recombinant human hyaluronidase PH20 [rHuPH20]; ENHANZE® drug delivery technology, Halozyme, Inc.) was shown to be noninferior to DARA IV, demonstrating similar efficacy and pharmacokinetics, with a decreased rate of infusion-related reactions (IRR) and a reduced administration time. The phase 2, open-label, multicenter PLEIADES study (MMY2040) assessed the efficacy, safety, and pharmacokinetics of DARA SC in combination with 4 SOC treatment regimens for patients with NDMM or RRMM, including D-Kd. Methods: In the D-Kd cohort, approximately 60 patients with RRMM will be enrolled to receive DARA SC (1,800 mg QW for Cycles 1-2, Q2W for Cycles 3-6, and Q4W for Cycles 7+) in combination with Kd (K 20 mg/m^2 IV Cycle 1 Day 1, escalated to 70 mg/m^2 on Cycle 1 Days 8 and 15, then 70 mg/m^2 Days 1, 8 and 15 of each cycle thereafter; d 40 mg weekly) until disease progression. Eligible patients have received only 1 prior line of therapy which included ≥2 consecutive cycles of lenalidomide therapy. Patients must have an Eastern Cooperative Oncology Group performance status ≤2, left ventricular ejection fraction ≥40%, and no uncontrolled hypertension. The primary endpoint for the D-Kd cohort was overall response rate (ORR), defined as patients achieving a partial response or better, assessed via International Myeloma Working Group criteria. Secondary endpoints included DARA SC pharmacokinetics, IRR rate, rates of very good partial response or better and complete response or better, duration of response, immunogenicity, and minimal residual disease-negativity rate. NCT03412565.

Keywords:
CD38

daratumumab

Multiple myeloma

Tracks:
Antibody Based Approaches to MM

FP-156

DNA methyltransferase inhibitors upregulate CD38 expression and enhance daratumumab efficacy in multiple myeloma

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Abstract:
Introduction: The anti-CD38 monoclonal antibody Daratumumab is highly effective against multiple myeloma and is well tolerated. Daratumumab resistance in patients is correlated with CD38 loss (Nijhof et al, 2016). As a result, there is significant interest in elucidating the regulation of CD38 in MM. Recently All Trans Retinoic Acid (ATRA) and the FDA-approved histone deacetylase inhibitor panobinostat were both demonstrated to upregulate CD38 in MM plasma cells. We hypothesized that demethylation of the CpG island in the promoter and first exon of CD38 may lead to increased CD38 protein at the cell surface in MM plasma cells. Here we demonstrate that DNA methyl-transferase inhibitors (DNMTis), currently FDA-approved for treatment of myelodysplastic syndrome, enhance daratumumab efficacy in MM. Methods: We treated MM cell lines (RPMI-8226, MM.1S, XG-1, KMS12-PE) with two different DNMTis, 5-Azacytidine and decitabine, and assessed CD38 cell surface expression by flow cytometry. Similarly, we treated MM patient bone marrow aspirates ex vivo and assessed CD38 expression in the CD138+ population. ATRA was used as a positive control in all experiments. We evaluated daratumumab efficacy using an Antibody Dependent Cell Cytotoxicity (ADCC) assay. Results: Both 5-Azacytidine and Decitabine treatment induced a 1.2-2 fold increase in CD38 surface expression in a dose-dependent manner across MM cell lines. This increase was consistently higher than that seen in ATRA- or panobinostat-treated cells. 5-Azacytidine increased CD38 mRNA expression 2.9 ± 0.1 fold, compared to 1.7 ± 0.8 fold increase with ATRA. In ADCC assays, DNMTi treatment also led to greater lysis than ATRA, and the combination of DNMTi and ATRA was additive. In contrast, in ex vivo-treated patient plasma cells, ATRA induced greater CD38 expression than DNMTis. This result is expected since patient plasma cells typically do not proliferate in standard ex vivo culture, and active DNA replication is required for successful DNMT inhibition. In patients, however, we anticipate that continual plasma cell proliferation will lead to effective increases in CD38 after DNMTi treatment. Surprisingly, targeted bisufite sequencing revealed that the CpG island at CD38 locus has low DNA methylation levels. We hypothesize that DNMTi treatment instead increases a positive transcriptional regulator of CD38. We are currently testing several cytokines that are known inducers of CD38, for their induction upon Azacytidine treatment and for their necessity in Azacytidine-induced CD38 upregulation. Summary and Conclusions: Our results here demonstrate that inhibiting DNMTs leads to CD38 upregulation and increased vulnerability to Daratumumab treatment. We propose that combination treatment with Azacytidine and Daratumumab can lead to higher efficacy of daratumumab in daratumumab-naïve MM, as well as reversal of daratumumab-resistance. We are currently planning a clinical trial to test this hypothesis.

Keywords:
Daratumumab resistance

DNA methylation

Immuno-oncology

Tracks:
Antibody Based Approaches to MM

FP-157

Targeting stromal-derived Gremlin1 to control Multiple Myeloma disease development

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Abstract:
Multiple myeloma (MM) is a fatal haematological malignancy characterised by the clonal proliferation of malignant plasma cells (PC) within the bone marrow (BM). In most instances, MM PCs are reliant on factors made by cells of the BM stroma for their survival and growth. To date, the nature and cellular composition of the BM tumour microenvironment and the critical factors which drive tumour progression remain imprecisely defined. To this end, our studies show that Gremlin 1 (Grem1), a highly conserved protein, which is abundantly secreted by a subset of BM mesenchymal stromal cells, plays a critical role in MM disease development. The studies presented here demonstrate, for the first time, a novel feed forward loop between MM PCs and BM stroma, and that inhibiting this vicious cycle with a neutralising antibody can dramatically reduce tumour burden in a preclinical mouse model of MM. Analysis of human BM stromal samples by quantitative PCR showed that GREM1 expression was significantly higher in MM patient-derived BM stromal cells compared to stromal cells from healthy, age-matched individuals ($p<0.01$ t-test). Additionally, a positive correlation between MM tumour burden and stromal-cell associated Grem1 expression was observed in 5TGM1 MM PC tumour-bearing mice ($p<0.05$, $R=0.64$, Pearson Correlation). Furthermore, BM-stromal cells cultured with 5TGM1 MM PCs expressed significantly higher levels of Grem1, compared to stromal cells alone ($p<0.01$, t-test), suggesting that MM PCs promote increased Grem1 expression in stromal cells. MM PC induction of stromal-Grem1 serves to drive a feed forward loop, as proliferation of the murine MM cell line, 5TGM1, was found to be significantly increased when co-cultured with Grem1-overexpressing stromal cells ($p<0.01$, t-test). To further examine the role of Grem1 in MM tumour establishment and growth in vivo, we utilized the 5TGM1/KaLwRij mouse model of MM. Following 5TGM1 tumour cell inoculation, mice (n=13/treatment group) were randomly assigned to either a neutralising Grem1 antibody or IgG control treatment arm. Our studies showed that compared to Ig control-treated mice, anti-Grem1-treated mice showed a 54.4% decrease in tumour burden ($p<0.01$, two-way ANOVA). This effect was even more pronounced when mice (n=7-8/treatment group) received treatment with a Grem1 neutralising antibody prior to 5TGM1 tumour cell inoculation, resulting in an 81.2% reduction in tumour burden ($p<0.05$, two-way ANOVA). Collectively, our data suggests that Grem1 is a key stromal-derived PC mitogen that promotes MM disease initiation and progression, and that antibody-mediated targeting of Grem1 significantly reduces disease burden. With few effective therapies that target the critical relationship between MM PC and BM, the findings presented here, represent a novel treatment strategy to limit MM disease burden.

Keywords:
Bone marrow microenvironment

therapy

Tracks:
Antibody Based Approaches to MM

FP-158

Preliminary results of Daratumumab, cyclophosphamide, thalidomide and dexamethasone- A quadruplet intensified treatment to newly diagnosed multiple myeloma transplant eligible patients

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Abstract:
Background: The best induction protocol to newly diagnosed MM transplant eligible (NDMMTE) patients was not established yet. Until now three drugs combo became the standard of care and one of the protocols worldwide largely used as induction is Cyclophosphamide(cyclo), Thalidomide(Thal) and Dexamethasone(Dex)- (CTD). Daratumumab (Dara), a MoAb against CD38 is one of the new drugs used in NDMMTE trials. Dara was approved in relapse cases and It is becoming approved as first line treatment for eligible and not eligible patients. Objective- To determine best response rate (better than VGPR) after transplant, to characterize safety, tolerability, overall survival, progression free survival, overall response rate and minimal residual disease. Besides that, we would like to evaluate the reflex of Daratumumab use just after ASCT as in an intensified mode (early D+30 consolidation). An exploratory endpoint is to analyze the immunologic profile changing during the treatment phases and the influence of Dara use in It. Patients and Methods: This is a single-center, open-label, phase II trial. Patients will be treated according to the following protocol: All patients will receive CTD-Dara up to four 28 day induction cycles: Cyclo-500mg PO D1-8-15, Thal- 100-200mg PO D1-D28, Dexa 40mg PO weekly and Dara 16mg/Kg/dose IV weekly during cycles 1-2 and every other week in cycles 3-4. After induction, patients will be submitted to conditioning with intravenous melphalan 140-200 mg/m², followed by autologous stem-cell transplantation. Consolidation will start after engraftment but not before D+30 from transplant. All patients will receive up to four 28 day consolidation cycles- Dara 16mg/Kg every other week associate with Thal 100mg PO D1-D28. During maintenance phase Dara 16mg/Kg will be used monthly until progression or limiting toxicity. The sample size calculation was based on phase II design exact one stage- 20 patients will be necessary to reject the hypothesis based on power of 93% and type 1 error of 9%- determine at least 18 patients that must obtain > VGPR. Results- The protocol was activated in November 2018. Nine patients were included and the recruitment is on-going. The median age at diagnose was 62(42-67) years, female represents seven cases and the R-ISS I, II and III were 0%,85% and 15% respectively. All patients achieved partial response after the first cycle of treatment. Two patients had performed Autologous Stem cell transplantation (ASCT) and CD34+/Kg collected cells of 3.17 and 5.3 x106 respectively. Both patients were MRD+ before ASCT. Conclusion- The expectative of the present study is to prove that association of CTD-Dara can represent a new and low-cost option of treatment for NDMMTE in comparison with the new protocols. Clinical trial information: NCT03792620

Keywords:
bone marrow transplantation

daratumumab

Multiple myeloma

Tracks:
Antibody Based Approaches to MM

FP-159

Daratumumab induces mechanisms of immune activation through CD38+NK cell targeting.

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Abstract:

Introduction: Daratumumab (Dara) is a human monoclonal antibody against the highly expressed multiple myeloma (MM) surface receptor CD38. Resistance eventually occurs in the majority of patients, but the mechanisms of acquired resistance are not well delineated. It was reported that CD38, in addition to its expression on malignant plasma cells (MM-PCs), is present on several immune effector cells, including NK cells and monocytes (Ghose et al., 2018). Results: A cell surface localization study of CD38 on MM-PCs was carried out in a cohort of MM patients (pts) who discontinued Dara therapy (Dara-RRMM) for at least ≥4 weeks but had not started a subsequent therapy (<16 weeks); results were compared to those in a cohort of heavily refractory patients (RRMM) who at the time of the analysis were progressing under a different therapeutic regimen. Dara-RRMM pts retained targetable CD38 in almost 100% of the MM-PCs. We also found that Dara-induced MM cell killing depends on the presence of surface CD38 on the cancer cells but is unaffected by its level. A flow cytometry-based killing assay showed that effector cells obtained from Dara-RRMM pts (n=6) are unable to kill CD38+ MM-PCs in the presence of Dara, in contrast to the killing ability of circulating immune subsets obtained from RRMM pts (n=4) and healthy donors. Moreover, we propose that concomitant Dara binding to CD38 and to the FcR (CD16) of immune effector cells may be critical for Dara-induced MM cell killing. Indeed, our data show that Dara-mediated cytotoxicity of MM cells by CD38+ immune effectors is dependent on CD38 surface expression on immune effector cells, which is fundamental for Dara immune activation against the cancer cells, an observation which is aligned with previous reports of a pivotal role of CD38 in orchestrating the Th1 immune response (Frasca L. et al., 2006). We also found that Dara induces CD38+ NK cell activation and degranulation, causing a significant increase in CD69 activation marker and a dose-responsive upregulation of IFN-γ and GM-CSF. This effect not only increases direct NK cell cytotoxicity against MM cells but also induces an increase in the T cell costimulatory molecules CD86/80 on monocytes, enhancing their anti-MM phagocytosis activity ex-vivo and in vivo.

Conclusions: We report that in the typical clinical scenario, MM patients progressing under Dara-based combinatorial therapies retain targetable levels of CD38 on the surface of MM cells, but tend to lose CD38 expression in their immune effector cells. We propose that Dara induces CD38+ NK cell activation and degranulation, leading to increased expression of T cell costimulatory molecules on monocytes, which induces monocyte polarization in M1 macrophages with anti-tumoral activity. Because MM cells retain targetable surface CD38, these findings may point to the efficacy of anti-CD38 antibodies with toxic payloads and CAR-T cells against CD38 for patients relapsing under daratumumab treatment.

Keywords:
daratumumab

Relapsed Refractory MM

Resistant

Tracks:
Antibody Based Approaches to MM

FP-160

Observational study to describe the impact of treatment combinations with Daratumumab versus other alternative regimens in patients with relapsed / refractory multiple myeloma. Spain real world evidence (RWE) data. GeminiS study.

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Abstract:
INTRODUCTION: The current national treatment scenario for relapsed / refractory multiple myeloma (RRMM) and the effectiveness of the different treatment alternatives in daily clinical practice outside clinical trials (CT) is unknown. In recent years, several treatment regimens have been approved representing effective treatment alternatives and a hope for a better-quality of life for patients, according to the results obtained in CT. It is necessary to evaluate the results of these treatments in daily clinical practice in order to elucidate the real impact of the incorporation of new treatments to the therapeutic arsenal already available and to know as objectively as possible the benefit they bring to the patients. METHODS: Observational, ambispective, descriptive study in patients with RRMM (first and second relapse) who started antineoplastic treatment within daily clinical practice. To describe the impact of the incorporation of monoclonal antibodies (mAb) in daily clinical practice, the results collected in two patient groups (before and after the commercial availability of the combinations that include the first and only mAb approved for the treatment of RRMM in Spain (daratumumab) will be presented. The results of effectiveness and tolerability of the patients included in the two groups will be described. Group A: starts treatment between 01/10/17 and 03/31/18 with a combination of ≥2 drugs. Group B: starts treatment between 04/01/18 and 09/30/18 with daratumumab in combination with lenalidomide or bortezomib and dexamethasone. RESULTS: The recruitment of this multicentre study is still ongoing. To date, 154 patients have been registered. Table 1 describes demographic data obtained from available patients (89). Table 2 presents the data obtained from the first line of treatment of available patients (84). The final data cut for this intermediate analysis will take place on July 19, 2019. Updated data on effectiveness and tolerability will be presented during the Congress. CONCLUSIONS: Multiple treatments have been incorporated into the therapeutic scenario of RRMM in the last years. However, it has not been described how their incorporation has affected the therapeutic panorama in Spain or its potential for patients outside CT and in an unselected patient population. Our objective through the GeminiS study is to systematically collect the results of effectiveness and tolerability of the incorporation of daratumumab treatment in combination in patients with RRMM in Spain in daily clinical practice.

Keywords:
monoclonal antibody

real-world evidence

Relapsed Refractory MM

Tracks:
Antibody Based Approaches to MM

FP-161

LONG TERM SAFETY AND EFFICACY OF DARATUMUMAB RAPID INTRAVENOUS INFUSION (90 MINUTES) AFTER THE THIRD DOSE IN MULTIPLE MYELOMA PATIENTS

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Abstract:
Background. The anti-CD38 IgG/k antibody Daratumumab is particularly efficient alone or combined with other drugs in multiple myeloma

(MM) patients. Long Infusion sched-ules of 4 to 8 hours however to avoid incidence of infusion related reactions (IRR) can reduce patients and health care professional compliance. Splitting of the first dose in two days has already reduced length of the first infusion (4 hours each). Strategies to reduce infusion time have been reported. One study (Barr H, et al., Leuke-mia 2018) showed safety in 28 patients with MM with an infusion time of 90 minutes start-ing from dose >10 in the majority. In 11 patients 90 minutes infusion was given from the third dose. Nothing was reported however on prolonged safety overtime and most of all efficacy. Patients and methods. During this observational prospective single center study, 16 patients with MM (M/F=12/4) median age 66 (61-83) received rapid infusion daratumumab allowed from the third dose. First dose of daratumumab was split day1,day2. Study period was December 2018-June 2019.The infusion rate was calculated to deliver 20% of the dose over 30 min (200 mL/hr), and then the rate was increased to deliver the remain-ing 80% over 60 min (450 mL/hr). This resulted in a 90 min estimated infusion time (total volume 550 mL). Premedication consisted in Dexamethasone 20 mg IV, Antipyretic (pa-racetamol 1.000 mg by mouth), antihistamine (diphenhydramine 25 mg intravenously), 2 puff inhalation of beta-adrenergic bronchodilator were given twenty minutes before infu-sion. Rapid infusion started from the third dose if no IRR was seen in the previous infu-sion (second). Results. Sixteen patient received daratumumab treatment (3 Dara-Rd, 4 Dara-VD, 9 Da-ra alone). Preexisting chronic obstructive pulmonary disease or asthma were absent in previous patient history. IRR's after first Daratumumab split infusion were seen in 5/16 patients (31%): all were Grade 2 (2 bronchospasm, 2 cough,1 rinhitis) and all happened during day 1. 16 patients received a total of 107 rapid infusions over a 6 months period. No reaction was seen in all patients during rapid infusion. All 5 patients that had a reaction during first split dose did not have other reactions. Premedication was also reduced after dose >10, i.e. oral antihistamine, dexamethasone 10 mg IV, paracetamol 500 mg oral. More importantly efficacy was maintained: 11/14 patients responded (ORR 78%, 3CR, all MRD negative by next generation flow, 5 VGPR, 3 PR), while 3 patients stopped for progression (2 patients treated at line 5 and 1 patient at line 8 of therapy). Conclusions. Rapid infusions of Daratumumab can be safely administered to MM pa-tients from the third dose. Safety is present over time. Importantly, efficacy of daratu-mumab treatment is mantained .

Keywords:
daratumumab

rapid infusion

Tracks:
Antibody Based Approaches to MM

FP-162

CD84: A Potential Novel Therapeutic Target in the Multiple Myeloma Microenvironment

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Abstract:
Introduction: CD84 (SLAMF5) is a cell surface receptor that modulates the immune response in the tumor microenvironment. Our study focused on the function of CD84 on immune checkpoint regulation in the multiple myeloma (MM) microenvironment. Results: CD84 surface expression was absent to low on human MM cell lines and primary myeloma cells (5.5-13%). However, CD84 was highly expressed on bone marrow (BM) stromal cells (20-26%) and CD14+ cells derived from MM patients (76-97%), versus that of matched CD14-negative fractions (2-

9%) (P<0.001). The monocytic myeloid-derived suppressor cells (M-MDSCs) were significantly expanded in the peripheral blood of MM patients (0.34-2.88%), in contrast to those in healthy donors (HD) (0.04-0.45%) (P<0.05). CD84 was also significantly up-regulated in MM patients (43-92%) compared to levels in HD (7-21%) (P<0.001). Activation of CD84 with an antibody on patient BM stromal and MM cells led to an increase of PD-L1 expression levels (P<0.05). In addition, elevated PD-L1 mRNA levels were detected in the 5TGM1 MM cell line when incubated with the activating antibody, whereas reduced PD-L1 mRNA levels were found with the anti-CD84 inhibitory antibody (B4), compared to IgG controls (P<0.05). Further, MM cell lines induced PD-L1 surface expression on CD14+ cells (P<0.01). Blocking of CD84 partially overcame the increase of PD-L1 on CD14+ cells (P<0.01) and PD-1 on T cells (P<0.05) in a co-culture setting with primary CD14+ cells, CD3+ cells and the MM1S MM cell line. To follow the in vivo role of CD84, we generated a chimeric mouse model. The lack of CD84 on stroma cells led to a reduction in tumor load in the BM (P<0.05) and smaller spleen and prolonged survival (40%). Furthermore, CD84 deficiency significantly reduced the expansion of M-MDSCs and expression of PD-L1 on MDSCs (P<0.05). T cells displayed reduced levels of exhaustion markers, among them PD-1 (P<0.05), as well as an increase in IL-2 (P<0.05), IFN-γ (P<0.01), GRZMB (P<0.05) and LAMP-1 (P<0.05). To further investigate CD84 activity in vivo, we analyzed the role of B4 in the MM mouse model. B4 treatment led to a significant decrease in CD138+ malignant cells (P<0.01) and increased survival of the mice (40%). Blocking CD84 reduced the accumulation of M-MDSCs in the BM and decreased expression of PD-L1 on these cells (P<0.01). A significant increase in T cell functionality was noted in B4-treated mice, as seen primarily by their increased production of IL-2 (P<0.05), IFN-γ (P<0.001), GRZMB (P<0.0001) and LAMP-1 (P<0.05), but also evidenced by the reduced expression of exhaustion markers such as PD-1 (P<0.05). Conclusion: Targeting CD84 both in vitro and in vivo abrogates CD84 signaling, resulting in decreased PD-L1/PD-1 expression as well as reduced M-MDSC expansion and increased T cell activation, inhibiting myeloma proliferation. These results indicate that CD84 may be a promising target representing a novel therapeutic approach for MM.

Keywords:
CD84

microenvironment

Multiple myeloma

Tracks:
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Patient tolerability and Estimation of Direct/Productivity costs associated with rapid infusion of daratumumab.

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Abstract:
Background: Daratumumab is an anti-CD38 monoclonal antibody FDA approved for use in newly diagnosed (NDMM) and relapsed/refractory multiple myeloma (RRMM). A phase 2 trial has demonstrated the safety of reducing daratumumab infusion time from 4.5 hours to 1.5 hours. We explored the utilization and cost impacts of a rapid infusion rate for daratumumab in a community-based, quasi-academic setting. METHODS: We constructed an Excel-based model to estimate direct and productivity costs incurred for the health system and patients diagnosed with RRMM treated with daratumumab. All costs estimated were for infusion initiation and continuation during a 12-month period. The clinical and infusion data of 100 RRMM

patients treated at Levine Cancer Institute from October 2013 to October 2018 were used. Infusion staffing inputs were obtained from LCI administration. Patient salary and travel distance were estimated from the US Census. Drug administration reimbursement were obtained from the US Centers for Medicare and Medicaid Services 2018 Outpatient Prospective Payment System. Wholesale acquisition costs for drugs were obtained from AnalySource. The model assumed once patients switched to rapid infusion rate on cycle 1, day 15 they remained on rapid infusion rates. All costs were estimated in 2018 US dollars. RESULTS: There was no statistically significant difference of infusion rates between the two cohorts (standard: n = 2, rapid: n = 1; p-value: 0.59). Total costs estimated for the standard rate was $137,200 and $122,200 for the rapid rate (p-value: < 0.001). Drug and administration costs were similar between the standard and rapid cohorts ($112,300 vs. $110,600). Costs associated with staffing and patient productivity were greatest in the standard cohort (staff: $21,600 vs. $10,100; patient: $3,300 vs. $1,500). CONCLUSIONS: Our data suggest that while drug costs are similar between rapid and standard cohorts, utilizing a rapid infusion rate could save patients lost productivity and allow infusion staff to increase efficiency.

Keywords:
Multiple myeloma

rapid infusion

Tracks:
Antibody Based Approaches to MM

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M-Protein semi-quantification in MM serum patients based on Immuno-Capture and Liquid Chromatography coupled to High Resolution Mass Spectrometry

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Abstract:
In order to determine the disease status, and response to treatment in Multiple Myeloma (MM) patients, the amount of M-Protein (most often IgG or IgA with kappa or lambda light chains) in the serum is measured. According to International Myeloma Working Group (IMWG) criteria, detection and quantification of M-Protein, by Serum Protein Electrophoresis (SPEP) and Immuno-Fixation Electrophoresis (IFE) are essential for patient response evaluation in MM. Isatuximab, an IgG-kappa, anti-CD38 monoclonal antibody (currently under clinical development) has recently been shown to prolong progression-free survival and improve tumor response in combination with pomalidomide-dexamethasone in Relapsed and Refractory Multiple Myeloma (RRMM). However, isatuximab may be detected on conventional SPEP and IFE assays that are used to monitor patients with IgG kappa type M-Protein. This interference could lead to false-positive assay results and, consequently, an inaccurate determination of patient's response to the treatment according to IMWG criteria. In order to overcome the potential interference of isatuximab in clinical samples, we developed and validated a hybrid assay based on Immuno-Capture and Liquid Chromatography coupled to High Resolution Mass Spectrometry (IC-LC-HRMS). The first step of this approach is to perform an Immuno-Capture (anti-LC kappa/lambda beads) of Igs and free Light Chains (LC) in serum of MM patients. Heavy Chains (HC) and LC are then dissociated (reduction with dithiothreitol) and sorted using Liquid Chromatography. M-Protein and isatuximab LC are analyzed using HRMS and are identified according to their monoisotopic intact mass. The association of Liquid Chromatography and HRMS enables to characterize and discriminate signals of isatuximab and M Protein. As M-Proteins are specific for each MM patient, no standards are available to allow their

quantification using a bioanalytical approach such as LC-HRMS. In this work, we used alemtuzumab (IgG kappa) as a standard to semi-quantify M-Protein in MM serum patients. This analytical assay was successfully validated from 10 to 200 µg/mL for M-Protein in serum, with precision and accuracy within 20% (25% at LLOQ level). This complex assay was developed in compliance with Good Clinical Laboratory Practices (GCLP) recommendations and Data Integrity policy. This new IC-LC-HRMS method was successfully applied to clinical samples evaluation and permits to abrogate potential interference of isatuximab in monitoring MM patients using SPEP and IFE. Representative clinical cases in which the MS approach assisted in response assessment will be described. In conclusion, this novel assay helps in accurate assessment of tumor response to isatuximab treatment. Moreover, this methodology may be adapted to new therapeutic antibodies to characterize a potential interference and distinguish endogenous M-protein from these antibodies.

Keywords:
isatuximab

M-protein

Mass spectrometry

Tracks:
Antibody Based Approaches to MM

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Durability of Response and Characterisation of Corneal events with Extended follow-up after Belantamab Mafodotin monotherapy for patients with relapsed/refractory Multiple Myeloma

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Abstract:
Background: Belantamab Mafodotin (B, GSK2857916) is an antibody drug conjugate targeting BCMA. In the first-in-human clinical trial, a response rate of 60% and median progression free survival of 12 months was demonstrated for patients with relapsed/ refractory myeloma (MM). Blurring of vision and thrombocytopenia were the most significant toxicities requiring dose reduction.
Methods: This is a case series of 5 consecutively treated patients with B at the recommended dose of 3.4mg/kg enrolled onto the BMA117159 Phase 1 trial. Patients received up to 16 doses 3 weeks apart. We report durability of response following extended follow-up and patient level detail of the management and resolution of corneal adverse events (AE).
Results: Patients had a median age of 57 years (51-66), median time from diagnosis of 3.8 years and had received a median of 4 prior lines (3-6). All patients with known cytogenetic results were adverse risk (n=4, 1 patient = del(17p)). A median of 16 doses was given (12-16) with a median of 5 dose interruptions lasting median 14 days (range 7-98 days) and 2 dose reductions (both of 25%) due to AEs. All patients achieved ≥ VGPR (VGPR 2; CR 1; sCR 2) and remain alive. Following a median follow-up of 32.6 months, the estimated PFS was 17.0 months (16.5-not reached (NR)) and the time-to-next treatment was 31 months (21.7-NR). Notably, a median treatment-free-interval (TFI) of 16.9 months (6.5-NR) was observed, with 2 patients continuing in CR without further treatment for >20 months. All patients reported corneal AEs, mainly blurring of vision and photophobia (grade 2 (n=3) and grade 3 (n=2)). This was managed by interruption/ dose reduction of B and a prolonged increased frequency of dexamethasone eye drops (median 4xday (range 1 hourly-3xday)) and artificial tears under ophthalmology guidance. Symptoms improved in all cases to grade 1 to allow further dosing and none withdrew due to ocular AEs. All patients maintained their response despite treatment interruptions of up to 98 days. Corneal AEs

completely resolved in all patients following a median of 9.5 months (3.3-12.0) from the last dose of B. All patients were hypogammaglobulinaemic at baseline which worsened during treatment. 2 required intravenous immunoglobulin for recurrent infections; however immunoglobulin levels recovered during the TFI. Conclusion: This case series highlights the importance of effective management of corneal AEs for patients receiving B. Dose interruptions, reductions and escalation of topical therapies under ophthalmology supervision appeared effective in improving symptoms thereby allowing further dosing. Corneal AEs were fully reversible and an overall good quality of life was achieved. With optimal management, durable responses were demonstrated. In contrast to the current treatment paradigm of extended therapy for multiply relapsed MM patients, TFIs of up to 20 months are unusual and indicate potential potency of this agent

Keywords:
clinical trials

immunotherapy

relapsed/refractory multiple myeloma

Tracks:
Antibody Based Approaches to MM

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Efficacy and safety of a modified daratumumab/bortezomib/dexamethasone regimen using once weekly bortezomib in relapsed refractory multiple myeloma

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Abstract:

Background: The combination of daratumumab (dara), subcutaneous (SC) bortezomib twice weekly, and dexamethasone (dex) [Dara-Vd] has become a common treatment for patients with relapsed and/or refractory multiple myeloma (MM) after the CASTOR trial data led to its inclusion in the NCCN guidelines. A common and notable non-hematologic adverse effect causing dose modifications, delays, or discontinuation of bortezomib in this regimen has been peripheral neuropathy (PN). This could impact a patient's quality of life or lead to suboptimal therapy. At Wake Forest Baptist Health (WFBH), patients with MM receive a modified Dara-Vd regimen using weekly SC bortezomib in order to reduce severity of PN. The purpose of this study is to evaluate response rates, progression free survival (PFS), and incidence and severity of PN of weekly bortezomib dosing in the modified Dara-Vd regimen. Methods: An observational, single-center, non-randomized, retrospective chart review of patients receiving treatment with a modified Dara-Vd was conducted between December 1, 2015 to July 1, 2018. This regimen consisted of: dara 16 mg/kg weekly for 8 doses followed by every other week for 8 doses, and then monthly; bortezomib 1.3 mg/m2 SC on days 1, 8, 15 of 28-day cycles for the first 2 cycles and then days 1 and 15 thereafter; dexamethasone 20 mg was given on days of dara infusion and the day after. The primary objective was to evaluate response rates among MM patients at WFBH receiving modified Dara-Vd. The secondary objectives were to assess PFS, quantify the impact of therapy on PN, and describe dose adjustments, delays, or discontinuation of therapy. Results: A total of 25 patients received the outlined regimen and were included in the analysis. Sixteen patients (64%) were refractory to a proteasome inhibitor (PI), with 9 patients (36%) deemed bortezomib resistant. The overall response rate was 56%. Of the 16 patients who were refractory to a PI, 7 (ORR = 43.8%; p value = 0.21) achieved a response, including 3 (ORR = 33%; p value = 0.12) resistant to bortezomib. The median PFS was 9.7 months and the PFS at 12 months was 44.7%. Eighteen patients (72%) experienced PN. Of those 18 patients, 15 (83.3%) had pre-existing PN with 8 (53.3%) of the patients' PN worsening during the

modified Dara-Vd treatment. All 8 patients who experienced worsening PN were classified as NCI-CTCAE grades 1 or 2. There were 3 (16.7%) patients who had dose reductions or delay of treatment due to PN; however, no patients discontinued the modified Dara-Vd regimen due to PN or any other toxicity. Conclusion: Overall, a favorable response was achieved in this heavily pre-treated population where the majority of patients were refractory to at least one PI. The once weekly SC bortezomib dosing in the modified Dara-Vd regimen had a tolerable side effect profile and no therapy discontinuations, making it a treatment option to explore prospectively in patients with relapsed MM and pre-existing PN.

Keywords:
bortezomib

neuropathy

Relapsed Refractory MM

Tracks:
Antibody Based Approaches to MM

FP-167

CD46 Antibody Drug Conjugate Impedes Myeloma Engraftment in Patient-Derived Xenografts

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Abstract:
Background: Multiple myeloma (MM) is incurable, implying that MM progenitor cells are inherently resistant to current agents and inevitably lead to relapse. We recently reported the potent anti-myeloma effect of an antibody-drug conjugate targeting CD46 conjugated to monomethyl auristatin F (MMAF) anti-tubulin payload (CD46-ADC). Interestingly, MM patients with high-risk gain of chromosome arm 1q (1q+), overexpress CD46 and primary cells with 1q+ are more sensitive to CD46-ADC. Thus, we hypothesized that CD46-ADC may have the unique potential to target 1q+ MM progenitors. Methods: CD46 expression was measured on subpopulations of primary MM cells with a progenitor phenotype. Ex vivo sensitivity of primary MM cells to CD46-ADC was measured in samples spanning from diagnosis to the multi-relapsed setting. Lastly, a patient-derived xenograft (PDX) model was implemented utilizing implanted human fetal bone fragments to provide a human bone marrow microenvironment. To optimize this PDX model, we tested newly diagnosed and multi-relapsed samples for engraftment efficiency. Engraftment was monitored weekly by serum human light chain ELISA, and at sacrifice bone marrow and bone fragment flow cytometry. We then tested MM regeneration in PDX by treating mice with CD46-ADC or a nonbinding control-ADC two weeks after cell injection. Comparisons made between groups were made by t-test. Results: Clonal MM progenitor cells from patients that exhibit high aldehyde dehydrogenase activity (a marker of quiescence) also have high expression of CD46 (n = 5). Thus far, we have found primary MM cells to have ex vivo response to CD46-ADC in 2/3 (66.7%) newly diagnosed and 5/8 (62.5%) relapsed/refractory patient samples tested at 10nM, showing a lack of cross-resistance in multi-relapsed disease. In PDX, newly diagnosed MM patient samples engrafted significantly more (70%) compared to relapsed/refractory samples (11%) (p = 0.02). Thus, we used newly diagnosed samples in testing CD46-ADC effect on PDX engraftment. Compared to control-ADC, CD46-ADC treated mice showed significantly lower human free light chain by week 3 (p=0.04) and this continued through the end of experiment at week 8 (p=0.005), and decreased bone marrow involvement was nearly significant (p=0.055). Overall, PDX injected mice treated with CD46-ADC had detectable MM in 23% (3/13 mice) compared to 69% (9/13 mice) with control-ADC (p = 0.047). Conclusions: Our data further support the

development of CD46-ADC for multiple myeloma. For the first time to our knowledge, we show preclinical drug efficacy in MM PDX. Interestingly, newly diagnosed patient samples engraft more often in MM PDX with fetal bone fragments, facilitating drug efficacy testing. The phase I clinical trial for CD46-ADC (FOR46, Fortis Therapeutics) in patients with MM is currently underway (NCT03650491), and further preclinical and correlative studies will be focused on the optimal application of this agent for myeloma patients.

Keywords:
immunotherapy

malignant stem cells

novel agents

Tracks:
Antibody Based Approaches to MM

FP-168

HDP-101, a Novel BCMA-targeted Antibody Conjugated to α-Amanitin, is Active against Myeloma with Preferential Efficacy against Pre-clinical Models of Deletion 17p

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Abstract:
Background: High risk multiple myeloma (MM) with deletion (del) of 17p has always been an adverse prognostic factor. Genomic TP53 deletion might cause the haploinsufficiency of nearby genes, such as RNA polymerase II subunit A (POLR2A), located on 17p13.1. We thus hypothesized that del 17p could reduce POLR2A expression and enhance sensitivity towards α -Amanitin, a potent and specific inhibitor of POLR2A. Methods: Pre-clinical studies were performed using HDP-101, a monoclonal antibody-drug conjugate (ADC), which comprises an anti-BCMA antibody conjugated to α -Amanitin, or a control antibody comprising an anti-digoxigenin antibody also coupled to α -Amanitin in MM cell lines. The cell line models included H929, MM1.S, and MOLP-8 TP53 wild-type (WT) and isogenic cells in which TP53 had been knocked out (KO) using CRISPR/Cas9. To further evaluate del 17p and POLR2A haploinsufficiency, POLR2A was knocked down (KD) using shRNAs. Results: Analysis of the MMRF database revealed that del 17p13 was associated with a significant reduction in POLR2A expression ($p<0.0001$), patients within the lower quartile of POLR2A expression (which included those with and without del 17p), displayed an inferior overall survival ($p<0.0011$) with a trend towards a worse progression-free survival; this suggesting low POLR2A levels alone are an adverse feature. HDP-101 induced a time and dose-dependent cell killing at concentrations in the low picomolar range. To further assess specificity, MM cells were co-cultured with HS-5 (Human stromal) cells, only α -Amanitin and, to a much greater extent, HDP-101 induced cell killing in MM cells, while the HS-5 was spared. Cell killing due to HDP-101 was associated with induction of apoptosis as judged by Annexin-V and PI staining, which was accompanied by cleavage of caspases 3/9, along with the loss of mitochondrial membrane potential. H929, MM1.S, and MOLP-8 TP53 WT/KO cells were equally sensitive to HDP-101, as these cells expressed high levels of BCMA regardless of TP53 or POLR2A status. Notably, the preferential impact was associated with increased expression of XBP-1, ATF-4 and -6, suggesting enhanced induction of endoplasmic reticulum stress. Interestingly, POLR2A-KD cells were more susceptible towards HDP-101 mediated cell killing in both H929 TP53 WT and KO cells, supporting the promise of this target. Evaluation of HDP-101 in primary relapsed samples showed a dose dependent decrease in MM viability. The treatment of mice with HDP-101 showed suppression of tumor burden in both, TP53 WT and KO models, interestingly, the POLR2A-KD cells were sensitive to HDP-101 at a fifty percent lower dose to that which was effective in the TP53 WT and KO models. Conclusions: Our preliminary

data supports the possibility that del 17p may have a therapeutic vulnerability towards HDP-101. Moreover, they suggest that it is a novel potent and specific therapeutic that could show enhanced activity against high-risk multiple myelom

Keywords:
HDP-101

Multiple myeloma

POLR2A

Tracks:
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CLINICAL CHARACTERISTICS AND TRANSFUSION MANAGEMENT OF PATIENTS DIAGNOSED OF MULTIPLE MYELOMA RECEIVING DARATUMUMAB: EXPERIENCE OF A SINGLE CENTRE

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Abstract:
Introduction: Daratumumab (Dara) is a monoclonal antibody against CD38 that has shown high efficacy and safety profile in relapsed Multiple Myeloma (MM) patients, also approved for front-line therapy in patients ineligible for hematopoietic stem cell transplantation. It is well recognized that Dara interferes with blood bank testing by binding to CD38 on red blood cells and causing panagglutination in the Indirect Antiglobulin test (IAT). To overcome the problem, use of DTT treated red blood cells (RBC) is currently the most widespread and validated method. Our objectives were to review the clinical characteristics and transfusion management of MM patients receiving Dara in a single centre. Material and methods: we reviewed the clinical charts and transfusion data of patients diagnosed of MM and treated with daratumumab at La Fe University Hospital. In order to optimize and to make the DTT technique available for 24 hours, DTT-treated RBC used for IAT were suspended in a RBC storage solution that extends the shelf life until 31 days. Results: We reviewed 44 patients who received Dara (21 male, 23 female) with a median of age of 70 years, for a two years and a half period. Patients received a median of 2 (range 1-7) prior lines of therapy. Dara was used as single therapy in 15 cases and in combination with other agents in 31 cases: with lenalidomide-DXM (DRd) in 21 patients (two of them after dara monotherapy), with bortezomib-DXM (DVD) in 7 patients and with carfilzomib-DXM (KDd) in 3 patients. Fourteen patients had previously received stem cell transplantation. High-risk cytogenetic was detected in 17 patients before Dara treatment. Ninety percent of patients (n=28) had ISS-R of 2-3 and 13 (29.3%) had extramedullary disease. One patient underwent autologous followed by haploidentical stem cell transplantation after Dara. Patients received a median of 16 Dara doses (range 1-39). A total of 39 patients were evaluable for response. Overall response and very good partial response (VGPR) was achieved in 66.6% and 51.3% of patients respectively, 41.6% and 25% with monotherapy, 66.6% and 50% with DVd, 77.7% and 61% with DRd, respectively, and two of three patients treated with KDd achieved VGPR. Fifty three IATs were performed to 13 patients (27.9 %) who received a median of 6 RBC transfusions (range 1-22). IAT was performed when transfusion was requested. Overall, 99 RBC units were transfused without delay or any adverse effect. In 2 patients a positive direct antiglobulin test was detected after starting Dara treatment. No patient developed red blood cell alloantibodies. Conclusions: Dara is a well-tolerated treatment that shows high efficiency in patients with relapsed MM. Using an in-house validated method to perform IAT with DTT treated RBC allows to quickly and safely transfuse to patients undergoing Dara therapy. A close

relationship between clinicians and blood bank is mandatory to provide the best transfusion support to MM patient

Keywords:
carfilzomib

daratumumab

transfusion

Tracks:
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EVALUATION OF CD319 (SLAMF7) AS A NOVEL GATING MARKER FOR PLASMA CELLS IN FLOW CYTOMETRIC IMMUNOPHENOTYPING OF MULTIPLE MYELOMA

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Abstract:
Introduction: Traditionally, plasma cells (PCs) are identified using strong CD38 and CD138 expression in flowcytometric Immunophenotyping (FCI). However, variable loss of CD138 and decreased-expression of CD38 is well-known in clonal-PCs. Furthermore, anti-CD38-monoclonal antibody (Daratumumab) therapy causes down-regulation of CD38 expression. In these scenario, traditional markers are not adequate for FCI of PCs, especially for monitoring of minimal residual disease (MRD). Recently, CD319 (SLAMF7) has been demonstrated to be useful for FCI-PC gating, but in a small cohort of samples and clinical-trial settings. However, its utility in routine laboratory practice for plasma cell gating is still not established. In this study, we have investigated the value of CD319 as gating marker in FCI of MM in routine laboratory practice.
Objectives: 1. To investigate the expression-pattern of CD319 in normal and clonal PCs 2. To study its utility as the gating marker in Flowcytometric Immunophenotyping of MM. Methods: We analyzed expression-pattern of CD319 (PE, clone-CRACC) in PCs from bone marrow (BM) of newly-diagnosed MM and control samples (uninvolved staging BM). FCI characterization was performed on Navios flow-cytometer and data-analysis was performed using Kaluza-v1.3-software. Expression-levels of CD319 in PCs against remaining hematopoietic cells (HCs) was determined as the ratio of mean fluorescent intensity (MFI) of CD319 in PCs to MFI of HCs (denoted as "MFI-R"). The pattern of expression (homogenous/heterogenous) was determined as coefficient-of-variation of immunofluorescence (CV-IF). Statistical analysis was performed using SPSS-v16. Results: CD319 expression was analysed in 207 BM (163 newly diagnosed MM and 44 control BM samples). Median (range) of total PCs/viable cells (TPCs) in MM and control samples were 22% (1 - 87%) and 5% (1 - 18%). Median & standard deviation (SD) of MFI-R of CD319 in abnormal PCs (aPCs) were 18.1 & 15 and normal PCs (nPCs) were 24 & 16.37 respectively. Median & SD of CV-IF of CD319-expression was 56 & 37. Thus, CD319 was strongly and homogeneously expressed in PCs than rest of HCs (Mann-Whitney-U test, $P<0.001$). There was no statistically significant difference in the expression-level of CD319 in nPC vesrus aPC. It was positive in 100% of PCs in all control-samples and 86% (140/163) MM-samples. Median (range) PC-percentages with CD319 negative expression in these 23 samples was 6.5% (3-60%). There was a high correlation between the PC percentages calculated using

CD138vsCD319 and CD38vsCD45vsCD138 gating-strategy (r=0.96) and CD45vsCD319 and CD38vsCD45vsCD138 gating-strategy (r=0.99). Conclusion: CD319 is stable immunophenotypic marker with strong and homogenous expression in PCs. It can be effectively used as a gating marker in addition to traditional markers for plasma cell quantitation, especially after daratumumab-therapy. It also provides a potential target for anti-CD319 (Elotuzumab) therapy.

Keywords:
CD319

Flow Cytometry

immunophenotype

Tracks:
Antibody Based Approaches to MM

FP-171

Inhibition of CD47 as a Novel Cancer Immunotherapy for Multiple Myeloma

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Abstract:
Introduction: CD47 is a protein highly expressed on the surface of various cancer cells, allowing them to escape innate immune recognition by sending inhibitory signals to macrophages (Ma), which further hinders the anti-tumor response by the adaptive immune system. This CD47 "don't-eat-me signal" has been identified as a novel therapeutic target in various cancers, including multiple myeloma (MM). Targeted reprogramming of this interaction using anti-CD47 monoclonal antibody (mAb; Vx1000R) represents a new class of checkpoint inhibitor that attack tumors via coordinating the innate and adaptive immune systems. In this study, our objectives were to: (1) analyze CD47 mRNA expression in MM patients; (2) test CD47 protein expression in MM cell lines by binding Vx1000R; (3) study the effect of hypoxia, tumor microenvironment (TME), and 3D tissue engineered bone marrow (3DTEBM) on the expression of CD47; (4) examine the effect of Vx1000R alone on MM cell survival in 2D vs 3DTEBM; and (5) examine the effect of Vx1000R on MΦ mediated MM cell phagocytosis and killing in 2D vs 3DTEBM. Methods: We performed analysis of CD47 mRNA expression in healthy, MGUS (pre-condition of MM), and MM subjects. We measured CD47 protein expression on MM cell lines with Vx1000R and analyzed through FACS. We cultured MM cell lines under various conditions for 72hrs to test the effect of hypoxia (1% O2), stromal cells, and 3DTEBM cultures on CD47 expression. Cytotoxicity of Vx1000R on MM cells was analyzed by MTT assay. The effect of Vx1000R on phagocytosis and killing of GFP-5TGM1 cells by mice-derived Ma (mMa, labeled with DiD) was tested at 4 and 24hrs with or without Vx1000R, in 2D and 3DTEBM cultures. Phagocytosis was determined as GFP+ DiD+ cells and MM survival as GFP+ by FACS. We also performed real-time live confocal imaging on 3DTEBM cultures of GFP-5TGM1 cells and DiD-mMa, with or without treatment of Vx1000R, to further visualize the effect of blocking CD47. Results: CD47 mRNA in patients increased with MM progression. CD47 protein was highly expressed in MM cells lines such as MM.1S, H929, U266, the expression was not altered by hypoxia or support of stromal cells; however, 3DTEBM cultures increased CD47 expression. Vx1000R treatment alone did not result in direct killing of MM cells in 2D monoculture, but resulted in extensive killing of MM cells in MM/mMa co-cultures in 2D and 3DTEBM---treatment in 3DTEBM induced 50% killing at 4hrs and ~95% killing at 24hrs. Conclusions: In summary, MM cells express high levels of CD47 which was not affected by hypoxia or TME. This expression, however, was

increased in 3DTEBM cultures. Blocking CD47 on MM cells with anti-CD47 mAb enhanced MM phagocytosis and killing by MΦ, especially in 3DTEBM. Our results suggest that anti-CD47 mAb is a promising immunotherapy for MM, and further studies are warranted to examine the biology behind changes in 3DTEBM, as well as the effect of anti-CD47 mAb in vivo and in patients.

Keywords:
CD47

immune checkpoint

Macrophage

Tracks:
Antibody Based Approaches to MM

FP-172

MEDI2228, a novel BCMA pyrrolobenzodiazepine antibody drug conjugate, overcomes drug resistance and synergizes with bortezomib and DNA damage response inhibitors in multiple myeloma

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Abstract:
We here investigate the potency and define molecular mechanisms whereby MEDI2228, a novel BCMA antibody drug conjugate (ADC) armed with the DNA cross-linking pyrrolobenzodiazepine (PBD) dimer tesirine, overcomes drug resistance in multiple myeloma (MM). In vitro preclinical studies show that MEDI2228 targets MM cells, including CD19+CD138- MM progenitor cells. The cytotoxicity of MEDI2228 is minimally impacted in the presence of soluble BCMA in preclinical models. MEDI2228, more effectively than its monomethyl auristatin-F (MMAF) ADC homolog, inhibits proliferation and survival of all MM cell lines and MM cells from patients with multiple relapsed and refractory disease, regardless of BCMA levels, p53 status, and the protection conferred by bone marrow stromal cells and IL-6. Specifically, MEDI2228, but not its MMAF ADC homolog, activates critical DNA damage responses (DDR) via phosphorylation of ATM/ATR kinases, checkpoint kinases (CHK)1/2, and H2AX, associated with induction of multiple DDR pathway-associated genes. Low doses of MEDI2228 and bortezomib (btz) synergistically induce apoptosis of drug-sensitive and -resistant MM cells, at least in part, through modulation of RAD51, a DNA damage and repair protein. Importantly, MEDI2228 triggers ATM/ATR-CHK1/2 signaling cascade, associated with increased phosphorylated H2AX, p21, and apoptosis molecules, in MM1S-xenografted tumors in mice. In vivo, a single sub-optimal dose of 0.4 mg/kg MEDI2228 induces superior targeted anti-MM activity than btz, indicating that MEDI2228 is significantly more effective than btz as single agent therapy in vivo. Further, combined treatments with MEDI2228 and btz result in potent tumor depletion and significantly prolonged host survival via increased nuclear phosphorylated H2AX-expressing microfoci, DNA damage-induced growth arrest and cell death. Significant tumor necrosis is observed earlier in mice receiving both drugs than either agent alone, and at 177d, 15% of mice in the combination treatment group remain alive and without any sign of tumor growth. Importantly, no weight loss is noted in all groups, indicating a favorable safety profile of MEDI2228 in vivo. Moreover, DDR checkpoint inhibitors, i.e., AZD0156 (ATMi), AZD6738 (ATRi), AZD1775 (WEE1i), synergize with MEDI2228 to enhance MM cell cytotoxicity. Taken together, these results further support current clinical development of MEDI2228 as a novel monotherapy (NCT03489525) and provide the framework for combination use of MEDI2228 with btz or DDRi(s) as an important next-generation immunotherapy to improve patient outcome in MM.

Keywords:
ADC

Bone marrow microenvironment

DNA damage

Tracks:
Antibody Based Approaches to MM

FP-173

Manual polybrene (MP), not dithiothreitol (DTT), is the recommended method for blood banking procedure in myeloma patients treated with anti-CD38 monoclonal antibody in Asia

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Abstract:
Background: Anti-CD38 monoclonal antibody treatment is known to interfere with the blood compatibility test. Dithiothreitol (DTT) pre-treatment to denature surface CD38 on the reagent erythrocytes is a robust method to mitigate this interference and has been validated internationally (Transfusion, 2016;56;2964-2972). However, the distribution of common alloreactive antibodies differed widely between Asian and Caucasian population. Furthermore, in addition to anti-K, it remains unknown whether DTT pretreatment will decrease the sensitivity in the detection of other allogeneic antibodies common in Asia like anti-Miltenberger (anti-Mia). We therefore conduct this study is to compare the sensitivity of using MP and DTT pretreatment followed by column agglutination technology (DTT-CAT) in the detection of common allogeneic antibodies in Asia. Method: Per hospital guideline, all the patients receiving anti-CD38 monoclonal antibody should have complete blood group typing and antibody screening prior to and after anti-CD38 treatment. Consecutive 11 patients receiving Daratumumab (N=7) and Isatuximab (N=4) at China Medical University Hospital were included. Direct antiglobulin test (DAT), indirect antiglobulin test (IAT), and antibody screening tests (using MP and DTT-CAT) were done. Since no alloantibody was detected in these patients, standard anti-sera (anti-c, D, E, Fyb, Jka, M, Mia) was added into patient's serum with serial dilution and MP and DTT-CAT were done to compare the sensitivity of these 2 methods in detecting these antibodies. Results: Before the treatment of anti-CD38, alloreactive antibody was not detected in all the 11 patients. After anti-CD38 treatment, all the specimens showed pan-reactivity to the reagent erythrocytes and DTT treatment mitigated this reaction. Interestingly, all the specimens tested by MP showed no agglutination. Adding test anti-sera serum with serial dilution into patient's serum and repeated the compatibility tests showed that MP method remained very sensitive in detecting all the test antibodies. However, after pretreatment with DTT, the senstivity of detecting anti-Mia and anti-M were markedly decreased by using CAT method. Anti-M was detected by MP at 1:256 and by DTT-CAT at 1:8. Anti-Mia was detected by MP at 1:64 and by DTT-CAT at 1:8. Conclusion: Our study for the first time showed that Anti-CD38 monoclonal antibody treatment (both Daratumumab and Isatuximab) do NOT interfere with the blood compatibility test and do not jeopardize the sensitivity of detecting allogeneic antibodies by using manual polybrene. On the other hand, the sensitivity of detecting anti-M and anti-Mia were compromised by using DTT-CAT method. Since anti-M and anti-Mia are the common allogeneic antibodies in China, Korean, Japan, Taiwan, Hong Kong, Thailand, and Malaysia, we recommend MP as a preferred method of blood banking procedure for myeloma patients treated with anti-CD38 monoclonal antibodies in Asia.

Keywords:
anti-CD38

Blood banking

Tracks:
Antibody Based Approaches to MM

FP-174

Daratumumab monotherapy in heavily pretreated Asians patients with relapsed and refractory multiple myeloma

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Abstract:
Background/Aim: Daratumumab is a first-in-class human immunoglobulin kappa monoclonal antibody targeting CD38. Clinical trials with daratumumab monotherapy in relapsed and refractory multiple myeloma (RRMM) have shown substantial efficacy and favorable safety profiles. However, these trials excluded patients with poor performance status and other significant co-morbidities, thus their results cannot be immediately implemented into real-world practice. There still lacks real-world data concerning daratumumab monotherapy, especially from the Asian population. To this end, we carried out this study. Materials and methods: This was a multicenter, retrospective, longitudinal cohort study set between January 2017 and April 2019. We collected and analyzed clinical and survival data of 21 patients treated with daratumumab monotherapy. Results: The median time from MM diagnosis to daratumumab monotherapy 54 months (range 12-119 months). The median previous line of therapy was 4 (range 3-8) and all the patients were previously exposed to at least one proteasome inhibitors (PI) and immunomodulatory drugs (IMiD), and the majority (76.2%) of the patients were double-refractory. Among the 19 patients with evaluable response, the overall response rate (ORR) was 42.1% (8/19), including 1 complete response (CR) and 3 very good partial response (VGPR). The clinical benefit was seen in 57.9% of the patients (11/19), and the median time to response for these patients was 2 months (range 1-6 months). The median PFS was 6 months (95% CI, 1.1-10.9 months) and the median OS was not reached. As for the safety of daratumumab, though no new toxicity signal was identified, infusion related reactions (IRR) occurred in 42.9% (9/18) of the patients. There were 4 cases with grade 3 or higher IRR in the form of severe nausea and vomiting combined with generalized rash leading to permanent daratumumab discontinuation in 1 patient, and dyspnea (bronchospasm) requiring immediate intervention in 3 patients. The latter 3 patients continued subsequent daratumumab treatment on desensitization protocol. There were 5 cases (23.8%) of serious infection: 1 with Pseudomonas bacteremia after cycle 3, 1 with gram negative rod bacteremia during cycle 1 leading to patient's demise, 1 with Corynebacterium bacteremia during cycle 1 to patient's demise, 1 with atypical pneumonia after cycle 5, and 1 with Pneumocystis pneumonia after cycle 3. The most common adverse event was fatigue, which was reported from 52.4% (11/21) of the patients. Conclusion: Daratumumab monotherapy showed fairly promising activity but modest tolerance in heavily treated Asian RRMM patients. Our study highlights the importance of real-world data to complement the results of published clinical trials, especially across different ethnicities.

Keywords:
Asia

daratumumab

real-world evidence

Tracks:
Antibody Based Approaches to MM

IMMUNOTHERAPEUTIC APPROACHES TO MULTIPLE MYELOMA

FP-175

Nanoparticle Multi-Specific T cell Engagers for the Treatment of Multiple Myeloma

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Abstract:
Introduction: Despite the compelling clinical success of chimeric antigen receptor (CAR)-T cells and bispecific T cell engagers (BiTEs) for the treatment of multiple myeloma (MM), many patients relapse due to tumor escape. A list of limitations exists for both immunotherapies. CAR-T cells, for instance, 1) only target one cancer antigen when it is evidently known that cancer cells express a landscape of heterotypic genes and moieties; and 2) are extremely expensive with a total cost of more than $1 million. With regards to BiTEs, limitations arise from: 1) the inability to target multiple cancer antigens; 2) the need to be continually infused into the patient to enable efficacy and distribution due to their very short half-lives (2 hours); and 3) the increased risk of infections and sepsis-related deaths due to continual infusion. In addition, BiTEs and CAR-T cells require the use of laborious techniques and sophisticated equipment for production. To circumvent these issues, we have developed a nanoparticle in which two antibodies are conjugated to the surface of a liposome; one to recognize an epitope on MM and the other to engage T cells, which we defined as the nanoparticle bispecific T cell engager (nanoBiTE). Moreover, we have made a nanoBiTE with more than three total targeting moieties; one to engage the T cells and the other two or more to target various epitopes on MM, defined as the nanoparticle multi-specific T cell engager (nanoMuTE). Methods: Liposomes were prepared using the thin-film hydration method followed by extrusion. nanoBiTEs and nanoMuTEs were developed by conjugating monoclonal antibodies against BCMA, CS1, and/or CD38; together with anti-CD3 onto the liposomes. We have tested the expression of BCMA, CS1, and CD38 antigens on MM cell lines and primary MM patient samples, and analyzed the binding of the CD38/CD3, BCMA/CD3, and CS1/CD3 nanoBiTEs, as well as the BCMA/CS1/CD38/CD3 nanoMuTEs to these cells by flow cytometry. Binding specificity was assessed by blocking the target with corresponding free antibodies. CD69 expression and cytokine release was assessed for T cells after four days when incubated with nanoBiTEs or nanoMuTEs in the 3D tissue engineered bone marrow (3DTEBM). Moreover, we tested the efficacy of the nanoBiTEs and nanoMuTEs against MM cells and patient samples in vitro using the 3DTEBM. Finally, we tested the efficacy of the nanoBiTEs and nanoMuTEs in a xenograft MM mouse model. Results: The binding of the nanoMuTEs was significantly higher compared to each nanoBiTE for all samples. The nanoBiTEs and nanoMuTEs were able to activate T cells only in the presence of the target cell in vitro. The nanoMuTEs induced greater activation of T cells and T cell-redirected MM cell lysis compared to each individual nanoBiTE in the 3DTEBM. In vivo, the nanoBiTEs and nanoMuTEs were able to redirect T cells to the tumor site and reduce tumor burden in the MM-bearing mice compared to control.

Keywords:
BiTE® (Bispecific T-cell Engager) molecule

Nanoparticles

T-Lymphocytes

Tracks:
Immunotherapeutic Approaches to MM

FP-176

Neoantigen-specific CD4+ T cells induce protective, tumor-specific CD8+ T cells in a mouse model of multiple myeloma.

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Abstract:
Cancer immunotherapies have primarily focused on generating tumoricidal CD8 T cells. However, recent data demonstrate a critical role for CD4 T cells in tumor immunity. CD4 T cells against epitopes derived from mutated tumor-associated neo-antigens (neoAg) conferred protection against tumor growth in animal models of neoAg vaccine therapy. In clinical studies, immunity elicited by neoAg vaccines was associated with improved survival, even though the majority of immune responses were CD4 T cells that did not have cytolytic activity. In these studies, CD8 T cells directed against immunized neoAg were rarely detected. These findings are even more striking because most tumor cells do not express MHC class II molecules and are invisible to CD4 T cells. To investigate the mechanisms of neoAg-specific CD4 T cells protection against tumor, we used a multiple myeloma cell line, MOPC315.BM (MOPC, BalB/C background), which produces a unique neoAg in the λ2 light chain called Idiotype λ2.315 (Id) and does not express MHC II. Our vaccine formulation, the Id peptide sequence fused with a high affinity HSP70 binding site and delivered with poly(I:C), elicited strong CD4 T cell immunity and protected against MOPC tumor growth even in the absence of direct cytolytic activity in vitro and without detectible Id-specific CD8 T or B cell responses. These findings lead to the hypothesis that Id-specific CD4 T cells confer protective immunity by cross-priming CD8 T cells against non-Id, MOPC-associated antigens. To investigate this hypothesis, splenocytes and bone marrow (BM) cells were harvested from three groups of mice; one group challenged with MOPC cells only, one group vaccinated with the Id peptide only, and one group Id vaccinated and challenged with MOPC cells with protection against tumor growth. CD4 and CD8 T cell activity was assessed by intracellular cytokine staining (ICS) for IFNγ and TNFα after in vitro restimulation with Id peptide and irradiated MOPC cells. In the absence of Id vaccination, very little Id-specific activity was observed in the spleen and BM. Id vaccination alone induced CD4 T cells in both compartments. In mice that received both Id vaccine and MOPC challenge, there was induction of tumor-specific CD8 T cells, with a trend towards high levels of activity in the BM. These CD8 T cells were not detected when cells from the same animals were restimulated with the Id peptide alone, indicating that these CD8 responses were against non-Id, MOPC-associated antigens. The protective effect of Id vaccination was lost when CD4 or CD8 T cells were depleted after vaccination and before MOPC challenge, confirming that the mechanism of protection was dependent on Id-specific CD4 T cells and supporting the model of cross-priming of CD8 T cells against distinct MOPC-associated antigens. Further investigation of the CD8 target antigens may lead to polyvalent vaccines of optimized CD4 and CD8 T cell antigens with improved efficacy.

Keywords:
CD4 T cells

Multiple myeloma

vaccination

Tracks:
Immunotherapeutic Approaches to MM

FP-177

Novel On-Target Restoration of a Split T Cell-Engaging Antibody for Precision Immunotherapy of Multiple Myeloma

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Abstract:
T cell-engaging immunotherapies are changing the therapeutic landscape of cancer. However, suitable target antigens are scarce, restricting these strategies to very few tumor types. To overcome this limitation, we developed a T cell-engaging antibody derivative, which comes in two complementary halves and addresses antigen combinations instead of single molecules. Each half, originally coined hemibody, contains an antigen specific single-chain variable fragment fused to either the variable light (VL) or variable heavy (VH) chain domain of an anti-CD3 antibody. When the two hemibodies simultaneously bind their respective antigens on a single cell, they become aligned and reconstitute the original CD3-binding site to engage T cells. This novel precision immunotherapy is named „Combinatorial hemibody retargeting therapy" (Cherry). Employing a preclinical model for multiple myeloma (MM), we show that by the combinatorial nature of this Cherry-Antibody approach, T lymphocytes react exclusively against dual antigen-positive MM cells while sparing single positive bystanders. After biological and biochemical screening of over 40 different hemibody fragments directed against several antigens associated with MM, we designed a final pair of Cherry-Myeloma Antibodies against CD38 and BCMA. The combination of the anti CD38- and the anti BCMA-Cherry-Myeloma-Antibodies induced substantial T-cell mediated lysis on double targets positive MM cells in vitro at nanomolar concentrations. Their effect was negligible on CD38 and BCMA single-positive cells. Importantly, classic BiTE-antibodies directed against CD38 and BCMA caused T-cell induced killing of cells expressing the cognate antigen but could not discriminate single- from double-antigen positives. To put the potential therapeutic applicability of Cherry-Myeloma-Antibodies to the test, in vivo studies with MM directed Cherry-Myeloma-Antibodies against different MM antigens are ongoing. By addressing an aberrant antigen combination on myeloma cells, Cherry-Antibodies are a new class of immunotherapeutics with the potential to perform a Boolean AND Gate operation and to improve safety and specificity for patients.

Keywords:
BCMA

CD38

immunotherapy

Tracks:
Immunotherapeutic Approaches to MM

FP-178

Reinstating anti-tumor activity of Natural Killer cells

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Abstract:
Despite new therapeutic options, MM still remains incurable and clearly, novel modalities complementing or improving current treatment options are needed. In this context, our group, as well as others, have previously reported that Natural Killer (NK) cells may be a feasible treatment modality. However individual patient NK cell myeloma cell interactions vary among patients and it is unclear if these interactions predict response to complementary treatments. Thus, with this project, we aim to identify therapeutic targets via systematic screening of NK cell/tumor cell interactions by using genetically modified autologous NK cells. We would like to elucidate the functional role of each single NK cell receptor in autologous MM recognition and killing. This method will allow the functional screening of activating receptors while accounting for the complex network of interactions between the NK cell and the MM cell. The results from such assays provide patient-specific data regarding the significance of each receptor in a possible NK cell-based immuno-gene therapy

setting. In order to generate genetically modified NK-cells and to identify key NK cell receptor/tumor interactions, we utilize bicistronic lentiviral vectors with fluorescent markers. Viral particles produced by transfection of HEK293FT cells with LeGO-iG2 vector carrying the gene of interest as well as the viral packaging plasmids. Supernatants from transfected cells are collected and viral particles are purified and concentrated. PBMCs isolated from peripheral blood of MM patients and plasma cells are isolated from the BM of the same patients. NK cells from the PBMCs isolated by AutoMACS separation and consequently expanded for 3 days by the addition of IL-2 and IL-21 followed by transduction with purified viral constructs coding for activating receptors in the presence of small molecule inhibitors. These small molecule inhibitors are used to enhance lentiviral gene delivery to NK cells. After transduction, NK cells are kept in culture for three more days and target cells are added to each well in order to assess NK cell degranulation and IFN-g release. We observed a general trend that upregulation of the activating receptors elevates the degranulation of NK cells against tumor cells when compared to spontaneous degranulation and to activation against autologous PBMCs. The results present the degree of involvement of each receptor in mediating the NK cell response and by comparing the responses against non-tumor cells and tumor cells, we will also obtain a measure of how specific the anti-tumor response is. Significance of this research for the myeloma field is to develop a predictive algorithm that will enable patient inclusion which will benefit from synergies between different receptor profile. This, in turn, enables patient-tailored cancer immunotherapy approaches based on NK cells.

Keywords:
Genetically modified primary NK cells

immunotherapy

Multiple myeloma

Tracks:
Immunotherapeutic Approaches to MM

FP-179

Ruxolitinib (RUX) reverses checkpoint inhibition by downregulating PD-L1 expression in both multiple myeloma (MM) tumor and stromal cells

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Abstract:
Multiple myeloma (MM) tumor cells evade host immunity through the interaction of programmed cell death ligand 1 (PD-L1) to PD-1. This creates an immunosuppressive milieu in the bone marrow microenvironment. The immune inhibitory proteins PD-L1 are highly expressed in MM bone marrow (BM). Moreover, increased expression of this protein is associated with resistance to treatment in MM. Ruxolitinib (RUX) is an inhibitor of the Janus kinase family of protein tyrosine kinases that is effective for the treatment of myeloproliferative diseases. In this study, we investigated the effects of RUX on expression of PD-L1 in MM, and the effect of RUX in combination with anti-MM agents in vitro and in vivo. We examined PD-L1 gene expression in MM patients with progressive disease (PD) or in complete remission (CR). The results showed that PD-L1 gene expression was markedly increased in BM mononuclear cells (MCs) from MM patients with PD compared with those patients in CR or with healthy subjects using quantitative PCR and flow cytometric assay. We further investigated the effects of RUX on PD-L1 expression of primary and stromal cells from MM patients' bone marrow samples in vitro. RUX treatment markedly reduced PD-L1 gene expression in the MM tumor cells cultured alone or co-cultured with stromal cells compared with cells not treated with the JAK1/2 inhibitor in a concentration dependent pattern. Next, we determined whether RUX can augment T-cellular anti-MM effects immunotherapy potency in vitro. We used anti-PD-1 and anti-PD-L1 blocking antibodies as a positive control. The results showed

that RUX (0, 0.1, 0.5, 1, and 5 μM), increased MM cell apoptosis in the presence of IL-2 stimulated T-cells in a concentration dependent fashion to a similar extent as observed with anti-PD-1 (0, 0.5, 1, 5, and 10 μg/ml) or anti-PD-L1 (0, 0.5, 1, 5, and 10 μg/ml) antibody treatment. Moreover, the combination of RUX with anti-PD-1 or anti-PD-L1 increased T-cell inducing MM cell apoptosis 5-10%. RUX had no effect on PD-1 expression on T-cells. To evaluate these drugs in vivo, the human MM xenograft LAGκ-2 model was used. The mice were then treated with RUX, the immunomodulatory agent lenalidomide (LEN) or dexamethasone (DEX) alone, doublets or the combination of all three drugs. RUX alone produced no anti-MM effects whereas the doublets showed more anti-MM effects than any single agent, and the combination of all three drugs showed the most marked anti-MM effects. Conclusion: The PD-L1/PD-1 pathway delivers inhibitory signals that regulate both peripheral and central tolerance and inhibit anti-tumor immune-mediated responses. This study demonstrated that the JAK inhibitor RUX downregulated PD-L1 expression in both MM tumor and stromal cells. We also demonstrated the combination of RUX with anti-PD-1 and anti-PD-L1 increased MM tumor cell apoptosis. The results suggest that JAK inhibitors may be effective for treating MM patients through their ability to reduce expression

Keywords:
immune checkpoint

JAK2 inhibitor

PD-L1

Tracks:
Immunotherapeutic Approaches to MM

FP-180

Frequent methylation of the tumor suppressor miR-1258 targeting PDL1: implication in multiple myeloma-specific cytotoxicity and prognostification

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Abstract:
Background miR-1258 is localized to the first intron of ZNF385B at chromosome 2q31.3. We postulated that miR-1258 is an intronic miRNA co-regulated with its host gene by promoter DNA methylation in multiple myeloma. Methods miR-1258 promoter methylation was studied a total of 147 samples including 10 normal buffy coat, eight normal bone marrow plasma cells, 16 human myeloma cell lines (HMCLs), 20 Monoclonal gammopathy of undetermined significance (MGUS), 63 diagnostic myeloma, and 30 relapsed myeloma samples by methylation-specific polymerase chain reaction. Results: In myeloma lines, miR-1258 methylation, verified by pyrosequencing, was detected in 62.5% HMCLs but not normal controls, and expression of miR-1258 correlated with that of ZNF385B. 5-Aza-2′-deoxycytidine resulted in promoter demethylation and ZNF385B/miR-1258 re-expression. Luciferase assay confirmed programmed cell death ligand-1 (PDL1) as the direct target of miR-1258. Over-expression of miR-1258 in completely methylated myeloma cells led to reduced cellular proliferation and enhanced apoptosis, hence a tumor suppressor role, in addition to repression of PDL1. In primary samples, methylation of miR-1258 was detected in 31 (49.2%) diagnostic myeloma, and 15 (50.0%) relapsed myeloma but not MGUS, and correlated with lower expression of miR-1258. Furthermore, methylation was associated with inferior PFS (P=0.034) that started to diverge at 12 months after treatment, and a trend of inferior OS. Conclusion miR-1258 is a tumor suppressor miRNA co-regulated with its host gene, and frequently hypermethylated in active myeloma instead of MGUS, hence acquired during myeloma progression. Methylation-mediated miR-1258 silencing led to overexpression PDL1 and inferior

PFS, implicating the role of miR-1258 in the modulation of myeloma-specific cytotoxicity.

Keywords:
methylation

miR-1258

PD-L1

Tracks:
Immunotherapeutic Approaches to MM

FP-181

Hypersialylation protects Myeloma cells from NK cell mediated killing and this can be overcome by targeted desialylation using a sialyltransferase inhibitor.

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Abstract:
Introduction: Evading Natural Killer (NK) cell-mediated immunosurveillance is key to the survival of Multiple Myeloma (MM) cells. Recently, attention has focused to the role of the hypersialylation in facilitating immune-evasion of NK cells. Abnormal cell surface sialylation is considered a hallmark of cancer, with growing evidence implicating hypersialylation in disease progression in MM. Certain sialylated glycans can act as ligands for the sialic acid-binding immunoglobulin-like lectin (Siglec) receptors expressed by NK cells (Siglec-7 and Siglec-9). These ITIM motif-containing inhibitory receptors are similar to PD-1, transmitting an inhibitory signal upon sialic acid engagement. We hypothesized that desialylation of MM cells or targeted interruption of Siglec expression could lead to enhanced NK cell killing of MM cells. Methodology: MM cells were treated with the sialidase neuraminidase for 45 mins prior to co-culture with NK cells. MM cells were treated with 300μM 3Fax-Neu5Ac (sialyltransferase inhibitor) for 7 days prior to co-cultures with NK cells. Primary NK cells were expanded, IL-2 activated (500U/ml) overnight, or naïve. Primary MM samples/MM cell lines were screened with Siglec-7/9 chimeras (10μg/ml) for 30 mins. Siglec-7 was targeted for knockout (KO) using the CRISPR/Cas9 system, a pre-designed guideRNA and the MaxCyte GT transfection system. Results: Using recombinant Siglec-7/9 chimeras a panel of commonly used MM cell lines (MM1S, RPMI-8226, H929, JJN3 and U266) were shown to express ligands for Siglec-7 and Siglec-9 (>85%). Primary MM cells isolated from BM of newly diagnosed (n=3) and relapsed patients (n=2) were also shown to express Siglec-7 ligands (72.5±17.5%, 36.5% respectively). Desialylation of the MM cell lines JJN3 and H929 using neuraminidase significantly enhanced killing of MM cells by healthy donor (HD) derived primary NK cells (expanded, IL-2 activated and naïve, n=7) at multiple Effector:Target (E:T) cell ratios. Desialylation using 3Fax-Neu5Ac resulted in strongly enhanced killing of MM1S by expanded HD NK cells at multiple E:T ratios (n=5, $p < 0.01$ at 0.5:1, $p < 0.001$ at 1:1, $p < 0.01$ at 2.5:1). De-sialylation of JJN3 and H929 using neuraminidase resulted in increased NK cell degranulation (CD107α expression), compared to a glycobuffer control (n=7). Targeted KO of Siglec-7 using CRISPR did not result in enhanced NK cell cytotoxicity against H929 and JJN3 MM cell lines (n=7). Discussion: Hypersialylation of MM cells facilitates immune evasion and targeted removal of sialic acid strongly enhances the cytotoxicity of NK cells against MM. However, to date the role of Siglecs remains inconclusive. Nevertheless, targeting hypersialylation in MM represents a novel therapeutic strategy to enhance NK cytotoxicity and improve disease control.

Keywords:
Hypersialylation

NK cells

Siglecs

Tracks:

Immunotherapeutic Approaches to MM

FP-182

Preclinical assessment of LCAR-B38M, a novel BCMA-targeting chimeric antigen receptor (CAR)-T cell therapy in relapsed/refractory multiple myeloma

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Abstract:
Multiple myeloma (MM) remains an incurable hematologic malignancy, partly due to its resistant microenvironment to immunotherapy. B-cell maturation antigen (BCMA) is expressed on MM cells and has emerged as a selective antigen that has been targeted by novel treatments for MM. Here, we discuss the in vitro and in vivo assessment of LCAR-B38M CAR-T cells, a novel T-cell therapy containing a 4-1BB co-stimulatory domain and two BCMA-targeting single-domain antibodies (sdAbs, also referred to as VHH domains). Recombinant llama-derived VHH domains of LCAR-B38M CAR-T were generated through phage display. Two individually identified VHH fragments were tandemly linked with a synthetic linker as the BCMA-targeting domain of the CAR. Both VHH domains and LCAR-B38M CAR-T cells demonstrated high binding affinities to BCMA in vitro. LCAR-B38M CAR-T cells selectively bind to human BCMA but not to BCMA from mouse or non-human primates. BCMA is almost exclusively expressed on plasma cells and MM cells. The selectivity and specificity of LCAR-B38M CAR-T cells for BCMA were studied in cell-based co-culture assays with various human tumor cell lines that express BCMA (RPMI8226, a human MM cell line) and do not express BCMA. Results from luciferase-based cytotoxicity assays showed that cytotoxicity and cytokine production of LCAR-B38M CAR-T cells were BCMA antigen dependent. Activity was observed on the human MM cell line, whereas no detectable activity was observed on HEK293-hERG cells or on other BCMA-negative tumor cell lines, such as A549 cells (lung carcinoma). LCAR-B38M CAR-T cells demonstrated BCMA antigen–dependent interferon gamma (IFNγ) release in co-culture with the human MM cell line, compared with un-transduced T-cells when co-cultured at a E/T=20:1 ratio. In addition, LCAR-B38M CAR-T cells did not exhibit IFNγ release in co-culture with any of the BCMA-negative human cell lines. These studies confirmed the specificity and activity of LCAR-B38M CAR-T cells against BCMA-positive cells. In vivo anti-tumor efficacy of LCAR-B38M CAR-T cells was evaluated utilizing a MM-derived luciferase-expressing cell line (RPMI8226.Luc) in NCG mice. LCAR-B38M CAR-T cell–treated mice showed statistically significant tumor reduction ($P<0.01$) and prolonged survival ($P<0.01$), with no obvious loss of animal body weight. In general, LCAR-B38M shows high affinity and specificity to human BCMA, with potent on-target anti-tumor activity. A phase 1b/2 clinical study is ongoing in the United States (CARTITUDE-1, NCT03548207, JNJ-68284528) and a phase 2 confirmatory study has been initiated in China (CARTIFAN-1, NCT03758417).

Keywords:
B-cell maturation antigen

Chimeric Antigen Receptor

Preclinical LCAR-B38M

Tracks:
Immunotherapeutic Approaches to MM

FP-183

Lenalidomide (Len) Refractory MM Patients' Outcomes

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Abstract:
BACKGROUND: Len refractoriness seems to constitute an adverse factor of survival in myeloma in spite of the recent therapeutic progress. It is taken in account in the current treatment recommendations. This statement is frightening considering that almost all MM patients will become at some time point Len refractory. However cautious evaluation (definitions) of Len resistance in various settings is lacking. AIMS: It was therefore the purpose of this study to assess this matter in a series of patients treated with Len according to EMA indications since 2008. PATIENTS AND METHODS: 172 Len – treated MM patients were studied and separated into 5 categories: (1) primary resistant MM (PRMM) defined as patients with no response within 2 months, (2) very resistant MM (VRMM) presenting progression under treatment after ≥ MR and within 6 months from Len initiation, (3) resistant MM (ResMM) presenting progression under treatment after ≥ MR within 7-12 months from Len initiation, (4) initially sensitive MM (ISMMP) progressing under treatment after ≥ MR and after more than 12 months and less than 4 years from Len initiation and (5) Resistant after long-lasting response (RALR) progressing under treatment after ≥ MR after more than 4 years from Len initiation, Statistical analysis was performed by conventional methods with the SPSS 21 software. RESULTS: 133 (77%) patients could be included in the afore mentioned categories: 14 PRMM, 27 VRMM, 24 ResMM, 61 ISMMP and 17 RALR. Their median time from diagnosis to Len treatment was 30, 17, 32, 41 and 15 months respectively and the overall median number of previous treatment lines was 2. The 14 PRMM patients (of whom 1, 5, 3, 3, 1 and 1 were in 1st, 2nd, 3rd, 4th , 5th and 6th line respectively) had a median overall survival (OS) after Len administration of 3 months and only 4 patients were in condition to receive one next line. The 27 VRMM patients, including 4, 8, 6, 5, 2 and 2 patient in 1st, 2nd, 3rd, 4th , 5th line and lenalidomide maintenance after ASCT respectively, had a median OS of 6 months after Len administration. Median OS after Len was of 12 months for ResMM, 39 months for ISMMP and 64 months for RALR (p<0,001). 74% of ISMMP and RALR received next lines and 20% more than 4 ones. Next treatment options that frequently induced responses, included PAD and other Bortezomib combinations, pomalidomide combinations, newer proteasome inhibitors (also with Len combinations such as KRD or IRD), Bendamustine combinations, ESHAP/DiCEP and Daratumumab alone or in combinations. CONCLUSIONS: Outcomes are indeed poor for PRMM and VRMM that constitute a minority of patients, intermediate for ResMM and favorable for ISMMP and RALR; for these last categories, there are still numerous treatment options

Keywords:
Lenalidomide

Patient stratification

resistance

Tracks:
Immunotherapeutic Approaches to MM

FP-184

DART4MM: DARATUMUMAB AS CONSOLIDATION THERAPY IN PATIENTS WHO ALREADY ACHIEVED OPTIMAL RESPONSE /MRD POSITIVITY BY NEXT GENERATION FLOW (NGF): PRELIMINARY RESULTS OF A PHASE 2 MULTICENTER STUDY

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Abstract:
CR is a prerequisite for long term responses, PFS, OS and cure. In the era of novel agents, many Multiple Myeloma (MM) patients can achieve stringent CR but still will relapse and minimal residual disease (MRD) negativity will be primary objective in many future trials. Strategies such as VTD consolidation therapy after autologous stem cell transplant (ASCT) showed increased complete response from 15 % to 49 % in patients who had previously achieved very good partial response (VGPR) and progression free survivals (PFS) doubled for patients in MRD negativity. Aim. Daratumumab therapy has unprecedented observed rate of CR and MRD negativity alone or with other agents. Aim of this study is to evaluate Daratumumab effect on MM patients who achieved VGPR/CR MRD positive after a first line therapy (ASCT, VMP). Patients and methods. Next generation flow (NGF) is centralized and measured at Siena Hospital with two 8 colors tubes panel developed by the EuroFlow Consortium (BD OneFLOW Tm PCSTe BD OneFLOW Tm PCD. BD BioSciences) with detection of MRD with a sensitivity (≥ 1 in 105 /10-6). Daratumumab 16 mg/kg administered at weekly intervals for 8 weeks, then every 2 weeks for an additional 8 weeks, will be given to 50 MM patients who achieved a VGPR or more defined as per IMWG criteria and MRD-positivity (by NGF). Daratumumab starts at least 12 weeks from ASCT and at least 4 weeks after VMP. Free light chain (FLC) and CT/PET are evaluated at time 0 and every 6 months. NGF is done on marrow aspirate at time 0, at 2 months and every 6 months for 2 years. Primary endpoint is achievement of MRD negativity at 6 months: if patients are MRD negative after 6 months of therapy, treatment is stopped. Otherwise treatment will continue every 4 weeks up to 2 years Recruitment started at the end of December 2018. Twenty-one patients were screened until May 2019 at 3 centers in Italy. At least 10 milliion cells were analyzed for sensitivity at flow for each sample. 10/21(45%) resulted MRD positive and eligible. M/F =5/5, median age was 61 (range 48-68). Previous therapy were single ASCT (7 patients), VMP (2 patients), KRD (1 patient). ISS stage was II in 4 patients, and III in the other 6 patients.Cytogenetics/FISH analysis at diagnosis was negative for 17p deletion, t(14q) and 1q amplification in 5 patients, 2 had t(4;14) , and 3 t(11;14). Grade 2 reaction (moderate infusion-related reactions) during first daratumumab infusion was seen in 3/10 (30%) patients and promptly resolved with corticosteroids administration and temporary infusion interruption. No serious adverse event was registered. Six patients completed 8 weeks of treatment (2 months) and evaluated MRD. 3/6 (50%) patients became MRD negative by NGF after 8 weeks of treatment (2 ASCT, 1 VMP). Daratumumab is safe as consolidation therapy, even soon after ASCT. First preliminary results seem to be promising for efficacy in the setting of very good responders. Study Co-financed by Jansenn Cilag SPA

Keywords:
consolidation

daratumumab

Minimal residual disease

Tracks:
Immunotherapeutic Approaches to MM

FP-185

Mechanisms, biologic sequelae and clinical benefits of bortezomib-induced immunogenic cell death in multiple myeloma

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Abstract:
Immunotherapy has achieved unprecedent long-term survival rates in solid tumors and has begun to transform myeloma (MM) treatment as well. Among strategies to enhance cancer cell immunogenicity, induction of immunogenic cell death (ICD) is particularly promising: the release of danger signals from dying cancer cells may, indeed, stimulate a specific anti-cancer immunity via T-cell priming by dendritic cells (DCs). Here, we sought to investigate the molecular basis and clinical relevance of bortezomib (BTZ)-induced ICD in MM. We show that BTZ can induce hallmarks of ICD in MM cells, including exposure of endoplasmic reticulum protein calreticulin (CALR) that functions as an "eat me signal". Specifically, our data show that co-culture with BTZ-treated MM cells can induce phenotypic and functional changes in immature DCs: they express higher levels of CD86/CD83 and engulf BTZ-treated MM cells, as assessed by flow cytometry- and confocal-based phagocytosis assay. Notably, we show that CALR has a key role in BTZ-induced immunogenicity, since these functional sequelae were abrogated when DCs were co-cultured with CALR KO MM cells. We validated these findings in 2 different in vivo models. First, we observed that anti-MM activity of BTZ resulted in more potent 5TGM1 tumor cell shrinkage in immunocompetent hosts; and that this effect was directly linked to ICD induction, since it was abrogated in mice bearing CALR KO tumors. Second, in vitro BTZ-treated 5TGM1 were used as a vaccine to enhance an anti-MM immune response: injection of live tumor cells resulted in palpable tumors in non-vaccinated mice by 1 week; conversely, injection of live tumor cells in vaccinated mice did not result in detectable tumor after 30 days. Mice were similarly vaccinated with BTZ-treated CALR KO 5TGM1 cells and challenged with injection of live WT cells: only 50% of vaccinated mice were tumor-free at day 30. Next, we performed RNAseq analysis of BTZ-treated vs untreated tumors from both immunodeficient or immunocompetent mice. We found that BTZ-induced signatures deeply change in the presence of the immune system, including regulation of type I interferon (IFN-I), inflammatory and immune responses. Importantly, we carried out an integrative analysis of RNAseq data from MM patients uniformly treated with BTZ-based regimes (IFM/DFCI 2009): increased expression of the human orthologs of the immune genes induced in mice by BTZ was strongly and positively correlated with clinical outcome (OS p=0.00089). These results were confirmed in an independent dataset (GSE9782) (OS p=0.024). Finally, our recent studies show that BTZ-mediated activation of the IFN-I signaling occurs through activation of the cGAS/STING pathway in MM cells. In conclusion, our studies demonstrate the mechanisms, biologic sequelae and clinical benefits of BTZ-induced ICD in MM. These studies provide the framework for novel combination treatments to trigger anti-MM immunity and improve patient outcome in MM.

Keywords:
bortezomib

immune modulation

immunotherapy

Tracks:
Immunotherapeutic Approaches to MM

FP-186

Immunotherapy in Multiple Myeloma: Boom or Bust? Investigating Oligoclonal Banding and Survival in Multiple Myeloma Patients Receiving Anti CD3-CD28 Co-Stimulated and Engineered Autologous T cells after Autologous Stem Cell Transplant.

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Abstract:
Introduction: In some patients with multiple myeloma (MM), the original M protein disappears and one or multiple smaller immunoglobulins, called oligoclonal bands (OCB), emerge following autologous stem cell transplant (ASCT). OCB are associated with improved disease-free survival (DFS) and may be associated with early immune system recovery. Patients in phase I/II clinical trials at the University of Maryland Greenebaum Cancer Center who received anti CD3-CD28 co-stimulated and engineered autologous T cells shortly after ASCT had early, rapid, and robust T cell recovery. Our research hypothesis was that patients who received these T cells after ASCT would develop OCB at a higher frequency than those who underwent conventional ASCT. We also aimed to assess whether receiving these T cells conferred any survival benefit. Methods: Our study cohort consisted of 60 MM patients enrolled in 1 of 3 phase I/II clinical trials (PI: Aaron Rapoport, MD) receiving either ex vivo vaccine-primed, anti CD3-CD28 autologous T cells targeting putative myeloma tumor antigens (hTERT, survivin, MAGE-A3) or autologous T cells genetically engineered to express a high-affinity NY-ESO-1 directed T-cell receptor two days after ASCT between 1/2007 - 9/2014. The control group had 203 MM patients who received conventional ASCT between 11/2009 - 8/2014. The last follow up date was 2/1/2019. Through retrospective chart review, we collected data on patients' demographic and clinical characteristics. Results: Study and control groups were well matched based on demographic and clinical characteristics; however, more patients in the study group did not receive maintenance therapy (18.3% vs 10.8 %, p = 0.1). There was no difference in frequency of OCB between the cohorts. Multivariable Cox regression model stratified by cytogenetic risk (n = 153) showed that the study cohort trended towards worse DFS (HR = 1.47, 95% CI [.92, 2.37], p = 0.11) and OS (HR = 1.52, 95% CI [0.83, 2.76], p = 0.17; median OS 8.9 years in controls vs 5.3 years in study cohort). A Fine-Gray competing risk multivariable model evaluating cumulative incidence of relapse demonstrated that study patients' hazard of relapse was 1.5 times higher than the control group (HR = 1.51, 95% CI [1.05, 2.18], p = 0.03) when adjusted for cytogenetic risk and presence of maintenance therapy. Discussion: Our data showed that use of engineered T cells did not increase frequency of OCB and was associated with shorter DFS and OS. This may be attributed to a lower rate of maintenance therapy among the study group, or an inherent selection bias in which study patients had more advanced disease, given their increased expression of cancer-testis antigens (MAGE-A3, NY-ESO-1), which are known to confer inferior prognosis. It may also reflect an unanticipated effect of these T cells on myeloma cells, such as inadvertent promotion of myeloma cell growth and survival by activated T cells which produce IL-6 and other cytokines.

Keywords:
immunotherapy

transplant

Trial

Tracks:
Immunotherapeutic Approaches to MM

FP-187

Potent anti-myeloma efficacy of dendritic cell therapy in combination with pomalidomide and programmed death-ligand 1 blockade in a preclinical model of multiple myeloma

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Abstract:
Dendritic cell (DC)-based vaccines are recognized as a promising immunotherapeutic strategy against cancer, and various combination approaches have

been developed to enhance DC function by modulating immune responses and tumor microenvironment. In this study, we investigated the efficacy of DC vaccination in combination with pomalidomide and programmed death ligand-1 (PD-L1) blockade in a murine model of multiple myeloma (MM). MOPC-315 cell lines were injected subcutaneously to establish MM bearing mice. Four test groups were used to mimic clinical protocol: (1) PBS control, (2) DCs + pomalidomide/dexamethasone, (3) Pomalidomide/dexamethasone + PD-L1 blockade, and (4) DCs + pomalidomide/dexamethasone + PD-L1 blockade. The combination of DCs + pomalidomide with dexamethasone + PD-L1 blockade inhibited more strongly tumor growth and prolonged survival of treated mice compared to the other groups. This effect was associated with a significant reduction in immune suppressor cells, such as myeloid-derived suppressor cells, regulatory T cells, and M2 macrophages, and level of immunosuppressive factors, such as vascular endothelial growth factor, transforming growth factor-β, and interleukin-10, and with the significant induction of immune effector cells, such as CD4+ and CD8+ T cells, memory T cells, natural killer (NK) cells, and M1 macrophages, in the spleen and tumor microenvironment. Functional activities of cytotoxic T lymphocytes and NK cells in spleen were also enhanced by the combination of DCs + pomalidomide with dexamethasone + PD-L1 blockade. The collective findings in the murine MM model suggest that DC vaccination combined with pomalidomide and PD-L1 blockade synergistically enhance antitumor immunity through two-way mechanism, which inhibits immunosuppressive cells while activating effector cells with superior polarization of the Th1/Th2 balance in favor of the tumor immune response.

Keywords:
dendritic cells

immunotherapy

Multiple myeloma

Tracks:
Immunotherapeutic Approaches to MM

FP-188

A novel antiCD38-CAR construct increases the in vitro responsiveness of NK cells against Multiple Myeloma cells

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Abstract:
Multiple myeloma (MM) is a plasma cell malignancy, that currently remains incurable. The identification of CD38, a transmembrane glycoprotein overexpressed on MM cells, led to the development of target-specific therapeutics such as the FDA-approved monoclonal antibody (mAb) Daratumumab. Although a valuable treatment option for refractory/relapsed MM patients, Daratumumab has a limiting response rate of about 30%, which highlights the clinical need for novel therapeutics. A modern alternative to antibody-based technologies is the genetic modification of effector cells into expressing highly-selective chimeric antigen receptors (CARs). While T-cells are the most commonly studied effector cells, both preclinically and clinically, NK cells may be of potential relevance due to their shorter life span and low risk of causing graft-versus-host disease. The increased attention towards CAR-NK therapies has led to multiple preclinical studies, which have already shown encouraging results. Here, we used a lentiviral approach to transduce NK cell lines with a CAR that consists of an antiCD38 extracellular domain and the intracellular domains of CD28 and CD3ζ. We show a reproducible transgene expression ranging between 11-68% depending on the NK cell line. In functional assays, CAR-positive NK cells display a 3-fold higher degranulation against the MM cell line RPMI8226, compared with CAR-negative NK cells. Furthermore, we generated genetically modified CD38-negative RPMI8226 cells using the CRISPR/Cas9 technology to test the selectivity of the CAR-NK cells. Ongoing efforts

also include the introduction of the CAR into primary NK cells from MM patients. Altogether, our findings show that antiCD38-CAR NK cells are strong candidates for the immunotherapy of MM.

Keywords:
CD38

cell therapy

Chimeric Antigen Receptor

Tracks:
Immunotherapeutic Approaches to MM

FP-189

CD38 and CD45 expression on plasma cells and response to daratumumab in Multiple Myeloma

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Abstract:
Background Studies that evaluated the relationship between CD38 expression on plasma cells and response to daratumumab in multiple myeloma patients show conflicting results. Whereas Nijhof et al. found a significantly higher CD38 expression in responders compared to non-responders, Pick et al. found no difference between these two groups. In addition, although Nijhof et al. showed a decrease in CD38 expression 14 weeks after start of treatment with daratumumab, CD38 expression was partly regained after 6 months. Case reports also describe this phenomenon, however the known interference of daratumumab with diagnostic CD38 antibodies in flow cytometry creates the need for these results to be approached with caution. Fc-receptor-mediated cross-linking induced apoptosis is a newly discovered mechanism of action of daratumumab. Kimlinger et al. found that CD45+ multiple myeloma cells show higher apoptotic rates, therefore we hypothesized that higher CD45 expression is associated with better response to daratumumab. The primary aim of this study is thus to compare CD38 expression before and after treatment between responders and non-responders to treatment with daratumumab, given as monotherapy or as combination treatment. The secondary aim is to compare CD45 expression between these groups. Methods In flow cytometry experiments, cells from bone marrow samples of relapsed myeloma patients were stained with CD38, CD138, CD45, CD56, CD19, and cytoplasmic kappa/lambda, as described by Nijhof et al. and Krejcik et al. Total plasma cells were defined as CD38+/CD138+ cells. Monoclonal plasma cells were gated as CD19- /CD56+ or CD56- and solely expressing either lambda or kappa light chains. Patient characteristics, including response evaluation - (at least PR or less than PR) - and progression-free survival, were retrieved from medical records. Mann-Whitney U tests were performed to compare median fluorescence intensity (median [IQR]) between groups. Preliminary results A total of 32 multiple myeloma patients were analyzed for CD38 and CD45 expression before start of daratumumab treatment. Results show that the CD38 expression in monoclonal plasma cells is higher in responders compared to non-responders (12963 [9913.5, 31016] vs. 11924 [6495, 15304]) ($p = 0.266$). In contrast, CD45 expression was lower in responders compared to non-responders (630.5 [528, 842.25] vs. 710 [590, 1051]) ($p = 0.427$). Conclusion Our preliminary results show a higher CD38 expression in patients that had a better response to daratumumab. CD45 seems not to play a role in daratumumab-mediated cell killing. Our results did not reach statistical significance due to the limited number of samples evaluated so far. Data from 15 or more patients will be included in the study in order to validate our findings. Understanding more about CD38 expression before and after treatment with daratumumab provides important information that guides clinicians in their choice of therapy.

Keywords:
CD38

CD45

daratumumab

Tracks:
Immunotherapeutic Approaches to MM

FP-190

Elotuzumab, Pomalidomide, and Dexamethasone for Relapsed/Refractory Multiple Myeloma: Efficacy After Additional Follow-Up of the ELOQUENT-3 Study

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Abstract:
Background: Elotuzumab, an immunostimulatory monoclonal antibody targeting SLAMF7, selectively kills multiple myeloma (MM) cells and synergizes with pomalidomide (pom). The primary analysis (minimum follow-up [FU]: 9.1 mo) of the open-label, randomized ELOQUENT-3 study (NCT02654132) demonstrated a median progression-free survival (PFS) of 10.3 mo for elotuzumab plus pom and dexamethasone (dex; EPd) vs 4.7 mo for pom and dex (Pd) alone (hazard ratio [HR] 0.54, p=0.008). Preliminary analysis of overall survival (OS) suggested a trend in favor of EPd (Dimopoulos MA et al. N Engl J Med 2018). Based on these data, EPd was approved in the USA for the treatment of adult patients (pts) with MM and ≥2 prior therapies including lenalidomide (len) and a proteasome inhibitor (PI). Aims: This non-prespecified analysis was conducted after a minimum FU of 18.3 mo to provide a descriptive assessment of OS with EPd vs Pd in ELOQUENT-3. PFS and safety were also assessed. Methods: Adults with MM that was refractory to last therapy and either refractory or relapsed and refractory to len and a PI, with ≥2 prior lines of therapy (LoTs, including len and a PI), were randomized 1:1 to receive EPd or Pd in 28-day cycles until disease progression or unacceptable toxicity. Elotuzumab: 10 mg/kg IV weekly in cycles 1–2 and 20 mg/kg IV every 4 weeks in cycles 3+. Pom: 4 mg orally on days 1–21 of each cycle. Dex: 40 mg (pts ≤75 y) or 20 mg (pts >75 y) weekly in each cycle. Primary endpoint was PFS by investigator assessment; secondary endpoints were overall response rate by investigator and OS. Results: In total, 60 pts were randomized to the EPd group and 57 to the Pd group. Clinically relevant baseline characteristics were balanced between treatment groups; median (range) age was 67 y (36–81). Median (range) number of prior LoTs was 3 (2–8), and 68% (EPd) and 72% (Pd) of pts had MM that was refractory to both len and a PI. As of database lock (29 Nov 2018, minimum FU 18.3 mo), there were a total of 90 PFS events (EPd: 40/60; Pd: 50/57). PFS rates (EPd vs Pd) were 43% vs 20% (12 mo) and 34% vs 11% (18 mo). With 48 (EPd: 20/60; Pd: 28/57) of the 78 (62%) deaths required for the final analysis, OS curves continued to diverge, with a 46% reduction in the risk of death with EPd vs Pd (HR 0.54, 95% CI 0.30–0.96). Median (95% CI) OS was not reached (24.9–not estimable [NE]) with EPd and was 17.4 mo (13.8–NE) with Pd. OS rates (EPd vs Pd) were 79% vs 68% (12 mo) and 68% vs 49% (18 mo). Safety results were consistent with the primary analysis. Conclusion: In this extended FU of ELOQUENT-3, EPd demonstrated a favorable trend in OS and a

sustained and clinically relevant PFS benefit vs Pd, with no new safety signals. These data support the long-term favorable efficacy–safety profile of EPd and suggest this regimen should be considered as a standard of care, where approved, for pts with relapsed/refractory MM after failure of len and a PI.

Keywords:
elotuzumab

Pomalidomide

Relapsed/Refractory

Tracks:
Immunotherapeutic Approaches to MM

FP-191

PD-L1 expression in bone marrow plasma cells as a biomarker to predict prognosis of newly diagnosed multiple myeloma patients: development of a nomogram-based prognostic model

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Abstract:
Introduction: Programmed death-ligand 1 (PD-L1) expression is known to correlate with unfavorable prognosis and resistance to anticancer therapies in some types of solid tumors and lymphomas; however, whether PD-L1 expression affects prognosis of hematologic malignancies originating in bone marrow such as multiple myeloma remains unclear. This study was designed to assess PD-L1 expression in bone marrow aspirated plasma cells using quantitative immunofluorescence (QIF), and evaluate the feasibility of predicting prognosis in patients with newly diagnosed multiple myeloma (NDMM). Methods: Two cohorts of NDMM patients who underwent bone marrow examination at Korea University Anam Hospital were included in this study: 1) a retrospective cohort of 84 patients enrolled between 2011 and 2018, and 2) a prospective cohort of 27 patients enrolled between 2018 and 2019. Formalin-fixed, paraffin-embedded bone marrow aspirates acquired from all 111 patients were reviewed, and available 87 bone marrow samples were analyzed. PD-L1 expression was measured by QIF, and expression was dichotomized as low or high. A prognostic nomogram was developed and compared to the Revised International Staging System (R-ISS). Results: By Kaplan–Meier analysis, overall survival (OS) was significantly shorter in the high PD-L1 expression group (P<.001). By multivariable Cox regression analysis, high PD-L1 expression was identified as a significant prognostic factor for OS (HR, 4.337; 95% CI, 1.712–10.986, P=.002). Next, we constructed a prognostic nomogram stratifying patients into 3 risk groups (low, intermediate, and high) by combining PD-L1 expression with significant clinical parameters (age, cytogenetics, LDH). This nomogram reveals good calibration and prediction accuracy (AUCs for 2-year OS, 0.835; 5-year OS, 0.701). Our prognostic model showed better discriminating power than that of R-ISS in this setting according to C-index values (0.758 vs. 0.647; 95% CI, 0.685–0.831 vs. 0.545–0.748). Kaplan–Meier analyses were performed on the 3 risk groups to compare effects of up-front immunomodulatory drug (IMiD)-based therapy and autologous stem cell transplantation (ASCT). In the high risk group, up-front IMiD-based therapy had no significant survival benefit; however, ASCT significantly improved OS (P=.017) and PFS (P=.002). No significant differences were observed in the low-risk and intermediate-risk groups. Multivariable Cox analysis confirmed that only ASCT in the high-risk group could predict improved OS (P=.041) and PFS (P=.008). Conclusions: High PD-L1 expression in bone marrow aspirated plasma cells as measured by QIF is associated with poor prognosis in NDMM. Thus, combining PD-L1 expression with clinical parameters can improve prognostic evaluation of NDMM patients. Our

prognostic model may be useful for identifying high-risk patients who would benefit from ASCT.

Keywords:
Multiple myeloma

PD-L1

prognostic impact

Tracks:
Immunotherapeutic Approaches to MM

FP-192

Super-resolution microscopy reveals ultra-low expression of CD19 on myeloma cells that triggers elimination by CAR-T cells

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Abstract:
Background: Especially since the transfer of chimeric antigen receptor (CAR) T cell therapy to the clinic, there has been controversy over the amount of target molecules necessary to activate T cells via a CAR. Here, we evaluate the use of CAR-modified T-cells targeting CD19 (CD19CART) in multiple myeloma. A highly recognized study (Garfall et al, NEJM 2015) reported complete remission in one patient that had received CD19CART, even though only 0.05% of myeloma cells expressed CD19 as judged by flow cytometry (FC). This has sparked debate over low level CD19 expression on myeloma cells that may be invisible to detection via FC but could trigger elimination by CD19CART. Methods: We generated expression profiles of CD19 on primary myeloma cells from n=14 patients by single-molecule sensitive super-resolution microscopy (dSTORM - direct stochastic optical reconstruction microscopy) and FC. In parallel, we treated myeloma cells with CD19 CART and control T cells in vitro. Results: In 10/14 patients, we detected CD19 on a fraction of myeloma cells (range: 10.3%-80%) by dSTORM, while FC detected CD19 only in 2/14 patients on a smaller cell fraction (range: 4.9%-30.4%). Four patients were classified as CD19-negative by dSTORM. The majority of myeloma cells expressed CD19 at very low levels, far below the FC detection limit. Treatment with CD19CART led to specific elimination of CD19dim myeloma cells, even when CD19 was undetectable by FC. Conclusions: In a prevailing subset of patients, CD19 is expressed on a large fraction of myeloma cells at a very low density, only detectable by super-resolution dSTORM microscopy. These patients might be candidates for a combination therapy including CD19 CART cells. Our data rationalize anti-myeloma responses that have been reported after CD19CART therapy. dSTORM analysis allowed defining the threshold of antigen expression for T cell activation via a CD19 CAR, which was found to be less than 100 molecules per cell.

Keywords:
CD19

Chimeric Antigen Receptor

super-resolution microscopy

Tracks:
Immunotherapeutic Approaches to MM

FP-193

CS1 Targeted Chimeric Antigen Receptors (CAR) for treatment of multiple myeloma (MM)

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Abstract:
BCMA-CAR-Ts induce complete responses in MM but not cure, indicating a need for other CAR targets. CS1 (SLAMF7) is uniformly expressed on MM with limited expression on normal cell types, so is a good CAR target. CS1-CAR-Ts expressing the scFv derived from Elotuzumab antibody (clone HuLuc63) show efficacy in preclinical MM models. Here, we report efficacy of CS1-CAR-Ts with an scFv derived from an antibody that binds a separate, more distal extracellular epitope on CS1 (clone Luc90; CS1-90). The MM.1S human myeloma cell line (CS1+; expressing luciferase and GFP; MM.1S-CG) were used as target cells in 4hr Chr51 release killing assays. CS1-CAR-Ts efficiently killed MM.1S-CGs while control CD19-CAR-T showed minimal killing. In vivo efficacy of CS1-CAR-T was tested by injecting 5X10^5 MM.1S-CG into NSG mice and 28 days later were treated with 2X10^6 CS1 or CD19-CAR-Ts. CS1-CAR-T treated mice (n=10) had a 3 log decrease in photon flux, and lived >90 days, while median survival of CD19-control mice (n=13) was 46 days. Mice engrafted with MM.1S lacking CS1 (CRISPR/Cas9) and treated with CS1-CAR-T had similar survival to controls (49 days), demonstrating in vivo specificity. A subset of CS1-CAR-T mice developed extramedullary tumors that retained expression of CS1 and were efficiently killed when used as targets in Chr51 killing assays, suggesting antigen escape did not occur. Consistent with the fact that some CD8+ T-cells express CS1, CS1+CD8+ cells were reduced in CS1-CAR-T cultures (9%+/- 2) but not in CD19-CAR-Ts (28%+/-10) suggesting fratricide. Deletion of CS1 from T cells (CRISPR/Cas9; CS1-CrispR-CAR-T-CS1) prior to transduction with CS1-CAR protected CS1+CD8+ cells from fratricide (30%+/-7). Similar killing of CS1-CS1-CrispR-CAR-T-CS1 and CS1-CAR-Ts was observed in 4-hr Chr51 assays. We are currently comparing efficacy of Luc90 and HuLuc63 CS1 CAR-T in both unedited and edited CS1-T cells. Comparable killing of CS1-Luc90 and CS1-63 CAR-T was observed in Cr51 killing assays. Both CS1-CAR-T-Luc90 and CS1-CAR-T-Luc63 reduced BLI signal 3 logs compared to controls (n=10) 49 days post injection of tumor cells (n=15); continued assessment of these mice will determine if efficacy remains equivalent long term. Invariant natural killer T-cells (iNKTs) harbor innate and adaptive immune cell properties and do not cause GvHD so are potentially useful in an allogeneic setting as an "off the shelf" CAR product. They may also offer reduced risk of CRS and neurotoxicity compared to CAR-Ts. We generated CS1-iNKT-CARs which killed MM.1S-CG targets in Chr51 assays. We have gene edited CS1 from these cells (CRISPR/Cas9) and are assessing fratricide and efficacy. Together, we have generated highly effective CAR-T cells targeting CS1. Future experiments are aimed at comparing CS1-CAR-T vs CS1-iNKT-CAR with and without CS1 gene editing. Our work further validates the utility of CS1 as an immunotherapeutic target for MM.

Keywords:
Chimeric Antigen Receptor

CS1

Multiple myeloma

Tracks:
Immunotherapeutic Approaches to MM

FP-194

Modulation of NK, T, & B cell sub-populations by Pomalidomide predicts favorable progression-free survival (PFS): Results from a large randomized clinical trial in relapsed/refractory myeloma.

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Institutions:

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Abstract:
Multiple myeloma (MM) is associated with significant immune dysfunction. Although, the impact of immunomodulatory agents has been demonstrated, however their impact in vivo on immune function is not fully understood. The large CC4047-MM007 (OPTIMISMM, NCT01734928) study in relapsed/refractory (RR) MM patients (N=540), who were randomized to receive pomalidomide (Pom, PVd) versus placebo (Vd), a combination of bortezomib and low-dose dexamethasone, provided unique opportunity to investigate impact of Pom on immune cell-subsets. We have analyzed 197 RRMM patients utilizing 366 peripheral blood samples collected at screening, day 8 of cycle 1 and day 8 of cycle 3 using 38 immune biomarker-panel with multi-color flow to identify changes with Pom exposure in various sub-populations of B, T, & NK cells. The primary objective of the investigation is to identify changes induced by Pom containing regimen. The analyzed patient-cohort had identical characteristics as the total patient population and was balanced for the 2-treatment arms, overall patient characteristics and response. The percentage of NK cells were significantly elevated following Pom containing regimen as early as day 8 of cycle 1 and persisted at cycle 3 compared with Vd arm. The double positive NK cells for activation markers (p46 and NKG2D) were significantly elevated following the treatment and the expression of CD159a (Kir molecule) on NK cells was significantly down-regulated at day 8 of cycle 1 & 3 with both Pom and Vd. However, increased cycle 3/screening ratio for p46 & NKG2D and cycle 1/screen ratio of CD159a expression on NK cells was associated with improved PFS (p value < 0.05 and FDR < 0.2) only in PVd compared to Vd. Investigation of four T cell -sub-populations including memory cell sub-types showed that the higher ratio of naïve T cells in cycle 3 to screening in Pom compared with placebo treatment yielded significantly improved PFS (p value < 0.05 and FDR < 0.2). Pom treatment restored the effector memory cells throughout the treatment despite the observed decline in these memory cells with Vd treatment. Among the B cell-subsets analyzed, PVd increased B1b cells and decrease in Bregs within 8 days of starting therapy (at cycle 1, day 8) which persisted after 2 cycles (Cycle 3, day 8). Reduction in B1a and Ira-B cells with Vd-regimen was restored by addition of Pom (PVd). A significant increase in MZB cells were observed in both arms, however, we observed significant improvement in PFS (p value < 0.05 and FDR < 0.2) association with increased ratio of MZB cells in cycle 1 to screening in the PVd arm compared with Vd arm. In summary, this large cohort study identifies significant and specific enhancement of immune stimulating subsets with PVd compared to Vd arm, with subsequent favorable impact on PFS. Our results identify immune profile changes as possible bio-markers of clinical response to pomalidomide-based therapy.

Keywords:
immunophenotype

Pomalidomide

Progression-free survival

Tracks:
Immunotherapeutic Approaches to MM

FP-195

Inhibition of Kynurenine-3-Monooxygenase in Tryptophan Catabolic Kynurenine Pathway Enhances Anti-Myeloma Immunity

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Institutions:
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Abstract:
Introduction Dysfuntional plasmacytoid dendritic cells (pDCs) contribute to multiple myeloma (MM) pathogenesis. In particular, pDCs interactions with tumor and T/NK effector cells in the bone marrow (BM) milieu induce immune suppression in MM. Delineation of the mechanism(s) mediating pDCs-MM-T-NK cells interactions will identify novel therapeutic targets to anti-MM immunity as well as enhance cytotoxicity. Using gene expression profiling, we show that pDC-MM interactions trigger upregulation of immunosuppressive tryptophan catabolic kynurenine (Kyn) pathway. Specifically, we show that Kyn pathway enzyme kynurenine-3-monooxygenase (KMO) is upregulated during pDC-MM interactions. Using our coculture models of patient autologous pDC-T-NK-MM cells, we show that biochemical inhibition of KMO activates pDCs and induces MM-specific cytotoxic T cell lymphocytes(CTL) and NK-cells cytolytic activity against MM cells. We also show that concurrent blockade of Kyn pathway and immune checkpoint PDL-1 enhances anti-MM immunity and cytotoxicity. These preclinical findings lay the framework for new immune-based therapeutic strategies targeting Kyn metabolic pathway enzyme KMO, alone or in combination with anti-PD-L1 Ab, to restore anti-MM immunity. Methods Gene expression profiling of MM cells cultured in the presence vs absence of pDCs were compared (>1.5-fold change taken as significant, CI>95%). MM-BM CD8+ T- or NK-cells were cultured with autologous pDCs (pDC:T/NK;1:10 ratio) in the presence or absence of KMO inhibitor Ro 61-8048 (100 nM) for 3 days; cells were then washed to remove the drug and resuspended in complete medium. Pre-stained autologous MM cells were then added for 24h (E/T ratio;10:1;T/NK:MM), followed by FACS quantification of viable MM cells. Results Normalized gene expression showed pDC-induced upregulation of KMO in MM cells (2.15-fold vs MM alone; n=3); KMO is expressed in both pDCs and MM cells; and importantly, pDC-MM coculture further increased KMO levels in MM cells (KMO:2-fold;$p<0.05$). Moreover, KMO+ cell population is increased after coculture (KMO:~1.2 fold;$p<0.05$). Biochemical or genetic blockade of KMO activates pDCs, as evidenced by increase in pDCs maturation/activation markers (CD80/CD83/CD86); moreover, coculture of these activated pDCs with autologous MM BM-CD8+T or NK cells triggers both MM-specific cytotoxic T cell lymphocytes (CTL) and NK-cells cytolytic activity against tumor cells. KMO inhibition increases expression of surface CD107a on NK and CD8+T cells (NK:1.41-fold;CD8+T:1.6-fold;$p<0.05$). Finally, the combination of KMO inhibitor and anti-PD-L1 Ab triggers a more robust MM-specific CD8+ CTL activity vs single agent (%MM viability: KMOi:72%;KMOi+anti-PD-L1-Ab:57%;n=7;$p=0.01$). Conclusions Our preclinical data provides the basis for novel immune-based therapeutic approaches targeting Kyn pathway enzyme KMO, alone or in combination with anti-PD-L1 Ab, to restore anti-MM responses and enhance cytotoxicity.

Keywords:
immunotherapy

Kynurenine Pathway

Plasmacytoid Dendritic Cells

Tracks:
Immunotherapeutic Approaches to MM

FP-196

Molecular markers of MM cell sensitivity and resistance to Natural Killer cells: implications for anti-MM immunotherapy

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Abstract:
Despite recent therapeutic advances, including monoclonal antibodies and T-cell-based therapies, multiple myeloma (MM) remains incurable. Natural

killer (NK) cells are highly cytotoxic in preclinical MM studies; while infusion of ex vivo expanded/activated NK cells in clinical studies has been feasible and safe, without graft-versus-host reactions. However, the molecular markers determining MM cell response vs. resistance to NK cells remain incompletely understood. To address this topic, we performed genome-wide CRISPR/Cas9 loss- (LOF) and gain-of-function (GOF) studies in MM.1S cells exposed to primary NK (pNK) cells and identified genes whose knock-out (KO) or activation led to NK cells resistance or sensitivity. Building on these results, we quantified the dose-dependent responses to pNK cells for 70 molecularly-annotated blood cancer cell lines, including 15 MM cell lines (examined in a pooled "DNA-barcoded" format, PRISM system), in presence vs absence of bone marrow stromal cells (BMSCs) and interferon gamma (IFNg), followed by integrated computational analyses to identify candidate molecular markers correlating with tumor cell sensitivity or resistance to NK cells. NK cell cytotoxicity, quantified by the relative abundance of barcodes in treated cells compared to controls, was correlated with the transcriptional, mutational and other molecular features of each of the 70 cell lines. Such data show that the coculture with BMSCs decreased to variable extent the NK cell responsiveness to a large majority of cell lines, underscoring the protective effect of stromal microenvironment in blood malignancies. Interestingly, baseline state of JAK-STAT signaling correlates with BMSCs-induced NK cell resistance, a result further confirmed by addition of IFNg to MM-NK cocultures in the absence of BMSCs. In terms of a gene- or pathway-level analyses, this study confirmed our observations from genome-scale LOF and GOF CRISPR studies and showed that NK cell sensitivity of tumor cells is modulated by activation of several metabolic and homeostatic genes, receptor kinases, and NK ligands such as ULBP1 and ULBP2. Importantly, this study confirms that gene lesions commonly associated with high-risk MM (e.g. LOF of TP53 or PTEN) , didn't affect NK-cell response. No significant differences in NK cell response were observed between MM vs. other neoplasias, suggesting that candidate markers from these studies (and their ongoing expansion to larger cell line panels) may be relevant across different hematologic neoplasias. In conclusion, this is a first study correlating the molecular annotation of different pooled "DNA-barcoded" hematologic cell lines with their response to a homogeneous cell-based treatment. This provided complementary and orthogonal information to our previous LOF and GOF screens, expanding our potential to identify and validate molecular markers for individualized use of NK cell-based therapies in MM and other hematologic malignancies.

Keywords:
DNA barcoding

NK cells

Tracks:
Immunotherapeutic Approaches to MM

FP-197

Combination of herpes-simplex based oncolytic viruses (HSV-OV) with natural killer (NK) cells in Multiple Myeloma

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Abstract:
Oncolytic viruses (OV) are genetically modified viruses that specifically infect and lyse tumor cells. So far, OV monotherapy shows only limited benefit in clinical practice. However, it holds great potential in combinatorial treatment approaches. Natural killer cells recognize and kill infected, stressed or malignant cells without prior antigen exposure. Patients who lack NK cells are highly susceptible to severe and recurrent herpesvirus (HSV) infections. Thus, the combination of HSV based OVs (HSV-OV) and NK cells has a strong rationale. We aim to

explore the synergy between clinically applied HSV-OV and NK cells. Our main interest is Multiple Myeloma (MM) - an aggressive hematological malignancy of the B-cell line. It is known that NK cell functionality is highly impaired in MM patients. Recent NK cell based immunotherapies against MM have shown encouraging results. We hypothesize that HSV-OV may increase NK cell functions and improve therapy outcome. To test this, we have infected both MM cell lines and primary NK cells from healthy donors with HSV-OV at different OV doses and measured their viability and phenotype at several time points by Flow Cytometry. We show that HSV-OV directly infects and lyses tumour cells while sparing NK cells from OV mediated killing. Our data furthermore indicate that HSV-OV activates primary NK cells and increases their cytokine release and killing ability at an early time point. We further elucidate the basis of this activation by an extensive phenotypic analysis of HSV-OV treated primary NK cells. Similarly, we test phenotypic changes of MM cells upon HSV-OV infection and evaluate their recognition and elimination by NK cells. These data will help to define the potential and accessibility of combinatorial HSV-OV and NK cell therapies. Both therapies are feasible and safe for patients with MM. HSV-OV could potentially increase therapy outcome in conjunction with autologous stem cell transplantation or NK cell infusion in patients with MM.

Keywords:
immunotherapy

NK cells

Oncolytic virus

Tracks:
Immunotherapeutic Approaches to MM

FP-198

Preclinical evaluation of CD8+ Anti-BCMA mRNA CAR T-Cells for control of multiple myeloma

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Abstract:
Chimeric antigen receptor (CAR) T cells targeting BCMA are positioned to transform treatment of multiple myeloma (MM), and virally-generated anti-BCMA CAR T cells have shown impressive early stage clinical results. However, the safety risk/benefit, manufacturing constraints, and relevant patient populations of viral anti-BCMA CAR T have yet to be fully defined. Here we present preclinical characterization of an autologous mRNA-generated anti-BCMA CAR T cell product (Descartes-08) designed to reduce safety risk and broaden the fitness-for-use of anti-BCMA CAR T cell therapy. Descartes-08 are autologous CD8+ T cells that express anti-BCMA CAR on up to 90% of cells with duration of CAR expression for several days with subsequent reduction in expression to background approximately 1 week after their generation. The manufacturing process is clinically scalable with high purity and viability of Descartes-08 following cryopreservation. Descartes-08 undergo cytotoxic degranulation and produce cytokines IFNγ, TNFα, IL-2, in response to multiple BCMA-expressing multiple myeloma target cell lines in an effector-to-target-ratio-dependent manner. Furthermore, Descartes-08 kills MM lines that are both resistant and sensitive to lenalidomide and pomalidomide, and/or MM cells that are grown in the presence of bone marrow stromal cells that clinically support MM survival. Moreover, Descartes-08 are highly cytotoxic against MM cells from both newly-diagnosed and relapsed patients. The magnitude of cytolytic and cytokine responses correlates with duration of anti-BCMA CAR expression and declines after 4 days, indicating a temporal limit in activity that is predicted to dramatically decrease the

risk of severe cytokine release syndrome. In a mouse model of disseminated human MM, Descartes-08 shows CAR-specific suppression of myeloma that is maintained throughout the duration of treatment. Taken together, these results illustrate features of RNA-generated anti-BCMA CAR T cells that promise key clinical advantages, thereby supporting ongoing clinical development of Descartes-08 for treatment of MM (NCT03448978).

Keywords:
B-cell maturation antigen

Chimeric Antigen Receptor

immunotherapy

Tracks:
Immunotherapeutic Approaches to MM

FP-199

Novel RNA construct increases cytotoxic proteins in lymphocytes and leads to prolonged survival in an experimental syngeneic immunocompetent Multiple Myeloma model

Authors:
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Abstract:
Stimulation and activation of the cytosolic RNA recognition receptors RIG-I and MDA-5 are desirable to boost the immune response of cytotoxic lymphocytes against cancer. Activation will stimulate the synthesis of a broad range of antiviral effector molecules, cytokines, and chemokines that have a crucial role for priming, expansion, and polarization of immune cells. In this study, we identified efficient inducers of perforin- (Prf) and granzyme B- (GrzB) production in cytotoxic lymphocytes. The present short RNA construct induced a significant increase of cytotoxic granule components, without causing an excessive type I interferon (IFN-I) response. This is in contrast to other published RIG-I agonists, that induce IFN-I but only minimal Prf or GrzB. Introduction to NK cells using transfection or extracellular vesicle-mediated delivery resulted in a rapid increase of both molecules, which could be further boosted by IL-2. The RNA construct led to increased killing of tumor targets by primary human NK cells with increased capacity to kill multiple targets (serial killing). Upon administration of the RNA construct to a syngeneic immunocompetent multiple myeloma (MM) mouse model in which activated NK cells are critical for MM rejection, the construct resulted in a significant delay in tumor development and increased survival compared to published RIG-I agonists. No off-target effects or toxicity were observed. Further studies are needed to elucidate the best platform and method of delivery for optimal anti-tumor activity in human MM.

Keywords:
immunomodulatory drugs

lymphocyte

novel agents

Tracks:
Immunotherapeutic Approaches to MM

MYELOMA RESPONSE ASSESSMENT INCLUDING MRD

FP-200

Evaluation and Dilution Verification of the Optilite FreeliteTM Assay show discordant results at high serum free light chain concentrations

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Abstract:
Introduction & Objectives: The International Myeloma Working Group updated diagnostic criteria for multiple myeloma and related plasma cell disorders recommend the use of serum-free light chains (sFLCs), with the ratio of involved to uninvolved sFLC>100 constituting a myeloma defining event. sFLCs also have utility in screening, prognosis, monitoring response to therapy, and recurrence. The Binding Site Freelite assay is the only sFLC assay currently included in national and international guidelines. The study objective was to evaluate the analytical performance of the Freelite assay on the Binding Site Optilite platform, with particular attention to dilution inaccuracies that may lead to clinical misinterpretation of sFLC results. Study Design & Methods: Serum free kappa light chain (FKLC) and free lambda light chain (FLLC) were measured using Freelite reagents on the Optilite platform (Binding Site, UK) according to manufacturer's instructions. Precision was assessed with quality control material. Method comparison to the Freelite assay on our predicate Siemens Advia 1800 platform was performed using 50 patient samples. For dilution validation, patient samples with a known result close to each dilution threshold were analyzed at increasing dilution factors. Results: Total imprecision was 2.5–3.8% for FKLC and 5.6-6.4% for FLLC. The assays were linear between 1.5–115.9 mg/L and 1.9–134.5 mg/L for FKLC and FLLC, respectively. Method comparison showed good agreement (R=0.98–0.99, slope=0.81-1.008) for both assays in the initial measuring range. However, for high concentration samples requiring dilution prior to analysis, we observed a significant negative bias on the Optilite compared to the Advia, with differences of up to 40% noted. This observation was not sample specific, and was replicated by measuring samples with sFLC values near the top of each dilution range at the next highest dilution. Discordance between sFLC results and serum protein electrophoresis and immunofixation patterns were also noted for several samples, with falsely low sFLC results when dilutions were not appropriately reflexed by the Optilite. Conclusions: The Optilite Freelite assays showed acceptable precision, linearity and agreement with the Advia Freelite assay in the initial linear range. Significant differences in sFLC results performed at different dilution factors were noted, resulting in sFLC values that erroneously fell below diagnostic cut points or fluctuated inconsistently with the patient's clinical progress. We recommend that clinicians are made aware of these anomalies and consult with their laboratories to investigate any suspected discrepant findings, since unpredictable sFLC results could lead to missed diagnosis, inappropriate changes in treatment or disease re-stratification. We also recommend that dilution factors be included in sFLC reports to help distinguish changes due to different assay dilutions from changes that reflect clinical pro

Keywords:
Free light chain assay Validation

Free Light Chains

Multiple myeloma

Tracks:
Myeloma Response Assessment including MRD

FP-201

Comparison of PET Reconstruction Algorithms on Assessment and Quantification of FDG-PETCT Findings in Patients with Multiple Myeloma

Authors:
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Abstract:
Background: PETCT is a constantly improving field; technologies for image formation as well as image interpretation are evolving. Improved image formation technology (such as Bayesian penalized likelihood reconstruction algorithm (BPL)) is now commercially available and increasingly used routinely. While improving image quality, the derived quantitative values (e.g. SUVmax) may differ from established methods (e.g. ordered subset expectation maximization (OSEM) time of flight (TOF)). On the other hand, image interpretation is being refined, with emphasis increasingly placed on (semi-)quantitative methods. An example is the IMPeTUs criteria1 , which proposes using an adapted Deauville score. Our study aims to assess how different image formation methods may impact on clinical image interpretation. Methods: FDG-PETCT performed for assessment in myeloma patients were retrospectively reviewed, and grouped under three broad indications: baseline assessment, response evaluation and suspected relapse. In each case, OSEM TOF and BPL were assessed. A qualified nuclear medicine physician evaluated the following parameters on both sets of PET images: mediastinal and liver SUVmax, number of focal FDG avid lesions (skeletal and extramedullary) & SUVmax of up to 3 focal skeletal lesions per patient. SUVmax values were compared using paired t-tests. Results: In the period evaluated, 71 PET-CT scans were identified in 68 patients (average age: 64.3±10.3 years). Indications were: baseline assessment (n=17), response evaluation (n= 27) and suspected relapse (n=27). In total, 112 skeletal lesions were identified. For mediastinal and liver measurements, in all three groups (baseline, response evaluation, suspected relapse), the SUVmax values are higher on OSEM TOF reconstruction i.e. 8.5%, 2.3% & 1.2% higher respectively in the mediastinum, and 10.2%, 7.5% & 8.9% higher respectively in the liver. For focal FDG avid skeletal lesions, average lesional SUVmax values are 1.9 ± 2.5, 2.1 ± 3.5, 2.0 ± 3.4 higher on the BPL reconstructions (24%, 12.8%, 27%, for baseline, response evaluation and suspected relapse groups respectively) ($p<0.001$ for all three groups). Additional focal avid skeletal sites are seen in one of the response evaluation and five of the suspected relapse cases on BPL reconstruction, not perceptible on routine TOF reconstructions. Using the Deauville score as per IMPeTUs criteria1, 8/27 (29.6%) patients would be 'upgraded' if BPL reconstruction images were used for clinical assessment of focal FDG avid skeletal lesions, instead of routine OSEM TOF. Conclusion: A shift in PET reconstruction algorithm used in the FDG PETCT assessment of multiple myeloma patients would have a potentially significant impact in the clinical interpretation of PETCT findings. 1. Nanni C, et al. Image interpretation criteria for FDG PET/CT in multiple myeloma. Eur J Nucl Med Mol Imaging. 2016; 43(3):414-21.

Keywords:
Deauville score

PET-CT

Tracks:
Myeloma Response Assessment including MRD

FP-202

Use of Quantitative Immunoprecipitation Mass Spectrometry to Resolve the Complexity of Plasma Cell Populations in Multiple Myeloma

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Abstract:
Background: Clonal heterogeneity and evolution of neoplastic plasma cells are common events in multiple myeloma (MM). Myeloma cells can

produce M-proteins as intact immunoglobulins (Ig) with or without excess free light chains (FLC), FLC only or, rarely, no detectable M-protein. Ig are characterized by serum immunofixation electrophoresis (IFE) whereas FLC are quantified by turbidimetry (Freelite), two methods that are not always in concordance. Approximately 95% of MM patients have an abnormal FLC ratio but do not always show the abnormal FLC by IFE. Since a light chain secreted by the same plasma cell-clone is predicted to have the same molecular mass, independently of whether it is free or bound to the heavy chain, determination of the molecular mass could be of clinical value. We evaluated the utility of quantitative immunoprecipitation mass spectrometry (QIP-MS) to aid interpretation of four patient-samples with discrepant electrophoretic and turbidimetric results. Methods. We studied 4 MM patients (2IgG, 1IgG, 1IgA) with an intact Ig but no monoclonal FLC on IFE and abnormal FLC results by turbidimetry. κ and λ serum FLCs were measured using Freelite® on an Optilite® instrument (The Binding Site Group Ltd., UK). For QIP-MS studies, samples were subjected to substrate-specific immunoprecipitation using paramagnetic beads coated with polyclonal anti-IgG, -IgA, -IgM, -total κ, -total λ, -free κ and -free λ. After separation of the light from the heavy chain, light chain mass spectra were acquired using a MALDI-TOF mass spectrometer. Results: Involved FLC levels were elevated and κ/λ FLC ratios were abnormal in all four patients. In the 2 IgGκ patients QIP-MS confirmed the presence of monoclonal IgGκ, with light-chain molecular weights of 23578 and 23252 Daltons (Da). It also identified smaller κFLC peaks with similar molecular weight (MW), indicating that the light chain arose from the same plasma cell as the heavy chain. In the 23758Da IgGκ patient, QIP-MS detected an additional clone producing IgGκ (23454Da) and not identified by IFE. QIP-MS identified the IgAλ monoclonal protein (22742Da) with λFLC protein at the same MW; and additional discrete IgGλ (22772Da) and IgMλ (22860Da) subtler clones in the same patient without apparent λFLC production. Finally, in the IgGλ patient there seemed to be polyclonal IgG only; however, a shifted protein was clearly identified as IgGλ by QIP-MS, and there were multiple putatively glycosylated proteins with multiple and sometimes discrete putatively glycosylated λFLCs present. Conclusion: The low sensitivity of electrophoresis-based techniques can lead to the erroneous conclusion that FLC or other subtle monoclonal clones are not present. QIP-MS improves the characterization of these patients by showing intact and FLC monoclonal immunoglobulins as well as additional monoclonal peaks, supporting previous work for the presence of multiple clones within individual patients

Keywords:
electrophoresis

Free Light Chains

MALDI Mass Spectrometry

Multiple myeloma

Tracks:
Myeloma Response Assessment including MRD

FP-203

Minimal Residual Disease (MRD) ratio before and after Autologous Stem Cell Transplantation (ASCT) in Multiple Myeloma.

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Abstract:

Background: In the last ten years, Multiparametric Flow Cytometry (MFC) has been standardized and routinely applied for the detection of MRD as a prognostic factor in MM patients across different lines of therapy. We assessed the MRD carried out before and after ASCT in a series of consecutive MM patients in order to investigate whether the ratio of the two determinations might increase the prognostic potential. Methods: We collected bone marrow samples for MRD assessment at the end of induction therapy and 3 months after ASCT from 75 MM patients treated between 2013 and 2018 achieving at least a Very Good Partial Remission (VGPR) with a bortezomib-based induction therapy, according to the most recent International Myeloma Working Group (IMWG) criteria (Kumar S et al, Lancet Oncol 2016). MFC-determined MRD was evaluated according to current guidelines (Arroz M et al, Cytometry 2016). All patients were examined with 18-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) scan before and after the ASCT. Results: Post-induction therapy MRD was found predictive of post-ASCT MRD status. Indeed, patients transplanted in a MRD positive status had a significantly increased risk to maintain a MRD positivity status after transplantation (Odds Ratio - OR - 7,682; $p < 0,001$). Detection of post-ASCT MRD had a negative impact on median PFS (31 months vs not reached respectively, $p = 0,005$). In Cox-Regression analysis, a complete remission status (CR) with an undetectable MRD after the ASCT resulted to be the major protective factor from relapse (Hazard Ratio - HR -0,054, $p = 0,005$), while patients with a detectable MRD before and after the ASCT had the worse PFS (22 months, HR 3,731; $p = 0,008$). Risk analysis showed 3 different PFS risk groups: "high" for the patients with MRD detectable before and after the ASCT, "intermediate" for patients with MRD positivity before the ASCT who achieve a negativity after, and "low" in the case of MRD undetectable before and after. In our study, response evaluated by FDG-PET/CT showed no correlation with PFS. Conclusions: Multiparametric flow cytometry is a relatively recent method to assay MM MRD, and its role in MM therapeutic path is still under investigation. According to our data, a detectable MRD after the ASCT is a major relapse risk. Interestingly we found that it can be early predicted by the post-induction MRD status and its negativization after ASCT has a modest impact on this. Therefore, we support the concept of treatment escalation when a CR is not reached after the induction treatment, in order to undergo to the ASCT in the best possible response. However, double MRD determination before and after ASCT may increase the prediction potency of currently validated.

Keywords:
autologous stem cell transplant

Minimal residual disease

Progression-free survival

Tracks:
Myeloma Response Assessment including MRD

FP-204

Myeloma plasma cell Multiparametric Flow Cytometry (MFC) detection in autograft products of Newly Diagnosed Multiple Myeloma (NDMM).

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Abstract:
Background. Over the last decades the incorporation of novel agents such as proteasome inihibitor (PI) and immunomodulatory drug (IMID) prior of autologous stem cell transplantation (ASCT) resulted in high response rate after induction therapy

in newly diagnosed Multiple Myeloma (NDMM). Nevertheless the relapse occurs in virtually all MM patients. Many authors suggested that the presence of myeloma plasma cells (PC) in the graft may contribute to the recurrence of myeloma after ASCT. Recent techniques of multiparameter flow cytometry (MFC) can be applied to detect such contamination. Methods. From December 2017 to May 2019 the apheresis products of 40 NDMM were collected before cryopreservation in order to assess the presence of myeloma PC by 8-colour MFC. All patients received bortezomib/thalidomide/dexamethasone (VTD) regimen for 4 cycles as induction and high doses cyclophosphamide plus G-CSF for mobilization. 300 mcl of the cell suspension was forwarded to the flow cytometry laboratory for PC assessment by MFC analysis in order to evaluate 3000000 events. According to the current guidelines, limit of detection (LOD) was set at 30 aberrant phenotype PC. Thirty-three out of 40 patients were also evaluated for bone marrow MFC minimal residual disease (MRD) after induction. Results. After VTD induction, 29 (72,5%) patients achieved a high quality response (21 VGPR, 8 CR), while the remainder 11 patients were in PR; 24 out of 33 (72,7%) had a detectable MFC-MRD in the bone marrow. Aberrant phenotype PC over the LOD were found in 6 (15%) apheresis products, whereas further 3 (7,5%) samples were below the LOD. Apheresis positivity was not significantly influenced by MRD status (11,1 vs 20,8% for negative and positive MRD status respectively, p = 0,467) post induction and also post ASCT (evaluated in only 18/40 patients). Factors known to have a prognostic significance on survival of NDMM, such as International Staging System (ISS) subgroup, cytogenetic risk and response status after induction therapy, were not found to be predictive about the apheresis contamination. No aberrant phenotype PC were found in the graft of 2 poor mobilizer patients treated with plerixafor. Conclusions. Eight-colour MFC is a reproducible and reliable method to detect myeloma PC in autograft products. Notewhorty, aberrant phenotype PC detection was not related to MRD status both after the induction therapy, and post-ASCT, and also to other prognostic factors. A too short follow-up time doesn't allow to evaluate the impact of this analysis on ASCT outcome, particularly on progression free survival.

Keywords:
Autograft products

Minimal residual disease

multiparameter flow cytometry

Tracks:
Myeloma Response Assessment including MRD

FP-205

Changes in Serum B-Cell Maturation Antigen Levels Rapidly Predict Progression Free Survival among Multiple Myeloma Patients undergoing New Treatment

Authors:
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Abstract:
Introduction: We have previously shown that MM patients (pts) have higher levels of serum (s) BCMA than healthy subjects and these levels can be used to monitor the course of disease of MM pts. There is a need for more rapid and accurate ways to assess the efficacy of therapy (Tx) for these pts. Thus, we compared changes in levels of sBCMA, sM-protein and SFLC among MM patients undergoing new treatments. Methods: Serum was obtained at baseline and then at least weekly during each pt's first cycle of Tx and the first day of their second cycle and monthly thereafter from all MM pts receiving Tx at a single clinic from March 2015 to

October 2017 (n=116). sM-protein and SFLC levels were measured, and sBCMA levels were determined using an ELISA (R&D Systems; Minneapolis, MN). Percentage changes in these levels during Tx were determined relative to levels at the start of treatment. Kaplan-Meier analysis was used to assess differences in progression free survival (PFS) based on the changes in biomarker levels starting on cycle 1 day 8 (C1D8) and during their treatment. Baseline sBCMA levels of at least 56 ng/mL (based on ROC curve analysis compared to healthy subjects) and measurable sM-protein and SFLC levels according to IMWG criteria were considered assessable levels for analysis. All pt samples were obtained following proper informed consent in accordance with the Declaration of Helsinki. Results: More patients were evaluable by sBCMA (86% [n=100] than by sM-protein (53% [n=62]; $p < 0.0001$) or SFLC (60% [n=70]; $p < 0.0001$). Most patients (85%) analyzed were receiving salvage treatment. Pts with a ≥25% increase in sBCMA on C1D8 (n=8) had a significantly shorter PFS than pts who did not (n=90; median PFS 0.89 vs 3.91 mo; $p < 0.0001$). Only 2 pts reached a ≥25% increase in sM-protein levels on C1D8. Among those with evaluable SFLC, 7 pts showed a ≥25% increase on C1D8 and their PFS was shorter than those that did not (n=50, median PFS 0.92 vs 3.45 mo; $p < 0.0001$). Pts with a ≥25% increase in sBCMA from baseline at any time during their first cycle (n=20 [31%]) had a markedly shorter PFS compared to those that did not show this increase (n=65, median PFS 1.15 vs 3.95 mo; $p < 0.0001$); all pts who showed a ≥25% increase showed a PFS < 5 mo except one pt. Fewer pts showed ≥25% increases in sM-protein (n=6) or SFLC (n=14) at any time during their first cycle. Among pts that were evaluable by all 3 markers and progressed (n=33), sBCMA (≥25% increase) identified progressive disease more rapidly (median 48 days [d]) compared with sM protein (121 d; $p = 0.0247$) or SFLC (114 d; $p = 0.0178$). Conclusions: We have shown that sBCMA is a biomarker that is evaluable in more pts starting new treatments than traditional serum MM markers. Increases (≥25%) in sBCMA levels from baseline during the first cycle indicate a shorter PFS for MM pts starting new therapies, and progressive disease can be identified more rapidly with sBCMA than sM-protein or SFLC.

Keywords:
BCMA

Biomarker

Progression-free survival

Tracks:
Myeloma Response Assessment including MRD

FP-206

Normalization of Serum B-cell Maturation Antigen Levels Predicts Progression Free and Overall Survival in Multiple Myeloma Patients Starting Treatment

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Institutions:
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Abstract:
Introduction: B-cell maturation antigen (BCMA) is increased in the serum (s) of multiple myeloma (MM) patients (pts). We have previously shown that baseline sBCMA levels predict outcomes for MM pts. The purpose of this study was to determine whether a decrease of sBCMA to normal levels (< 56.0 ng/mL) after initiating treatment predicts both progression free survival (PFS) and overall survival (OS) among MM pts and its relationship to complete remission (CR) in this pt population. Methods: sBCMA samples from 147 consecutive MM pts whose first treatment was in the frontline (n=87 [59%]) or salvage (n=60 [41%]) settings in a single clinic specializing in MM from February 2009 to May 2019 were analyzed using an ELISA (R&D

Systems; Minneapolis, MN). We determined sBCMA weekly during the first cycle and then monthly thereafter (median follow-up= 24 mo). A ROC curve analysis of age- and sex-matched healthy donors and active MM pts was used to determine a normal sBCMA level threshold of 56.0 ng/mL. We defined normalization of sBCMA as a decrease in its levels to < 56.0 ng/mL on two consecutive measurements. Kaplan-Meier analysis was used to compare PFS and OS among these pts and compared with CR as defined using the IMWG criteria. All pt samples were obtained following informed consent in accordance with the Declaration of Helsinki. Results: One hundred twenty-four pts (84%) had a baseline sBCMA ≥ 56.0 ng/mL (median 364.7 ng/mL; range, 56.5 9,153.8 ng/mL), and the remaining 23 pts (16%) with baseline levels below 56.0 ng/mL were excluded from our analyses. sBCMA levels normalized (< 56.0 ng/mL) in nearly half (49%) of pts (n=61), and these pts showed a markedly longer PFS (median 42.3 mo) than pts that did not (median 4.1 mo [n=63]; p<0.0001). Furthermore, those normalizing their sBCMA levels showed improved OS (p=0.0008); all pts who normalized their sBCMA whose baseline was below the median level of all normalizing patients (255.3 ng/mL) survived ([n=30]; median follow-up 27.8 mo, range 2.5 97.2 mo). Among those evaluated during their frontline treatment (n=80), those who normalized (n=51) also showed a longer PFS (median 63.5 mo vs 12.8 mo [n=29]; p<0.0001). Only 10 out of 44 pts undergoing salvage treatment normalized and their PFS was longer (median 8.7 mo vs 3.3 mo) but not significantly so (p=0.1346). Pts whose sBCMA levels normalized had similar PFS (p=0.7768) and OS (p=0.3844) to those who achieved CR (n=25). Notably, every pt who achieved CR had normalized sBCMA and all pts who failed to normalize did not achieve CR (n=63). Conclusion: This is the first study to assess whether decreases in sBCMA levels following new treatment predict outcomes for MM pts. We have demonstrated that among MM pts starting new treatment with baseline elevated sBCMA levels, normalization of sBCMA levels (< 56 ng/mL) predicts markedly longer PFS and OS. Therefore, sBCMA may be a novel approach to predict clinical outcomes for MM pts starting new treatment.

Keywords:
BCMA

Biomarker

Progression Free and Overall Survival

Tracks:
Myeloma Response Assessment including MRD

FP-207

CD200 expression level is associated with outcome in multiple myeloma

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Abstract:
CD200, formerly known as OX-2, is a type I glycoprotein that is expressed by thymocytes, activated T cell, B cells, endothelial cells, and neurons. CD200 interacts with receptor for CD200 (CD200R), which is restricted to myeloid-derived antigen presenting cells and a subset of T cells. Through the ligation of CD200R, CD200 delivers an inhibitory signal, leading to the suppression of the T-cell-mediated immune activation. Increasing studies focus on the clinical impact of CD200 expression in patients with newly diagnosed multiple myeloma (NDMM), both on the diagnostic judgement and treatment efficacy monitoring. However, the prognostic value of CD200 remains controversial. We applied immunophenotyping by multi-parameter flow cytometry (MFC) to detect the expressions of CD200 prior to induction therapy and during the progression of treatment, to evaluate its correlation with clinical indicators of MM patients and its prognostic significance. We respectively studied 131 patients who were diagnosed from September 2011 to December 2016. All the patients were followed up until June 2018, with the median follow-up time of

30.0 (range, 7.0-80.5) months. The immunophenotypic studies were performed at diagnosis using fresh bone marrow (BM) samples. The frequencies of cell surface and intracytoplasmic antigen expressions were evaluated with following antibody combinations: CD38, CD138, CD19, CD56, CD45, CD200, ckappa and clamba. Using a CD200 positive cutoff of 20%, 71.0% (93/131) patients were CD200 positive expression. CD200 positive patients had a significant shorter overall survival (OS) than those negative (median OS, 48.0 vs. not reached, P=0.015), as well as 2-year OS rate (71% vs. 92%, P=0.019). Furthermore, in multivariate analysis, CD200 positive expression was the unique risk factors of OS for NDMM patients, as well as higher LDH and high risk cytogenetic abnormal. Interestingly, we found that the ratio of CD4+ to CD8+ T cells (CD4/CD8 ratio) was decreased in CD200 positive patients and this decrease was significantly related to an increase of CD8+ (but not CD4+) T cells (P=0.021). In addition, we analyzed the change of CD200 expression level after treatment in 47 patients who expressed higher level of CD200. Further analysis demonstrated that 80.9% patients became CD200 negative after therapy. In our results, absence of CD200 after therapy was highly predictive of a favorable outcome (OS, not reached vs. not reached, P=0.019). There were 32 patients (84.2%) with CD200 positive converted negative reached very good partial remission (VGPR), compared with 1 patient (11.1%) who kept CD200 positive (P<0.001). In conclusion, our study identified CD200 as a potential prognostic factor in MM.

Keywords:
CD200

Multiple myeloma

Outcome

Tracks:
Myeloma Response Assessment including MRD

FP-208

Standardized minimal residual disease detection by next generation sequencing in multiple myeloma

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Abstract:
Background Next generation sequencing (NGS) has been applied to monitor minimal residual disease (MRD) in multiple myeloma (MM). Standardized DNA input and sequencing depth is essential for achieving a uniform sensitivity in NGS-based MRD study. Method We applied a standardized protocol for MRD assessment of four myeloma cases using the LymphoTrack-Miseq platform based on the use of triplicates of 1 μg DNA input for each MRD sample and a sequencing depth of 1 million sequencing reads per replicate. The number of cells contained in 1μg of each sample was validated by the real time PCR standard curve method using plasmids, in which the albumin gene is cloned. Two plasmids containing unique IGH sequences were added to each replicate, one at the concentration of 10-5 (copy number equivalent to 0.001% of the number of total cells in a replicate) for validation of the sensitivity of 10-5, and the other at 5x10-5 or 10-4 for obtaining an amplification factor. The MRD level in each replicate was calculated from the corresponding reads of the myeloma-specific sequence and the amplification factor. The final MRD level of a sample was defined as the mean MRD levels of the triplicates. In addition, one normal bone marrow sample was used as normal control to evaluate the feasibility of identified clonal sequences as MRD target. Result First of all, five clonal sequences identified in the four myeloma cases were not detected in the normal control except one (sequencing reads of 7), however, of which the complementarity-determining region 3 is in high diversity. The presence of this myeloma-specific sequence in normal control is more likely caused by

index misassignment. The spike-in control of 0.001% MRD was consistently detected in all samples, i.e. seven samples of the four myeloma cases, confirming a sensitivity of 10-5. Moreover, the spike-in control at 10-4 appears appropriate for MRD normalization as variation lower then 2.8 folds in frequency among triplicates achieved in 4/5 samples. Furthermore, this standardized NGS approach yielded MRD+ or MRD- results concordant with allele-specific oligonucleotide (ASO) real-time quantitative (RQ)-PCR. NGS showed expected decrease of MRD levels associated with the change in serological response in three follow up samples from one case. NGS showed an improved sensitivity and provided quantification of MRD for cases assigned "positive but not quantifiable" (PNQ) by ASO RQ-PCR, without the use of patient-specific probes/primers. Conclusion The standardized LymphoTrack-MiSeq-based method is verified to carry a sensitivity of 10-5, hence an effective tool for MRD monitoring in MM. As only a small number of samples are tested here, further study with a larger number of patients is warranted.

Keywords:
DNA

Minimal residual disease

Next Generation Sequencing

Tracks:
Myeloma Response Assessment including MRD

FP-209

Upgraded standardized minimal residual disease detection by next generation sequencing in multiple myeloma

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Abstract:
Background We have previously validated the sensitivity of 10-5 using spike-in plasmid controls in a standardized experimental design based on triplicate of bone marrow DNA that acquired one million sequencing reads by next generation sequencing (NGS) in each replicate of 1 μg DNA input using the LymphoTrack-MiSeq platform. Herein, we attempted to simplify operation by the use of spike-in controls with genomic instead of plasmid DNA in an additional 19 myeloma patients, which was compared with minimal residual disease (MRD) data derived from allele-specific oligonucleotide (ASO) real-time quantitative (RQ)-PCR. Methods To simplify operation of the spike-in controls, we replaced spike-in plasmid controls of immunoglobulin heavy chain sequences with genomic DNA from CD138 sorted cells of MM patients with clonal IGH/IGK rearrangement with highly diverse sequence for two reasons. First, diluting plasmid from stored concentration to appropriate concentration for use (generally from 109 to 6 copies per microliter) is too tedious and susceptible to possible pipeting error. Secondly, the concentration of spike-in controls is more accurate with the use of gDNA since the cell numbers of both the spike-in controls and MRD samples are measured by real-time PCR. On the other hand, calculation of number of copies of plasmid is based on the assumption that the average weight of a base pair is 650 Daltons. MRD assessment was based on the use of triplicates of 1 μg DNA input and a sequencing depth of 1 million sequencing reads per replicate as previously. The number of cells contained in 1μg of each sample was measured by the real time PCR standard curve method using plasmids, in which the albumin gene is cloned. Two spike-in controls generated from genomic DNA of myeloma cells were added to each replicate, one at the concentration of 10-5 for validation of the sensitivity of 10-5, and the other at 10-4 for obtaining an amplification factor, i.e. percentage of tumor alleles per sequence read. The MRD level in each replicate was calculated from the corresponding reads of the myeloma-specific sequence and the amplification factor. The final MRD level of a sample was defined as the mean MRD levels of the triplicates. Results The spike-in control of 0.001% concentration was consistently detected in all 19 follow up samples tested, confirming a uniform

sensitivity of 10-5 of this standardized experimental protocol. Moreover, this standardized NGS approach demonstrated MRD positivity in 9/13 (69%) patients achieving complete response. Furthermore, NGS showed an improved sensitivity and provided quantification of MRD for cases assigned "positive but not quantifiable" by ASO RQ-PCR, without the use of patient-specific probes/primers. Conclusion The use of genomic DNA has simplified verification of the sensitivity of 10-5, and operation of the standardized LymphoTrack-MiSeq-based MRD detection, hence an effective tool for MRD monitoring in MM.

Keywords:
Minimal residual disease

Next Generation Sequencing

Tracks:
Myeloma Response Assessment including MRD

FP-210

Recovery of policlonal immunoglobulins as a predictor factor of increased progression-free survival and overall survival in patients with multiple myeloma ineligible for ASCT

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Abstract:
Background: Immunoparesis is the suppression of polyclonal immunoglobulins (Igs) and is present in about 85% of patients diagnosed of multiple myeloma (MM). Our group recently demonstrated that the normalization of polyclonal Igs after ASCT is a predictor factor for longer progression-free survival (PFS) and overall survival (OS). However, the impact of this factor in patients who are ASCT-ineligible has not been determined yet. Aims and methods: To determine the immunoparesis status of ASCT-ineligible MM patients at diagnosis; and its impact, along with its normalization with induction treatment, on prognosis. This study retrospectively analyzed 210 patients from different centers from our region diagnosed of MM between 1998 and 2017. Igs data were collected at diagnosis; 1, 2 and 3 months since the beginning of treatment, and then at intervals of 3 months until progression disease or a maximum of 36 months. Immunoparesis was defined as at least a 25% decrease in one or more polyclonal Igs relative to the lowest limit of normality. Results: The evaluation of the baseline characteristics of the patients showed that immunoparesis was present in 81.7% of patients at diagnosis, with similar distribution among the different isotypes of MM. Patients presenting with immunoparesis had higher percentage of aberrant plasma cells within the plasma cell bone marrow compartment, but no significant correlation with gender, age, FLC ratio, ISS, R-ISS, LDH, cytogenetics or leukocytes. As far as treatment is concerned, 53.3% of the patients received a PI-based treatment, 5.2% an IMID-based treatment, 4.8% both drugs and 36.7% any conventional treatment without any novel agent. Among patients presenting with immunoparesis at diagnosis, 43 of them (25.3%) did recover the polyclonal Igs during the follow-up, with a median time to recovery of 9 months. There was no difference between polyclonal Igs recovery and the type of treatment. Immunoparesis recovery was associated with better quality of responses: 46.5% of patients with

recovered immunoparesis achieved CR, vs only in 10.3% of patients with persistent immunoparesis (p=0.000). Most interestingly, PFS was significantly longer in the group of patients who did recover immunoparesis (32 months) vs those with persistent immunoparesis (16 months);p=0.000. The same association was observed with OS (82 vs 31 months;p=0.000). To rule out the potential influence of the response to treatment in the recovery of immunoparesis, we also performed a Landmark analysis at 9 months (median time to recover the polyclonal Igs). This analysis confirmed the previous data with a PFS of 32 vs 23 months; p=0.000 and an OS of 82 vs 48 months;p=0.004. Discussion: Our study suggests that the presence of immunoparesis at diagnosis is only associated with higher clonal plasma cell bone marrow infiltration. The recovery of immunoparesis after treatment, is a surrogate marker predicting significantly longer PFS and OS.

Keywords:
Autologous stem cell transplantation ineligible

immunoparesis

Progression-free survival

Tracks:
Myeloma Response Assessment including MRD

FP-211

Minimal Residual Disease Measurement in Multiple Myeloma: Survey of Clinician Practices

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Abstract:
Background: Minimal residual disease (MRD) in multiple myeloma (MM) is evaluated by multiparametric flow cytometry (MFC), next generation sequencing (NGS), and positron emission tomography (PET-CT). MRD negativity is associated with improved survival, but there is no consensus on its value, modality, and timing. We surveyed MM clinicians regarding MRD measurement in MM. Methods: An online survey of practices and attitudes toward MRD measurement in MM was distributed by direct e-mail (DE) to 255 MM clinicians identified through public directories, by e-mail solicitation via the MM Research Foundation, and by twitter between September and November 2018. Results: All 84 respondents (31% DE response rate) were familiar with MRD. 89% were academic clinicians; median experience was 16 yrs. Respondents were from 6 continents: North America (65.5%), Europe (22.6%), Asia (5.9%), South America (3.6%), Africa (1.2%), and Australia (1.2%). Of the 76 (91%) clinicians who use MRD, 49% preferred MFC, 45% NGS, and 6% PET-CT. There was no statistical difference in NGS usage between respondents before and after FDA approval date (9/28/2018) of the ClonoSEQ NGS MRD assay (39/46 pre-approval vs. 37/38 post-approval, p=0.067). Most respondents (88%) use a MRD modality with a sensitivity of 10-5 or greater; 50% use a modality with a sensitivity of 10-6. 37% of clinicians use MRD to guide decision-making. Academic clinicians were more likely to measure MRD at each response assessment compared to private practice clinicians (43/63 vs. 4/13, p=0.025). The most preferred times of MRD assessment are (of 6 timepoints): during standard response assessment (62%), after stem cell transplantation (51%), and after 1 year of maintenance (30%). The areas of greatest perceived value provided by MRD include (of 6 choices): prognostication (71%), guiding future decision making (61%), prompting a change in the duration of treatment (51%), and serving as a surrogate endpoint for clinical trials (50%). The leading areas of concern about MRD testing include (of 7 choices): unknown timing of testing (54%), unknown utility (37%), cost of testing (34%), and value as a surrogate endpoint (26%). Conclusions: While 91% of MM clinicians measure MRD, only 50% measure at a depth of 10-6 and only 37% are making treatment decisions based on the result. There is similar preference for using MFC and NGS. Lack of consensus on appropriate timing of testing

and concerns about the utility and cost of testing may be limiting its use beyond prognostication. Half of respondents perceived value in using MRD status to change duration of therapy. These results support the need for clinical trials with MRD-guided therapeutic strategies to establish clinical utility and endpoint surrogacy.

Keywords:
Minimal residual disease

Multiple myeloma

Survey

Tracks:
Myeloma Response Assessment including MRD

FP-212

Predicting Treatment Response of Multiple Myeloma Patients Using Tumor Specific cell-free DNA

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Abstract:
Great progress achieved in treatment of multiple myeloma (MM) over the past decade changed overall perception of importance of minimal residual disease (MRD) assessment. Since new drugs induce deep responses, MRD must be evaluated using sensitive techniques, such as allele specific PCR (ASO-PCR), next-generation sequencing (NGS) or flow cytometry. MM is a genetically heterogeneous disease characterized by multiple focal lesions in the bone marrow (BM). BM samples are typically used for analysis, but currently an alternative approach called liquid biopsies, which utilize body fluids for analysis of various molecules and cells, is intensively studied. Cell-free DNA as one type of the molecule which can be analyzed using liquid biopsy approach. In our study, patient-specific, clonotypic rearrangement of immunoglobulin heavy chain (IgH) gene, identified in BM samples, was used for qPCR analysis of cfDNA samples from peripheral blood. We demonstrate that dynamics and quantity of patient-specific, clonotypic IgH rearrangement found in cfDNA can predict the outcomes and response of MM patients. Methods: Total of 45 patients enrolled in the study. Samples of BM were collected at diagnosis. At diagnosis and at three-month intervals, samples of peripheral blood (PB) were collected for cfDNA extraction and analysis until a patient reached complete remission (CR). If CR was not reached, samples were collected for 24 months after diagnosis. Two more samples of PB were collected (CR+3, CR+6) if patients reached CR. Patient-specific VDJ rearrangement was identified using previously described PCR method from genomic DNA extracted from CD138+ cell fraction; based on the results, patient-specific primers and probes were designed for use in ASO-PCR. Obtained data were evaluated by absolute and relative frequencies of categorical variables and median (minimum–maximum) of quantitative variables. Results: First, we assessed time to complete remission (CR). Patients were classified according to the quantity of cfDNA measured at time of diagnosis into three groups: negative, PNQ (= positive non-quantifiable) and positive. As PNQ had a similar profile to negative-classified samples (in K-M plot), PNQ were grouped together with negative results except extremely high values (>5, n=2) which were reclassified from PNQ to positive group. The Kaplan-Meier estimates at 12 months were reported and supplemented by the 95% confidence interval derived using Greenwood formula. The results show that significantly higher number of patients classified as negative or PNQ with quantity < 5 have reached CR in contrast to

patients classified as positive or PNQ with quantity > 5. Our results demonstrate that MM patient-specific cfDNA fragments are released into the bloodstream and that patients either with no or very few DNA fragments have a higher chance of achieving better treatment response. This work was supported by grant AZV 17-29343A.

Keywords:
cell-free DNA

Liquid biopsy

Minimal residual disease

Tracks:
Myeloma Response Assessment including MRD

FP-213

PROGNOSTIC SIGNIFICANCE OF RED BLOOD CELL DISTRIBUTION WIDTH (RDW) AND DIVERSE HEMOGRAM RATIOS IN NEWLY DIAGNOSED MULTIPLE MYELOMA (NDMM)

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Abstract:

INTRODUCTION Complete blood count is considered as an important baseline test for NDMM. The RDW, the neutrophil-to-lymphocyte ratio (NLR), platelets-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR) and absolute lymphocyte count (ALC) have been shown to be associated with adverse prognosis in several malignancies including hematologic diseases. However, there are limited reports in the literature regarding the use of these parameters as prognostic markers for MM. AIM The aim of our study was to investigate the prognostic value of these parameters in our cohort of patients with NDMM, in terms of overall survival (OS) and progression free survival (PFS). METHODS Multicentric study where data of 122 patients from 3 hospitals from the Balearic Islands were retrospectively obtained. All NDMM from January 2012 until October 2018 were included. Data including age at diagnosis, gender, follow-up duration, disease staging, treatment received, number of deaths and losses to follow-up were collected. We also obtained the following laboratory parameters: hemoglobin, RDW, white cell blood count, platelets and biochemical parameters. We determined the optimum cutoff points for the NLR, LMR, PLR, ALC and RDW as a predictor for OS and PFS with the Maxstat statistic. Uni and multivariate analysis were performed for these variables. RESULTS We analyzed 122 patients, which 66 (54%) were males. The median age at diagnosis was 68 years (range 59-76). 29 patients (28%) had R-ISS1, 56 (53%) R-ISS2 and 20 (19%) R-ISS3. All patients received chemotherapy and 53 (43%) received or were planned to do an autologous stem cell transplantation. The median follow up was 2 years. In the univariate analysis, the patients with a RDW value at diagnosis <12.2 have better overall survival outcomes compared with those patients with RDW>12.2 (p=0.0036). These results remained statistically significant regardless of age. We also found statistically significant differences in terms of OS for NLR with a cutoff of 4.09 (p=0.035), LMR with a cutoff of 3.38 (p=0.0049), PLR with a cutoff of 146.9 (p=0.019) and ALC with a cutoff of 2590/µL (p=0.022). In the multivariate analysis, we did not find statistically significant differences for those variables.

CONCLUSION In our experience, an elevated RDW, as well as an elevated NLR, LMR, ALC and PLR at diagnosis were an adverse prognostic factor in terms of PFS and OS for NDMM in the univariate analysis, which was not confirmed in the multivariate analysis. RDW was stadistically significative regardless of patients age. Bigger studies are needed to confirm these results. RDW and the other parameters could have a potential role in prognostic index in NDMM.

Keywords:
Newly diagnosed multiple myeloma

Platelet count

prognostic factors

Tracks:
Myeloma Response Assessment including MRD

FP-214

Minimal residual disease and quality sample evaluation by Next Generation Flow cytometry in multiple myeloma patients: a Brazilian experience

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Abstract:
Introduction: Increasing evidence suggests that of minimal residual disease (MRD) in bone marrow (BM) is one of the most relevant independent prognostic factors in multiple myeloma (MM). Recently, EuroFlow consortium developed and validates the Next Generation Flow cytometry (NGF) approach to evaluate BM MRD in MM patients, at very low levels and, simultaneously is able to estimate the sample hemodilution. Here, we evaluated flow-MRD by NGF in MM patients after autologous stem cell transplantation (ASCT) and compared with conventional techniques for response criteria in serum. Material and Method: Overall, 32 BM samples were obtained from MM patients undergoing ASCT – 62% F and 38% M (median age of 60 years old, range 41-72y), collected at 100 days (D+100) after ASCT. Patients received the induction protocol:
ciclophosphamide+thalidomide+dexamethasone (CTD) n=12 and
borthezomide+ciclophosphamide+dexamethasone (VCD) n=20. In addition, MM patients were evaluated according to the IMWG conventional response criteria. The samples were processed according to the EuroFlow NGF MM-MRD protocol (www.euroflow.org). The percentage of CD117hi mast cells ($\leq 0.002\%$) were used to discriminate samples with hemodilution. Infinicyt® software (version 2.0, Cytognos®) used for data analysis. For statistical analysis, the SPSS software (version 21, IBM) was used. The Kaplan–Meier were used to compare progression-free survival (PFS) curves. PFS was defined as time from ASCT to either disease progression or death by any reason. Statistical significance was set at p values <0.05. Results: The sensitivity of flow-MRD achieved by NGF was 10-6 cells in all samples evaluated. Aberrant phenotypes associated with MM were found in all MRD+ samples (65%; 21/32). Hemodilution was observed in 03/11 MRD-, in this group only one patient progressed. On the other hand, in 02/21 MRD+ hemodiluted progressed early. As expected, MM patients who were MRD+ (21/32) had shorter PFS vs. MRD- cases at D+100 (26 vs. 36 months). According to conventional criteria response, 59% of patients (19/32) achieved complete response (CR) or stringent CR. Among this group of patients, 53% (10/19) maintained MRD+. Conversely, in patients with partial response (PR) or very good PR 41% (13/32), the percentage of MRD+ was 85% (11/13). Conclusion: NGF became an excellent method for high sensitivity and standardized measure of MRD in MM patients after

therapy; in addition allow the evaluation simultaneously of the quality of BM samples studied. This study suggests that MRD+ in BM at D+100 after ASCT is associated with a shorter PFS in MM patients. Besides careful evaluation for hemodilution cases independently status MRD is necessary. Whether evaluation of an additional sample is required in such cases remains to be established

Keywords:
Minimal residual disease

Multiple myeloma

next generation flow

Tracks:
Myeloma Response Assessment including MRD

FP-215

Clinical relevance of Minimal residual Disease assessment by NGS in Multiple Myeloma

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Abstract:
Background: Minimal residual disease (MRD) assessment is a known surrogate marker for survival in multiple myeloma (MM). The majority of data comes from retrospective or subset analyses of patients enrolled in clinical trials. We present here a single institution's experience assessing MRD in MM patients receiving frontline therapy as well as those receiving therapy for relapsed disease. We describe the impact of depth of response, duration of response, and direction of response, on prognosis. Patients and methods: 181 multiple myeloma patients treated at The University of California, San Francisco (UCSF) from 2008 to 2016 were included. 126 were newly diagnosed patients versus 55 in second line or later. Patients received anti-MM therapy per provider preference with the aim of obtaining maximal response by International Myeloma Working Group (IMWG) criteria and MRD was assessed in those achieving VGPR or better. MRD assessment was performed by commercially available next generation sequencing (NGS) of immunoglobulin genes (Adaptive biotechnologies, Seattle, WA, USA). The sensitivity of this technique ranged from 10-4-to-10-6) and was 10-6 in most cases. Results: A total of 398 MRD samples were analyzed at various time points during the disease course. MRD data was available at ≥ 3 time points for 59 patients, 2 time points for 36 patients and 1 time point for 86. Median follow up was 26 months. Overall, 66 of 181 total patients (36%) achieved MRD negativity (<10-6) on one or multiple assessments. Also, when we analyzed the effects of depth of response on survival, patients who were MRD negative or who were MRD positive at a very low level (between 10-5 and 10-6), had a better prognosis than those with higher disease burdens (>10-5)(p 0.001). Then, we analyzed the effect of repeated MRD monitoring on PFS. Three categories were identified in newly diagnosed patients: (A) patients with ≥3 MRD- samples, (B) patients with continuously declining detectable clones, and (C) patients with a stable number of clones. Groups A and B had a more prolonged PFS than group C (NR vs 31m, p<0.0001). Finally, we will show several cases with MRD driven decision. Conclusion. This study shows that MRD assessment in a real world setting likely has the same predictive power as that seen in clinical trials. MRD dynamics can accurately predict disease evolution and ultimately could drive clinical decision-making. MRD is an important predictor of PFS in newly diagnosed and relapsed patients.

Keywords:
Minimal residual disease

Next Generation Sequencing

Tracks:
Myeloma Response Assessment including MRD

FP-216

Post-transplant minimal residual disease assessment in Multiple myeloma

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Abstract:
Background: MRD status was assessed in MM patients undergoing high-dose Melphalan and autologous stem cell transplantation (ASCT). The primary objective of this study was to determine the MRD negativity rate in this population. Methods: Between April 2016 and January 2019, 110 MM patients underwent ASCT at our center. 10 color flow cytometry was used to assess MRD in the bone marrow on day 100 (± 15 days) after transplant; limit of detection was 0.001%. Along with this, 18F FDG whole body PET-CT scan was also performed. CD138 enriched plasma cells were used for cytogenetic analysis by FISH. IMWG criteria were used for response assessment for MRD. Results: Baseline characteristics of patients were similar with respect to age, gender, ISS and DS stage and immunoglobulin subtype. MRD status was negative in 80 (group A) and positive in 30 patients (group B); MRD negativity was 73%. Patients' median age: 52 years (range 31-71) group A vs 51 years (range 31-64) group B; gender M/F 51/29 vs 24/6; ISS stage III 33 (41%) vs 10 (33%) respectively. Renal failure at presentation occurred in 10 (13%) vs 6 (20%) respectively, p=0.4. IgG/IgA/light chain subtypes: 53/10/17 and 18/4/8 patients, respectively. Cytogenetic profile was available for 47 patients; 2 have high risk disease. All patients received novel agents as induction therapy: triplet 84 (76%), doublet 23 (21%) and 4-drug 3 (3%) patients. Majority received one line of therapy prior to transplant 59 (73%) vs 19 (63%) respectively, p=0.4; 22 (28%) vs 11(37%) had received >1 line of therapy. Disease status at transplant: sCR+CR 43 (54%) and 12 (40%) respectively, p=0.28; VGPR 17 (21%) vs 7 (23%), p=0.8. 41 (51.2%) vs 16 (53.3%) patients, respectively underwent ASCT within 1 year of diagnosis. Melphalan 200mg/m2 was the conditioning regimen used. Complete suppression of FDG uptake was observed in 61(76.2%) vs 17 (56.6%) patients respectively, p=0.1. Bortezomib lenalidomide dexamethasone (VRd) consolidation was received by 68 (85%) and 30 (100%) respectively in groups A and B, p=0.03; the remaining received lenalidomide maintenance. Following consolidation, patients received lenalidomide maintenance. Mean OS from date of transplant is 36.5 (95% CI 35.6-37.5) vs 35.7 months (95% CI 33.2-38.2) for MRD negative & positive patients (p=0.2). At a median follow up of 19 months (range 5-38) from transplant, mean OS and PFS from transplant were 18.5 (95% CI 15.9-21.1),19 (95% CI 14.6-23.4), 22.9 (95% CI 18.8-26.9) and 23.3 months (95% CI 16.2-30.4), p=0.2 and 17.7 (95% CI 15.2-20.2),18.6 (95% CI 14.2-22.8),19.9 (95% CI 16.2-23.6) and 23.3 months (95% CI 16.2-30.4), p=0.3 respectively in MRD-PET -, MRD-PET +,MRD +PET - and MRD+PET + patients. 5 patients have progressed in MRD negative vs 6 in the MRD positive group (p=0.07). Conclusion: Patients who were MRD negative and PET negative had trend for better OS and PFS. Longer follow up is needed to see the impact of MRD negativity on OS and PFS.

Keywords:
Minimal residual disease

multiparameter flow cytometry

PET-CT

Tracks:

Myeloma Response Assessment including MRD

FP-217

Urine immunofixation is not necessary for CR definition in myeloma patients with complete M protein molecule

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Abstract:
Introduction: The standard definition of complete remission (CR) in multiple myeloma (MM) requires negative urine immunofixation (IF). This has been recently challenged by Ubieto et al. (Blood 2018 132:474) showing that patients with unavailable urine IF show same disease course as those negative for M protein in urine. Aim was to test if patients with negative serum IF and urine not available have the same outcomes in terms of overall survival (OS) and progression free survival (PFS) as patients with negative urine IF on real life patient´s population.
Patients and methods: This is a retrospective registry-based analysis from the Registry of monoclonal gammopathies of the Czech Myeloma Group. Patients with newly diagnosed MM between 2007 and 2018 and with complete M protein molecule at diagnosis were included in the study. Patients were divided into 4 groups: patients with negative immunofixation in serum after the first treatment and urine negative (CR), patients with negative immunofixation in serum after the first treatment and urine not available (uCR), patients with VGPR and patients with negative serum immunofixation and positive urine. Basic demographic data and disease characteristics were obtained. The Kaplan-Meier estimates were completed by the Greenwood confidence interval. The log-rank test was used to estimate the statistical significance of the difference between the curves.
Results: Overall 1151 patients were identified (CR group n=301, uCR group n=180, VGPR group n=654, negative serum IF and positive urine IF n=16). Only 3.2% (16/497) were identified. Of note, 301/317 (95%) patients with negative serum IF, had also negative urine IF. All groups were balanced except the fact that uCR group included significantly more patients with high risk cytogenetics (27.7% high risk in CR group, 53.1% in uCR group and

34.8% in VGPR group, p=0.011). Median OS in CR group was 91.9 months (95th CI: 70.4-113.4), in uCR 79.0 months (95th CI: 56.4-101.6), and in VGPR 64.0 months (54.2-68.9). The difference between CR and uCR group was not statistically significant (p=0.314). The difference between CR and uCR groups versus VGPR group was statistically significant (p<0.001). Median PFS in CR group was 39.7 months (95th CI: 33.2-46.2), in uCR 36.2 months (95th CI: 32.1-40.2) and VGPR 25.5 months (23.9-27.1). The difference between CR and uCR group was not statistically significant (p=0.1). The difference between CR and uCR groups and VGPR group was statistically significant (p<0.001). Conclusion: Based on the presented real world data we conclude that negative IF in urine is not necessary to define CR in individuals with complete M protein molecule. Patients in CR but with urine IF not available display similar outcomes in terms of PFS and OS to those in CR with negative urine IF. Both the

Keywords:
complete Ig molecule

complete response

urine immunofixation

Tracks:
Myeloma Response Assessment including MRD

FP-218

Comparison of three different assays demonstrates heterogeneity in determination of serum free light chains - implications on diagnostic and therapeutic monitoring of multiple myeloma

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Abstract:
Determination of serum free light chains (FLC) is established as standard for diagnosis and monitoring of multiple myeloma (MM) and other plasma cell dyscrasias. In 2014, the revised IMWG criteria implemented the serum free light chain ratio of involved FLC (iFLC) / non-involved FLC (niFLC) > 100 as a biomarker defining MM requiring treatment. This recommendation was based on Freelite assay, which relies on polyclonal antisera. Additionally, the monoclonal N-Latex FLC assay and more recently, the polyclonal Sebia FLC assay are available and approved for determination of FLC. The aim of this trial was to compare the three different assays for correlation and potential implication for diagnostic and clinical use. Blood samples from patients with MM were collected at the beginning of the study and after a maximum of six follow-up visits. A total of 187 samples from 47 patients with newly diagnosed (n = 31) or relapsed / refractory multiple myeloma (n = 16) were examined. Determination of FLC was conducted. N Latex reagents (Siemens Healthineers, Germany) and Freelite reagents (The Binding Site (TBS), United Kingdom) were used on a Siemens BN II nephelometer. Sebia FLC (Sebia, France) was performed manually. Statistical analyses included Passing-Bablok regression analyses, Spearman rank correlation, Bland-Altman plots and Cohens Kappa coefficient. Comparison of Freelite and N Latex assay shows higher total values for Freelite kappa (κ), lambda (λ) and κ/λ ratio compared to N Latex. Comparison of Sebia FLC to N Latex and Freelite shows similar results for Sebia FLC and N Latex with markedly lower values compared to Freelite. Using Freelite to determine the iFLC/niFLC ratio, 18 of 42 patients exhibited a ratio >100. With N Latex and Sebia FLC just 10 and 9 patients respectively were quantified as FLC ratio >100. Using the recently proposed modified thresholds for N Latex (> 30) or Sebia FLC (> 16) comparable results to the Freelite assay were achieved. This is

the first report on comparing three different assays to determine serum free light chain values. Our data show that the assays should not be used interchangeably to monitor patients. Absolute values differ as well as the FLC ratio, which shows high discrepancy between the different assays. In light of these results, the current international guidelines based on the Freelite assay should therefore not be translated to N Latex FLC and Sebia FLC assays. Treating physicians should be aware of potentially misleading results and the fact, that individual patients may not meet diagnosis criteria for requiring treatment or were mistreated because of misleading information regarding response.

Keywords:
free light chain assay

free light chain ratio

Tracks:
Myeloma Response Assessment including MRD

FP-219

The use of Cancer/Testis antigens to monitor levels of circulating malignant stem cells in Multiple Myeloma.

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Abstract:
Despite the development of sensitive methods to monitor the residual malignant plasma cell component in Multiple Myeloma (MM) patients, the current assays are limited in that they do not necessarily assess the complete malignant cellular component of the disease, cannot be applied to all MM patients and require painful BM assessments on a regular basis. There is therefore potential room for a completely different approach, investigating the monitoring of the proposed malignant stem cell feeder population circulating in the PB. Following the finding that MAGEC1, a cancer/testis antigen (CTA), is highly expressed in MM patients at diagnosis, we used the expression of this aberrant antigen to identify an abnormal pro-B to pre-B progenitor cell that was present in both BM and PB compartments of the disease. Using flow cytometry and QRTPCR we determined that the levels of this cell type mimicked treatment responses determined using basic biochemical methodology yet provided a deeper sensitivity for the detection of residual disease. A separate assessment of MM patients diagnosed at different stages of the disease demonstrated a cascade-like pattern of expression of several key CTAs: MAGEC1, PRAME, MAGEA3 and BAGE2, that was linked to defining features of advancing disease. Through multiplex QRTPCR assessment of all 4 CTAs we were able to show that this cascade-like pattern occurred sequentially in sub-populations of the same stem cells as the disease advanced and assessment of multiple CTAs could be used to monitor both the level of this malignant progenitor cell and its clonal evolution. This research opens an interesting alternate avenue to the assessment of minimal residual disease in MM, allowing for the development of a molecular assay that could offer a deeper look at the cells that potentially drive the disease forward and result in the inevitable relapse.

Keywords:
Cancer/Testis antigen

MAGEC1

malignant stem cells

Tracks:
Myeloma Response Assessment including MRD

FP-220

Bone marrow lymphocytes reconstructive pattern in multiple myeloma patients after autologous transplant has no prognostic significance

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Abstract:
In the last 20 years, the modern anti-myeloma drugs and autologous stem cell transplant (ASCT) significantly improved prognosis of multiple myeloma (MM) patients. Despite high efficiency of current induction regimens, most patients relapse over time. The link between changes in the immune system and prognosis of the disease is still not entirely clear. Therefore, we analyzed whether the reconstructive pattern of bone marrow (BM) lymphocytes during routine BM examination after ASCT is related to disease prognosis and whether there is a typical reconstructive pattern in patients with MRD negative complete remission. From September 2009 to October 2018, 98 MM patients underwent routine BM testing after the first ASCT at the Department of Internal medicine, Hematology and Oncology, University Hospital Brno in the Czech Republic. By multi-parametric flowcytometry, four BM lymphocyte subtypes were analyzed - T cells (CD19-CD5+), mature B cells (CD19+CD20+) immature B cells (CD19+CD20-) and NK cells (CD19-CD5-CD56+). In 60% of patients who achieved complete response (CR), MRD by flowcytometric analysis (sensitivity threshold 10-5) was evaluated. We analyzed correlation of changes in BM lymphocyte populations to length of progression free survival (PFS) and overall survival (OS) or minimal residual disease (MRD) negativity achievement. Changes in counts of any lymphocyte subtypes were not associated with significant PFS or OS benefit. No significant association of BM lymphocyte subtypes count with MRD negative status was found. Our results showed that the reconstructive post-transplant BM lymphocyte pattern is not connected to further newly diagnosed MM patients` prognosis after intensive treatment including ASCT.

Keywords:
Flow Cytometry

Immunorecovery

Multiple myeloma

Tracks:
Myeloma Response Assessment including MRD

FP-221

STANDARDIZATION OF HIGH SENSITIVITY MINIMAL RESIDUAL DISEASE MONITORING IN MULTIPLE MYELOMA: AN EXPERIENCE IN TERTIARY CANCER CENTRE

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Abstract:
Introduction: Minimal residual disease (MRD) status is the most relevant prognostic marker in multiple myeloma (MM). Recently, IMWG has incorporated MRD-negative status as a criterion to define stringent clinical response (sCR) using next-generation flow cytometry (NGF) i.e. high-sensitivity flow cytometry (HSFC). Herein, we present our experience in the standardization of HSFC and MRD monitoring in MM. Methods: HSFC MRD-assay in MM was standardized using Euroflow bulk-lysis and stain method. A ten-color

two-tube antibody panel was used which included antibodies against CD19, CD20, CD27, CD28, CD38, CD45, CD56, CD81, CD117, CD138, CD229, CD319 and Cytoplasmic-kappa and lambda. Sample were acquired using Navios flow-cytometer and data was analyzed using Kaluza-software. Limit of detection (LOD) and lower limit of quantitation (LLOQ) were determined using spiking and dilution experiments. Results: LOD and LLOQ of the HSFC-MRD was found to be 10 events at a sensitivity of 0.0003% and 25 events (CV of 23.8%) at a sensitivity of 0.0008%. We studied HSFC-MRD in 128 bone marrow samples from 99 MM patients (age- median-54 years, range-29 to 74 years and M:F ratio-4.2). Number of cells studied for MRD ranged from 700,000-9,900,000 with median of 3,400,000. We could obtain more than 2 million events (sensitivity of 0.00125%) in 84.4% of the samples and more than 5 million events (sensitivity of 0.0005%) in 59.4% of the samples. MRD was detectable in 62.7% (79/128) samples and MRD levels ranged from 0.0002% to 23.4% with median of 0.2%. Only seven samples (5.5% of total) with total event less than 2 million had undetectable residual disease. Correlation with serum M protein showed a correlation coefficient of 0.59 and 12 (9.4%) samples had detectable MRD without detectable M-protein. CD19, CD45, CD27, and CD56 demonstrated highest frequency of abnormal expression in MRD detection (i.e. 100.0%, 90.9%, 87.0%, and 87.0%), followed by CD117, CD200, CD81, CD28, CD38, and CD20 in decreasing order (i.e. 62.3%, 54.5%, 50.6%, 35.1%, 16.9% and 10.4%). Median (range) of LAIP detected in MRD was 6 (2-8) using these markers. We were also able to develop infinicyt-based database using clonal and normal plasma cells in which would allow us automated objective identification of clonal plasma cells. Conclusion: We standardized a highly sensitive 10-color flow cytometric MRD assay for MM that can detect at a sensitivity of 0.001% in nearly 95% of the samples. CD19, CD45, CD27, CD56, CD117, CD200, CD81 were found highly useful markers in MM MRD detection and must be included in the MM-MRD panel.

Keywords:
Flow Cytometry

Minimal residual disease

Multiple myeloma

Tracks:
Myeloma Response Assessment including MRD

FP-222

Comparison of minimal residual disease detection in multiple myeloma between SRL 8-color single-tube and EuroFlow 8-color 2-tube multiparameter flow cytometry methods

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Abstract:
Background: Most patients with multiple myeloma (MM) are considered to be incurable, and relapse owing to minimal residual disease (MRD) is the main cause of death among these patients. Therefore, new technologies to assess deeper responses are required. Next-generation sequencing (NGS) and multiparameter flow cytometry (MFC) methods have been used to assess MRD. However, NGS and MFC methods are generally expensive. Aims: We sought to determine the efficacy of a new, inexpensive, single-tube 8-color MFC method (SRL-Flow), which is based on the EuroFlow-next generation flow (NGF) (tube 2 only), to assess MRD-negative status. MRD-negative status is considered a treatment milestone in multiple myeloma (MM). Methods: We used 45 bone marrow samples from patients with MM, including 11 cases treated with anti-CD38 monoclonal antibody (10 daratumumab and one isatuximab cases). The NGF method was based on a standardized lyse-wash-and-stain sample preparation protocol, the measurement of high numbers of cells and an optimized 8-color,

2-tubes, antibody panel, for accurate identification of plasma cells (PCs) and discrimination between phenotypically aberrant (aPC) and normal PC (nPC) (J Flores-Montero et al., Leukemia 2017). The SRL-Flow sample preparation protocol was identical to that of EuroFlow-NGF. The antibody panel for SRL-Flow was as follows: CD138V450/CD27V500/CD38ME (multiepitope)FITC/CD56PE/CD45PerCP-Cy5.5/CD19PE-Cy7/cytoplasmic (Cy) immunoglobulin (Ig) κAPC/CyIgλAPC-H7. To identify abnormal plasma cells (aPCs) of patients with MM who received anti-CD38 monoclonal antibody, we used a panel of anti-CD45 and anti-CD138 antibodies (Abs) rather than a panel of anti-CD45 and anti-CD38 Abs. We compared the total nucleated cell (NCC) numbers, total PC levels, and MRD levels between the EuroFlow and SRL-Flow methods. The data of EuroFlow (tube 2 only) was extracted from that of EuroFlow-NGF (tubes 1 and 2). Results: We compared the total PC and MRD levels among SRL-Flow, EuroFlow-NGF (tubes 1 and 2), and EuroFlow (tube 2 only) because the panel of SRL-Flow is based on that of EuroFlow (tube 2 only). The correlations of total PC and MRD levels between SRL-Flow and EuroFlow-NGF (tubes 1 and 2) were good ($r > 0.9$). Similarly, the correlations of the levels between EuroFlow (tube 2 only) and EuroFlow-NGF (tubes 1 and 2) or SRL-Flow were also high ($r > 0.9$). We examined the discrepancies in MRD positivity/negativity. No disagreements were observed among SRL-Flow, EuroFlow-NGF (2 tubes), and EuroFlow (tube 2 only). Conclusions: High correlations ($r > 0.9$) in total PC and MRD levels were noted among SRL-Flow, original EuroFlow-NGF (2 tubes), and EuroFlow-NGF (tube 2 only), suggesting that SRL-Flow is an inexpensive (< $200 USD/sample as of January of 2019) alternative to EuroFlow-NGF (< $350 USD/sample) for assessing MRD in MM.

Keywords:
Minimal residual disease

multiparameter flow cytometry

Tracks:
Myeloma Response Assessment including MRD

FP-223

Minimal residual disease assessment using EuroFlow in patients with relapsed/refractory multiple myeloma who received carfilzomib+lenalidomide+dexamethasone (KRD) therapy

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Abstract:
Background: Deep response has a great impact on prognosis in multiple myeloma (MM). We treated patients with MM with carfilzomib+lenalidomide+dexamethasone (KRD) therapy and analyzed the response depth using multiparameter flow cytometry and the survival of these patients. Methods: We assessed the response in 21 patients with MM who started KRD between September 2016 and October 2018. We used the Euroflow-Next Generation Flow (NGF) method to assess minimal residual disease (MRD) level in bone marrow (BM) cells (cutoff: $1\times10-5$). The NGF method was based on a standardized lyse-wash-and-stain sample preparation protocol, the measurement of high numbers of cells and an optimized 8-color, 2-tubes, antibody panel, for accurate identification of plasma cells (PCs) and discrimination between phenotypically aberrant (aPC) and normal PC (nPC) (J Flores-Montero et al., Leukemia 2017). High-risk cytogenetics (del 17p, t(4;14) and t(14;16)) in BM cells were analyzed using FISH. Results: Patients (12 males; 9 females) had a median age of 66 years (range, 30-83) at KRD initiation. Patients had ISS stage 1 (n=11), 2 (n=6), and 3 (n=4). The median number of therapy lines pre-KRD, patients receiving KRD, and therapy lines post-KRD was 3, 4, and 1,

respectively. The pre-KRD response was 2 sCR, 7 VGPR, 6 PR, 3 SD, 3 PD; the post-KRD response was 13 sCR, 2 CR, 3 VGPR, 3 PR; and the best response was 20 sCR and 1 VGPR. Treatment response was upgraded in 19 patients (90%) and maintained in two PR cases (10%) post-KRD therapy. During KRD and post-KRD therapy, MRD negativity was achieved in 12 of 16 (75%) and 15 of 21 (71%) cases, respectively. All four high-risk cytogenetics cases (1 t(14;16) and 3 del17p) could achieve MRD negativity. The 2-year PFS/OS from the start of KRD therapy were 100%/100% and 88%/100% in MRD-positive and -negative cases, respectively (median follow-up, 1.8 years). One MRD-negative case showed extramedullary relapse. Conclusions: KRD therapy can induce a deep response in patients with MM, showing excellent survival.

Keywords:
KRD

Minimal residual disease

Tracks:
Myeloma Response Assessment including MRD

FP-224

Absence of Aberrant Plasma Cells in the Apheresis Product Predicts for Minimal Residual Disease Negativity after Autologous Transplantation in Myeloma Patients Who Receive First Line Therapy

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Abstract:
Background: Despite recent therapeutic advances, multiple myeloma (MM) remains an incurable disease. High-dose chemotherapy with autologous stem cell support (ASCT) is the standard frontline therapy for eligible patients. "Contamination" of leukapheresis products with aberrant plasma cells has been considered as a possible predictive factor for response and outcome, though there are limited data in the literature and concerns regarding the sensitivity of the techniques applied for their enumeration. We evaluated the frequency and the clinical value of the remaining clonal plasma cells in leukapheresis products, by utilizing highly-sensitive next generation flow (NGFC) cytometry, able to detect aberrant clonal cells at levels reaching 10-6. Patients & Methods: Leukapheresis products from 98 MM patients, who received four cycles of induction therapy based on bortezomib (VCD or VRD), were assessed for the presence of clonal plasma cells. Sample evaluation was performed with the 8-color NGFC protocol suggested by EuroFlow. Following this method, 8-10 million cells were examined; the median sensitivity of the test was 2-4x10(-6) per sample. All patients received high-dose melphalan and ASCT. Using the same NGFC protocol, 53 patients who achieved complete response (CR) post-ASCT, based on the IMWG criteria, were also examined for the presence of minimal residual disease (MRD) Results: Our analysis revealed 58/98 (59%) "uncontaminated" (con-) and 40/98 (41%) "contaminated" (con+) leukapheresis products. Interestingly, the majority of con+ cases had very low numbers of aberrant plasma cells detected; 18/40 (45%) at the level of 10(-6), 15/40 (38%) at the level of 10(-4) and 7/40 (18%) at levels ≥10(-3). On day +100 post-ASCT, MRD evaluation was performed in 33 con- and 20 con+ patients, who had achieved CR. MRD positivity was found in 11/53 (20.8%) cases. Of note, only 3/33 (9.1%) con- patients were found MRD+, all of which at very low levels, <10(-5). On the other hand, 8/20 (40%) con+ patients were MRD+ at levels varying from 10(-2) to 10(-5). Conclusions: Using NGFC, we were able to detect aberrant

plasma cells in 40% of apheresis products at the level of 10(-6). The absence of clonal plasma cells in the apheresis products predicted for MRD- in our series of patients. These results highlight the necessity of highly sensitive techniques for the detection of the clonal plasma cells that may be present in the stem cell collection. Despite the relatively low number of patients in this analysis, presence of aberrant plasma cells in the apheresis products correlates with higher probability for MRD+ after ASCT.

Keywords:
apheresis product

MRD

Multiple myeloma

Tracks:
Myeloma Response Assessment including MRD

FP-225

Longitudinal Evaluation of Minimal Residual Disease in Patients with Multiple Myeloma who Achieve Complete Response After First Line Therapy

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Abstract:
Background: Novel treatments have significantly increased the rates of complete response (CR) in patients with multiple myeloma (MM), however most of them will eventually relapse. The presence of minimal residual disease (MRD) has emerged as a valuable biomarker as it discriminates patients with a higher risk of progression despite the achievement of CR. Previous studies have highlighted the prognostic value of MRD negativity at the time of CR after frontline therapy; there is limited data on the impact of MRD in patients achieving long-term CR. In this prospective study, we evaluated the incidence of MRD- in MM patients at first CT, at prolonged CR and the probability of achieving sustained MRD- after frontline treatment. Patients & Methods: A total of 173 MM patients have been tested for the presence of MRD after achieving CR post frontline therapy, using the EuroFlow next generation flow cytometry (NGFC) approach. The cohort was divided in two groups: (A) 109 patients were tested at the time of CR and (B) 64 patients were tested after achieving long-term CR (≥2 years; median period 61 months). MRD evaluation was repeated after 6 and 12 months post the first MRD-test. Results: All patients had received bortezomib-based triplets as induction therapy: in group A, 98/109 patients had received VRD combination, while 67 patients received an autologous transplantation (ASCT) after 4 cycles of VRD; in group B all patients had received 4 cycles of a bortezomib-based triplet (mainly VCD) followed by ASCT. MRD was negative in 63/109 (57.7%) of group A and in 37/64 (57.8%) patients of group B. Among MRD+ patients in both groups (n=73), 31 (42.4%) showed very low numbers of residual clonal cells (≤10-5), irrespective of their CR status (first CR, 19/46 or prolonged CR, 12/27). Over a median follow-up period of 18-months after their MRD evaluation, 22/46 (47.8%) MRD+ patients of group A and 8/27 (29.6%) MRD+ patients of the long-term CR group progressed. Twenty-nine patients of group A and 22 patients of group B, who were MRD-, had subsequent MRD evaluation after 6 and 12 months post their first test. During the first year of follow-up, 4/29 (13.7%) of MRD- patients of group A and 6/22 (27.2%) of MRD- patients of group B became MRD+. These 4 patients of group A and 2/6 patients of group B progressed (IMWG criteria for progression) within the following 18 months of follow-up. Conclusions: MRD negativity, using NGFC EuroFlow methodology, was achieved in

approximately 58% of both patients at first CR and at prolonged CR, after first line therapy based on bortezomib. Sustained MRD- (i.e. MRD- 12 months after the first evaluation) was observed in 85% of patients at first CR. Although the number of patients in this study is relatively small to have final conclusions, the transition of MRD- to MRD+ within a year correlates with high rates of progression.

Keywords:
complete response

MRD

Multiple myeloma

Tracks:
Myeloma Response Assessment including MRD

FP-226

Saliva-omics in Plasma Cell Disorders-proof of concept and potential as a non-invasive tool for monitoring disease burden and MRD status.

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Abstract:
Salivaomics has exciting potential for the diagnosis and monitoring of malignancy, evidence of which has been reported in oral cancer, head and neck malignancies and ovarian cancer. It has been observed that approximately 40% of cancer, stroke and cardiovascular disease biomarkers are present in whole saliva. Salivaomics has become an area of great interest in disease diagnosis over the last number of years, following the footsteps of the other "omics" based diagnostic tools. Saliva is a fast, inexpensive and non-invasive method of sample collection therefore it might be considered as the biofluid of choice for the diagnosis, early detection, monitoring and prediction of progression of disease. Serum and saliva samples were collected from 18 newly diagnosed MM patients and 8 MGUS patients, peptides were purified using the filter aided sample preparation (FASP) method and samples were prepared for label-free liquid chromatography mass spectrometry (LC-MS/MS) using a Q-Exactive mass spectrometer (Thermo Fisher Scientific). Proteins were analysed using the MaxQuant and Perseus software for mass-spectrometry (MS)-based proteomics data analysis, UniProtKB-Swiss Prot database and KEGG Pathway database. The abundance of proteins in saliva from MGUS compared to newly diagnosed MM was analysed. Fatty Acid Binding Protein 5 (FABP5) was detected in elevated levels in saliva from MM patients compared to MGUS. FABP5 is known to promote cell proliferation, survival and migration and has been seen to be overexpressed in multiple cancer types such as breast, prostate and HCC. FABP5 is observed to link closely with poor outcome and unfavourable clinical parameters in MM. Additionally, analysis was performed on serial MM patient saliva samples during treatment. A panel of significant proteins was identified when comparing the saliva proteome during treatment. The abundance of many of the detected proteins mirrored response to treatment. A decreased abundance of transglutaminase 3 (TGM3) was observed in saliva from patients in remission. Overexpression of TGM3 has been observed to induce oesophageal cancer (EC) cell invasion, migration and proliferation. This study provides proof of concept that a range of biologically significant proteins of interest can be reliably detected in the saliva of MM and MGUS patients. The observation of differential abundance of FABP5 between MGUS and MM identified these as candidate proteins relevant to malignant transformation of MGUS to symptomatic MM. The demonstration of decreased abundance of FABP5 after achieving remission indicates a correlation with tumour burden. This opens the opportunity to explore candidate salivary biomarkers for use in the clinic for disease monitoring and Minimal Residual Disease (MRD) assessment.

Keywords:
Biomarker

Mass spectrometry

Proteomics

Tracks:
Myeloma Response Assessment including MRD

FP-227

Circulating tumor DNA in the peripheral blood as early predictor of clinical outcome in relapsed/ refractory multiple myeloma

Authors:
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Abstract:
Introduction: Treatment of multiple myeloma (MM) has improved over the last decade. Although long-term survival is noted in some patients, emergence of resistant disease still prevents cures. The objective of this study was to define "liquid biopsy" parameters that identify patients who do not benefit from a particular treatment before relapse becomes evident by serological markers. Having such parameters at hand will potentially inform changes in treatment. Methods: Here, we apply low-pass whole genome sequencing to profile a uniform cohort of 45 relapsed and/or refractory MM (RRMM) patients who have been treated in a multicenter phase II trial evaluating the efficacy of a combination treatment with elotuzumab, pomalidomide, bortezomib and dexamethasone (elo-PVd; NCT02718833). Peripheral blood plasma samples were acquired for circulating tumor DNA (ctDNA) evaluation at four different timepoints (screening, cycle 3 day 1 (C3D1), cycle 5 day 1 and end of treatment). The concentration, relative fraction and copy number profile of myeloma-derived ctDNA were determined across all timepoints. Results: Thus far, 17 patients (35%) continue on treatment whereas 28 patients (58%) have developed progressive disease (PD). Our data suggests that ctDNA levels at C3D1 strongly correlate with progression-free survival (PFS). Patients with reported PD and available follow-up samples (n=24) were stratified according to ctDNA levels at C3D1 of treatment. Patients with a ctDNA level <10% showed a significantly longer PFS (mean/ SEM 9.4 ± 1.3 months) as compared to those with ctDNA levels >10% (mean/ SEM 3.8 ± 0.5 months, Wilcoxon rank test P=0.0004). The kinetics of ctDNA were largely concordant with the M protein and serum-free light chains (SFLC). Importantly, we identified a subgroup of patients for whom a prediction of PFS was particularly challenging by serological markers (MR/SD at C3D1 by IMWG criteria). In this cohort of 12/24 (50%) patients, a residual ctDNA fraction >10% at C3D1 translated into a significantly shorter mean PFS (4.1 ± 1.1 months) as compared to ctDNA levels <10% (7.6 ± 1.2 months, P=0.0006). Conclusions: This preliminary data indicates that "liquid biopsy" evaluation of ctDNA may provide more accurate prognostication than serological markers alone. While in the large majority of cases ctDNA has excellent concordance with M protein and SFLC for monitoring of MM disease progression, it may provide greater accuracy to identify those patients for whom relapse is imminent before it can be detected by serological parameters. This approach may therefore refine our framework for treatment decisions. Notably, this approach is highly scalable, cost-efficient and provides information about the clonal evolution of MM without the need for bone marrow biopsy.

Keywords:
Genetic profiling

Liquid biopsy

Minimal residual disease

Tracks:
Myeloma Response Assessment including MRD

FP-228

Monitoring the cytogenetic architecture of minimal residual plasma cells indicates the therapy-induced clonal selection in multiple myeloma

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Abstract:
Background: The importance of deep response is now well-accepted in multiple myeloma (MM). So far techniques for detection of minimal residual disease (MRD) mainly focus on identifying fewer magnitude of residual cells using more sensitive technologies. However, limit attention has been paid to explore the biological and genetic features of the minimal residual cells. Methods: A cohort of 193 patients with at least one cytogenetic abnormalities (CA) at diagnosis were analyzed using data from the prospective, non-randomized clinical trial (BDH 2008/02), and iFISH analyses were performed in patient-paired diagnostic and post-therapy samples. Results: Persistent CA in residual tumor cells were observed for the majority of patients (63%), even detectable in 28/63 (44%) patients with MRD negativity (<10-4). The absence of CA in residual PCs was associated with prolonged survival regardless of MRD status. It was noted that MRD-positive but FISH-negative patients experienced similar survival to MRD-negative patients (m-TTP 4.5 vs. 5.1 years, P=0.983). According to the change of the clonal size of specific CA, patients were clustered into five groups, reflecting five patterns of clone selection under therapy pressure. 1) Pattern A were observed in 36 (19%) patients where a minor subpopulation or undetectable subclone in the pre-treatment sample became dominant after therapy. 2) Pattern B was identified in 29 (15%) patients whose fractions of PCs harboring different CA were decreased with inconsistent extent. 3) Identical CA fraction in residual PCs were found in 22 (11%) patients as Pattern C. 4) Pattern D. The fractions of PCs harboring specific CA in 35 patients (18%) were uniformly declined. 5) 71 patients lost their abnormal cytogenetic clone after therapy (less than cut-off level) were classified as Pattern E. The cytogenetic dynamics of pattern A and B can be interpreted as a therapy-induced selection process with comparable inferior survival (m-TTP 1.2 vs. 1.6 years, respectively). Patients with pattern E experienced the most favorable outcome (m-TTP 5.0 years), following those with pattern D and C (m-TTP 3.5 and 2.5 years). Longitudinal cytogenetic studies at relapse were available in 43 patients. The results suggested that sequential cytogenetic dynamics were observed in most patients, and the cytogenetic architecture of residual cells could to some extent predict the evolutional pattern at relapse. Conclusions: The repeat cytogenetic evaluation in residual cells could not only serves as a good complementary tool for MRD detection, but also provides a better understanding of clinical response and clonal evolution. Therapy-induced clonal selection was associated with inferior outcome regardless of the baseline cytogenetic profiles. The early identification of resistant clone may contribute to guide better tailored therapy strategies based on the feature of the residual tumor cells.

Keywords:
clonal evolution

FISH

Minimal residual disease

Tracks:
Myeloma Response Assessment including MRD

FP-229

Concordance Analysis of PET-CT and 10 Color MFC used for MRD assessment with other serological remission markers in Newly Diagnosed Multiple Myeloma patients Post-ASCT

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Abstract:
Background & Introduction: Autologous Stem Cell Transplantation (ASCT) has a proven role in patients with Multiple Myeloma. Different serological markers are used traditionally to monitor the remission status of the patients' post-ASCT including protein electrophoresis (SPEP), immunofixation (SIFE), and free light chain assay (SFLC). Multicolour Flow Cytometry (MFC) and PET-CT imaging post-transplantation are increasingly being used for testing residual disease. We tried to study the concordance between MFC and PET-CT in multiple myeloma patients post-ASCT. Patients and Methods: This is a concordance analysis of MFC and PET-CT (at different time points) in patients who have undergone ASCT at a tertiary care center in North India between 01 Jan 2017 till 31 Mar 2019. Flow Cytometry was done using Beckman Coulter 10-color Flow cytometer. PET-CT was done using Siemens Cyclotron. All these patients were also subjected to simultaneous serum protein electrophoresis (SPEP), serum immunofixation electrophoresis SIFE, and serum free light chain assay (SFLC). All the tests were done within a gap of 7 days. Statistical analysis was done using JMP ver 13.1.0 software. Results: A total of 60 simultaneous evaluations were assessed. The median age of the study population was 52 years (35-66). 61.3 % of the study population were males. Of all the patients analyzed 18.3% were positive for MRD by MFC and 30% were positive for PET (using PIPET scoring). On 2x2 analysis, 83.3% patients negative for PET were also negative for MFC while only 36.36% of the patients positive for MRD were positive for PET. As per the Likelihood ratio and Pearson test, the concordance between MFC and PET-CT was not statistically significant (Chi-square - 0.6152 and 0.6103 respectively). The concordance between SPEP and PET-CT was statistically significant as per the Likelihood ratio (Chi-square - 0.01) and the Pearson test (Chi-square - 0.01). The concordance between all other variables was not statistically significant. Conclusions: The results signify that these tests are not interchangeable and none of these can be used as a surrogate for the others.

Keywords:
Minimal residual disease

multiparameter flow cytometry

PET-CT

Tracks:
Myeloma Response Assessment including MRD

FP-230

IgH-V(D)J NGS Study on Non-CR patients with Negative MRD by Next Generation Flow

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Abstract:
Background: According to the treatment response criteria by International Myeloma Working Group (IMWG), treatment response is categorized on the basis of bone marrow (BM) plasma cell (PC) percentage, and the amount of remaining light chain and M-proteins. Recently, the survival and complete response (CR) rates of multiple myeloma (MM) patients have rapidly increased with the development of novel agents. However, despite the high CR rate, the recurrence rate remains high. Therefore, there is a great need for a more sensitive and accurate method to detect minimal residual disease (MRD). In 2016, IMWG included MRD in the treatment response criteria. Next Generation Flow (NGF), one of the selected methods for MRD detection, is an excellent modality with high sensitivity. We conducted MRD tests using NGF on MM patients on follow-up care. For non-CR patients with negative MRD results by NGF, a next-generation sequencing (NGS) study of IgH rearrangements was conducted for a more in-depth exploration of such contradictory results. Methods: Thirty-four patients receiving treatment for MM were included in the study. NGF was conducted with follow-up BM from all patients. At the time of the NGF tests, 11 patients showed CR, 21 showed non-CR, and two showed non-evaluable responses based on the IMWG treatment response criteria. Four out of 21 non-CR patients showed MRD-negative results by the NGF despite being non-CR. The IgH rearrangement test was conducted via NGS on those four patients with paired BM samples collected at the time of diagnosis, and follow-up. Results: NGS IgH rearrangement results at the time of diagnosis and follow-up were analyzed in the four non-CR patients with MRD-negative results by NGF. In all four of those patients, NGS study of IgH rearrangement revealed the presence of residual abnormal PCs, which were not detected by NGF. Upon NGS analysis, one patient showed same dominant clones from the time of diagnosis, two patients were found to acquire new dominant clones, and one showed heterogeneous clones. Conclusion: There is no need to further emphasize the importance of MRD detection. Many studies have shown that MRD were detected by the NGF methods in MM patients who achieved CR. In such cases (CR with MRD-positive), patients can benefit from more frequent follow-up or more intensive treatment regimen. On the other hand, the MRD-negative results by NGF in non-CR patients poses a more difficult question. IMWG treatment response criteria mainly rely on M-protein and light chain levels without consideration for the BM PC%, except in the definition of CR, which requires the BM PC% <5. Immunoglobulins have a relatively longer half-lives, due to the recycling process by FcRn receptors. If the M-protein is cleared too slowly from the system, a patient who has virtually reached CR can be miscategorized as non-CR. In such a case, a negative MRD result by NGF is justified, and there is a need to improve upon the oversight in

Keywords:
IgH-next generation sequencing

Minimal residual disease

next generation flow

Tracks:
Myeloma Response Assessment including MRD

MULTIPLE MYELOMA BONE DISEASE

FP-231

NONSECRETORY MUTIPLE MYELOMA. A RARE HEMATHOLOGIC ENTITY AND POSSIBLE MISDIAGNOSIS. A CASE REPORT WARNING

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Abstract:
Introduction. Nonsecretory multiple myeloma (NSMM) is a rare subtype of mutiple myeloma (MM). MM is normally associated with the secretion of monoclonal Ig (M spike) detected by serum or urine immunofixation/ electrphoresis; however in NSMM an M spike is not dedected, thus leading to either a misdiagnosis or a delayed diagnosis. A recent method of assessment for plasma cell disorders, serum free light chain assay (SFLC), individuates cases with measurable amounts of FLC, i.e., oligosecretory multiple mieloma (OSMM) or FLC-MMs. FLC-negative NSMM are divided into several subtypes: non-secretors in which there is Ig production without secretion; non-producers in which there no Ig production; and false non-secretors in which there is Ig production but no detected extracellular components despite pathological evidence of their secretion. The present report describes a case of OSMM in a adult male with recurrent vertebral compression fractures without monoclonal Ig in either serum or urine which misled doctors Case. A 55-year-old man with a history of sudden and recurrent back pain and difficulty walking was given a routine work-up. MRI findings showed diffuse spinal degeneration and D7 and L4 vertebral collapse. Serum gamma globulin and urine protein levels were normal, and neither serum nor urine immunofixation /ectrophoresis showed an M spike. The standard biohumoral data were normal. These results suggested a diffuse skeletal metastasis. The patient then underwent kyphoplasy and a trephine biopsy on the D7 and L4 vertebrae that showed plasma cell CD138+ K+ infiltration (50–55%). Consequently an extensive myeloma workup was performed that showed: k-FLC and λ-FLC levels at 91.20 and 5.77 mg/L, respectively, with the κ/λ ratio 15.8; a β2-microglobin level at 2.557 mg/mL; and PET-TC with an increased uptake in the sternum, left humerus, sacrum bone and left femoral diaphysis. The final diagnosis was OSMM. Chemotherapy regimen based on the proteasome inhibitor bortezomib, thalidomide and dexamethasone was performed resulting in the complete disappearance of FLC. Discussion. Paraprotein absence does not exclude a multiple myeloma diagnosis. FLC assays can suggest an oligosecretory type of NSMM, which must be confirmed by bone marrow or osteolytic lesion biopsy. In our case only a delayed bone lesion biopsy unexpectedly showed the presence of clonal/atypical plasma cells which suggested NSMM as the cause of the patient's pain and pathologic fractures. Secretory activity was then confirmed by the presence of FLC. Conclusions.This case confirms that the complete list of exams indicated by IMWG for the diagnosis of MM, which includes SFLC detection, must be performed in order to identify OSMM/NSMM, thus reducing the probability of either misdiagnoses or delayed diagnoses of MM. Moreover, a pre-treatment and monitoring FLC assays should be performed to evaluate treatment response.

Keywords:
Free Light Chains

Non secretory myeloma

Oligosecretory

Tracks:
Multiple Myeloma Bone Disease

FP-232

18F-FDG PET/CT in patients with multiple myeloma presenting with renal impairment

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Abstract:
Background 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT) has become a standard imaging technique for predicting prognosis in multiple myeloma (MM), but have potential inaccuracies in patients with renal impairment (RI).

In this study, we investigated the prognostic role of 18F-FDG PET/CT in patients with MM presenting with RI. Method Retrospective data for 209 patients with MM between June 2011 and November 2018 were analyzed. Renal function was assessed using the estimated glomerular filtration rate (eGFR), which was calculated by the simplified Modification of Diet in Renal Disease (MDRD) formula. RI was defined as an eGFR of <60 mL/min/1.73 m2 at initial diagnosis. Severe RI was defined as eGFR <30 mL/min/1.73 m2. 18F-FDG PET/CT was performed prior to induction therapy. Results. Ninety (43.1%) of 209 patients had RI at the time of diagnosis. A total of 41 patients (45.6%) had more than three focal lesions (FLs) and 16 (17.8%) had extramedullary disease on baseline 18F-FDG PET/CT. The median eGFR was 37.9 mL/min (range 3.0-59.8) and 29 (32.2%) had severe RI at initial diagnosis. Over the median follow-up duration of 33.7 months, the median progression free survival (PFS) was 23.1 months (95% CI, 16.0-30.2) and the median overall survival (OS) was 68.3 months (95% CI, 43.3-93.2). By multivariate analyses, presence of more than three FLs on PET/CT was independently prognostic factor for PFS and OS in patients with RI. Patients with more than 3FLs had significantly inferior survival outcomes than those with ≤ 3FLs (PFS, 12.7 months vs. 34.0 months, P < 0.001; OS, 42.2 months vs. not reached, P = 0.001). In patients with severe RI, >3 FLs on PET/CT was significantly associated with poorer PFS and OS (PFS, 12.7 months vs 34.4 months, P = 0.024; OS, 42.2 vs not reached, P = 0.019). Conclusion 18F-FDG PET/CT may be useful imaging technique for predicting survival outcomes in patients with MM presenting with RI.

Keywords:
Multiple myeloma

PET-CT

Renal impairment

Tracks:
Multiple Myeloma Bone Disease

FP-233

Real-world Data on Incidence, Clinical Characteristics and Outcome of Patients with Macrofocal Multiple Myeloma in the Novel Therapeutic Era: A study of the Greco-Israeli Collaborative Myeloma Working Group

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Abstract:
Macrofocal Multiple Myeloma (MFMM) was described as a distinct entity of Multiple Myeloma (MM), characterized by young age (≤40), multiple lytic lesions, limited bone marrow (BM) infiltration, absence of anemia, renal insufficiency or hypercalcemia, and favorable prognosis. Our aim was to investigate the incidence, characteristics and outcome of a large cohort of patients, regardless of age, meeting the criteria of MFMM and treated mainly with novel therapies. Patients were considered to have MFMM if BM infiltration was <20% and they had multiple lytic lesions without anemia, renal insufficiency or hypercalcemia; among 4650 MM patients (3%) registered in the MM databases of Greek and Israeli centers during 2001-2017, we identified 140 patients with MFMM (M/F: 93/47, median age: 61, range: 26-89, IgG: 86, IgA: 12, light chain: 21, IgD: 4, non-secretory: 16, IgM: 1). Twice the number of patients with typical MM treated during the same period were used for comparisons; 60% of MFMM patients were <65 years, whereas only 7/140 were ≤40 years; 68% had good performance status and 70% had advanced bone disease. Plasmacytomas present at diagnosis or during disease course were more common in MFMM compared with standard myeloma (68% vs. 15%; p<0.05). Solitary bone plasmacytoma (SBP) preceded MFMM diagnosis in 14%. Adverse prognostic parameters (i.e. high LDH, advanced age, high β2 microglobulin, high risk cytogenetics) and immunoparesis were infrequent in patients with MFMM compared with controls (p<0.05). According to the International staging system (ISS) 4% of patients with MFMM were stratified in advanced stage (ISS3) whereas none of the patients was classified in the revised-ISS3, both displaying significant difference compared with controls (ISS3:29% and R-ISS3:13%; p<0.05); 90% of patients with MFMM received novel drugs, mainly bortezomib-based (PI-based) regimens and 47% underwent autologous transplantation upfront; 90% achieved an objective response (ORR) and 70% had at least very good partial response (vgPR), both significantly higher compared with typical myeloma (p<0.05). After a median follow-up of 52 months, 33 patients have died (disease progression:19/33). Early deaths (i.e. <12 months) were uncommon (5% of patients). Median progression-free survival and overall survival (OS) were 46 and 129 months respectively, both significantly longer compared with controls (p<0.001); PI-based therapy upfront, was the only independent predictor for OS in the multivariate analysis (HR: 3.9; p<0.001). In conclusion, MFMM is a distinct entity characterized by limited bone marrow involvement, advanced bone disease and frequent development of plasmacytomas. In an appreciable number of patients, SBP precedes MFMM diagnosis suggesting a different natural history of MFMM; MFMM may occur regardless of age and it has less often adverse prognostic features. Patients with MFMM enjoy high response rates and prolonged OS when treated with PI-based therapies.

Keywords:
Macrofocal

Multiple myeloma

Outcome

Tracks:
Multiple Myeloma Bone Disease

FP-234

COMPARISON OF RADIODIAGNOSTIC METHODS (CONVENTIONAL RADIOGRAPHY, LOW-DOSE COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING) WITH SELECTED MARKERS OF BONE METABOLISM AND BONE MARROW MICROENVIRONMENT

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Abstract:
Objective Our aim was to compare the extent of myeloma bone disease (MBD) evaluated by radiodiagnostic methods, conventional radiography (X-ray), low-dose computed tomography (LD-CT) and magnetic resonance imaging (MRI), to selected markers of bone metabolism and bone marrow microenvironment. Material and Methods We prospectively examined 93 patients with newly diagnosed MM. All patients were examined by X-ray, MRI and LD-CT. We chose 10 parameters of bone marrow microenvironment that are known to be dysregulated in MBD. Following parameters of bone marrow microenvironment derived from bone marrow (trephine biopsy) were assessed: osteoprotegerin (OPG), macrophage inflammatory protein 1α (MIP-1α), receptor activator of nuclear factor kB (RANK) and its ligand (RANKL), Annexin A2, Activin A, tartrate-resistant acid phosphatase (TRAP), Dickkopf related protein (DKK-1), Runt-related transcription factor 2 (Runx2) and Matrix Metalloproteinase-9 (MMP-9). To assess these parametrs, we used immunohistochemistry techniques. For statistics we used Spearman's correlation analysis and a Kruskal-Wallis test with a post-hoc test by Dunn, at $p<0,05$. Results The assessment of osteolytic involvement in MM using X-ray is not very sensitive, especially within the spine. There was no correlation between X-ray findings and the levels of the parameters reflecting bone microenvironment and bone turnover. We found positive correlation between the extent of osteolytic involvement on LD-CT and OPG ($kk = 0,206$, $p = 0,026$), with a trend towards higher levels of MIP-1α in patients with advanced involvement on LD-CT. We also found correlation between extent osteolytic involvement on MRI and DKK-1 ($kk = 0,305$, $p = 0,035$). For other parameters the correlation was not statistically significant. Conclusion We found three parameters of bone marrow microenvironment with positive correlation to the extent of myeloma bone disease, evaluated by advanced imaging: OPG, MIP-1α and DKK-1. These three markers have the potential to predict the extent of myeloma bone disease As we expected, there was no correlation between X-ray and and the levels of the parameters reflecting bone microenvironment and bone turnover. Supported by the grant MZ ČR – RVO (FNOl, 00098892), IGA_LF_2019_001, NV18-03-00500

Keywords:
Bone marrow microenvironment

Tracks:
Multiple Myeloma Bone Disease

FP-235

Cryoablative Surgery for Patients with Radiotherapy Resistant Solitary Plasmacytoma: Report of Two Cases

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Abstract:
Background: Solitary plasmacytoma (SPC) is an infrequent form of plasma cell (PC) dyscrasia that presents as a single mass of monoclonal PCs, either extramedullary or intraosseous, with limited (<10% PC infiltration) or no bone marrow (BM) involvement. High dose radiotherapy (RT) is recommended, however, 50% of the patients later progress to multiple myeloma. The role of chemotherapy is controversial. Method: Cryoablative surgery (CryoS) is a conservative surgical technique aimed to kill remaining tumor cells after intra-lesional debulking and excision, while preserving anatomy and function. It has been

applied in benign and malignant bone tumors, however experience in myeloma is anecdotal, and to the best of our knowledge, not yet reported. CryoS induces tissue necrosis via rapid cooling, to temperature of -40 C or below. Pre-Op 3D surgical planning includes segmentation of the lesion on imaging and creation of a 3D printed guidance tool to guide the positioning of the cryo probes. During surgery, the lesion is curetted, then the lesion bed is filled with sterile gel which is frozen into an ice-ball using cryo- probes and an Argon/Helium gas system. Thereafter, the ice-ball thaws and the tumor bed is filled with PolyMethyl Methacrylate or allograft bone chips. Case descriptions: Case #1: A 37-year old women, 19 weeks pregnant, presented with a 7X8X9cm painful mass in the Lt iliac bone plasmacytoma (kappa). Whole body MRI confirmed SPC, there was no BM involvement. Serum kappa FLC was 246 mg/L. Patient received corticosteroids until delivery, then RT (45 Gy), with no response (by PETCT & repeat biopsy). She later was resistant to bortezomib/thalidomide/dexa and had partial response to carfilzomib/lenalidomide/dexa and high-dose melphalan but remained with pain and persistent active tumor. She was therefore referred to CryoS, after which she achieved for the first time normalization FLC, and local tumor control as evident, by eradication of PETCT FDG uptake and ongoing symptomatic improvement in pain control and ambulation (13 months). Case #2: A 45-year old man, presented with a painful Rt clavicular mass 3.8X4.2 cm SPC (lambda) with minimal BM involvement (0.27% clonal PCs on FACS). No further lesions on PETCT. Patient was resistant to RT (50 cGy) and refused systemic therapy; he was referred to CryoS. Local tumor response was achieved with reduced swelling and pain, PETCT showed residual updtake compatible with postoperative changes. On followup (12 months), remaining positive immunofixation IgG Lambda, non-quantifiable M-spike, and ongoing local control. Summary and conclusions: We present application of CryoS in 2 patients with radiotherapy resistant SPC. Durable tumor response with local disease control was achieved, long term outcomes are pending. This method developed and studied in various primary bone-tumors and metastatic lesions may be considered in cases of SPM resistant to standard treatment. Further studies are warranted

Keywords:
Cryoablative surgery

Radiotheraoy resistant

Solitary Plasmocytoma

Tracks:
Multiple Myeloma Bone Disease

FP-236

Imaging in Multiple Myeloma - Independent review perspective for IMWG 2016 response assessment

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Abstract:
As per the International Myeloma Working Group (IMWG) 2016 criteria, response evaluation in multiple myeloma takes into consideration two main components: clinical data (e.g., SPEP, UPEP, Immunofixation, etc.) and imaging-based plasmacytoma/ myeloma-lesions assessment. Independent central review of imaging and clinical data may be required for clinical trial submission. Currently, no clear guidance is available on acceptable imaging modalities and various types of myeloma lesions seen on imaging. The purpose of this abstract is to describe in detail how to perform and incorporate imaging assessment in a clinical trial charter; this will facilitate the independent review process as well as address the most common questions related to imaging assessment. Historically, a skeletal survey/radiography has been the most commonly used imaging modality to assess disease burden at screening and inconsistently at

post-treatment for response assessment in patients with multiple myeloma. However, skeletal survey often displays low sensitivity and resolution in identifying myeloma-lesions. With the more widespread availability of newer imaging techniques, there has been a shift in the image evaluation paradigm towards the modalities with superior resolution and sensitivity for early detection of myeloma progression, such as whole-body low dose CT, whole-body MRI and FDG-PET. The advantages and disadvantages of each modality need to be considered when designing the evaluation criteria for multiple myeloma clinical trials, tailored to suit the needs of the trial. This is especially important in the response assessment of patients who are receiving novel targeted therapeutic agents. For instance, with more modern myeloma treatments where a rapid objective response is typically achieved, assessing the metabolic activity of lesions on FDG-PET/CT can prove more valuable than using a skeletal survey. Documenting the changes in metabolic activity of the disease can be useful in the early evaluation of response or progression. Medullary and extramedullary myeloma-lesions/plasmacytomas show a varied appearance on different imaging modalities. Therefore, it is important to assess all myeloma-lesions consistently across various investigator sites involved in a clinical trial. We propose to assess soft tissue myeloma-lesions, including medullary and extramedullary plasmacytomas as measurable (target) lesions and pure lytic bony lesions as non-measurable (non-target) lesions. This approach allows for quantitative assessment of measurable lesions and qualitative assessment of the rest of the disease burden. A consistent imaging assessment by a Musculoskeletal Radiologist can then be integrated with clinical data by an Oncologist for IMWG response assessment. This can result in a guide for imaging-based independent review assessment in multiple myeloma clinical trials

Keywords:
Imaging

PLASMACYTOMA

Response Criteria

Tracks:
Multiple Myeloma Bone Disease

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New factors involved in the appearance of Mandibular Osteonecrosis by Bisphosphonates in Multiple Myeloma. A multicentric study.

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Abstract:
Introduction Osteonecrosis of the jaw (ONJ) is a complication associated with the use of bisphosphonates (BPs) in patients with multiple mieloma (MM). It is known that the previous dental procedures can precipitate the development of ONJ, but other risk factors remain unexplored. Recently, has been described the implication of other drugs in ONJ, mainly antiangiogenic treatments, but their study in the context of MM has not been performed. Objective To study the characteristics and risk factors currently implicated in the development of ONJ in patients with symptomatic MM in 13 Spanish hospitals in the last 10 years.

Methods:
Methods We studied 44 patients with sympthomatic MM, receiving BPs, that have been diagnosed with ONJ during at least 8 weeks. Patients with local bone involvement or local radiotherapy were excluded. We analyzed the possible risk factors for developing ONJ, depending on the characteristics of the patient, the underlying disease and the treatment received.

Results:
Results The demographics of the patients were: 34% MM IgG kappa, 43% stage IIIA, 45% ISS2, 41% ISSR-2 and 16% adverse cytogenetics. Of the 44 patients with ONJ, only 29% smoked and 16% had a diagnosis of diabetes mellitus. Eighty-two percent were in response of their MM when ONJ was diagnosed. Four percent of patients were diagnosed in ONJ stage 0, 25% s1, 25% s2 and 46% s3. Sixty-one percent of the patients had previously performed a dental procedure. Of these, 48% had performed an extraction with a median of 4.3 months (2-10) prior to diagnosis; 37% were carriers of a dental implant, with a median of 5 years prior to diagnosis (0.8-12) and 15% had performed other procedures such as endodontics. The treatment was observation in 4% of patients, antibiotic in 8%, surgery in 12%, surgery plus antibiotic in 74% and surgery plus hyperbaric O2 in 2% of patients. Thirthy-one percent of patients presented relapse, although cure was obtained in 45% of the patients and improvement in 32%. Sixty six percent of patients received treatment for MM with lenalidomide before or during the ONJ diagnosis, or at the relapse, with a median duration of treatment of 8 months (0-59) until the ONJ resolution. Only 20% of patients have received thalidomide and 12% pomalidomide. Median time of treatment with steroids and BPs was 16 months in both cases. Interestingly, 90% of patients had not dental revision prior to the beginning of BPs. Of the patients with ONJ who did not perform dental procedures previously, 88% received lenalidomide before or during the diagnosis while in the group of patients with dental procedures the use of lenalidomide was 51% (p 0.021). No other factor related to ONJ was found in the group that did not perform dental procedures.

Conclusion:
Conclusions - The performance of dental procedures precedes the ONJ in 61% of the patients. - In patients who did not perform dental procedures, the use of lenalidomide, antiangiogenic drug, could be a risk factor to consider for study in larger series.

Keywords:
bisphosphonates

jaw

osteonecrosis

Tracks:
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Osteolytic disease in IL-6 and Myc dependent mouse model of human myeloma

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Abstract:
Introduction: Myeloma bone disease (MBD) is an important unmet medical need characterized by focal and generalized bone loss causing severe pain,

pathological fractures, instability of the vertebral column, and medullary cord / spinal nerve root compression. MBD is a disease-defining feature of multiple myeloma, the second most common blood cancer in the United States. MBD is poorly recapitulated in genetically engineered mouse models (GEMMs) of human myeloma developed in the past. Objective: To address this shortcoming, we determined onset, incidence and severity of osteolytic disease in a new GEMM of human myeloma developed in our laboratory. The model is designated IL6Myc. It relies on deregulated expression of human IL-6 and mouse c-Myc to drive myeloma-like neoplasms and MBD-like disease in transgenic mice on the genetic background of BALB/c. Our long-term goal is to validate and use this model for preclinical studies of human MBD. Methods: We used whole-body ex vivo µCT imaging to analyze MBD-like changes in IL6Myc-transgenic mice. Parameters of bone loss, such as bone volume and trabecular space and thickness were determined with the assistance of the BoneJ software tool. Bone-eating osteoclasts in tissue sections were enumerated using cytochemical detection of tartrate-resistant acid phosphatase (TRAP). ELISA was employed to measure serum levels of soluble receptor activator of nuclear factor kappa-B ligand (RANKL) and its decoy receptor, osteoprotegerin (OPG). The abundance of IL-17 producing T helper cells (Th17) in the bone marrow was determined using flow cytometry. Results: We found that IL6Myc mice that harbor primary myeloma-like plasma cell tumors (PCTs) exhibit a pattern of skeletal decay that mimics important features of human MBD. Osteolytic disease was detected in 10 of 10 PCT-bearing IL6Myc mice and was more pronounced in long bones than axial skeleton and skull. Mechanistically, MBD-like changes in mice were caused, at least in part, by increased osteoclast-dependent bone resorption that led to heightened serum levels of TRAP and RANKL and reduced serum levels of OPG. Just like in patients with myeloma, bone disease in mice was associated with increased numbers of Th17 cells in the bone marrow. Conclusions: In conclusion, the main finding of this study is the pronounced proclivity of IL6Myc mice to MBD-like disease. The IL6Myc model holds great promise for the elucidation of the natural history of MBD and the design and testing of new approaches to the treatment and prevention of bone loss in patients with myeloma. Significance: IL6Myc-dependent bone disease occurs in a tumor microenvironment that contains a fully intact immune system. This makes the mouse model ideal for translational myeloma studies, especially for the preclinical development of immunotherapies that play a growing role in the clinical management of myeloma including MBD.

Keywords:
Genetically engineered mouse models of human cancer

Osteopenia

Small-animal ex vivo imaging

Tracks:
Multiple Myeloma Bone Disease

FP-239

Initial extramedullary myeloma impacts overall survival via affecting post progression survival

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Abstract:
[Background] Recent progress of multiple myeloma (MM) treatment has been significantly improving prognosis, however subset of MM remains to be dismal. Extramedullary myeloma (EMM) is a disease growing outside of the bone marrow. It has been repeatedly shown poor prognosis, however how it impacts survival is not fully documented. [Method] We retrospectively analyzed consecutive 149 MM patients who were diagnosed between 2006 and 2016 and treated with novel agents. EMM was diagnosed with either CT scan and/or FDG-PET scan. Extramedullary disease (EMD) defined as the presence of plasma cell tumor outside of the bone marrow, either in the form of soft-tissue mass spreading from bone or arising in extra-osseous regions. [Results] Fifty-one patients presented EMM including twenty-one EMD patients and thirty bone related plasmacytoma (BP) patients. Overall survival (OS) was significantly shorter in MM with EMD with 2.9 years compare to MM without EMD with 5.9 years ($p<0.0001$). EMD showed worse prognosis 1.9 years as usual, and BP also showed shorter survival with 3.9 years ($p<0.0001$). Impact of EMM on progression free survival (PFS) was not so significant with 1.9 years vs 2.2 years ($p=0.08$). Interestingly, PFS was significantly shorter in MM with EMD with 1.0 years compared with MM with BP with 2.2 years ($p<0.05$) and MM without EMD with 2.2 years ($p<0.05$). Overall response rate (ORR) for initial treatment and early death rate was the same. We found that post progression survival (PPS) was significantly shorter in EMM with 1.1 years vs 3.4 years ($p<0.0001$). EMM was associated with del 17p but not with other chromosomal abnormalities, high LDH, ISS or R-ISS. EMM appearance after progression was associated with initial EMM presentation. Cox proportional hazard model revealed that the presence of del 17p, EMM at diagnosis and autologous hematopoietic stem cell transplant (ASCT) were the independent prognostic factors meaning that intensive chemotherapy could partly overcome EMM. [Conclusion] Our finding again pointed out importance of advanced imaging modality to identify dismal MM subtype. It may serve as changing treatment strategy as well as predicting prognosis.

Keywords:
extramedullary disease

Multiple myeloma

prognostic factors

Tracks:
Multiple Myeloma Bone Disease

FP-240

Ixazomib inhibits osteoclastogenesis and promotes osteogenic differentiation in vitro

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Abstract:
Multiple myeloma (MM) is a clonal B-cell malignancy characterized by an accumulation of clonal plasma cells (PC) in the bone marrow (BM) leading to bone destruction and BM failure. Osteolytic bone disease is a common manifestation of MM that leads to progressive skeleton destruction

and is the most severe cause of morbidity in MM patients. Proteasome inhibitors (PIs) are the most important drugs for the treatment of multiple myeloma. Pathogenetic mechanisms of MM bone destruction are closely linked to MM PC and osteoclasts (OCs) hyperactivity coupled with defective osteoblast (OB) function unable to counteract bone resorption. We recently demonstrated that the PI Bortezomib was capable to inhibit osteoclastic differentiation modulating chitinase family genes. In this work we investigated the effect of Ixazomib (IXA), a third generation PI, on osteoclastogenesis and osteogenic differentiation. Human monocytes were differentiated in OCs in presence of OC medium (supplemented with RANKL and M-CSF), and/or 10nM IXA. We observed that IXA was able to inhibit the expression of different OCs markers such as RANK, CTSK, TRAP, and MMP9 when added in OC medium respect to OC medium alone ($p<0.001$). In addition, IXA treatment reduced CHIT1 enzymatic activity and downregulated CHIT1 and YKL40 (both mRNA and proteins). Immunofluorescence evaluation confirmed that IXA inhibited the mature OCs formation with five or more nuclei. Moreover, IXA was able to stimulate osteogenic differentiation of human mesenchymal stem cells (MSCs). After 21 days of treatment, IXA alone or added to osteogenic medium increased the osteogenic markers genes (BMP2, RUNX2, Osteocalcin and Osteonectin). Immunofluorescence assay confirmed the increase of BMP2 after IXA treatment alone or in combination with osteogenic medium. In conclusion, we showed that IXA was able to decrease osteoclastogenesis and promote osteogenic differentiation representing a good therapeutic option to improve the complex pathological condition of patients with MM.

Keywords:
bone target

ixazomib

Multiple myeloma

Tracks:
Multiple Myeloma Bone Disease

POSTER SESSION II

TREATMENT OF NEWLY DIAGNOSED MYELOMA TRANSPLANT ELIGIBLE

SP-001

Risk of developing Venous Thromboembolism in Multiple Myeloma; Based on current VTE risk assessment models : Impede VTE Score & IMWG guidelines

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Abstract:
Risk of developing Venous Thromboembolism in Multiple Myeloma; Based on current VTE risk assessment models : Impede VTE Score & IMWG guidelines Introduction.Venous thromboembolic events (VTE) are a common cause of morbid-mortality in patients with multiple myeloma(MM),occurring in about 10% of patients.The pathogenesis of thrombosis in the MM is multifactorial and includes patient, treatment and disease-related factors.It is demonstrated that the risk of VTE increases during the active phase and the risk is higher with the use of certain agents such as immunomodulators (IMIDs),especially in combination with high-dose of Dexamethasone.Although thromboprophylaxis is an

effective strategy to reduce the risk of VTE, currently there is no validated scale that can predict the risk of VTE in MM. In this study,we analyzed and compared the IMPEDE score and the IMWG guidelines as predictors of VTE risk and also evaluated additional factors not included in these assessment models in patients who developed VTE, despite antithrombotic prophylaxis. Patients and method. A retrospective observational study that includes 107 patients diagnosed with MM in a single center, between 2014 and 2018. Demographic data and thrombotic risk factors were included. The IMPEDE VTE Score and the IMWG Score were applied, and their sensitivity and specificity were evaluated with a ROC curve to predict a thrombotic event in the first 6 months of diagnosis.Chi-Square were used to compare proportions depending of the expected count of the cells. Results The average age was 74 years (40-97) with median follow-up of 14 months. The incidence of thrombosis was 7.4% (n = 9). Six pulmonary embolism (66.6%) and 3 deep venous thrombosis (33.3%). A higher risk of thrombosis was observed in patients with a GFR<60 ml/min (p=0.063), high R-ISS (p <0.05) and in those with high dose dexamenthasone (p = 0.063). All patients who developed VTE, have had adverse cytogenetics (p=0.001).According to the IMWG score, 36.8% were low risk (n = 39) and 63.6% high risk (n = 68); while the IMPEDE Score 54.2% were low risk (n = 58), 37.4% intermediate risk (n = 40), and 6.5% high risk (n = 7). No patient with low risk IMEPEDE Score, had VTE. IMPEDE score showed an AUC slightly greater than IMWG (0.683 vs 0.669). No differences in the type of MM, comorbidities, history of VTE and the use of IMIDs with incidence of VTE. Conclusions Our study confirmed that VTE is an adverse event that occurred in nearly 8% of patients with MM, with pulmonary embolism being the most common thromboembolic event. The thrombotic risk may change overtime which suggests that it is necessary to perform an ongoing assessment of VTE risk through the disease course. Although none of the scores is a validated model for predicting thrombosis, the IMPEDE Score appears to be more sensitive in our study to predict VTE in high and intermediate-risk patients. In our study all patients that developed VTE, had high-risk cytogeneti

Keywords:
Multiple myeloma

VTE RISK

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-002

Impact of 18F-FDG PET/CT as a valuable prognostic tool for the newly diagnosed multiple myeloma with extramedullary disease

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Abstract:
Purpose 18F-FDG PET/CT (PET/CT) could be considered as a valuable tool to predict the long-term survivals in patients with newly diagnosed multiple myeloma (MM). It has the ability to distinguish metabolically active sites such as extramedullary disease (EMD) as well as bone damage with relatively high sensitivity and specificity. In this study, we attempted to evaluate the PET-CT as a prognostic tool for patients with newly diagnosed MM who have EMD. Patients and Methods This study included 211 patients who were newly diagnosed with multiple myeloma from Kyunpook National University Hospital and Chonnam National University Hwasun Hospital. We retrospectively analyzed the medical records of enrolled patients. PET/CT was performed at the diagnosis and EMD was identified in 36 patients (17.1%). Results With a median follow-up duration of 21.5 months (range

1.4-67.7), the estimated 2-year PFS and OS rates were 46.1%±4.2% and 79.6%±3.2%, respectively. The presence of EMD and high maximum standardized uptake value (SUVmax) on baseline PET/CT were significantly associated with inferior long-term survivals in terms of PFS (p=0.007, p=0.013) and OS (p=0.004, p=0.002). Among the patients with PET/CT positive EMD, Revised-International Staging System (R-ISS) significantly correlated with the PFS (p=0.026) and OS (p=0.017) than the patients without PET/CT positive lesion. In addition, patients with EMD who underwent autologous stem cell transplantation (auto-SCT) showed superior PFS (p=0.005) and OS (p=0.022). In the R-ISS stage III group, patients with EMD showed statistically poor prognosis (PFS; p=0.002, OS; p=0.001). In the multivariate analysis, LDH level was an independent prognostic factor of OS (hazard ratio 3.086, 95% confidence interval 1.114-8.548, p=0.030) in patients with EMD. Conclusion PET/CT at diagnosis showed a significant prognostic value for newly diagnosed MM with EMD. Plus, PET/CT might be an important tool to determine clinical outcome in patients with R-ISS III. Therefore, patients with EMD should be considered auto-SCT to improve long-term survivals.

Keywords:
extramedullary disease

PET-CT

RISK ASSESSMENT MODEL

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-003

NEGATIVE IMPACT OF HIGH LDH AT DIAGNOSIS ON OS, BUT NOT PFS, CAN BE OVERCOME BY AUTOLOGOUS STEM CELL TRANSPLANTATION

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Abstract:
Background: Multiple myeloma (MM) is a plasma cell neoplasia characterized by a diffuse clonal plasma cell infiltration of the bone marrow. Serum lactate dehydrogenase (LDH) is a relevant biomarker and a fundamental element of the R-ISS. Methods: This single center retrospective study included 213 consecutive myeloma patients who underwent autologous stem cell transplantation (ASCT) between January 2008 - May 2019. Baseline ISS and serum LDH values (ULN) were compared with response and survival outcomes . Results: High LDH: 44 (20.7 %) and normal LDH: 169 (79.3 %)) was found among (median age at diagnosis:63 years (range, 36-77 years))all patients. The median time of follow-up was 44 months (range, 2.8-197.5 months). There was no statistically significant difference in gender, MM subtype, ISS stage, induction treatment and chemotherapy lines prior to ASCT when stratified by LDH. In both groups, most of the patients received VCD (high LDH: 20 (45.5 %) normal LDH: 99 (58.6 %)). Induction therapy consisted of 3 drugs in 81.9 % and 2 drugs in 18.2 %. Forty-eight (75 %) patients with high LDH received a bortezomib-based induction and 26 patients (59.1 %) achieved ≥ very good partial remission (VGPR) after the induction therapy. Number of ASCT was balanced between high and normal LDH groups: One hundred sixty-one patients received single (high LDH: 33 (75 %) normal LDH: 128 (75.7 %)) where as 52 received double (high LDH: 11 (25 %) normal LDH: 41 (24.3 %)) ASCT as salvage treatment (p>0.5). Median PFS was 73.2 months (95 % CI: 63-83.4) in high LDH group and 92.3 months (95 % CI: 66.8-117.9) in normal LDH group (p=0.26). According to the long-rank test, estimated 5-year OS was not significantly different between normal and high LDH categories (58.9 %±0.4 % vs. 58.3 %±0.9 %; p=0.41). ISS I vs II/III patients exhibited an OS 101 months (95 % CI 83.8-

119.4) vs 65.2 months (95 % CI 43.4-87.1) (p=0.01). Conclusion: In our consecutive series of 213 patients who received 1-2 ASCT, we were able to validate prognostic role of ISS but not able to observe a negative impact of LDH on OS. However, a statistically insignificant difference in response rates and PFS in favor of normal LDH was observed.

Keywords:
autologous stem cell transplant

lactate dehydrogenase

Multiple myeloma

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-004

Selecting transplant in the elderly: validation of IMWG frailty score and Revised Myeloma Comorbidity Index compared to clinical judgment

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Institutions:
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Abstract:
Background: Autologous stem cell transplantation (ASCT) has proven safe and effective in selected elderly patients (pts) with Multiple Myeloma (MM); several comorbidities scores have been proposed but specific criteria for evaluating ASCT eligibility in elderly MM pts still need to be established. We performed an external validation of the IMWG frailty score and the revised Myeloma Comorbidity Index (R-MCI) in unselected elderly pts considered for ASCT at our center and treated according to clinical judgment. Methods: From January 2013 to December 2018 167 consecutive newly diagnosed symptomatic MM pts aged 65-75 were evaluated: the IMWG frailty score and the R-MCI were obtained at diagnosis; the intensity of treatment was left to physician's clinical judgment, irrespective of the above mentioned scores. The predictive role of the scores on progression-free survival (PFS) of pts selected or not for ASCT was analyzed. Results: Of 167 pts, 98 (59%) were judged transplant eligible (ASCT group) by the clinician and received bortezomib-based induction (VTD 98%); 85 of them (87%) actually underwent ASCT (73% single, 27% double; melphalan 200 mg/sqm in 73% of cases). The 69 (41%) pts considered ineligible to ASCT received a less intensive first line treatment (82% VMP). CR rate after the first ASCT was higher in the ASCT vs the NO-ASCT group (44,8% vs 19%, respectively; p 0.0005). Transplant related mortality (TRM) was 0%. By intention to treat (ITT), after a median of 32 months, PFS was 34,6 in the ASCT group vs 18,4 months in NO-ASCT pts, respectively (p 0,0001). No pts classified as FRAIL had been considered eligible to ASCT by clinical decision; their outcome was significantly worse compared to FIT and UNFIT pts according to IMWG frailty score [median PFS 7,1 vs 34,6 and 28,12 months, respectively ($p < 0,0001$)] and to R-MCI, [median PFS 10,1 vs 33,3 vs 24 months ($p<0,0028$)]. In FIT&UNFIT pts selected for ASCT according to clinical judgment, PFS was better than with NO-ASCT: median 34,6 vs 23,6 months by IMWG frailty score (p 0,0045), 34,6 vs 21,9 months by R-MCI (p 0,0004). In the ASCT group, the age group 65-69 years fared better than pts 70 (34,6 vs 24 months, p 0,0035). However, while in UNFIT pts aged 65-69, PFS was superior with ASCT (42,6 vs 21,2 months (p 0.011, IMWG frailty score); 35,6 vs 22,3 months (p 0,028, R-MCI), the PFS of the ASCT group was comparable to NO ASCT in pts aged 70 considered UNFIT both according to IMWG frailty score (28,1 vs 24,5 months, p 0,96) and to R-MCI (29,8 vs 18 months, p 0,17,). Conclusion: In an unselected series of elderly MM pts aged 65-75 undergoing ASCT according to clinical judgment the outcome of ASCT pts was better than those of NO-ASCT. However both the IMWG frailty score

and the R-MCI have proven particularly useful in the age group 70-75 since patients identified as UNFIT by any of the two scores did not benefit from ASCT selected according to clinical judgment compared to less intensive treatments.

Keywords:
Elderly

frailty

transplantation

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-005

Early mortality in Transplant-eligible Multiple Myeloma patients in Latin America. An International Study of GELAMM.

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Abstract:
Background: Early mortality (EM) is still an unsolved problem in the treatment of multiple myeloma (MM). Age, renal failure, infections and active disease have been associated to inferior survival. There is scarce information about this topic in Latin America (LA). The aim of this study was to evaluate EM in a Latin-American transplant eligible MM cohort, and to determine associated risk factors. Methods: A retrospective, multicenter, observational cohort study was performed in 5 countries from LA. Patients included were consecutive newly diagnosed (ND), transplant-eligible MM, older than 18 years, diagnosed between 2010 and 2018. EM was defined as death from any cause in the first 6 months from diagnosis. Survival curve was estimated using the Kaplan–Meier method, comparisons among groups were carried out with the chi-square test. Risk factors were analyzed as independent variables in multivariate Cox regression model. In all cases, $p<0.05$ was considered significant. Results: Data from 930 patients from Argentina, Chile, Uruguay, Ecuador and Mexico were collected. Anemia and bone lesions were the prevailing symptoms at diagnosis. More than 70% of patients were ISS2-3 and 25.6% had renal failure. A 9% EM rate was found. Patients with EM had higher incidence of hypercalcemia 47.3%vs16.8% ($p<0,001$), anemia 77.3%vs54.3% ($p<0,001$), renal failure 60%vs22% ($p<0,001$), ISS3 77%vs35.9% ($p<0,001$) and light chain MM 36.4%vs15.6% (LCMM) ($p<0,001$) at

diagnosis. Twelve percent of patients treated in the public setting died early compared to 3.2% from the private setting (p<0.001). Ninety-eight percent of whole cohort received at least one treatment dose. Only 28.6% of patients with EM received bortezomib in frontline treatment vs 51.9% in those surviving >6 months (p<0.001). Bortezomib was included in frontline therapy in 32.8% in the public vs 75.8% in private centers (p<0.001). With a median follow-up of 26 months, median overall survival of the whole cohort was 72 months (95% CI 63.7–80.3). Causes of EM were detailed in 28 patients: MM progression in 71.4% and infections in 25%. In the multivariable analysis, treatment in the public setting (p=0.014), no bortezomib frontline therapy (p=0.001), LCMM type (p=0.001), renal failure (p=0.002) and ISS3 (p=0.006) were independent factors associated to EM. Conclusion: EM was 9%, similar to reported by others studies. The results of this study provide real-world data concerning risk factors for EM in MM in LA. Some features help identify ND transplant-eligible patients at risk of EM: LCMM, ISS 3, renal failure, treated in a public setting, not receiving bortezomib. Most early deaths were attributed to disease progression. This study has limitations, particularly due to its retrospective nature and a high number of missing data regarding cause of death. Improving frontline therapy according to current evidence and a more effective prevention of infections must be prioritized to help decrease EM.

Keywords:
Mortality

Multiple myeloma

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-006

Daratumumab Plus Lenalidomide Versus Lenalidomide Alone as Maintenance Treatment in Patients With Newly Diagnosed Multiple Myeloma After Frontline Transplant: A Multicenter, Randomized, Phase 3 Study (AURIGA)

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Abstract:
Trial in Progress Background: Daratumumab, a human anti-CD38 IgGκ monoclonal antibody, is approved in many countries as monotherapy in relapsed/refractory multiple myeloma (RRMM), and in combination with standard-of-care regimens in RRMM and transplant-ineligible newly diagnosed multiple myeloma (NDMM). Daratumumab is also under investigation as induction, consolidation, and maintenance treatment in transplant-eligible NDMM. The phase 3 AURIGA (MMY3021) study will evaluate the conversion rate to minimal residual disease (MRD) negativity after 1 year of maintenance treatment with daratumumab plus lenalidomide versus lenalidomide alone following autologous stem cell transplant (ASCT). Methods: In this ongoing multicenter, open-label, randomized phase 3 study, approximately 214 patients from up to 60 sites in the United States will be randomized 1:1 to daratumumab plus lenalidomide versus lenalidomide alone, stratified by cytogenetic risk. Eligible patients (18-79 years of age) are those with NDMM who have completed 4-8 total cycles of induction therapy (and/or consolidation therapy), have undergone ASCT, and are MRD-positive by next-generation flow (NGF) or next-generation sequencing (NGS). At the time of randomization, patients must be 60-100 days post-ASCT (≤60 days post-treatment for patients receiving consolidation therapy) and must have achieved a very good partial response or better per International Myeloma Working Group criteria. Patients previously treated with anti-CD38 antibodies are excluded. Patients

will receive 10 mg lenalidomide orally continuously during each 28-day cycle. After Cycle 3, if lenalidomide is well tolerated, the dose may be increased to 15 mg per investigator decision. Patients in the daratumumab plus lenalidomide group will receive subcutaneous daratumumab (1,800 mg co-formulated with recombinant human hyaluronidase PH20 [rHuPH20; Halozyme]) QW in Cycles 1-2, Q2W in Cycles 3-6, and Q4W thereafter. Treatment will continue until disease progression, unacceptable toxicity, withdrawal, or for a maximum of 36 cycles. The primary endpoint is the MRD-negativity conversion rate (10^-5 sensitivity threshold) at 12 months, assessed via NGS. MRD will also be assessed at 6, 18, 24, and 36 months. Secondary endpoints include progression-free survival, overall MRD-negativity rate, durable MRD negativity, rate of complete response or better (≥CR), duration of ≥CR, overall survival, health-related quality of life, and safety. The ClinicalTrials.gov identifier is NCT03901963.

Keywords:
daratumumab

maintenance

Newly diagnosed multiple myeloma

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-007

A Matching-Adjusted Indirect Comparison (MAIC) of Daratumumab-Bortezomib-Thalidomide-Dexamethasone (D-VTd) Versus Bortezomib-Lenalidomide-Dexamethasone (VRd) in Patients (Pts) With Newly Diagnosed Multiple Myeloma (NDMM) who are Transplant Eligible

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Abstract:
Introduction: In Part 1 of the phase 3 CASSIOPEIA trial, patients (pts) received four 28-day pre-autologous stem cell transplant (ASCT) induction and two 28-day post-ASCT consolidation cycles of D-VTd or VTd. D-VTd improved progression-free survival (PFS) and rates of stringent complete response (sCR) and minimal residual disease (MRD) vs VTd alone. Overall survival (OS) remains immature. In Part 2 (ongoing), pts were re-randomized to daratumumab maintenance or observation for 2 yrs. In the phase 3 IFM2009 trial, all pts received three 21-day cycles VRd induction followed by either an additional 5 cycles of VRd or ASCT followed by 2 post-ASCT consolidation cycles of VRd (all pts then received 1 yr lenalidomide maintenance). VRd + ASCT improved PFS vs VRd and OS was similar between groups. Indirect, naïve comparisons of CASSIOPEIA and IFM2009 may introduce bias due to differences pt populations. As no randomized controlled studies have directly compared D-VTd to VRd in transplant-eligible NDMM, an unanchored MAIC was conducted to assess relative differences in OS, PFS, and MRD negativity in D-VTd vs VRd + ASCT. Methods: For each analysis, a naïve comparison without adjustments and MAIC were performed. The MAIC weighted individual D-VTd pts in CASSIOPEIA (based on propensity scores) to match published summary baseline characteristics of VRd + ASCT pts in IFM2009, and weighted outcomes were calculated. Matched characteristics were median age, sex, ISS stage, and IgG disease.

IFM2009 pt-level OS and PFS data were generated by the Guyot algorithm. IFM2009 assessed MRD (10^–4 sensitivity threshold) in ≥VGPR pts during consolidation and maintenance. CASSIOPEIA assessed MRD at a 10^–5 sensitivity threshold regardless of response; therefore a post-hoc analysis was used to estimate a similar variable from this study, limiting MRD results to post-consolidation. Results: A total of 543 D-VTd pts in CASSIOPEIA and 350 VRd + ASCT pts in IFM2009 were treated in their respective studies. There were no notable differences in baseline characteristics between treatment arms after matching. Naïve comparisons for OS, PFS, and MRD negativity were all significantly in favor of D-VTd vs VRd. After matching, OS, PFS, and MRD negativity were also all significantly in favor of D-VTd vs VRd. In the MAIC, D-VTd performed significantly better than VRd for OS (hazard ratio [HR], 0.305; 95% CI, 0.165-0.565; P <0.001). The PFS HR in the MAIC was 0.473 (95% CI, 0.328-0.683; P <0.001) for D-VTd vs VRd. A total of 73.8% D-VTd vs 62.9% VRd pts achieved MRD negativity (10^–4), with a rate difference of 10.98 (95% CI, 4.7-17.26; P = 0.001), after matching. Conclusions: This MAIC demonstrates that D-VTd + ASCT in CASSIOPEIA significantly improved efficacy in terms of PFS and MRD negativity vs VRd + ASCT in IFM2009 for transplant-eligible NDMM. Although the MAIC demonstrates significant improvement in OS for D-VTd + ASCT vs VRd + ASCT, the OS results from CASSIOPEIA remain immature.

Keywords:
comparative effectiveness

daratumumab

Newly diagnosed multiple myeloma

Tracks:
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SP-008

A Matching-adjusted Indirect Comparison (MAIC) of Bortezomib-Thalidomide-Dexamethasone (VTd) and Daratumumab Plus VTd (D-VTd) Versus Bortezomib-Dexamethasone (Vd) in Patients with Newly Diagnosed Multiple Myeloma (NDMM) who are Transplant Eligible (TE)

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Abstract:
Introduction: In Part 1 of the phase 3 CASSIOPEIA study, patients (pts) received D-VTd or bortezomib-thalidomide-dexamethasone (VTd) as pre-autologous stem cell transplant (ASCT) induction (four 28-day cycles) and post-ASCT consolidation therapy (two 28-day cycles). D-VTd improved progression-free survival (PFS) and rates of stringent complete response (sCR) and minimal residual disease-negativity rate vs VTd. In Part 2 (ongoing), pts were re-randomized to D maintenance or observation for 2 years. In the phase 3 IFM 2005-01 study, pts received vincristine-doxorubicin-dexamethasone (VAd) induction (four 28-day cycles) with or without dexamethasone-cyclophosphamide-etoposide-cisplatin (dCEP) consolidation (two 28-day cycles), or Vd induction

(four 21-day cycles) with or without dCEP consolidation therapy; all pts with a partial response or better post-ASCT were randomized (1:1) to receive lenalidomide maintenance or placebo until relapse. Vd induction improved median PFS and overall response rate compared with VAd induction; response rates were similar with and without dCEP consolidation. As indirect naive comparisons may introduce bias due to differences in patient populations, we compared relative differences in efficacy outcomes (PFS and OS) for D-VTd or VTd+ASCT vs Vd+ASCT using an unanchored MAIC. Methods: In each analysis, a naïve comparison without adjustments and MAIC were performed. The MAIC weighted individual D-VTd or VTd pts in CASSIOPEIA (based on propensity scores) to matched published summary baseline characteristics of Vd pts in IMF 2005-01, and weighted outcomes were calculated. Matched characteristics were age, sex, ISS stage, β-2 microglobulin level, cytogenetic profile, hemoglobin level, and serum calcium level. A sensitivity analysis was performed that also matched pts on creatinine level. IFM2005-01 patient level OS and PFS data were generated by the Guyot algorithm. Results: A total of 543 D-VTd and 542 VTd pts in CASSIOPEIA and 240 Vd pts in IFM 2005-01 were treated. After matching, all baseline characteristics were balanced between treatment arms. Naive comparisons of PFS and OS were all significantly in favor of D-VTd vs Vd. After matching, PFS and OS were also significantly in favor of D-VTd vs Vd. D-VTd performed significantly better than Vd for PFS (HR, 0.42 [95% CI: 0.28-0.63], P<0.0001) and OS (HR, 0.38 [95% CI: 0.18-0.77], P=0.0072). The sensitivity analysis including baseline creatinine level showed similar significant results for PFS and OS, although these results should be interpreted with caution due to a marked reduction in effective sample size, immaturity of data in the D-VTd arm, and presence of outliers. Naïve comparisons and MAICs showed that PFS and OS were not significantly different for VTd vs Vd. Conclusion: In this MAIC, D-VTd+ASCT from CASSIOPEIA significantly improved PFS and OS compared with Vd+ASCT from IFM2005-01 for pts with NDMM who were TE, although the CASSIOPEIA OS data remain immature.

Keywords:
autologous stem cell transplant

daratumumab

Newly diagnosed multiple myeloma

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SP-009

A Matching-adjusted Indirect Comparison (MAIC) of Bortezomib-Thalidomide-Dexamethasone (VTd) and Daratumumab Plus VTd (D-VTd) Versus Bortezomib-Cyclophosphamide- Dexamethasone (VCd) in Patients (Pts) with Newly Diagnosed Multiple Myeloma (NDMM) who are Transplant Eligible (TE)

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Abstract:

Introduction: In Part 1 of the phase 3 CASSIOPEIA study, pts with NDMM who were TE received D-VTd or VTd as pre-autologous stem cell transplant (ASCT) induction (four 28-day cycles) and post-ASCT consolidation therapy (two 28-day cycles). D-VTd improved rates of stringent complete response (sCR), minimal residual disease-negativity, and progression-free survival (PFS) compared with VTd. In Part 2 (ongoing), pts with a partial response or better were rerandomized to daratumumab maintenance or observation for 2 years. In the phase 3 GMMG-MM5 study, pts with NDMM who were TE received induction with bortezomib-cyclophosphamide-dexamethasone (VCd; three 21-day cycles) or doxorubicin-dexamethasone (PAd; three 28-day cycles) pre-ASCT induction followed by lenalidomide consolidation (two 28-day cycles) and maintenance for 2 years (LEN-2Y) or until CR (LEN-CR). The estimated 36-months overall survival (OS) rate was significantly improved in the VCd- and PAd- LEN-2Y groups vs the VCd- and PAd- LEN-CR groups; however, PFS (the primary endpoint) was not statistically different for any group. In the absence of randomized controlled trials comparing D-VTd or VTd to standard-of-care VCd as induction and consolidation therapy, an unanchored MAIC was used to compare PFS and OS for D-VTd or VTd vs VCd-LEN-2Y. Methods: Naïve comparisons and MAICs were performed. The MAIC weighted individual D-VTd or VTd pts from Part 1 of CASSIOPEIA (based on propensity scores) to matched published baseline characteristics of pooled data for the VCd-LEN-2Y and VCd-LEN-CR pts in GMMG-MM5 (VCd-LEN-2Y baseline data were not available separately). Matched characteristics were age, sex, ISS stage, ECOG/WHO status, cytogenetic profile, creatinine level, bone disease, serum calcium level, platelet count, LDH level, and heavy-chain isotype distribution. GMMG-MM5 patient-level PFS and OS data were generated by the Guyot algorithm. Results: 543 D-VTd and 542 VTd pts in CASSIOPEIA and 251 VCd pts (n=126 VCd-LEN-2Y; n=125 VCd-LEN-CR) in GMMG-MM5 were treated in their respective studies. All clinically relevant baseline characteristics were similar between the treatment arms with the exception of the number of pts with elevated LDH. Naïve comparisons of PFS and OS favored D-VTd vs VCd-LEN-2Y, and no differences between VTd vs VCd-LEN-2Y were observed. After matching, PFS and OS remained improved for D-VTd vs VCd-LEN-2Y (PFS HR, 0.35 [95% CI: 0.21-0.58], P<0.0001; OS HR, 0.34 [95% CI: 0.14-0.86], P=0.0223). PFS and OS for VTd vs VCd-LEN-2Y were similar after matching (PFS HR, 1.00 [95% CI: 0.62-1.61], P=1.0000; OS HR, 0.94 [95% CI: 0.42-2.13], P=0.8868). Conclusion: This MAIC supports use of D-VTd+ASCT as a valid treatment option for pts with NDMM who are TE; D-VTd+ASCT from CASSIOPEIA improved PFS and OS vs VCd-LEN-2Y+ASCT from GMMG-MM5, although the CASSIOPEIA OS data remain immature. PFS and OS were not different for the control VTd group+ASCT from CASSIOPEIA and VCd-LEN-2Y+ASCT from GMMG-M5.

Keywords:
autologous stem cell transplant

daratumumab

Newly diagnosed multiple myeloma

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SP-010

Bortezomib-based regimens for primary multiple myeloma patients in China: from 2006 to 2018

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Abstract:
Since the approval of Bortezomib for the treatment of Chinese MM patients in 2006, the understanding of the efficacy and adverse reactions of the drug has gradually become clear, therefore the clinical application form also have corresponding changes and thereby affect the characteristics of the patient population who receiving treatment and the treatment effect. A total of 530 MM patients who received bortezomib-based treatment in 4 hematological disease treatment centers in China from February 2006 to August 2018 were enrolled in this study ,the general characteristics, treatment regimen, treatment course, efficacy, survival and adverse reactions of the patients in this group who received treatment before and after August 2013 were analyzed and compared.The results indicated that optimized treatment regimen and administration enable patients to complete more courses of treatment after 2013, the ORR was similar in this two group (88.6% vs 90.5%), but there was a higher rate of CR (39.1% vs 28.6%) and a better PFS after 2013.Subgroup analysis suggested that non-high-risk patients with D-S stage, ISS stage and R-ISS stage had significant PFS benefits in elderly patients aged 65 and above.Therefore, in the clinical practice in China,by reducing the financial burden of patients' treatment and optimizing the treatment regimen, more patients can adopt the better regimen and receive more treatment, thus achieving better efficacy and survival.

Keywords:
bortezomib

Multiple myeloma

optimizing the treatment regimen

Tracks:
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SP-011

Real-time prediction of myeloma clinical responses using an ex vivo, 3-dimensional culture system

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Abstract:
Introduction Though major therapeutic advances have extended median overall survival in myeloma from 3-5 years to 8-10 years, these new therapies are costly. Further, these treatments are not without significant side effects. Individual treatment responses are difficult to predict. In this study, we proposed that this prediction can be achieved by testing sensitivity on the diagnostic bone marrow biopsy. Methods Following ethics approval, consecutive myeloma patients were accrued in a prospective, observational manner. Additional aspirate from the diagnostic sample and a same-day blood sample underwent Ficoll separation to isolate bone marrow (BMNCs) and peripheral blood mononuclear cells (PBMCs). BMNCs and PBMCs were placed 1:1 in a 24-well plate prepared with Matrigel (Corning) and fibronectin to create a 3-dimensional (3D) lattice system. Newly diagnosed patient marrows were treated with increasing titrations of cyclophosphamide (50, 100, 1000, and 2000 mcg/L) and bortezomib (1, 10, 50, and 100 mcg/L); the combination of cyclophosphamide (Cy, 500 and 100 mcg/L), bortezomib (Bor, 50 and 100 mcg/L), and dexamethasone (D, 2 mcg/L); and a negative control all in duplicate. Media (patient serum) was exchanged and cultures retreated based on their assigned well on day 3. Cultures were harvested on day 7 following enzymatic degradation as previously described. Cells were subsequently quantified and assessed for viability by light microscopy first and subsequently confirmed by

flow cytometry. Percentage of myeloma cell death ex vivo was compared to both serum free light chain (SFLC) and monoclonal protein (M-protein) response following 4 cycles of CyBorD. Results 12 consecutive patients were accrued to this study consisting of 8 males, median age of 66 (range 48-70), and a majority having ISS stage III. 3 patients prematurely stopped therapy and were not included for final analysis (cardiac reasons [n=1] or treatment complications [n=2]). Of the 9 remaining patients, concordance between ex vivo and clinical response (by either SFLC or M-protein) was relatively high (r2=0.80 with SFLC and r2=0.78 with M-protein) with higher association between ex vivo and clinical response occurring in those achieving a very good partial response (VGPR) or better. By separating the individual therapies in culture, only 22.2% (n=2) in fact demonstrate any sensitivity to cyclophosphamide. In 1 patient who did not achieve a VGPR, a unique CD20+, CD138+ clone began to expand following treatment. Conclusions Our preliminary data demonstrates that ex vivo, 3D culture of patient-derived bone marrow treated according to their clinical situation can be predictive and quick. This timing is important as it can fit concurrently with a clinical lab's bone marrow analysis and could be available prior to treatment start. Further optimization is being explored now such as shortening culture duration and testing for resistance mechanisms particularly in those not in VGPR.

Keywords:
Ex-Vivo

Multiple myeloma

Predicting Treatment Response

Tracks:
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SP-012

Outcomes with different administration schedules of VRD as first-line therapy in multiple myeloma: a retrospective analysis

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Abstract:
Introduction: Induction therapy for multiple myeloma with subcutaneous (SQ) bortezomib (V), lenalidomide (R), and dexamethasone (D) (VRD) has traditionally been administered as a three-week cycle regimen, with SQ bortezomib given on days 1,4,8,11 and lenalidomide on days 1 to14. A modified schedule of weekly bortezomib over a 21 [len: days 1-14] or 28 day cycle [len: days 1-21] is frequently used in practice to reduce the risk of neuropathy. This study evaluates the response rates and outcomes with different schedules of subcutaneous (SQ) bortezomib and lenalidomide. Methods: Electronic records of newly diagnosed multiple myeloma patients from 2008 to 2016 were retrospectively reviewed for administration frequency of bortezomib: weekly or twice weekly and on a 21 or 28 day cycle. Weekly bortezomib was given on days 1,8,15 on 21 day cycle and days 1,8,15,22 with a 28 day cycle. Patients who received alternate schedules of bortezomib administration or switched from weekly to twice weekly or vice versa during their induction were excluded. Response rates per IMWG criteria and PFS with different schedules is reported Results: 109 patients met inclusion criteria. The cohort included 63% men (n=69), 37% women (n=40); 84% were <70 yrs (n=91) and 66% underwent ASCT (n=72). SQ bortezomib was administered twice weekly in 67% (n=73) and once weekly in 33% (n=33). In the once weekly

bortezomib group, treatment cycles were every 21 days in 36% (n=13) and every 28 days in 64% (n=23). Median no. of treatment cycles was as follows: twice weekly: 5, weekly q21:4, weekly q28: 4. Treatment was discontinued due to toxicity in 15%, 8% and 13% of patients in the three groups respectively, p=0.8. VGPR or better response was seen in 59%, 54% and 48% patients in the three groups respectively, p=0.6. Time to best response was also similar [median: 3.5, 2.9, 3.9 months; p=0.09]. Estimated median PFS in the twice weekly, weekly q21 and weekly q28 schedules was 25.9, 16.3 and 27.6 months, p=0.28. On multivariate analysis incorporating treatment schedule, ASCT and high-risk cytogenetics [del 17p, t(4;14), t(14;16) and t(14;20)], there was no difference in PFS based on treatment schedule (weekly q21 vs. twice weekly: HR 1.5, 95%CI 0.7-3.3, p=0.3; weekly q28 vs weekly q21: HR 0.7, 95% CI 0.3-1.6, p=0.4; weekly q28 vs. twice weekly HR 1.0, 95% CI:0.6-1.8, p=0.98). Conclusion: VRD treatment with weekly SQ bortezomib on a 21 or 28 day cycle resulted in similar response rates, time to response and PFS as conventional VRD on a 21 day cycle with twice weekly bortezomib. Weekly bortezomib is preferred as it results in lower rates of neuropathy, which was not evaluated in this study due to difficulty in ascertaining neuropathy retrospectively. Given equivalence of both 21 and 28 day cycle of weekly VRD, either may be selected based on physician and patient preferences.

Keywords:
Multiple myeloma

treatment patterns and outcomes

VRD

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-013

Tandem autologous stem cell transplantation in high-risk patients with newly diagnosed multiple myeloma: Feasibility and preliminary results.

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Abstract:
Aim: High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) remains the mainstay of treatment of eligible patients with newly diagnosed multiple myeloma (MM). However, results of ASCT in high-risk (HR) patients, i.e., those with adverse cytogenetics and/or ≤PR after induction are suboptimal. Retrospective data suggest that double ASCT (tandem) can improve prognosis in this subgroup of patients. We analyze the feasibility and the efficacy of tandem ASCT in terms of progression-free survival (PFS) and overall survival (OS) in HR patients with MM and compare the results with a series of patients with standard-risk (RS) undergoing a single ASCT. Material and methods: This is a prospective study with a retrospective initial phase. We present the initialresults of the preliminary phase. Patients with MM aged ≤70 years undergoing front-line ASCT (single or tandem) and diagnosed between 2014-2018 in our institution have been included. Recruitment is still ongoing. Currently, 45 patients have been included: 30 SR and 15 HR (13 due to bad-prognosis cytogenetics and 2 due to ≤PR after induction). The median, mean, and range for continuous variables and frequency (percentage) for categorical variables were calculated using standard methods. Estimation of PFS and OS was performed using Kaplan-Meier method. Results: Baseline characteristics at diagnosis were similar between both groups except for cytogenetics. Eleven (73%) out of 15 patients in the HR group underwent the tandem ASCT, in the remaining four, second ASCT was not performed due to: poor stem cell collection (1), severe thrombocytopenia, relapse after first ASCT (1 each), and patient refusal (1). The overall response rate (ORR) after induction in the HR group was 100% (≥PR: 15, ≥VGPR: 11, ≥CR: 7) and after first ASCT was 93.3% (≥PR: 14, ≥VGPR: 13, ≥CR:

8) with one patient progressing after ASCT. Response after second ASCT was ≥PR: 9, ≥VGPR: 8, ≥CR: 6 (response evaluation is pending in one patient). Response after second ASCT was improved in 4 (40%) out of 10 evaluable patients. Among SR patients the ORR after induction and after ASCT was 96.7% (≥PR: 29, ≥VGPR: 24, ≥CR: 16) and 96.7% (≥PR: 29, ≥VGPR: 25, ≥CR: 20), respectively. In this group, 11 (36.7%) patients improved response after ASCT. With a median follow-up of 33.36 months, median PFS in HR group was 30 months (95%CI, 15.30-44.69) and 38 months (95%CI, 13.58-62.51) in SR group (p=0.3). Median OS has not been reached in any group. Eight patients have died, 3 in the HR group (MM progression, 2; other causes, 1) and 5 in the SR group (MM progression, 2; transplant-related mortality, 1; other causes, 2). Conclusions: Tandem ASCT approach seems to be a feasible option for most patients with HR MM. Our preliminary results did not show differences in terms of PFS when compared with SR patients receiving a single ASCT. A high number of patients and a longer follow-up are required to confirm these data.

Keywords:
autologous stem cell transplant

High risk

Tandem Transplant

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-014

Comparative Effectiveness of Induction Treatment Regimens in NDMM: Results of an SLR to Inform Clinical Decision-Making in the US

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Abstract:
Introduction Numerous induction regimens have proven effective in patients with newly diagnosed multiple myeloma (NDMM). Lately, new drug combinations have been evaluated, with important implications for NDMM treatment. This systematic literature review (SLR) aimed to identify recently published evidence investigating the effectiveness and impact on patient quality of life (QoL) of lenalidomide (LEN)-based regimens as induction therapy in NDMM, in order to inform clinical decision-making. Methods and Population The SLR followed the methods recommended by the Cochrane Collaboration and is reported according to the PRISMA guidelines. On May 13, 2019, studies were identified through a systematic search of biomedical literature databases (EMBASE, MEDLINE, and Cochrane Database of Systematic Reviews) using Population, Intervention, Comparison, Outcomes, and Study design (PICOS)-based inclusion/exclusion criteria. Relevant congress presentations were also searched. Key inclusion criteria were: (a) treatments: induction regimens that included LEN versus any comparator; and (b) study design: randomized controlled trials (RCT; any phase), meta-analyses (MA), indirect treatment comparisons/network meta-analyses (ITC/NMA), real-world evidence (RWE), and QoL. Exclusion criteria were: (a) case series; or (b) RWE and QoL studies with <10 patients. Only studies relevant to the USA were included for RWE and QoL analyses. The search was restricted to studies published in the English language between 2016 and May 10, 2019. Results The search identified 1,242 records. Of these, 13 RCTs, 2 MAs, 7 ITC/NMAs, 16 RWE studies, and 6 QoL studies were extracted. Evidence from these selected studies showed LEN+dexamethasone (DEX)-based induction therapies were associated with significantly longer progression-free survival compared with prednisone (PRED)+melphalan (MEL)-based induction therapy (hazard ratio [HR] 0.39), thalidomide (THAL)+PRED+MEL (HR 0.69), and bortezomib (BORT)+PRED+MEL (HR 0.70); only LEN+BORT+DEX was superior to LEN+DEX-based therapies (HR 0.71) (all P<0.05). For overall survival, LEN+DEX was superior to THAL+PRED+MEL (HR 0.78) and inferior to

LEN+BORT+DEX (HR 0.71) (all P<0.05). In the RWE setting, LEN+BORT+DEX treatment was associated with significantly longer duration of treatment and time to next treatment compared with all other induction regimens. LEN+DEX induction was associated with a significant improvement in global QoL compared with baseline, which was maintained through 48 months of therapy. Patients utilizing an oral regimen (LEN+DEX) were more adherent compared with patients using an injectable regimen (BORT+DEX). Conclusions Recent clinical and RWE data indicate superior efficacy and high patient preference for LEN-based induction regimens in patients with NDMM in the USA.

Keywords:
induction

Lenalidomide

Multiple myeloma

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-015

Bortezomib, Liposome Doxorubicin and Dexamethasone (PDd) is Superior in Safety and Not Inferior in Efficiency to Bortezomib, Doxorubicin and Dexamethasone (PAd) As Induction Therapy in New-Diagnosed Multiple Myeloma Patients

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Abstract:
Purpose: Bortezomib, doxorubicin and dexamethasone (PAd) and bortezomib, liposome doxorubicin and dexamethasone (PDd) are widely used as induction chemotherapy regimens in China in the new-diagnosed multiple myeloma patients before autologous stem cell transplantation. There was no data on the comparison in safety and efficiency between those two regimens, so we designed this open-label, randomized, multicenter clinical trial in 10 centers in China （NCT02577783）. Method: Until April 30th 2018, 95 cases have finished 4-cycle induction therapy, 48 cases treated by PAd （bortezomib1.3mg/m2 d1,4,8,11,doxorubicin40mg/m2 d1and dexamethasone 20mg/d d1-2,4-5,8-9,11-12）and 47 cases treated by PDd（bortezomib1.3mg/m2 d1,4,8,11, liposome doxorubicin 25mg/m2 d1and dexamethasone 20mg/d d1-2,4-5,8-9,11-12）, every 28 days. After induction therapy, Eligible patients underwent autologous hematopoietic stem cell transplantation and then maintenance therapy. Other patients were treated by primary regimen for another 2 cycles as consolidation therapy and then underwent maintenance treatment. Outcomes of adverse effects and response evaluation were compared here. Median follow up was 13 months. Results: There was no significant difference in gender, ISS stage, R-ISS stage, D-S stage between the two groups. But the patients are elder in PDd group than in PAd group (median age 60y vs 55y, p=0.049), as well as More IgA and light chain type in PAd group (p=0.0002) . There was no difference in ORR between the PAd and PDd group (75.6% vs 77.2%, p=0.795), as well as in VGPR or better between two groups (60% vs 61.4%, p=0.895). MRD by 10-colour flow-cytometry at the level of 10-4 is also no difference between two groups. But, except incident of grade I to II ALT elevation in the PDd group is higher than in the PAd group (21/47 vs 7/48, p=0.003), the incidence of grade III-IV leukocytopenia (2/47 vs 24/48, p=0.000), neutropenia (4/47 vs 23/48, p=0.000) and thrombocytopenia (5/47 vs 30/48, p=0.000) is significantly lower in the PDd group than in the PAd group. No difference is observed in active infection, febrile, herpes.Besides, two patients in PAd group had to stop induction therapy because of serious adverse event, one for heart attack after three circles, and another one for liver failure after the first circle. Though there is no significant difference in PFS and OS between the two groups, patients show a higher probability of overall survival in the PDd group (100% vs 87.1%) at the median 13 months follow

up, which may owe to the lower toxicity of PDd. Conclusion: There is no difference in the efficiency after 4-cycle induction chemotherapy between the PDd group and the PAd group in the newly diagnosed MM patients, but the PDd regimen showed advantages in less cytotoxicities and a higher probability of overall survival.

Keywords:
bortezomib

liposome doxorubicin

safety

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-016

Impact of t(11;14) on the outcome of autologous transplantation in Multiple Myeloma: A multiple centers retrospective analysis from China

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Abstract:
Background: Patients with t(11;14) have traditionally been classified as having standard risk MM, based on studies conducted before novel agents were available. But in novel agent era, there are some conflicting results among the different study. Methods: We reviewed medical records of de novo MM patients who received ASCT from 3 Chinese hospitals from 2012 to 2018 and 455 MM patients were included in the study. Conventional chemotherapy was administered as induction regimen in 45 patients (9.9%), whereas novel agents were used in 410 patients（90.1%). 65 MM patients were identified with t(11;14) and 399 were identified without t(4;14). In addition, 55 MM patients with t(11;14) and without t(4;14), t(14;16), or del 17p, and 400 matched controls: 248 patients for standard risk without t(11;14), t(4;14), t(14;16), or del 17p and 152 patients for high risk with t(4;14), t(14;16), and/or del 17p. Responses were evaluated according to IMWG uniform response criteria. Results At least VGPR after induction therapy was lower in patients with t(11;14) compared to those with standard risk or high risk (56.4% versus 73.8% versus 76.9%, respectively, P=0.014). The estimated median PFS for patients with (n=65) and without t (11;14) (n=390) were 75 (95% CI, 29–121) and 44 (95% CI, 34–53) months, respectively (P=0.312). The estimated median OS for patients with (n=65) and without t (11;14) (n=390) were 86 (95% CI, 29–143) and 100 (95% CI, 80–120) months, respectively (P=0.936). There was no difference in the estimated PFS [52 (95% CI, 26–78) vs 63 (95% CI, 44–82) months, P=0.935] and OS (86 vs 100 months, P=0.836) between patients with t (11;14) alone (n=55) and patients with standard group (n=248). . In addition, estimated PFS was significantly longer in patients with t(11;14) compared to patients with high risk (52 vs 33months, P=0.009). The similar tendency was observed for OS between patients with t(11;14) and high risk (86 vs 71 months, P=0.041). We performed univariate analysis to determine their association with PFS and OS in the t(11;14) alone group . Variables with a P-value <0.4 on univariate analysis were included as predictor variables in multivariate Cox proportional hazards model. Only presence of 1q gains/amplification was associated with reduced PFS and however it had no impact on OS. Conclusions With the use of novel agent based induction regimens consolidated with ASCT, MM patients with t(11;14) alone have lower rates of ≥VGPR post-induction, but have similar PFS and OS compared to the standard risk patients. For the t(11;14) alone group, only 1q gains/amplification at diagnosis predicted reduced PFS but not OS.

Keywords:
autologous stem cell transplant

novel agents

t(11;14)

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-017

Treosulfan Conditioning for Allogeneic Transplantation in Multiple Myeloma – Improved Overall Survival in first line Hematopoietic Stem Cell Transplantation

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Abstract:
Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) is a potentially curative treatment for multiple myeloma (MM) utilizing the graft versus myeloma effect. However, the treatment remains controversial mainly due to a high non-relapse mortality (NRM), partly due to the type of conditioning. Treosulfan is a prodrug of a bifunctional alkylating agent which has both myelotoxic and immunosuppressive properties. Previous small studies on the use of treosulfan conditioning (Treo) in Allo-HSCT for MM have indicated feasibility, stable engraftment and low NRM. In this study, we present the results of a retrospective analysis of patients with MM undergoing Allo-HSCT in first line of treatment after receiving Treo based conditioning between 2008 to 2016 reported to the EBMT registry. One thousand and ninety-eight patients transplanted in first line, were analyzed in cohorts based on the conditioning regimens; those receiving Treo in their conditioning regimen, n = 136, and those receiving RIC, n = 587, or MAC, n = 375. First line of treatment included upfront Allo-HSCT (n = 38, 143, and 227 for Treo, RIC and MAC, respectively) and first line tandem Auto-HSCT-Allo-HSCT (n = 98, 444, and 148 for Treo, RIC, and MAC, respectively). The 5-year overall survival (OS) in first line Treo was significantly superior, compared to the RIC and MAC patients which was 62%, 57% and 47% (CI, 95% 52-71, 52-62 and 41-54, p = 0.04), respectively. In patients receiving tandem Auto-Allo-HSCT, no significant difference was observed between condition regimens for 5-year OS (p=0.3). The same result was observed in patients

with upfront Allo-HSCT without prior Auto-HSCT (p=0.7). A trend of lower non-relapse mortality (NRM) was observed with Treo (10%), in comparison to RIC (17%) and MAC (19%) (p = 0.096), as was the tendency of higher relapse in Treo, 59%, 50% and 49% for Treo, RIC and MAC, respectively (p=0.079). No significant difference was observed for the conditioning regimen for relapse-free survival, aGvHD or cGvHD. In multivariate analyses Treo retained a significant superiority in OS when compared to MAC, (HR 0.57; CI 95% 0.38-0.85, p = 0.006) as did RIC (HR 0.65; CI 95% 0.51-0.83, p = <0.005). When using tandem Auto-HSCT-Allo-HSCT transplant as strata, significans for treosulfan remained superior to MAC (HR 0.63; CI 95% 0.42-0.96, p = 0.03) while RIC also exhibited a trend of improved OS (HR 0.77; CI 95% 0.59-1.00, p = 0.05) compared to MAC. In the multivariate analysis, no significant difference was observed between Treo, RIC, or MAC for relapse free survival, relapse, NRM, aGvHD or cGvHD. In this large retrospective study of the outcomes in 1098 MM patients undergoing Allo-HSCT after Treo conditioning, we demonstrated a superior OS without an increased relapse in Treo when compared to RIC or MAC. In conclusion, these findings suggest that conditioning with Treo is of benefit in first-line Allo-HSCT for patients with multiple myeloma.

Keywords:
Allogeneic hematopoietic stem cell transplantation

Conditioning regimens

Multiple myeloma

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-018

BASELINE CHARACTERISTICS AND OUTCOMES OF PATIENTS WITH MULTIPLE MYELOMA: INDIAN PERSPECTIVE

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Abstract:
Introduction: Multiple myeloma is an incurable plasma cell dyscrasia with an annual incidence of 1 % of all malignancies. Because of lack of adequate healthcare and infrastructure problems with access to novel drugs in our country, treatment of MM is still a challenge. The aim of this study is to determine the baseline clinical and biochemical characteristics and therapeutic outcomes in Indian population. Methodology: We retrospectively collected data from medical records of multiple myeloma patients treated at our institute's Hematology department from January 2015 to December 2018. Baseline characteristics of patients were noted. Event free survival (EFS) was defined from the date of first remission to date of first relapse, death or date of last follow up. Responses were defined by IMWG 2016 criteria. Results: A total of 115 patients was recruited for our study. Median age was 56 years (range 28-79 years). 16% patients were younger than 40 years of age. Majority (68%) were males. The most common symptoms at presentation were pain in back (90%), followed by fatigue (88.7%), fever (18%), weight loss (11.3%) and pathological fracture (11%). Lytic lesions on imaging (majority X- ray), hemoglobin < 10 g/dl, serum creatinine >2 mg/dl & serum calcium > 11 mg/dl, were found in 84 %, 83.5%, 18.26% & 15.65% patients respectively. The mean bone marrow plasma cell percentage and SPEP before therapy was found to be 39.2 ± 24.5 % and 3.3 ± 2.33 g/dl. On serum IFE majority (39%) patients had IgG kappa subtype and 22 % patients had only light chains. ISS stage 1,2,3 was seen in 39%, 29% and 31% patients respectively. Majority received bortezomib thalidomide dexamethasone (VTD) based triplet therapy (64%) rest received lenalidomide or cyclophosphamide-based triplet therapies. Majority patients received thalidomide

maintenance. 38 patients (33%) underwent autologous stem cell transplant. Median time from diagnosis to transplant was 12.76 months. 95 patients (83 %) attained VGPR and higher response. Median EFS patients was 45.2 months (95%CI-34.8-58.8). Ten patients were either in stable or progressive disease and never attained remission. 43 patients (37%) relapsed after first line therapy. On univariate analysis, female sex (p value - 0.033), albumin <3.5 g/dl (p value – 0.042) were found to be statistically significant predictors of relapse. Age, anemia, hypercalcemia, beta 2 micro-globulin, bone marrow plasma cell, renal dysfunction, ISS & RISS were found to be non predictors for relapse. Conclusions: Based on our results, Indian population has onset of MM at relatively younger age and higher proportion of symptomatic patients at presentation. Majority patients received bortezomib based therapy. EFS in our study was similar compared to published literature. Transplant could be done in only one third of patients. The quality of life and survival in MM patients may be improved if there is access to early transplant and newer therapies.

Keywords:
bortezomib

Multiple myeloma

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-019

Modified risk stratification (MRS) for Multiple Myeloma- A simplified model using machine learning

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Abstract:
Introduction: Risk stratification provides an important clue that helps clinicians decide differential medical treatment. The staging system for multiple myeloma (MM) has evolved with advancement of treatment protocols, from Salmon Durie staging to International Staging System (ISS) to Revised-ISS (R-ISS). The R-ISS is based on serum levels of albumin (alb), β2 microglobulin (β2m), lactate dehydrogenase (LDH) and cytogenetic aberrations using fluorescent in-situ hybridization (FISH). Because of limited availability of FISH-based testing, R-ISS for MM has not been applied widely in most developing countries. In this study, we attempt to devise a staging system based on simple laboratory parameters in MM patients treated with novel agents. Methods: Patients diagnosed with MM and treated with novel agents over a period of 10 years (2007-2017) for whom baseline information of at least 3 basic parameters alb, β2m and LDH were available (n=630) were analyzed. In the proposed modified risk stratification (MRS), 6 baseline parameters: alb, β2m, LDH, hemoglobin, calcium, and creatinine, were evaluated. Cut-off values for each parameter was used to draw Kaplan Meier (KM) curves for progression-free survival (PFS) and overall survival (OS) and weights were then assigned to each of the 6 parameters by applying computations on p-value of log-rank test between high-risk and low-risk groups. A weighted score was calculated for each patient followed by Birch algorithm based clustering into three groups. The data points with above-mentioned 6 parameters were classified into one of the three stages using supervised machine learning techniques and thus, obtained the rules for our proposed MRS system. The efficiencies of R-ISS and proposed MRS for risk prediction for PFS and OS were judged based on the p-values obtained with KM tests. Results: Using the proposed MRS, 314 patients were assigned to low, 280 to intermediate, and 36 to high-risk category. The median PFS for low, intermediate, and high-risk categories as per MRS was 188.6, 98.1, and 46.7 weeks, respectively (p=3.52e-14). The median OS was not reached for

low and intermediate categories and was 69 weeks for high-risk category (p=5.16e-13). The accuracy of classification into one of the three stages using J48 tree based classifier in 10-fold cross-validation was 97.30%. Using RISS, the median PFS was 184.1, 88.7 and 51.3 weeks (p=3.59e-15) and; OS was not reached, 182.4, and 155.9 weeks for R-ISS1, R-ISS2 and R-ISS3 respectively (p=1.25e-7). Conclusion: This work presents a new risk stratification model using simple baseline parameters. The method has been verified successfully using KM plots and 10-fold cross-validation. It is simple, easily applicable and is comparable to RISS in patients treated with novel agents. Acknowledgements We gratefully acknowledge the Department of Biotechnology (BT/ MED/ 30/ SP11006/ 2015), Ministry of Science & Technology, Government of India for research funding

Keywords:
machine learning

modified risk stratification

Revised ISS

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-020

Normalization of serum free light chains during therapy in the MM5 trial predicts prolonged progression free survival and overall survival

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Abstract:
Introduction According to the guidelines of the International Myeloma Working Group serum free light chains (sFLC) in multiple myeloma (MM) should be assessed in the context of screening, as prognostic factor at baseline, for response evaluation in patients with oligosecretory disease and for determination of stringent complete response. So far, there is no recommendation for the serial assessment of sFLC in patients with secretory MM. The aim of

this analysis was to investigate the prognostic impact of sFLC ratio normalization and simultaneous normalization of kappa and lambda sFLC during therapy in patients with secretory MM treated within the German-speaking Myeloma Multicenter Group trial MM5. Methods In the prospective randomized multicenter phase 3 trial MM5 sFLC were quantified centrally by Freelite test (The Binding Site Group Ltd., Birmingham, Great Britain) at inclusion, after induction, mobilization, high-dose therapy and consolidation. In multivariate time-dependent cox regression analyses the prognostic impact on progression-free survival (PFS) and overall survival (OS) of both sFLC ratio normalization as well as normalization of absolute sFLC values during the course of first-line treatment were assessed. The effect of time-dependent sFLC ratio and sFLC normalization was adjusted for age, sex, International Staging System (ISS) and arm of randomization. Results In total data of 601 patients were available. The sFLC ratio was normal at baseline in 3.5%, after induction in 22.3%, after high-dose therapy in 42.1% and after consolidation in 50.8% of the patients. In multivariate time-dependent cox regression analyses ISS ($p<0.001$) and the achievement of sFLC ratio normalization at any time before start of maintenance ($p=0.001$, hazard ratio (HR)=0.68, 95% confidence interval (95%-CI)=0.54-0.86) had a statistically significant impact on PFS. Furthermore, ISS ($p<0.001$) and sFLC ratio normalization ($p=0.01$, HR=0.66, 95%-CI=0.48-0.91) significantly affected OS. The kappa and lambda sFLC were normal at baseline in 3.5%, after induction in 13.6%, after high-dose therapy in 31.6% and after consolidation in 32.1% of the patients. In multivariate analyses, ISS ($p<0.001$) and normalization of absolute sFLC values at any time before start of maintenance ($p=0.01$, HR=0.76, 95%-CI=0.61-0.95) showed a statistically significant impact on PFS. In addition, ISS ($p<0.001$) and sFLC normalization ($p=0.02$, HR=0.70, 95%-CI=0.51-0.95) significantly affected OS. Conclusion In conclusion, normalization of both sFLC ratio and sFLC during therapy in the MM5-trial were associated with prolonged PFS and OS. These results indicate that sFLC ratio and sFLC normalization are important favorable prognostic factors and support continuous monitoring of sFLC during therapy in patients with secretory MM.

Keywords:
Multiple myeloma

prognostic impact

serum free light chains

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-021

Over 10 years relative median survival in MM patients ≤ 65 years with VGPR or better on 1st line treatment. Population-based data on patients diagnosed 2008-2018 from the Swedish Myeloma Registry

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Abstract:

Background: The Swedish Myeloma Registry (SMR) is a prospective observational registry documenting real-world management and outcomes in multiple myeloma (MM), smoldering multiple myeloma (SMM), solitary skeletal plasmacytoma, extramedullary plasmacytoma, and plasma cell leukemia since 2008 Aims: We present data showing improvement in response on treatment and in survival in Swedish MM patients since the forming of the national Swedish Myeloma Registry (SMR). Methods: Data are collected through report-sheets to all clinicians at diagnosis and 1-year follow-up. Using data at diagnosis on MM-patients diagnosed 2008-2018 and follow-up data on patients diagnosed 2008-2017, we studied diagnostics and 1st line treatment according to the Swedish Myeloma guidelines in the study period. We estimated response rate and relative survival (RS). A cox regression analysis was performed to evaluate the proportion of patients with ≥ VGPR over time, a log rank test to study the difference in survival in patients obtaining ≥VGPR or better. End of follow-up was at death or June 6, 2019. Results: We present data on 7608 patients (coverage 97% compared to Swedish Cancer Registry) and from 1-year-follow-up on 5565 MM patients. The median age was 71 years (range 19-100), 70 % of patients were >65 years. In the study period, we found that the number of patients with ISS-staging at diagnosis increased from 59% to 81%, and an elevation in reported cytogenetic risk factors to 70 % in 2017-2018 from less than 20% 2008-2009. An increasing part of patients received PI-or IMID-based 1st line treatment, from 38% in 2008 to 91% in 2017. The number of patients ≤ 65 years receiving high dose Melphalan with ASCT remained stable (80%) in the study period, but in patients 66-70 years they are rising, and since 2016 given in 40% of patients. The response ≥VGPR on 1st line treatment was increasing significantly in the period in patients ≤ 65 and 66-80 years (P<0.01), but not in patients > 80 years. However, a significant superior survival in patients with VGPR and better was seen in all patients, with a relative median survival in patients ≤ 65 years of 10.2 years (95% CI:8.45-NR). The proportion of patients with reported relapse in the first year after diagnosis decreased from 62% 2009 to 26% 2017, which can partly explain the improved 1-, -3, -5, and 7-year survival in all patients since forming of the registry 2008. Conclusion: Our data show a superior survival in all patients obtaining ≥VGPR after 1st line treatment, with excellent survival in patients ≤65 years, supporting the importance of high response rates to treatment. Improvements in diagnostics, treatment outcome and survival in all age cohorts and regions can be followed and made public after the introduction of a national Swedish Myeloma Registry 2008. Sharing registry data contributes to the harmonization of treatment strategies in all regions and increased coherence to national treatment guidelines.

Keywords:
registry

survival

VGPR

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-022

The differential presentation patterns and outcomes of young (AYA) myeloma patients... A single center two-decade experience

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Abstract:
Background: Myeloma is primarily a disease of the elderly with a median age of 71. Adult/young adult myeloma (AYA-MM) is less often encountered in

clinics with an incidence on the rise and with apparent different presentation patterns. Methods: We investigated presentation patterns and outcomes of 190 AYA-MM patients (<50 y.o) diagnosed over two decades (4/1993 - 3/2014) with respect to novel agent (NA) use Results : Median age of cohort was 46 (25-50) which included 104 males (55%), 86 females (45%). Racial distribution was as follows: Caucasian (n=94, 49%), Black (n=86, 45%), Other (n=10, 6%). 72 (38%) presented with skeletal pain followed by other symptoms. Median lab values were as follows: Hemoglobin 10.4 g/dL, calcium 9.4 g/dL, creatinine 1 g/dL, b2m 2.5 mg/dL, albumin 3.6 g/dL, LDH 216 U/L, CRP 1.5 mg/dL, serum M-spike 2.8 g/dL. Median plasma cell involvement (BMPC) was 40.5%. 20 had high-risk karyotype with hypodiploidy (6.3%) and complex karyotypes (4.2%). 14 had high-risk FISH (7.3%) including del17p (4.2%), t(4;14) (2.6%) and t(14;16) (0.5%). 139 (73%) were treated with NAs (bortezomib, thalidomide or lenalidomide). Status was unknown in 18 patients (9%). 77 and 74 patients respectively received IMiDs and bortezomib (41% and 39%). 114 and 76 patients were treated before- and after-2005, a landmark chosen for NA utilization that resulted in 26 CR (14%), 10 VGPR (5%), 68 PR (36%) and 27 PD (9%). All patients had hematopoietic stem cell transplantation (HSCT), 177 (93%) upfront auto (ASCT), 13 upfront allo (7%) leading to 80 CR (42%), 6 VGPR (3%), 41 PR (22%), 1 SD (5%), 40 PD (21%). 35 patients had more than one HSCT: 24 with second auto (13%), 9 with allo (5%). 2 patients went for a third HSCT. PFS and OS were analyzed via univariable Kaplan-Meier and Cox-regression methods. LDH (p=0.001), calcium (p=0.002), NA treatment (p-0.031), IgA subtype (p-0.036) and age with cutoff 46 (p=0.049) were characteristics that were frequent (>5 cases) and statistically significant. BMPC, hyperdiploidy and monosomy were significant (p=0.07, p=0.07, and p=0.09 respectively). Del 17p and hypodiploidy were not. Sex, race and other labs (including ISS determinants b2m and albumin, M-spike magnitude and type) were not. Multivariable Cox-regression (n=160) suggested an increased risk of death for older age at diagnosis (p=0.025, HR 1.84, CI 1.08-3.15) and in those who did not receive NAs (p= 0.011, HR 2.03, CI 1.17-3.54). Race did not have impact (p=0.23, HR 1.36, CI 0.81-2.29). Conclusions: Young myeloma patients do present with different patterns possibly indicating unique biological features of AYA-MM and appear to benefit from novel agent use leading to improved outcomes, irrespective of age and sex. Given the unique needs, the remarkable paucity of literature and rising incidence, prospective studies of AYA-MM are needed.

Keywords:
AYA-MM

disease presentation

Young myeloma

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-023

RVD with weekly subcutaneous bortezomib minimizes neuropathy and maintains efficacy in a diverse multiple myeloma cohort

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Abstract:
Introduction: Lenalidomide, bortezomib, and dexamethasone (RVD) is standard-of-care induction for fit multiple myeloma patients, with response rate (RR)>90% in first line. Standard RVD utilizes a 21-day cycle with bortezomib IV 1.3 mg/m2 days 1, 4, 8, and 11; lenalidomide 25 mg days 1-14; and dexamethasone 160-320 mg per cycle. Bortezomib-induced neuropathy may be treatment-limiting, occurring in up to 80% of patients. Weekly administration of bortezomib, subcutaneous (SC) dosing, and extending the cycle to 28 or 35 days may optimize tolerance. Those adjustments were

studied primarily in transplant-ineligible or relapsed/refractory patients. We report the results of a retrospective analysis of patients who received RVD on a 21-day cycle with weekly subcutaneous bortezomib to improve tolerability or logistics. Methods: We reviewed charts of patients who received RVD at these starting doses: lenalidomide 25 mg days 1-14 of 21; bortezomib 1.5 mg/m2 SC days 1, 8, and 15; and dexamethasone 40 mg days 1, 8, and 15. We noted demographics, ISS stage, performance status, cytogenetic risk, line of therapy, history of autologous transplant, degree of response (PD, SD, PR, VGPR, and CR based on IMWG criteria), EFS, OS, and toxicities. EFS and OS were calculated using the Kaplan-Meier method. Results: 41 patients received RVD with weekly bortezomib between 2009 and 2019. Median age was 59 (range 37-78); 37% were 65 or older. 58% were male. 63% were Caucasian. ISS stages were I in 29%, II in 22%, III in 34%, and missing in 6 patients; ECOG status was 0 in 27%, 1 in 44%, and 2 in 20%. 59% of patients underwent autologous transplant. Renal dysfunction (eGFR<60) was present in 27%. 34% were treated in the community. Line of therapy (range 1-8) was 1 in 68% and 2 or later in 32%. Median number of cycles was 5 (range 1-64). Dose reductions occurred in 22%, and 1 patient discontinued after 1 cycle. Treatment-emergent neuropathy was seen in 22%; 20% experienced grade 1 or 2, and 2% experienced grade 3 neuropathy. 37% had treatment-related cytopenias, with 2% grade 3. Response was assessable in all patients; 90% of patients across all lines achieved PR or better; 20% achieved CR, 37% VGPR, and 34% PR. Among first-line patients (n=28), RR was 100%, with 18% CR, 50% VGPR, and 32% PR. Median follow-up was 13 months (range 1-111). Median EFS trended longer in transplanted patients, 40 vs. 14 months (p=0.06). Relapse was not associated with ISS stage (p=0.154), ECOG score (p=0.314), or cytogenetic risk (p=0.641). Conclusions: 21-day RVD with weekly SC bortezomib caused no loss of efficacy compared to standard RVD in both transplant and non-transplant candidates; transplant recipients experienced longer EFS. Toxicity, especially neuropathy, was low with SC administration. Dose reductions were uncommon, and discontinuation was rare. RVD with weekly SC bortezomib optimizes efficacy, tolerability, and administration and is appropriate for transplant candidates.

Keywords:
bortezomib

neuropathy

Tolerability

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-024

Characteristics and Outcome of Relapsed Myeloma after Single Autologous Stem Cell Transplant: 20-year Experience.

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Abstract:
Relapse following autologous stem cell transplantation (ASCT) for multiple myeloma (MM) remains a major cause of treatment failure. We analyzed case records of 327 consecutive MM patients who underwent ASCT between 1995 and 2016 at our centre. Patient's median age was 52 years ranging from 29 to 68 years; 226 (68.9%) were males, 33.4% had ISS stage III disease, 80(24.9%) patients had light chain myeloma. 240 (73.2%) patients had received novel agents for induction, 34.3% of patients had received more than one induction regimen prior to transplant. Median interval from diagnosis to transplant was 10 months, ranging from 2 to 128 months. Median follow up for study population is 86 months (95% CI 74.70-97.30). The cumulative incidence of relapse at 1 year and 2 years is 9.8 % and 22%, respectively. Median

time to progression (TTP) was 8.5 months (95% CI 5.0-11.96) for those with very early relapse (<12 months), 18.0 months (95% CI 17.6-18.4) and 45.50 months (95% CI 39.8-51.2) for those relapsing between 12 to 24 months and >24 months post ASCT, respectively, p<0.0001. Clinical (symptomatic), biochemical (asymptomatic), localized plasmacytoma and relapse into plasma cell leukemia (PCL) was seen in 72.5% (n=140), 18.7% (n=36), 1.6% (n=3), and 7.3% (n=14) patients, respectively. Median TTP was 37.50 months (95% CI 33.83-41.2) for biochemical relapse compared to 21 months (95% CI 18.8-23.2) for clinical relapse and 18 months (95% CI 15.6-20.4) for PCL, p<0.0001. Median overall survival (OS) for all patients is 100 months (95% CI 83.24-116.76) from date of transplant. Corresponding figures for those with biochemical, clinical and PCL relapse are 174 months , 51 months (41.1-60.9) and 26 months (0-57.2), respectively (p<0.0001). 12 patients have died of unrelated causes (second malignancy-5, cardiac-2, stroke-1, dementia-1, accident-1, viral infection-2). Currently, 122 (37.3%) patients are alive without relapse. On comparison of three relapse groups (<12 , 12-24 and >24 months) - presence of extramedullary disease (p<0.003), >one line of induction therapy (p<0.008), Conclusion:. Identification of patients at high risk for early relapse (with symptomatic disease) and pre-emptive use of alternative strategies to improve outcome are potential areas of research in future studies.

Keywords:
early relapse

Multiple myeloma

survival

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-025

Once-Weekly 1.6mg/m2 Bortezomib BCD Regimen in Newly Diagnosed Multiple Myeloma: Better Response and Lower Incidence of Peripheral Neuropathy

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Abstract:
In the present study, the effect and toxicity of 1.6mg/m2 and 1.3mg/m2 bortezomib BCD on multiple myeloma (MM) were analyzed retrospectively. From January 2016 to December 2018, 82 newly diagnosed MM patients received minimal 4 cycles of either 1.6mg/m2 (bortezomib 1.6mg/m2, d1, d8, d15, d22; cyclophosphamide 300 mg/m2 d1, d8, d15; dexamethasone 20 mg d1, d2, d8, d9, d15, d16, d22, d23; 35 days per cycle) or 1.3mg/m2 (bortezomib 1.3mg/m2, d1, d4, d8, d11; cyclophosphamide 300 mg/m2 d1, d8, d15; dexamethasone 20 mg d1, d2, d4, d5, d8, d9, d11, d12; 21 days per cycle) bortezomib BCD regimen. There was no difference between the two groups with respect to clinical characteristics. Among these patients, 43 patients, the median age of 56 (35-76) years old, were treated with 1.6mg/m2, while 39 patients, the median age of 56 (27-74) years old, were given 1.3mg/m2. All the patients were assessed every 2 cycles. The analysis showed that there is no significant difference of effects (overall response rate ORR and complete rate CR) between 1.6 and 1.3 mg/m2 groups after 2 cycles of treatments, although 88.4% (38/43) patients achieved ORR with 18.6% (8/43) patients in CR in 1.6 mg/m2 group. After 4 cycles of treatment, the 1.6 mg/m2 group showed significantly higher CR as compared to 1.3 mg/m2 group (44.2% vs 23.1%, p=0.044) with no difference of ORR (83.7% vs 92.3%, P=0.249). In addition, 4 cycles of treatment had significantly higher CR (44.2% vs 18.6%, p=0.011) as compared to 2 cycles of treatment in the 1.6 mg/m2 group. In adverse events, there is no significant difference of peripheral neuropathy (PN) between 1.6 mg/m2 and 1.3 mg/m2 between groups in 2 cycle assessment (p=1). However, the incidence of PN in 4 cycle assessment is lower significantly in 1.6mg/m2 group than in 1.3mg/m2 (4.8% vs31.6%, p=0.04). In

respect to hematologic, infective, gastrointestinal toxicities, no significant difference was observed between the two groups. In summary, the 1.6 mg/m2 group achieved deeper and quicker response with reduced PN than 1.3mg/m2 group in after 4-cycle induction regimen, suggesting more effective and safer outcomes with the treatment of the 1.6mg/m2 BCD regiment in MM.

Keywords:
bortezomib

complete response

Multiple myeloma

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-026

Impact of Regional Income and Insurance Status on Survival of Multiple Myeloma Patients: Autologous Stem Cell Transplant as an Equalizer

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Abstract:
Patients with Multiple Myeloma (MM) are enjoying significant improvement in overall survival as the result of advent of novel anti-myeloma agent that replace traditional chemotherapy, in addition to the increased use of transplant. The prices of novel agents, especially oral ones, have been rapidly escalating and there are well-described issues with affordability (Shih et al. JCO 2017). We therefore hypothesized that insurance status influences MM patients (pts) survival. National Cancer Database (NCDB), covering 70% of MM patient nationwide was utilized. to test this hypothesis. Methods: Data from 117,926 MM pts diagnosed between year 2005 and 2014 was analyzed. MM (ICD-O 9732) diagnosed between year 2005 and 2014. Primary outcome was overall survival (OS) which was analyzed using Kaplan-Meier method and Cox model. Results: Median age at diagnosis was 67 years (19-90); 55% were males. 57% of pts lived in areas where the median income was < $46k/year (individual income data was not available); Primary insurance was Medicare (52%), private insurance (35%) or Medicaid (5%), and 3% were uninsured. 40% were treated in academic institutions. Median follow up was 30.2 (range, 0-145.2) months. By univariate analysis, better OS was observed in pts with primary MM, lower Charlson Comorbidity Index (CCI), treatment in academic institutions, higher median regional income, or private insurance ($p<0.001$ for all). Ninety six percent of patients were treated in facilities located ≤ 120 miles from area of residence. More patients with private insurance (5.7%) travelled > 120 miles to the treatment facility than patients with Medicare (3%). For patients younger than 65 years, 33% of patients with private insurance received transplant compared to 20% of those on Medicare ($p<0.001$). For those 65 years and older, 11% of privately insured patients had transplant compared to only 6 % for those on Medicare ($p<0.001$). Median age of pts on Medicare, private insurance, was 74 and 57, respectively. When restricting the analysis to pts ≥ 65 years old, pts with private insurance had longer OS compared to Medicare pts ($p<0.0001$). Multivariate analysis showed co-morbidity score, insurance and income as determinant of OS. When limiting the comparison to patients who were 65 years or older only, we found a statistically significant difference in survival between patients with private insurance and those with Medicare in favor of the private insurance group. The median OS for privately insured patients was 41.9 months compared to 30.8 months for patients with Medicare ($p<0.001$). When considering patients who received transplant, there was no difference in survival between privately insured patients and Medicare regardless of age. Conclusions: Although insurance type and regional

income are associated with MM survival (i.e., potentially related to affordability of novel agents), however transplant seems to be an equalizer for OS. This finding merits further investigation.

Keywords:
Insurance

Multiple myeloma

survival

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-027

Long term remissions, late relapses and prolonged survival in patients with multiple myeloma before the era of novel agents

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Abstract:
Immunomodulatory agents and proteasome inhibitors plus megatherapy and autologous stem cell transplantation have a dramatic impact in overall survival of multiple myeloma (MM) patients. However, there are patients in the early 2000s who remain in remission and survive for long time without having been exposed to novel agents. We present the clinical characteristics of long term – more than 10 years- survivors independent of cytogenetic or molecular findings. 39 MM patients (26 males, 13 females), age 44-76, median 60yrs, M-protein 16 IgGk, 10 IgGλ, 4 IgAk, 3 IgAλ, 3 light chain(λ), 2 non secretory and one triple M-component (IgGk/IgAk/IgDk), fulfilled criteria (CRAB) for initiation of treatment. Retrospectively one of them had smoldering myeloma. 27 patients presented with bone disease, 16 with renal impairment, 3 with hypercalcemia and 19 with anemia. In 12/39 patients MGUS preceded the diagnosis for more than 24 months. Staging according to Durie- Salmon prognostic system was: 9/39stage I, 13 stage II, 17 stage III, while according to ISS 17/39 were at stage I, 13 stage II and 9 stage III. G-banding karyotype was performed in 28/39 pts but findings were scarce and irrelevant. At that time FISH was not routinely performed. 33/39 received chemotherapy VAD or VAD-Caelyx, 5 were treated with melphalan -steroids and only 1 with bortezomib-dexamethazone. Radiotherapy was applied to patients with bone disease (26/39). 25/39 received megatherapy and stem cell transplantation, 4/25 tandem. 29/39 were given maintenance, mainly thalidomide. All pts achieved complete or very good partial remission and survived 10-20 (median 14) years. 15/39 pts relapsed at least five years after diagnosis and received 2nd line treatment. 5/15 achieved second long-term remission. 16 pts died, 10 with progressive disease and 6 from other causes. 8/39 remain in complete remission 10-18, median 13years after diagnosis. Two subgroups of pts emerge from our sample. One subgroup consists of rather young patients whose main clinical feature was lytic symptomatic bone disease. After conventional chemotherapy they proceeded to high dose melphalan and autologous transplantation and received prolonged maintenance therapy. They all achieved complete remission according to the contemporary response criteria. The other subgroup includes patients of older age with a history of long-lasting presence of MGUS (mostly IgGk). Although these patients did not achieve complete remission they remained for a long time out of treatment. The Durie-Salmon system failed to identify pts with good clinical course, while the International Scoring System was more relevant. In the lack of adverse molecular findings, younger MM pts with no comorbidities and bone disease as the main clinical feature may achieve long remissions and survival even with conventional drugs. Older patients with a

preceding history of MGUS progressing to MM seem to achieve long-lasting remissions. In any case

Keywords:
Long term outcome

multiple myeloma-specific survival

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-028

Pacific Islanders with multiple myeloma are younger and have inferior survival when compared to other ethnicities: a study from the Australian and New Zealand Myeloma and Related Diseases Registry (MRDR)

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Abstract:

Aim: To compare demographics and outcomes of patients with multiple myeloma (MM) in New Zealand (NZ) who have Pacific Islander (PI) ethnicity to the rest of the NZ MM cohort in the MRDR. Method: PI ethnicity included those listed with one or more grandparents of the following genetic heritages: Melanesian (including Fijian), Polynesian (including Maori). Of 377 NZ MM patients on the MRDR (Sep 2012 - Apr 2019), 90 met this definition and 59 were of unknown ethnicity, providing a control group of 228 non-PI of predominantly European heritage. Overall survival (OS) was calculated using Kaplan-Meier survival analysis. Results: PI patients were younger (median age 63 [IQR: 57-72] v 70 years [IQR: 64-77], $p<0.001$) had poorer ECOG performance status (ECOG 2-4: 17 v 31%, $p=0.02$) and higher median BMI (32 [27-37] v 27 kg/m2 [24-30], $p<0.001$) at diagnosis when compared to controls. Diabetes (22% v 6%, $p<0.001$) and renal insufficiency (eGFR>177µmol/L or eGFR<40ml/min [13% v 6%], $p=0.04$) were more common in PI compared to controls. PI were more likely to have karyotypic abnormalities when compared to controls (41% v 22%) including t(4:14) (15 v 7%, $p=0.04$) and del(13q) (10 v 3%, $p=0.04$). Fewer PI received chemotherapy (84% v 93%, $p=0.01$) and there was a trend for shorter OS in PI (HR 1.47 [0.94-2.29], $p=0.09$). However, age-adjusted OS was significantly shorter for PI versus controls (HR: 2.0 [1.3-3.2], $p<0.001$). When adjusted for age and (not) receiving chemotherapy, PI still had a significantly shorter OS (HR 1.68 [1.05-2.71], $p=0.03$). The same held when non-chemotherapy recipients were excluded (HR for PI: 1.89 [1.13-2.16], $p=0.016$). Conclusions: PI patients with MM are younger, have more co-morbidities and are more likely to have adverse karyotypes at diagnosis than non-PI MM patients. Moreover, PI with MM have a significantly inferior OS, even after adjustment for age and for (not) receiving chemotherapy. Investigation of modifiable factors that could improve outcomes for PI with MM, and to elucidate reasons why MM occurs at a younger age in PI is urgently required.

Keywords:
EPIDEMIOLOGY

prognostic factors

registry

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-029

Development of an Individualized, Supervised Exercise Intervention as Standard Care for Patients with Multiple Myeloma

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Abstract:
Patients with multiple myeloma (MM) often suffer from disease symptoms and treatment toxicities that may be alleviated through physical activity (PA). The attitudes and practices of treating physicians and their patients regarding PA participation for MM patients remains to be elucidated. This study aimed to explore the perspectives of hematologists and patients on PA for patients diagnosed with MM to assist with the development of an individualized, supervised exercise intervention as standard care. Paper-based surveys, with responses rated on a 5-point Likert scale, were distributed to clinical hematologists across Australia, and to patients with MM at public and private clinics. The hematologist survey asked questions regarding the importance of, or agreeance to, the benefits and barriers of PA participation. The patient survey included questions regarding the incidence of disease symptoms and personal perspectives and preferences for the design of an exercise program. Patients with MM (n=119; 79% response rate) and hematologists (n=34; 68% response rate) completed the surveys. The hematologists cumulatively treated approximately 340 patients each week. The patient population was well-represented in the older age groups with 57% aged 65 years or older. Almost all hematologists (97%) agreed that PA was important for patients with MM, with 85% reporting at least occasionally recommending PA to their patients. Exercise recommendations by hematologists diverged for MM patients who were experiencing disease complications; 55% did not recommend exercise when patients had spine fractures or were physically unwell. However 44% never referred patients for supervised PA with accredited exercise physiologists (AEP). An overwhelming majority of patient respondents (84%) experienced at least one symptom to a moderate intensity in the past month. Fatigue was experienced with the highest incidence (55%), with nerve symptoms (46%), back pain (44%) and lethargy (44%) also reported. There was a preference for PA programs during both active treatment and remission (69%) and for them to be guided by an AEP with an interest in cancer (62%). Programs of low-cost (91%), with flexible times (82%) and at locations close to home (77%) were considered important features for participation. Utilizing the information gained from the surveys, an exercise intervention has been developed for patients with MM, with 20 participants currently commenced and recruitment continuing. Hematologists perceive PA as very important for MM patients, however often do not recommend exercise for those experiencing disease complications. Patients are interested in participating in PA with a strong preference for convenient, low-cost programs, supervised by accredited exercise professionals. Availability of dedicated MM programs with clear referral pathways will increase the number of MM patients being referred by their hematologists.

Keywords:
exercise

Supportive Care

symptom management

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-030

Bortezomib, lenalidomide, and dexamethasone in transplant-eligible newly diagnosed multiple myeloma: A multicenter retrospective comparative analysis

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Abstract:
Introduction: Combination of bortezomib, lenalidomide, and dexamethasone (VRD) is a standard of care as induction treatment in patients with multiple myeloma. Twice-weekly VRD (twVRD) is the most popular regimen for transplant-eligible patients, whereas, VRd-lite is preferred for elderly, transplant-ineligible patients. It remains controversial what schedule is best as an induction regimen before auto stem-cell transplantation (SCT). Methods: We treated patients with twice-weekly VRD (twVRD: bortezomib [1.3 mg/m2 on days 1, 4, 8, and 11), lenalidomide [25 mg/body on days 1-14], and dexamethasone [40mg/body weekly] over 21-day cycles) or modified VRD-lite (bortezomib [1.3 mg/m2 on days 1, 8, 15, and 22) and lenalidomide [15 mg/body on days 2-7, 9-14, 16-21], and dexamethasone [40mg/body weekly] over 28-day cycles) in the newly diagnosed transplant-eligible myeloma patients before auto SCT, at four institute hospital between May 2015 and December 2017. Consolidation and maintenance therapy was depending on the physician's choice. The purpose of this study was to compare twVRD to once-weekly VRD in terms of activity and tolerability as induction treatment in transplant-eligible patients with multiple myeloma. Results: Fifty-five patients with a median age of 61 years were included; 22 patients treated with conventional twVRD and 33 was modified VRD-lite. Overall response, very good partial response, and complete response rates after 4 cycles of VRD were 96.4%, 45.5%, and 20.0% in total. There was no significant difference in OR, VGPR, or CR ratios between the two groups; OR, VGPR and CR rates of the twVRD and modified VRD-lite groups were 95.4% and 97.0% (P=0.999), 36.3% and 51.5% (P=0.407), and 18.2% and 21.2% (P=0.999), respectively. With the median follow-up period of 17.7 months, one-year PFS and 1-year OS were 95.8% and 98.2% in two groups, respectively. Response rate and PFS were similar between the groups. The incidence of peripheral neuropathy (PN) ≥grade 2 was higher in the twVRD group than in the modified VRD-lite group (27.2% vs. 0.0%, P=0.003); there was no significant difference between the groups regarding any grade of PN (31.8% vs. 27.2%, P=0.768). The incidence of thrombocytopenia grade 3-4 was higher in the twVRD group than in the modified VRD-lite group (27.2% vs. 0.0%, P=0.003). Conclusion: modified VRD-lite had a similar activity but better tolerability than twVRD as induction treatment for newly-diagnosed transplant eligible myeloma patients.

Keywords:
Induction therapy

peripheral neuropathy

RVD

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-031

Bortezomib-Dexamethasone vs Bortezomib-Dexamethasone and chemotherapeutic agents in Transplant-Eligible Newly Diagnosed Myeloma

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Abstract:
BACKGROUND Bortezomib (Btz) and dexamethasone (Dex) plus thalidomide (VTD) or lenalidomide (VRD) are recommended induction regimens for transplant-eligible patients with newly-diagnosed multiple myeloma (NDMM). However, Btz+Dex combined with cyclophosphamide (Cy) or doxorubicin (Dox) are still used either to avoid thalidomide related side effects or because of limited access to lenalidomide. The benefit of such combinations over Btz+dex alone has not been explored. METHODS Prospective, non-controlled evaluation of consecutive and unselected NDMM patients treated with btz+dex (VD group) vs btz+dex plus Cy, Dox or both (QV group) before ASCT during the 2005-2015 decade at a single institution. Noninferiority of VD in terms of PFS and PFS2 was the primary endpoint. RESULTS From 2005, NDMM patients at a single institution were treated with VD or QV before ASCT according to physicians preference. From 2015 VTD was established as standard and the prospective study was terminated including 122 evaluable individuals with a median follow-up of 6 years at time of analysis. VD (N=78) and QV patients (N=44) had comparable demographic characteristics and MM features. Median age was 58 years (range 28-73) and 57% were male. Overall response (ORR)and complete remission (CR) rates to induction were 79% and 18% for QV and 86 and 15% for VD pts respectively (NS differences). 13% vs 5% of patients progressed or died before ASCT in QV vs VD and 70% vs 83% received ASCT first line. Post-ASCT ORR and CR rates were 79% and 34% for QV and 87% and 36% for VD (NS). Median PFS was 2.78 years (95%CI 2.32-3.30), 3.36 years (95%CI 2.33-3.85) for QV and 2.56 (95%CI 1.81-3.17) for VD pts (p= 0.935). At time of analysis, 94 pts had relapsed (37 in QV and 57 in VD) and received similar second line treatments obtaining a median second line PFS of 1.08 years (95%CI 0.71-1.63), 0.69 years (95%CI 0.42-1.08) for QV and 1.51 (95%CI 0.96-2.09) for VD (p=0.282), making a global PFS2 of 4.54 years (95%CI 3.98-6.07), 3.95 years (95%CI 2.51-6.07) for QV and 4.84 (95%CI 4.18-6.54) for VD (p=0.236). Seventy patients (29 in QV and 41 in VD) have received 3 or more lines of treatment. OS is 7.88 years (95%CI 7.16-9.41), 7.49 years (95%CI 5.29-9.41) for QV and 8.85 (95%CI 7.16-NA) for VD (p=0.166). CONCLUSIONS Four cycles of VD induction led to similar ORR, CR, PFS, PFS2 and OS results than combinations of bortezomib and dexamethasone with cyclophosphamide (VCD), doxorubicin (PAD) or both (VBCMP/VBAD/Btz) while induction toxicity may be higher. Overall results are inferior than those reported for VTD or VRD in similar patient populations.

Keywords:
bortezomib

Induction therapy

Newly diagnosed multiple myeloma

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-032

Polyclonal immunoglobulin recovery after autologous stem cell transplantation is an independent prognosis factor for survival in patients with multiple myeloma

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Abstract:
Multiple myeloma (MM) is a plasma cell neoplasm characterized by the presence of monoclonal immunoglobulin (Ig) in serum and/or urine and clinical symptoms related to the CRAB features and myeloma-defining events. MM is a clinically and cytogenetically heterogeneous disease and survival outcome varies considerably depending on the risk status and treatment of each patient. Until now, treatment strategy for MM has been evolving rapidly by the introduction of several new classes of agents such as proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies. These highly effective modalities including autologous stem cell transplantation (ASCT) have led to deeper and durable responses such as minimal residual disease negativity that is now considered as a major prognostic factor for progression-free survival (PFS) and overall survival (OS). On the other hand, most patients present with immunoparesis defined by the suppression of normal Ig at diagnosis and during treatment. Recent studies have shown that recovery of patient immunity such as serum levels of Ig and lymphocyte counts in the peripheral blood are also involved in a favorable prognosis. In the present study, we assessed the impact of polyclonal Ig recovery after ASCT on survival outcome. A total of 50 patients (23 male and 27 female) were included. The median age was 57 (range, 35-71) years. The type of monoclonal immunoglobulin was 24 IgG, 9 IgA, 2 IgD, 13 light-chain only, and 2 non-secretory. The ISS stages I, II, and III were 16, 20, and 13; and the R-ISS stages were 9, 25, and 5, respectively. All patients received upfront ASCT after induction therapy either vincristine + doxorubicin + dexamethasone (n=20) or novel agent-based therapy (n=30). Best response after ASCT was 14 sCR, 7 CR, 14 VGPR, 13 PR, and 2 SD. Maintenance therapy was not performed after ASCT. The recovery of polyclonal Ig was defined as normalization of all values of serum IgG, IgA, and IgM. One year after ASCT, 26 patients (52%) showed polyclonal Ig recovery (14 in the ≥CR group and 12 in the non-CR group, respectively). The median PFS and OS in all patients were 35.0 and 118.3 months, respectively. Notably, the group with Ig recovery had a significantly better outcome than the group with persistent immunoparesis in PFS (median, 46.8 vs 26.7 months, p=0.0071) and in OS (median, not reached vs 65.3 months, p<0.00001). This tendency was also observed in the non-CR group (i.e., median PFS, 45.3 vs 23.0 months, p=0.016; and median OS, not reached vs 53.2 months, p=0.00016). Multivariate analysis revealed that persistent immunoparesis was a more significant prognostic factor than non-CR for OS (HR, 44.8, 95%CI [3.87-518.1], p=0.0023 vs HR, 17.0, 95%CI [2.00-145.5], p=0.0096, respectively) regardless of the type of induction therapy. Therefore, in addition to the depth of response, the recovery of polyclonal Ig after ASCT is an independent prognostic factor especially for long-term outcome in patients with MM.

Keywords:
autologous stem cell transplant

immunoglobulin

Immunorecovery

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-033

A phase I/II, open-label, prospective, multicenter study to evaluate the efficacy and safety of lower doses of bortezomib plus busulfan and melphalan as a conditioning regimen in patients with multiple myeloma undergoing autologous peripheral blood stem cell transplantation: The KMM103 study

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Abstract:
A phase I/II trial was conducted to explore the safety and activity of addition of bortezomib on days -6, -3, and +1 relative to the day of autologous stem cell transplantation to a conditioning regimen with busulfan and melphalan (BuMel; 3.2 mg/kg/day busulfan on days -5 to -3 and 140 mg/m2/day melphalan on day -2) in patients with multiple myeloma (MM) following bortezomib-based induction chemotherapy. In phase I, doses of bortezomib (0.7, 1.0, and 1.3 mg/m2) with BuMel were administered to groups of three patients each. No dose-limiting toxicities were observed. The maximum tolerated dose of bortezomib was 1.3 mg/m2/day. A subsequent cohort with 41 patients was analyzed in a phase II trial to identify safety and efficacy. The phase II trial showed 75% of response rates including very good partial response (VGPR) or better, and 55% of complete response (CR) rates at 3 months; For post-transplant best response, 83% of VGPR or better response rate (68% of CR rate) was observed. With a median follow-up duration of 31.4 months, median progression-free survival (PFS) was 26.8 months. The probability of 2 year-PFS was 56.5%, and median overall survival was unable to be calculated. Specifically, high-risk cytogenetics were associated with adverse survival outcomes compared to standard-risk cytogenetics (median PFS, 12.2 vs. 35.7 months, p=0.039; median OS, 26.7 vs. 73.3 months, p=0.086). With a median of 11 days and 10 days for neutrophil and platelet engraftments, respectively, no graft failure or delayed engraft was observed. The most common grade 3 or severe non-hematological adverse events included neutropenic fever (73.2%) and stomatitis (14.6%). Except for three cases with transplant-related mortality due to sepsis, other adverse events were manageable. These results demonstrate that bortezomib is safe and has a potential role in a conditioning regimen in combination with BuMel for patients with transplant-eligible MM. (This trial was registered at http://www.clinicaltrials.gov NCT01255527)

Keywords:
autologous stem cell transplant

bortezomib

myeloma

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-034

Impact of autologous stem cell transplantation on renal response in multiple myeloma patients with advanced renal failure

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Abstract:
Background This study aimed to evaluate the impact of autologous stem cell transplantation (ASCT) on renal outcomes of multiple myeloma (MM) patients who had advanced renal failure with estimated glomerular filtration rates (eGFR) ≤60 ml/min/1.73m2 at the time point of transplantation Patients and methods In our ASCT database from July 2009 to September 2018, 76 MM patients with median eGFR of 36.6 (range, 5.4-59.8) ml/min/1.73m2 at ASCT were included: 47 (61.8%) with eGFR ≥30 and <60ml/min/1.73m2; 16 (21.1%) with eGFR ≥15 and <30ml/min/1.73m2; and 13 (16.9%) with eGFR <15ml/min/1.73m2 and/or hemodialysis-dependent. Myeloma and renal response after ASCT were evaluated using the

international myeloma working group response criteria. Results: During median follow-up of 37.3 (range 0.9-108.3) months, transplant-related mortality occurred in seven patients (9.1%). Overall myeloma response was achieved in 70 patients (92.1%): 6 (7.9%) of partial response (PR), 12 (15.8%) of very good partial response (VGPR), and 52 (68.4%) of complete response (CR). Median myeloma progression-free survival (PFS) and overall survival were 23.2 (95% CI, 16.9-32.1) and 61.5 (95% CI, 43.6-69.8) months, respectively. Among 20 patients (26.3%) who achieved renal response, including 19 (25.0%) of renal CR and 1 (1.3%) of renal PR, median time to achieve partial response was 267 days (range, 3-2022). In subgroup (n=29) with baseline eGFR <30 ml/min/1.73m2, 21 patients (53.8%) achieved renal response after median 53 (3-1756) days post ASCT. In multivariate analysis, IgA type, advanced eGFR (<30 ml/min/1.73m2), and shorter duration from diagnosis to ASCT (<6.6 months) were associated with higher cumulative rate for achieving renal response. Conclusion: Clinical outcome of myeloma patients after ASCT was favorable. Patients with advanced renal failure may benefit from early ASCT.

Keywords:
autologous stem cell transplant

Multiple myeloma

Renal impairment

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-035

Carfilzomib-based induction improves progression free survival and rate of minimal residual disease negativity following autologous transplant in high risk multiple myeloma patients: a retrospective analysis

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Abstract:
Background: High-risk multiple myeloma (HRMM) is an aggressive disease with a poor prognosis. In this study, HRMM was defined by the presence of t(4;14), t(14;16), t(14;20), 1q gain, or del(17p) on interphase FISH. Our study aims to identify factors that prolong survival in HRMM. Methods: A retrospective analysis of HRMM patients who were diagnosed between 2002 and 2015 at Hackensack University and Mayo Clinic FL was performed. 110 patients were identified. Treatment-related data were analyzed using fisher's exact test, cox proportional hazard models and Kaplan-Meier analysis. Results: 31(28%) patients were ISS III, 43 (39%) had del 17p, 49 (45%) had 1q gain, 26 (24%) had t(4;14), 11 (10%) had t(14;16). Median age was 63, 51 (46%) were men. 91 (83%) received triplet induction, 31 (28%) received carfilzomib (K)-based induction, 73 (66%) received bortezomib (V)-based induction. 77 (70%) had single ASCT, 16 (13%) underwent a tandem ASCT, 13 (11%) underwent a salvage allogeneic transplant. The median follow-up time for all patients was 22m. The median OS of patients who underwent single ASCT was 60m and the median PFS was 20m. The median PFS for the entire population of patients who received K-based induction was not reached (NR) compared to 21m for patients who received V-based induction (p = 0.00). Among patients who underwent a single ASCT, the median PFS was NR for those who received K-based induction compared to 19m for those who received V-based induction (p=0.08). Patients who received K-based induction had a superior minimal residual disease negativity (MRD) rate compared to V-based induction following single ASCT (31.8% vs. 10.3%, p=0.027). Patients who achieved MRD negativity following ASCT had a superior PFS compared to those who did not (47m vs. 19m, p=0.054). In univariate analysis, MRD

negativity after ASCT (HR 0.44, 95% CI: 0.23-0.86, p=0.016), K-based induction (HR 0.32, 95% CI: 0.15-0.72, p=0.006), post-ASCT consolidation (HR 0.31, 95% CI: 0.09-0.99, p=0.049) and tandem ASCT (HR 0.47, 95% CI: 0.25-0.89, p=0.021) were associated with a reduced risk of progression. In multivariate analysis only K-based induction was associated with reduced risk of progression (HR = 0.42, 95% CI: 0.18-0.95, p = 0.04). Median PFS was NR for patients who received K-lenalidomide (R)-Dexamethasone(D) induction. When the PFS endpoint was set at the population median PFS of 20m, there were no PFS differences among patients who received KRD vs. VRD induction (20m vs. 16.5m, p = 0.44) followed by ASCT. Conclusions: K-based induction followed by ASCT is associated with a deeper hematologic response and reduced risk of progression in HRMM. No differences in PFS were noted when comparing KRD vs. VRD induction followed by ASCT. Longer follow-up is needed. The results of the ENDURANCE trial will prospectively determine if K-based induction confers a survival benefit in patients with multiple myeloma.

Keywords:
autologous stem cell transplant

carfilzomib

Minimal residual disease

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-036

Assessing efficacy and tolerability of a modified lenalidomide/bortezomib/dexamethasone (VRd-28) regimen using weekly bortezomib in multiple myeloma

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Abstract:
Background: The use of bortezomib in treatment of multiple myeloma (MM) has become a backbone of many induction regimens. Its efficacy when given twice weekly is often at the expense of peripheral neuropathy (PN) despite of adopting subcutaneous (SQ) administration. In an attempt to reduce the impact on quality of life (QOL) without compromising response, studies using weekly bortezomib with cyclophosphamide and dexamethasone (VCD) or lenalidomide and dexamethasone (RVD-lite) in transplant ineligible patients have demonstrated to be effective treatment regimens. At Wake Forest Baptist Health (WFBH), transplant eligible MM patients receive a modified RVD-lite regimen using a 28-day cycle with weekly SQ bortezomib (termed VRd-28) to minimize PN. The purpose of this study is to evaluate response rates, progression free survival (PFS), and safety (including PN) when using VRd-28. Methods: An observational, single-center, non-randomized, retrospective chart review of transplant eligible patients treated between October 2012 and May 2019. Patients included in this analysis received induction or salvage chemotherapy with bortezomib 1.3 mg/m2 SQ on days 1, 8, and 15 of a 28-day cycle; lenalidomide 25 mg on days 1 through 21; dexamethasone 40 mg on days 1, 8, and 15 (VRd-28). The primary objective was to evaluate overall response rates in MM patients at WFBH treated with VRd-28. Secondary objectives looked at PFS, effect of therapy on PN, and dose delays or changes related to weekly-dosed bortezomib. Results: Sixty-eight patients received VRd-28 for a minimum of 2 cycles and were considered evaluable for this study. Nineteen patients (27.9%) were classified as having high risk cytogenetics based on the presence of one or more of the following: 17p deletion, t(4;14), t(14;16), or 1q gain. The overall response rate (ORR) was 87.0% with 63% of cases achieving a very good partial response or better. Those who received VRd-28 as induction treatment (N=58) had an ORR of 88.8% compared to 75% for those who received it as salvage in the relapse setting (N=10).

Baseline PN was reported in 8 patients (11.6%) and increased to 26 cases (38.2%) after completing 4 cycles of therapy. None of the reported cases were NCI-CTCAE grade 3 or higher. Dose reductions or treatment delays for adverse events in general occurred in 27.9% of patients. Only one patient discontinued therapy. Conclusion: Transplant eligible patients treated with VRd-28 had favorable responses with tolerable side effects. This regimen echoes the reduced incidence of PN as those seen in RVD-lite and VCD when compared to regimen using bi-weekly bortezomib dosing. Randomized prospective studies to evaluate efficacy and safety of weekly vs twice weekly bortezomib dosing in treatments for MM is warranted.

Keywords:
bortezomib

neuropathy

RVD

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-037

Impact of cytogenetics versus FISH detected t(11;14) in newly diagnosed multiple myeloma patients with upfront transplantation

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Abstract:
Intro Traditionally, multiple myeloma (MM) patients with t(11;14) have been considered to have standard-risk disease. However, a few recent reports have challenged this notion. One of the several factors which could explain the disparate outcomes is inclusion of patients with t(11;14) on both fluorescence in situ hybridization (FISH) testing and conventional cytogenetics (CC) analysis. That's because abnormalities on CC analysis represent high proliferation rates in clonal plasma cells and portend poor survival in comparison to abnormalities detected through FISH alone. With the aim of comparing cytogenetics versus FISH detected t(11;14) abnormality, we designed this retrospective study in newly diagnosed MM patients who received upfront autologous hematopoietic stem cell transplant (auto-HCT) at our center. Methods From January, 2001 to December, 2015, we identified 27 MM patients with t(11;14) abnormalities detected on CC who underwent upfront auto-HCT at our center. Among these 27 patients, 13 patients were also positive for t(11;14) by FISH testing as well. In the FISH group, we identified 82 MM patients who were positive by FISH alone without t911;14) detected by CC. Results Patient characteristics are presented in Table 1. The median follow-up time for this cohort was 43.7 months. As shown in Table 1, more patients in CC arm received no maintenance therapy. The median PFS time was 22.3 (95%CI: 17.8-37.1) and 37.6 (95%CI: 26.6-not reached) months for CC and FISH positive patients, respectively (p=0.004). The four-year PFS rate was 17.8% (95%CI: 7.8%-40.8%) and 46.7% (95%CI: 35.3%-61.8%) for CC and FISH positive patients, respectively (Figure 1). The median OS time was 53.7 (95%CI:38.2-Not reached) months for CC positive patients, and was not reached for FISH positive patients (p=0.003). The four-year OS rate were 59.5% (95%CI: 42.8%-82.8%) and 81.4% (95%CI: 71.5% - 92.8%) for CC and FISH positive patients, respectively (Figure 2). For both univariate and multivariate analyses, we observed that CC positive patients had statistically worse PFS with HR=2.13 (95%CI: 1.26-3.59, P-value=0.007) and HR= 2.98 (95%CI: 1.40-6.34, P-value=0.004), respectively. Similarly, on both univariate and multivariate analyses, CC positive patients had statistically worse OS with HR=3.03 (95%CI: 1.40, 6.58, P-value=0.005) and HR=5.56 (95%CI: 2.09, 14.78, P-value<0.001), respectively. Conclusion In newly diagnosed MM with upfront autologous

transplantation, t(11;14) detected by conventional cytogenetics in comparison to FISH predicts poor overall survival outcomes.

Keywords:
t(11;14)

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-038

Multiple myeloma and comorbidity: a population-based study

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Abstract:
Introduction: The literature on comorbidity in MM is limited and based on small series. However, according to these studies, up to 80% of patients with newly diagnosed MM suffer from comorbidities. Comorbidity in MM patients may increase risk of therapy-related complications, lead to life-threatening conditions and decrease survival. Therefore population-based studies can be a valuable tool to estimate survival and comorbidities in a whole population. Aims: To evaluate the prevalence of comorbidities and to study the impact of comorbidities on survival among patients with multiple myeloma. Material and methods: All patients diagnosed with MM from January 1st 1990 to December 31st 2013 in Sweden were included in the study. Using the Swedish Patient Registry, all discharge diagnosis were gathered from January 1st 1985. Comorbid conditions were defined as chronic illnesses which demand life-long treatment. Only those diagnoses made prior to MM were used. Using ICD 8, 9, and 10 codes, comorbidities were identified. Kaplan-Meier curves were used to estimate survival. Risk of death was compared among multiple myeloma patients with a comorbid condition to those without a comorbidity, using Cox's proportional hazards regression. Results: A total of 13,656 patients with MM were included in the study and 21 groups of comorbidities were identified. The most common diseases were hypertension (20%), cancer (13%), and arrhythmia (10%). Other diseases had a prevalence <10%. In total, 6,471 (47%) had no prior history of comorbidity, 25% had one comorbidity, 14% had two comorbidities, and 14% had three or more comorbid conditions. The risk of death was significantly increased in patients with arrhythmia (hazard ratio (HR)=1.10; 95% confidence interval (CI): 1.03-1.17), cancer (1.09; 1.03-1.15), cerebrovascular disease (1.20; 1.10-1.29), chronic lung disease (1.20; 1.11-1.31), chronic kidney disease (1.25;1.03-1.51), dementia (1.70; 1.43-2.03), diabetes (1.12; 1.03-1.23), heart failure (1.56; 1.4 - 1.68), inflammatory bowel disease (1.37; 1.05-1.78), neurological disease (1.21; 1.09-1.36), peptic ulcer (1.17; 1.03-1.33), peripheral vascular disease (1.23; 1.09-1.39), and psychological disease (1.30; 1.19-1.41). Furthermore, risk of death was significantly increased for those with only one comorbidity at diagnosis (1.18; 1.13-1.24) and this risk was even higher for those with two (1.38; 1.30-1.46) and more than three comorbidities (1.73; 1.62-1.84). Conclusion: In this large, population-based study including almost 14,000 patients, we have shown that comorbidities are common among multiple myeloma patients and that comorbidities are associated with an inferior survival. Importantly, increasing number of comorbidities had a dose-response relationship with worse survival. The importance of comorbidities should be taken into account when evaluating patients and deciding on treatment strategies for individuals with multiple myeloma.

Keywords:
comorbidity

survival

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-039

Retrospective study on various peripheral blood stem cell collection regimens

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Abstract:
Background: Although multiple myeloma remains incurable, the use of novel agents has improved the prognosis. Autologous PBSCT is considered effective because it extends the disease-free survival even in this era and in some cases can be able to obtain MRD negative. Recently, triplet therapy including lenalidomide has become the mainstream in induction therapy, and the outcome after transplantation is further improved. However, it is a fact that stem cell collection has become difficult due to the use of lenalidomide, and in some cases it is simply difficult to collect G-CSF alone. The use of Plerixafor in combination with G-CSF improves the amount collected, and the use cases are gradually increasing in Japan. However, the combined use of chemotherapy and G-CSF is still the mainstream since the use of Plerixafo is only permitted in cases where it is difficult to collect due to insurance adaptation in Japan. It is unclear as to whether the combination of chemotherapy will improve the prognosis of multiple myeloma. Here, we report retrospectively on the efficacy and prognosis of the various harvesting methods. Materials and methods: According to the IMW criteria, patients younger than 65 years with symptomatic multiple myeloma , and signed research consents approved by the Institutional Review Board could be in this study. The exclusion criteria were a serum creatinine level of 2.05 mg/dL or more at time of collection; liver insufficiency, for example, a serum total bilirubin level of 2.0 mg/dL or more, serum aspartate/alanine aminotransferase levels or alkaline phosphatases levels more than 2.5 times the upper limit of normal; poor performance status (grade 3 or worth); and a history of any other malignant disease with the exception of basal cell carcinoma and stage I cervical cancer. All patients received 4 cycles of BD (Bortezomib 1.3 mg/m2×4d; Dexamethasone 20mg×8d) therapy as induction therapy. EDAP (Etoposide (100 mg/m2/d×4d); cis-Platin (25mg/m2/d×4d); Arabinosyl-cytosine (1g/m2/d×1); Dexamethasone 40 mg d1-5) regimen which was described in total therapy 1 (B. Barlogie et al.). All patients received lenoglastim (5μg/kg once a day. High dose cyclophosphamide (2g/m2/d×2) regimen was traditionally used. Results: We analyzed about 90 cases (51 men and 39 women). There were 58 cases in the EDAP group and 32 cases in the high dose cyclophosphamide group. There was no difference between the two groups in the success rate of stem cell collection. However, the amount of CD34 positive cells that could be collected was clearly higher in the EDPA group. Moreover, regarding the treatment results after transplantation, there was no difference between the two groups in overall survival rate at 60 months (81% vs. 78%). Conclusion: With both the anticancer drug and the G-CSF combination therapy, sufficient CD34 positive cells for transplantation could be collected with either treatment, and there was no difference in prognosis between the two groups

Keywords:
Stem Cell Mobilization

Stem Cell Transplant

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-040

ALPINA: Real World Analysis of 1st line RVd treatment in Transplant Eligible &

Transplant-non-Eligible MM patients with a focus on tolerability and efficacy

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Abstract:
Background: The triplet combination of Lenalidomid, Bortezomib and Dexamethasone (RVd) has shown high activity in Myeloma first line treatment in both transplant-eligible (TE) and transplant non-eligible (TNE) patients in clinical trials. In multiple myeloma (MM), the achievement and duration of complete response (CR) or at least very good partial response (VGPR) has been shown to be of major importance. This is particularly relevant in high dose therapy (HDT) followed by autologous stem cell transplantation (ASCT). In Europe, this regimen is not approved yet. In order to analyse the outcome of RVd-patients in a clinical routine setting, "ALPINA" was initiated. Methods: Patients receiving RVd off-label were identified using the Austrian Myeloma Registry (AMR) and local data repositories. A minimum of four completed cycles of RVd were required for TE patients, while at least 6 completed cycles of RVd were necessary for TNE patients to qualify for the analysis, making the cohorts comparable to the published trial populations (e.g. SWOG S0777, IFM 2009, GEM 2012). Besides outcome variables (best response, transplant use, etc.) safety, tolerability, side effects (e.g. neuropathy) and the RW use of regimen modifications were investigated using descriptive statistics. Results: Out of 141 patients, 87 patients met the inclusion criteria [TE (n = 59, 69 %, cohort 1), TNE (n = 28, 31% cohort 2)]. Among the patients not included (n = 54), 17 patients discontinued therapy before reaching the specified number of cycles, while 28 patients are still on RVd-treatment As these 28 patients are currently being treated with RVd, we are confident that the cohort will grow even further until the conference. Baseline characteristics of the cohorts were: 58 male and 28 female MM patients, diagnosed at a median age of 64 (male; range 43 - 64) and 59 (female; range 45 - 66) years. 59 (69 %) MM patients received an ASCT, and 28 (31 %) patients were TNE. Bortezomib was given exclusively s.c. in all patients. RVd was applied uniformly 14/21 in cohort1 (V 1.3 mg/m², R 25 mg (55 pts. (93 %) & 10 mg (4 pts. (7 %)) and Dexamethasone 40 mg/week (59 pts., 100 %). RVd was used in modified fashions in 39 % of pts. in C2 (RVd weekly, reduced DEX or V dosage). Dose delays were observed in 57 % of pts. In detail cohort 1 (TE) shows a distribution of best overall response in partial response (PD, 25 %), VGPR (27 %) and CR (41 %). In comparison the distribution of best overall response in cohort 2 (TNE) was SD (11 %), PR (32 %), VGPR (39 %) and 18 % of MM pts. reached a CR. Conclusion: RVd is a safe and well tolerated therapy over 4 cycles pre-ASCT and at least 6 cycles in TNE patients also under RW conditions. Deep responses (≥VGPR) were frequently achieved (68% in C1, 57% in C2). Despite a high dose intensity there were no therapy impeding toxicities. Detailed data including relevant side effects and a comparison to relevant clinical trials will be presented.

Keywords:
Multiple myeloma

Stem Cell Transplant

triplet therapy

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-041

Eight versus four induction cycles of Carfilzomib, Thalidomide and Low-dose Dexamethasone: the Carthadex trial.

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Abstract:
Introduction This phase 2 dose escalation trial investigates the combination of carfilzomib with thalidomide and dexamethasone (KTd) for induction and consolidation in transplant eligible patients with newly diagnosed multiple myeloma. Results of the first four cohorts have recently been published (Haematologica 2019). We here present the effect of intensified induction with 8 KTd as compared with 4 KTd on depth of response before and after high-dose melphalan (HDM). Methods Four or 8 induction cycles of KTd were used. Dose of carfilzomib was 20 mg/m2 i.v. on days 1, 2 followed by 27, 36, 45 or 56 mg/m2 on days 8, 9, 15, 16 of cycle 1 and on days 1, 2, 8, 9, 15 and 16 of cycles 2 to 4 or 8. Thalidomide dose was 200 mg orally, days 1 through 28. Dexamethasone dose was 40 mg orally, days 1, 8, 15 and 22. After induction, stem cell harvest was performed after cyclophosphamide priming (2 to 4 g/m2) and G-CSF. Following HDM (200 mg/m2) and autologous stem cell transplantation, consolidation treatment consisted of 4 cycles KTd in the same schedule, thalidomide dose was 50mg. The primary endpoint was response after induction therapy, specifically complete response (CR) and very good partial response (VGPR). Other endpoints were safety, progression-free survival (PFS) and overall survival (OS). Results A total of 137 eligible patients were included. We report the response of 26 patients treated with 8 cycles KTd induction therapy versus 20 patients treated with 4 KTd, with carfilzomib at the highest dose level (56 mg/m2). Median age was 57 years. Median follow-up was 40.2 months [range 19.3-60.7 months]. Response with 8 KTd after induction was CR in 27%, ≥ VGPR in 92% and ≥ PR in 96%. With 4 KTd response after induction was CR in 20%, ≥ VGPR in 80% and ≥ PR in 90%. CR rate with 8 KTd increased to 35% after HDM and to 58% after consolidation treatment. With 4 KTd CR rate increased to 30% after HDM and 65% after consolidation treatment. Induction treatment with 8 KTd resulted in a higher level of premature stop of carfilzomib (12%) and dexamethasone (12%) than with 4 KTd (5% and 5% respectively). Cardiac events grade 3 and 4 in patients treated with 8 KTd occurred in 4 patients (15%, heart failure (2 patients) and hypertension (2 patients)). With 4 KTd heart failure grade 3 was reported in one patient (5%). However, the small sample size preclude firm conclusions about differences in toxicity and response. In patients treated with 8 KTd PFS and OS at 36 months were 66% and 92% respectively. With 4 KTd PFS and OS were 60% and 85% respectively. Conclusions Treatment with 8 KTd resulted in a deeper response before HDM and ASCT. However, depth of response was comparable after consolidation treatment between patients treated with 4 and 8 KTd. Cardiac toxicity and premature stop was higher in 8 KTd than with 4 KTd. Also, 8 KTd showed no improvement in PFS and OS. Therefore, we conclude that 8 KTd is not superior to 4 KTd.

Keywords:
survival

Tolerability

treatment

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-042

The prognostic impact of dynamic changing of cytogenetic abnormalities under the treatment options in multiple myeloma

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Abstract:
BACKGROUND: Cytogenetic abnormalities (CAs) play a critical part in wide heterogeneity in multiple myeloma (MM) with significantly prognostic impact. It is not clear whether the dynamic changing of CAs and transformed genetic risk stratification matter in prognosis evaluation and individualized treatment in multiple myeloma. METHODS: We analyzed the prognostic impact of consecutive CAs by FISH with a cohort of 80 paired patients with complete cytogenetic data both at the time of diagnosis and progression among 568 consecutive treated NDMM, who received at least 4 cycles bortezomib or thalidomide based induction following ASCT or subsequent chemotherapy. The presence of t(4;14), t(14;16) ,17P13 deletion and 1q21 gains (≥4 copies) were defined as high-risk (HR) CAs. Patients without such abnormalities were classified as standard risk(SR) . RESULTS: We established 3 patterns of progression by comparing the cytogenetic data at the time of diagnosis and progression at a individual level: Pattern A (40%) containing 32 patients without new CAs at the time of progression; Pattern B(15%) containing 12 patients get new CAs without HR CAs；Pattern C(45%) containing 36 patients acquire new HR CAs. The mOS of Pattern A，B and C are 62.0 months(95% CI，35.8-88.3)，78.2momths，and 43.2 months(95% CI，23.6-62.8) respectively(P=0.000)，mPFS are 22.5 months(95%CI，11.2-33.9)，25.0 months(95%CI，12.6-37.4) and 16.9months(95%CI，13.3-20.9) respectively(P=0.013) with significant difference. The prognostic impact of progression patterns also exist in bortezomib and thalidomide group，SR and HR group classification (P＜0,05). 4 risk-changing groups including 60 patients are further established，with 15 patients keep SR both at diagnosis and progression named group A(25%)；12 SR patients evolving into HR group at disease progression named group B(20%)；17 HR patients without harboring new HR CAs at progression named group C(28%)；16 HR patients harbor new HR CAs at progression named group D(27%).The mOS of patients of group A，B and C and D are not reached，48.6 months(95% CI，10.3-86.9) ,48.1 months(95% CI，45.4-50.7) and 24.7 months(95% CI，16.8-32.5) respectively with significant difference(P=0.001)，mPFS are 26.0 months(95%CI，10.3-41.8)，18.1 months(95%CI，16.3-19.9)，14.5 months(95%CI，11.3-17.6) and 12.2 months(95%CI，9.8-14.7) respectively (P=0.143). CONCLUSION: The FISH analysis matters in evaluating dynamic cytogenetic changes and transformed genetic risk stratification with prognostic significance in the whole course of MM especially at the time of progression. Patients harboring new HR CAs when progressed have worse outcomes than those don't，no matter which genetic risk stratification or treatment group they belonged to at the very beginning.

Keywords:
dynamic cytogenetic abnormality changes

Multiple myeloma

prognostic impact

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-043

Real-world Outcomes of Chinese patients with high-risk Multiple Myeloma

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Abstract:
OBJECTIVE: At present, there is no report on the diagnosis and treatment of high-risk MM in the real world in China. Therefore, this study aims to record and describe the diagnosis and treatment status of high-risk MM patients in the real world through retrospective, single-center, observational cohort studies. METHODS:The data of real-world outcomes were collected from of the patients with high-risk multiple myeloma diagnosed in the CAMS&PUMC from January 2013 to June 2017. The current status of diagnosis and treatment of high-risk MM patients in the real world was studied by retrospective cohort study.RESULTS:A total of 160 patients were enrolled. In 107 patients received standardized treatment, the median age 56 years (31-77), 37 underwent stem cell transplantation (SCT) at any time during treatment. 4 received double ASCT, 2 cases of allo-SCT, and the other 31 received single ASCT. Immunological subtype IgA was found in 21 cases (19.6%), IgG in 42 cases (39.3%), IgD in 18 cases (16.8%), and light chain in 23 cases (21.4%), non secretory 3 cases(2.8%).The proportion of IgD subtypes was significantly higher than that of MM patients in the same period (5.8%).Extramedullary myeloma was found in 24 cases (22.4%), primary plasma cell leukemia in 12 cases (11.2%). 9.3%(10 cases) of the patients had received bortezomib-based therapy without thalidomide/lenalidomide, 8.4%(9 cases) had received thalidomide/lenalidomide-based therapy without bortezomib, and 82.2%(88 cases) had received bortezomib plus thalidomide/ lenalidomide-based therapy as frontline treatment, respectively. After a median follow-up of 22.31 months, the median disease-free survival (PFS) and overall survival (OS) were 28.52 and 48.10 months, respectively. The SCT group had a better survival benefit than the non SCT group. The median PFS in the two group was 46.78 months vs 24.84 months (p=0.037), the SCT group had not reached the median OS, but the median OS in the non SCT group was 43.30 months, and the SCT group could obtain longer survival time than the non SCT group, p=0.012.However, the PFS of single, double and allo-SCT in the SCT group was 46.78, 19.32 and 54.51 months respectively (P single vs double = 0.770, P single vs allo = 0.547, P double vs allo = 0.317), and the three subgroups had not reached the median OS. In addition, we found that the longest PFS was found in non-DPACE induction combined SCT group (p = 0.016): 54.51m vs 17.08m (DPACE + SCT) and 24.84m (non-SCT group).CONCLUSION:The proportion of IgD subtypes was significantly higher in HR group. HR MM who receive HSCT can obtain longer remission time and have significant survival benefits even in the novel drugs era. At present, we recommend that the high-risk MM patients receive novel-drugs-based treatment without DPACE in induction phase , and then combined transplantation ,which can significantly prolong PFS1.

Keywords:
High risk

real-world evidence

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-044

The impact of response kinetics following initial therapy for multiple myeloma in the era of novel agents

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Abstract:
Background: Rapid remission has long been recognized as an important predictor for long-time survival in acute leukemia (AL). However, the effects of response kinetics on survival seems to be different from those in AL. A rapid reduction of tumor burden probably indicates a chemotherapy-sensitive population. But on the other hand, a high proliferative activity of plasma cell may be responsible for the rapid response. The effects of response kinetics on outcome for MM remain largely unexplored. Method: The relationship between response kinetics and outcome were prospectively assessed in 626 patients with newly diagnosed MM that were included in a prospective, non-randomized clinical trial (BDH 2008/02). Patients were assigned to either immunomodulatory drugs-based or proteasome inhibitors-based therapy. The response depth, time to best response (TBR) and duration of best response (DBR) were collected. Modified progression-free survival (mPFS) and overall survival (mOS) from time of first detectable best response were calculated. Results: Depth of response was associated with superior outcomes. However, the early responders (defined as TBR $\leq$ 3 months) showed significantly worse survival compared with late responders. There was no significant difference in survival between patients with a rapid complete remission (CR) and those with a late partial remission (PR) (mPFS 33.4 vs. 36.2 months, P=0.382). TBR remained an independent predictor of outcome in multivariate analysis (HR = 1.9 and 2.8 for mPFS and mOS). Moreover, four distinct response kinetic patterns were identified: 1) late response and late relapse ("U-valley" pattern) (n=157, 25%); 2) early response and late relapse (n=101, 16%); 3) late response and early relapse (n=130, 21%); 4) early response and early relapse ("Roller coaster" pattern) (n=172, 25%), and best response less than PR (n=66, 11%). Response kinetics based stratification resulted in remarkable differences in outcome. Patients with gradual and sustained remission identified as "U-valley" pattern experienced superior outcomes, followed by patients with "early response and late relapse" and "late response and early relapse", while poorest outcomes were observed in rapid and transient responders ("Roller coaster" pattern) (median OS 126, 81, 44 and 30 months, respectively). The effects of response patterns on survival were confirmed in patients at different stages of disease and cytogenetic risk, including transplant-eligible patients and those attaining different extents of response depth. Conclusions: Our data indicate that a slow and gradual response is a good prognostic factor for survival, arguing against premature change to more intensive regimens, especially for elderly or unfit patients. In addition to response depth, the kinetic pattern of response is a simple and powerful predictor for survival even in the era of novel agents.

Keywords:
complete response

Minimal residual disease

myeloma

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

SP-045

COMMON REASONS FOR CHANGE OF CHEMOREGIMENS IN MULTIPLE MYELOMA: REAL WORLD, COMPARISON OF TWO TERTIARY CARE CENTERS

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Abstract:
Introduction: Multiple Myeloma (MM) is considered a relapsing-remitting incurable disease in spite of the expanded therapeutic armamentarium. The aim of the disease management is to achieve deeper remissions to prolong PFS best achieved by ASCT. Chemotherapy remains backbone in the treatment of MM in a real-world scenario not affording for ASCT. Change in chemotherapeutic regimens in day-to-day practice in the West is based on the clinical trials which are more systematic and organized. We tried to study the major reasons for the change in chemotherapeutic regimens in the real-world outside the clinical trial settings. Patients and methods: It is a retrospective study conducted at two government tertiary care centers from North India. The first institute (I-1) provides a free consultation with subsidized testing and in-hospital care, whereas patient has to procure the drugs at his own expense (n-415). The second institute (I-2) provides care with no out of pocket expense for OPD care and in-hospital care including sponsored free drugs (n-400). Records of all these consecutive patients of either gender were reviewed. The treatment profile of these patients was assessed. All recorded causes for the change of therapy were analyzed. Results: In a group of 815 patients who either refused, unwilling or non-affording for ASCT, a total of 1232 treatment changes were done in a period of 5 years with a mean follow up of 2.8y (SD-2.3y).In patients with a mean follow up of 3y (n-384), all but for 12 patients underwent treatment changes. The mean time to change of therapy was 1.1y (SD-0.94y). In a total of 462 patients (I-1:102, I-2:360) receiving 2nd-line therapy, the 1st line therapy was changed primarily based on the type of response achieved i.e., due to clinical or biochemical relapse (I-1:25.4%, I-2:21.1%), and change from consolidation to maintenance phase (remission) (I-1:21.5%, I-2:31.1%). Other major reasons were therapy-related toxicity (21.5%, 33.05%), financial non-affordability (I-1:24.9%, I-2:0%), and non-availability of prescribed drugs (I-1:0%, I-2:11.05%). Financial constraints were a major reason (79%) for choosing the first line regimen in I-1, whereas it was the availability of free drug supply in I-2 (82%) other than prevailing guidelines. Among patients requiring beyond the 2nd line of therapy in wither institutions, 2.4% and 21.1% were taken up for salvage ASCT. The commonest cause of change more than 5th line therapy was the non-responsive disease in both institutes, with the same set of patients requiring up to 9th line therapy with multiple drugs. Conclusion: Maximum change of therapy is from 1st to 2nd line therapy, which was mainly guided by the response achieved in either institution and not dictated by the financial constraints/ drug availability. Financial constraint and the availability of desired free-drugs played a major role in therapeutic decision making than the prevailing guidelines.

Keywords:
Change

Chemotherapy

real-world

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

TREATMENT OF NEWLY DIAGNOSED MYELOMA NON-TRANSPLANT ELIGIBLE

SP-046

What do costly tests add to baseline profile? Diagnostic work up of Myeloma in resource constraint setting

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Abstract:
Introduction: Multiple Myeloma is one of the common hematological neoplasms affecting elderly. This disease has seen lots of advances not only in treatment modalities but also in diagnostic and prognostic tools. Despite being aware of recent IMWG recommendation on work up of myeloma patients, health care in developing world faces unique challenges. Many a times what is "ideal" is not affordable to the majority of patients. We intend to analyze whether any additional information is obtained by adding to baseline work up two costly tests namely serum free light chain assay (sFLC) and FISH in these patients. Method: We retrospectively analyzed data of 130 myeloma patients enrolled to our institute between years 2016 to 2019. Subset analyses of 71 patients who had results of all the three tests, namely serum protein electrophoresis (SPEP), immunofixation electrophoresis (IFE) and serum free light chain assay (sFLC) for monoclonal protein detection at baseline. Relative efficiency of each of these tests in detecting M protein at baseline was compared. Another subset of patients (70) underwent FISH testing on sorted plasma cells for high risk cytogenetic abnormalities and serum LDH level. ISS and Revised International staging system (RISS) categories were compared amongst this group of patients. Results: Among the 71 patients who had all three tests done for monoclonal protein detection, SPEP detected and quantified M protein in 55 (77.4%) patients. IFE detected M protein in 68 (95.7%) patients, and sFLC ratio was abnormal in 66(92.6%) patients. Both IFE and sFLC were more sensitive in detecting monoclonal protein as compared to SPEP (p value 0.001 and 0.009). For 70 patients FISH, LDH and ISS results were available. 20(28.5%) were ISS stage I, 22 (31.4%) stage II and 28 (40%) were ISS stage III. Seven patients (10%) had high risk karyotype and LDH was raised in 5(7.1%) patients. Based on results of LDH and FISH 3 (4.2%) patients who were ISS stageI were upgraded to RISS stage II. 21(30%) ISS-III patients were shifted to RISS-II category due to absence of high risk karyotypic abnormalities and normal serum LDH. Conclusion: IFE was highly sensitive in detecting M protein but is not meant to quantify M band. In resource constraint setting utilizing sFLC sequentially when SPEP is non informative but UPEP/IFE shows M band can be viable approach. However, sFLC will be indispensable for application of sLIM criteria for diagnosis when CRAB features are absent and follow up of light chain Myeloma. FISH for high risk karyotypic abnormalities was informative and helped in better prognostication of 34% of our patient group. Routine testing for high risk cytogenetic abnormalities by FISH is of paramount importance.

Keywords:
FISH

free light chain assay

Risk stratification

Tracks:
Treatment of Newly Diagnosed Myeloma Non-Transplant

SP-047

Multiple myeloma treatment patterns, outcomes, and costs during 2009-2016, identified with multiple data sources from a hospital district in Finland

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Abstract:
BACKGROUND: Multiple myeloma (MM) and its complications require treatment, regular hospital visits, and intense patient follow-up. MM treatment patterns and outcomes are not fully known in the Finnish setting. This observational study describes patient characteristics, treatment patterns, outcomes,

and costs among adults treated for active MM during 2009-2016 at a hospital in Finland. METHODS: Three data sources were used: the hospital's database, the hospital's medical charts, and interviews with healthcare professionals. Patients with at least one diagnosis code for active MM (ICD-10: C90.0) and who received MM treatment between 2009-2016 in the hospital's database were eligible for the study. Patients receiving allogeneic transplantation were excluded. Descriptive analyses examined patient characteristics, MM treatment patterns, outcomes, and healthcare costs. RESULTS: Ninety-seven MM patients were analyzed in this study - 53 men (54.6%), median age at diagnosis: 70.0 years. The incidence of MM was 7.1/100,000, which is comparable to other settings. Median patient follow-up time was 33.6 months; median overall survival from diagnosis date was approximately 67.7 months. Bortezomib-cyclophosphamide-dexamethasone was the most common first-line (1L) treatment (30 patients, 30.9%); lenalidomide-dexamethasone was the most common treatment in 2L (22/57 patients followed, 38.6%), 3L (12/34 patients, 35.3%), and 4L (5/20 patients, 25.0%). Among patients receiving a subsequent line of therapy, mean time-to-next-treatment ranged from 229 days (3L to 4L) to 450 days (2L to 3L). Seventy-two patients (74.2%) had an objective response (OR) in 1L; 13 patients (13.4%) had stable or progressive disease. OR was observed in 2L, 3L, and 4L therapy for 42 (73.7%), 19 (55.9%), and 10 (50.0%) patients, respectively. Stable or progressive disease was observed in 2L, 3L, and 4L therapy for 10 (17.5%), 11 (32.4%), and 7 (35.0%) patients, respectively. Mean per patient drug costs per 28 days ranged from €2328 (in 1L) to €4930 (in 2L); drug costs represented the greatest proportion of total healthcare costs across all lines of MM therapy and increased from 1L to 4L: 34% to 63%. Mean, one-way distanced travelled to healthcare visits was 35.4km; mean per patient travel costs per 28 days for oral treatment were lower across 1L - 4L (range: €75.13 – €151.80) vs. non-oral treatment (€266.82 – €447.79) (n=63, treated between 2015-2016). CONCLUSION: OR was observed across 1L to 4L therapy in approximately 50%-75% of this sample of active MM patients treated in Finland. Treatment costs represented the greatest proportion of direct healthcare costs, and (for a sub-group of these patients) treatment with non-oral therapies incurred greater travel costs to healthcare visits vs. oral treatment. These findings indicate a need for more efficient treatments to provide better outcomes for patients, at lower healthcare costs.

Keywords:
Newly diagnosed multiple myeloma

treatment patterns and outcomes

treatment-associated costs

Tracks:
Treatment of Newly Diagnosed Myeloma Non-Transplant

SP-048

Phase 3 FIRST Trial in Transplant-Ineligible Newly Diagnosed Multiple Myeloma: Subgroup Analysis of Patients From Canada and the United States

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Abstract:
BACKGROUND In the FIRST trial, lenalidomide (LEN) + low-dose dexamethasone until disease progression (Rd cont) showed significant PFS and OS benefits compared with melphalan, prednisone, and thalidomide (MPT) in transplant-ineligible (TNE) pts with NDMM. PFS was also extended with Rd cont vs Rd for 18 cycles (Rd18). These results support the use of frontline alkylator-free continuous oral therapy for TNE pts with NDMM and established Rd cont as a standard of care, as reflected by clinical guidelines in Canada, the US, and Europe. Outcomes in the subset of pts from Canada and the US are reported. METHODS Pts with TNE NDMM were randomized 1:1:1 to Rd cont (28-day cycles until progression), Rd18 (18 × 28-day cycles), or MPT (12 × 42-day cycles). Rd18 and MPT both had a duration of 72 wks. LEN was given on days 1-21 of each cycle. Stratification factors included country. The primary comparison was Rd cont vs MPT. PFS was the primary endpoint; secondary endpoints included OS, time to next therapy (TTNT), and safety. Time from randomization to second progression or death (PFS2) was an exploratory analysis. The final OS analysis data cutoff (21 January 2016) was used. RESULTS A total of 312 pts from Canada (n = 252) and the US (n = 60) were enrolled (104 in each arm). The median age was 74 yrs, and 27%, 51%, and 21% of pts had an ECOG performance status of 0, 1, and ≥ 2, respectively. Consistent with results from the intent-to-treat (ITT) analysis, the Canada/US subgroup had a significant improvement in PFS with Rd cont vs MPT (median, 29.3 vs 20.2 mos; HR = 0.69 [95% CI, 0.49-0.97]; P = .03326) and an improvement vs Rd18 (median, 21.9 mos). Median OS was 56.9 vs 46.8 mos with Rd cont vs MPT (0.77 [0.53-1.11]; P = .15346) and 59.5 mos with Rd18. Median PFS2 was longer with Rd cont vs MPT (median, 39.3 vs 35.1 mos; 0.69 [0.50-0.95]) as was TTNT (median, 39.1 vs 24.6 mos; 0.54 [0.37-0.78]). Median PFS2 and TTNT were 39.8 and 29.9 mos with Rd18, respectively. ORR was higher in LEN regimens (78.8%, 65.4%, and 79.8% with Rd cont, MPT, and Rd18, respectively). In the 49.0%, 29.8%, and 52.9% of pts with ≥ VGPR, median PFS was 56.0, 40.2, and 30.9 mos. The most common grade 3/4 treatment-emergent adverse events were neutropenia (28.4%, 52.0%, and 30.1%) and anemia (23.5%, 23.5%, and 21.4% with Rd cont, MPT, and Rd18, respectively). CONCLUSION Results of this subanalysis from the phase 3 FIRST study of pts from Canada and the US showed that Rd cont extended median PFS by 9 mos vs MPT and > 7 mos vs Rd18. Rd cont also delayed median TTNT by > 14 mos and resulted in a longer PFS2 vs MPT, suggesting that the benefit of frontline Rd cont is maintained at relapse. These results are consistent with those in the ITT population confirming the benefit of Rd cont vs MPT in the Canada/US subgroup and supporting the role of Rd cont as a standard of care for TNE pts with NDMM.

Keywords:
Lenalidomide

newly diagnosed MM

Transplant-ineligible

Tracks:
Treatment of Newly Diagnosed Myeloma Non-Transplant

SP-049

Daratumumab, Lenalidomide, and Dexamethasone (D-Rd) Delivers a Reduction and Delay in Worsening of Pain Symptoms for Patients with Newly Diagnosed Multiple Myeloma Ineligible for Transplant

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Abstract:
Background. An ongoing phase 3 trial of transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM) demonstrated significant improvement in progression-free survival with daratumumab, lenalidomide, and dexamethasone (D-Rd) vs Rd alone (MAIA clinical trial; Facon T, et al. N Engl J Med. 2019;380:2104-15). Bone pain is a common presenting symptom in patients with multiple myeloma (MM), and pain has a significant impact on a person's everyday activity and health-related quality of life (HRQoL). Herein we explore the change in pain symptoms with D-Rd vs Rd treatment for patients with NDMM who were not eligible for autologous stem cell transplant (ASCT) from MAIA. Methods. Within the MAIA clinical trial, patients' self-report of their symptoms, the impacts, and general HRQoL were assessed by the EORTC QLQ-C30 questionnaire. The EORTC QLQ-C30 was completed using an electronic device at baseline, every 3 cycles during the first year of treatment, every 6 cycles thereafter, and at 8 and 16 weeks after disease progression. We report results from a prespecified interim analysis (Facon T, et al. N Engl J Med. 2019;380:2104-15). Treatment effects were assessed using mixed model repeated measures. Thresholds for clinically meaningful benefit were based on established criteria from the literature, which ranges from a 10-point to a 16.7-point improvement (Kvam AK, et al. Eur J Haematol. 2010;84(4):345-53; EORTC Quality of Life Group: Guidelines for assessing quality of life in EORTC clinical trials). The median time to worsening was calculated using the Kaplan Meier method. Hazard ratios (HRs) were estimated based on a proportional hazard model. Results. Compliance rates were high and comparable at baseline (>90%; D-Rd [n = 368]; Rd [n = 369) and through Cycle 12 (>80%) for both groups. Statistically significant greater reduction in pain was reported early with D-Rd (LS mean change at Cycle 3; D-Rd: –17.9 [95% CI: –20.7, –15.0], Rd: –11.0 [95% CI: –14.0, –8.1]; P = 0.0007]). The large, clinically meaningful reduction in pain symptoms with D-Rd was sustained through Cycle 12. Median time to worsening of ≥10 points on the EORTC QLQ-C30 pain subscale was 32.20 months (95% CI: 24.12, NE) for the D-Rd group and 17.97 months (95% CI: 10.74, 24.31) for the Rd group (HR = 0.69; 95% CI: 0.55, 0.87; P = 0.0017). When using a worsening of ≥16.67 points as a sensitivity analysis, the median time was not reached in either group, but there was a difference of 11.4 months delay with D-Rd treatment for the Kaplan Meier 25% quantile estimate over the Rd group (HR = 0.72; 95% CI: 0.53, 0.97; P = 0.0274). Conclusion. When treated with D-Rd, patients with transplant-ineligible NDMM experienced larger reductions in pain early during therapy and a delay of time to worsening

from their baseline pain level by about 14 months compared with patients treated with Rd.

Keywords:
CD38

daratumumab

Multiple myeloma

Tracks:
Treatment of Newly Diagnosed Myeloma Non-Transplant

SP-050

Post-Authorization Safety Study of Lenalidomide-Based vs Non–Lenalidomide-Based Treatment in Transplant-Ineligible Newly Diagnosed Multiple Myeloma

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Abstract:
BACKGROUND Lenalidomide (LEN)-based treatment (Tx) until disease progression is a standard approach in newly diagnosed multiple myeloma (NDMM). The safety and efficacy of LEN-based Tx in transplant-ineligible (TNE) NDMM pts has been validated in multiple clinical trials, including the phase 3 FIRST trial. Results from an ongoing observational, non-interventional post-authorization safety study (NCT03106324) investigating the safety and tolerability of LEN-based Tx (LEN cohort) vs non–LEN-based Tx (non-LEN cohort) in TNE NDMM are reported. METHODS TNE NDMM pts initiating their first antimyeloma Tx are eligible if they have received < 2 cycles. Tx is per routine clinical practice and determined before enrollment. The primary endpoint is incidence of cardiovascular events. Secondary endpoints are incidences of renal impairment, infections, and second primary malignancies (SPMs) and further characterization of safety. The observation period is < 3 yrs on Tx, and follow-up is 5 yrs for assessment of SPMs and survival. RESULTS As of 12 April 2019, 165 and 162 pts were enrolled in the LEN and non-LEN cohorts, respectively. Bortezomib-based Tx, the most common Tx in the non-LEN cohort, included combinations with dexamethasone (n = 70) and melphalan + prednisone (n = 83). Median age was 79.0 yrs (LEN cohort) and 76.0 yrs (non-LEN cohort). Tx was ongoing in 108 pts (65.5%) and 87 pts (53.7%), respectively, and median Tx duration was similar in both cohorts (21.9 and 23.6 wks). Thromboprophylaxis was given to 112 pts (67.9%) and 51 pts (31.5%) in the LEN and non-LEN cohorts. There were 11 cardiovascular events in the LEN cohort (6 cardiac failure, 3 angina pectoris, and 1 each of increased troponin and acute pulmonary edema) and 12 events in the non-LEN cohort (7 cardiac failure, 2 myocardial infarction, and 1 each of arterial bypass occlusion, cardiopulmonary failure, and stress cardiomyopathy). Similar percentages of pts experienced ≥ 1 grade 3/4 AE (LEN, 42.4%; non-LEN, 47.5%); neutropenia (5.5%; 7.4%), anemia (6.7%; 4.9%), and thrombocytopenia (3.0%; 7.4%) were the most common. In the LEN cohort, 78 pts (47.3%) had ≥ 1 LEN-related AE. LEN discontinuations and reductions/interruptions due to ≥ 1 AE occurred in 18 pts (10.9%) and 74 pts (44.8%), respectively. There were 3 SPMs reported in the LEN cohort (1 each of lung cancer, prostate cancer, and nonmelanoma skin cancer) and 4 SPMs in the non-LEN cohort (1 each of bladder cancer, lung cancer, cholangiocarcinoma, and recurrent

nonmelanoma skin cancer). CONCLUSION Current results of this ongoing observational, non-interventional study show that the safety profile of LEN-based Tx in TNE NDMM pts in a real-world setting is consistent with that observed in clinical trials. The incidence of cardiovascular events and other AEs was low, and no new safety signals for LEN-based Tx were identified.

Keywords:
Lenalidomide

newly diagnosed MM

real-world

Tracks:
Treatment of Newly Diagnosed Myeloma Non-Transplant

SP-051

PROFILE AND TREATMENT OUTCOMES OF FILIPINO MULTIPLE MYELOMA PATIENTS MANAGED AT A TERTIARY INSTITUTION: A SIX-YEAR RETROSPECTIVE STUDY

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Abstract:
Introduction: Multiple Myeloma remains to be an incurable hematologic entity, but with the advent of novel agents more patients experience significantly longer survival. In a third world country like the Philippines, autologous bone marrow transplant after chemotherapy for newly diagnosed cases which is the standard of care is difficult to comply. Management paradigm for Myeloma has shifted over the years, hence this study. Objective: Determine the clinical profile and treatment outcome of Filipino Multiple Myeloma patients diagnosed and managed at University of Santo Tomas Hospital from January 2013 to December 2018. Methodology: Retrospective, observational and cross-sectional study of eligible symptomatic Myeloma patients. Results: Data for six years were retrospectively collected from a single tertiary institution. The clinical characteristics at diagnosis, treatment, and survival rates of 109 active Myeloma patients were described. Median age was 61 years (range, 28–83), with 51.4% being female. Median overall survival was 49.5 months (95% CI 42.7–56.2). The frontline treatments of patients were also analyzed. The combined deep responses (complete and very good partial) of our patients at 31.7% was higher than of Asian Myeloma Network Study at 30.9%. None yet underwent autologous bone marrow transplantation as of date. Novel agents especially Bortezomib were used in 35.7% and significantly improved overall and progression-free survivals when used as a firstline treatment. Because of its cost and limited availability thru charity or access programs in our country, Thomasian clinicians practice "Bortezomib-sharing" amongst Myeloma patients, making almost all of our patients on Bortezomib-based therapy receive the drug on treatment schedule using available stocks. It could not be denied that this practice helped a lot of patients on Bortezomib achieve a desirable, sustainable response. Though most patients did not comply with all the stringent laboratories to earlier detect biochemical relapse due to financial challenges, most of them came on tight follow-up schedule. Understanding the non-curative nature of Multiple Myeloma and the current limited set of treatment available in our setting, patients' commitment to strict follow-up contributed significantly to the desirable results of this study. Conclusion: This retrospective analysis demonstrated the paradigm shift in the treatment modality of Myeloma, and the survival outcomes has significantly improved especially on best response to chemotherapy. Short of the ideal management in a third world country like the Philippines, we can now set our new standard of care based on the treatments available including novel agents like Bortezomib, and the best practices that our institution offers.

Keywords:
Multiple myeloma

Outcome

Profile

Tracks:
Treatment of Newly Diagnosed Myeloma Non-Transplant

SP-052

Impact of Early vs Late Relapse in Patients With Newly Diagnosed Multiple Myeloma Ineligible for Transplant: A Phase 3 FIRST Trial Subanalysis

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Abstract:
BACKGROUND Many transplant-ineligible (TNE) NDMM pts remain at risk of relapse within 1 year of Tx, which may be driven by pt characteristics and disease biology. Conversely, continuous therapy prolongs time to relapse, as demonstrated in the pivotal FIRST trial studying lenalidomide + low-dose dexamethasone until disease progression (Rd cont), Rd for 18 cycles (Rd18), and melphalan + prednisone + thalidomide (MPT) in TNE NDMM. Indeed, ≈26% of pts in FIRST received Rd cont >3 yrs. This analysis identified factors associated with early vs late relapse and further assessed the impact of continuous therapy.

Methods:
METHODS In FIRST, pts with TNE NDMM were randomized 1:1:1 to Rd cont, Rd18, or MPT. Rd18 and MPT were both 72 wks in duration. The primary comparison was Rd cont vs MPT. Predictors of early relapse were identified by univariate and multivariate analyses using a binary outcome (relapse < vs ≥ 12 mos) in 11 pt-, 18 disease-, and 2 Tx-specific baseline variables.

Results:
RESULTS After censoring, the remaining pts were categorized as those who relapsed early (< 12 mos; n=271) and those who relapsed or were censored ≥ 12 mos (n=975). Five factors were associated with risk of early progression (LDH ≥ 200 U/L, ISS Stage III, high-risk cytogenetics, EORTC My20 ≥ 50, and baseline platelet count ≤ 150×109/L). Due to infrequent use of EORTC in clinical practice, it was replaced with ECOG PS ≥ 2 without impact. As expected, there was a lower percentage of pts with these factors in late relapse which continued to decrease in pts who relapsed after 2 yrs. Validation was performed using MM-015 data (Palumbo, NEJM 2012). Independent of Tx arm, pts with early relapse had a lower ORR vs those with late relapse (59.8% vs 95.6%, with a ≥ VGPR rate of 13.3% vs 61.6%). Responses deepened over time, and the depth of response was higher in pts with later relapse: ≥ VGPR was 86.8% vs 60.9% in pts who relapsed ≥ 3 yrs treated with Rd cont (n=159) vs MPT (n=87), respectively. The median time to ≥ VGPR was 5.8 cycles, and in those pts who entered cycle 6 with ≥ VGPR, the ability to maintain responses with Rd cont resulted in prolonged remission (median PFS not reached vs 25.8 mos with MPT). While high-risk cytogenetics is associated with poor outcomes, pts with favorable hyperdiploidy (t(11;14) or gain of chromosome 5, 9, or 15) had prolonged remissions (median PFS 44.6 vs 27.4 mos with Rd cont vs MPT). Early relapse (< 12 mos) was associated with shorter OS after 12-mo landmark vs late relapse in Rd cont (median 27.9 vs 67.5 mos) and MPT (18.7 vs 54.0 mos).

Conclusion:
CONCLUSIONS These results highlight the importance of achieving and maintaining a response to frontline Tx to delay relapse. Pts with early relapse had lower ORR and ≥ VGPR rates and poor OS. The predictive factors identified suggest that the individual risk of progression appears to be a combination of disease biology, genetics, and pt-specific factors and could be used to help optimize Tx strategies to improve outcomes in TNE NDMM.

Keywords:
Lenalidomide

Long term outcome

Transplant-ineligible

Tracks:
Treatment of Newly Diagnosed Myeloma Non-Transplant

SP-053

The Characteristics, Treatment Patterns, and Outcomes of Older Adults with Multiple Myeloma.

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Abstract:
Background: Tremendous progress has been made in the treatment of multiple myeloma (MM) over the past two decades, however the majority of this success has been demonstrated in younger patients. With 36% of patients >80 years-old at diagnosis, it is important to understand if older patients are receiving similar benefits. In this study, we sought to better understand the characteristics, treatment, and outcomes of older patients with MM. Methods: We identified all patients diagnosed with MM at age 80 or older in the Surveillance, Epidemiology, and End Results Program (SEER)-Medicare database from 2007-2013. Patients who were enrolled in Medicare Parts A, B, and D were included in the analysis of treatment patterns and patient outcomes. A cohort of similar patients diagnosed with MM at age 70-79 was used for comparison using a difference-in-differences design. Results: Median overall survival (OS) for patients diagnosed at age 80+ was 13.4 months (95% CI 12.2-15.2). Only 51% of patients received systemic treatment. Those who received systemic treatment had a median OS of 21.4 months (95% CI 18.7-23.4), compared to 6.4 months (95% CI 5.3-7.3) ($p < 0.0001$) for those not receiving treatment. MM treatment was associated with a 26% decrease in hazard for death (adjusted hazard ratio [aHR] 0.74; 95% CI 0.67-0.82; $p < 0.0001$) independent of age, race, gender, poverty, comorbidities, and proxy measures of performance status. Outcomes improved for patients in more recent years; the hazard for death decreased by 3% (HR 0.97; 95% CI 0.94-0.99; $p = 0.0096$) each year 2007-2013, in conjunction with increasing treatment rates. In 2007, only 41% of patients received treatment compared to 61% in 2013. After controlling for MM treatment, the year of diagnosis was no longer a significant predictor of survival. In the comparator cohort (age 70-79), MM treatment was associated with a 22% decrease in hazard for death (aHR 0.78; 95% CI 0.70-0.86; $p < 0.0001$) independent of the same factors as above. Based on the difference-in-difference design, there is no statistically significant difference in treatment benefit based on age cohort. More specifically, patients 80+ at MM diagnosis who receive systemic treatment obtain proportional benefit to those age 70-79, relative to the untreated patients in the same age group. Conclusions: The results of our study indicate that novel agents produce a similar mortality benefit in older and younger patients. Regardless of age, treatment with novel agents improves survival. The population over 80, when MM incidence peaks, will triple over the next few decades. It is imperative that we continue to advance our understanding of the needs of this vulnerable subgroup of patients with MM.

Keywords:
Elderly

Elderly patients

novel agents

Tracks:
Treatment of Newly Diagnosed Myeloma Non-Transplant

SP-054

Treatment Pattern and Overall Survival in Newly Diagnosed Multiple Myeloma Patients

who are not Eligible for Autologous Stem Cell Transplantation

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Abstract:
Background: Current population-based analysis aims to describe treatment patterns and outcomes among patients with multiple myeloma (MM) who have not received autologous stem cell transplantation (ASCT). Methods: Data were extracted from the US SEER-Medicare database between Jan 2007 and Dec 2016 and from the Optum databases (DoD and EHR) between Jan 2007 and Sep 2018. Patients >45 years of age, diagnosed with MM, and who did not receive ASCT were in their follow-up period were included. Patients without insurance coverage at the time of diagnosis and with prior cancer were excluded. Demographic characteristics such as age, sex, duration of diagnosis, and comorbidities (Charlson Comorbidity Index and Elixhauser Comorbidity) were reported. Patient baseline characteristics were compared among the following groups: Velcade and Revlimid regimen (bortezomib + lenalidomide +/- dexamethasone, VRd cohort), Revlimid-containing regimen (lenalidomide +/- dexamethasone, Rd cohort), Velcade-containing regimen (cyclophosphamide + bortezomib + dexamethasone, CyBorD cohort and bortezomib +/- dexamethasone, Vd cohort). Cox proportional hazard model of overall survival were compared for VRd, Rd, Vd and CyBorD. Results: Of the 125,832 patients diagnosed with MM, 20,452 meeting the eligibility criteria were included (SEER-Medicare: 5,155; Optum: 15,297). Half of eligible patients were men (50.4%), patients had a mean (SD) age of 71.3 (9.66) years at index diagnosis. Mean (SD) duration from MM diagnosis to the start of treatment was 3.5 (8.86) months and a majority of the patients were covered by Medicare (61.3%). Velcade and Revlimid-based combinations were the most common treatment modalities. At baseline, hypertension (62.4%), diabetes (26.6%), and cardiac arrhythmia (24.4%) were among the most common Elixhauser comorbidities. Patients receiving Velcade-containing regimens had the highest mean (SD) Charlson Comorbidity Index of 2.8 (2.69) and that for the overall study population was 2.2 (2.56). Compared to 31.7% of the overall group, 43.2% of patients treated with Velcade containing regimens had renal failure. Patients receiving VRd were younger and more likely to have commercial insurance vs other regimens. VRd group was associated with better over survival compared to Rd, Vd and CyBorD groups (Hazards ratio: 0.82 [95%CI: 0.76-0.88], 0.60 [0.56-0.65], and 0.87 [0.78-0.98] respectively). Conclusion: The frontline combination therapies of MM patients not eligible for ASCT are consistent with NCCN guidelines. Patients initiating with VRd are associated with better OS. However, these results do not adjust for patient prognostic factors and subsequent therapies. The longtime lag of reporting in the SEER-Medicare database and under-reporting of deaths in the Optum database are limitations of the present study.

Keywords:
Multiple myeloma

multiple myeloma-specific survival

multiple-myeloma specific survival

Tracks:
Treatment of Newly Diagnosed Myeloma Non-Transplant

SP-055

A review of diagnostic features of multiple myeloma in Sub-Saharan black subjects Africa.

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Abstract:
Introduction: Multiple myeloma (MM) is the proliferation of a clone of abnormal blood cells that infiltrate into the bone marrow and elicit a monoclonal immunoglobulin. Many studies have been conducted on MM in Africa.. In this review, we comprehensively did a descriptive analyses of the clinical, biological and therapeutic features of myeloma African black individuals from studies conducted in sub-Saharan countries. Methodology: Bibliographic databases including African Index Medicus search engines, PubMed, EMBASE, The Cochrane Central Library, Google Scholar, Crossref, Zotero, ResearchGate were consulted for extraction studies published between 1985 and 2017. Clinical, biological and therapeutic data of MM from each peer-reviewed publication were extracted and keyed in a Microsoft Excel spreadsheet. Results: Twenty-one (21) studies, corresponding to a total population of 1417 individuals diagnosed with MM, were included in the review. All studies presented sociodemographic information whereas hematological, electrophoretic, immunological and biochemical information were available in 11, 8, 12 an14 studies respectively. In the overall mean age of individuals was 58.26 ± 6.53 years. Patients aged 50-59 years accounted for 29.32% of the total, the followed by those aged 60-69 years (25.30%). Bone pain (75.72%), anemia (47.85%), impaired general status and nephropathies (20.18%) were the main symptoms presented by patients. Peak in gamma globulins was mostly reported (n = 342, 53.27%) while Immunoglobulins G and A were found in 494 (48.14%) and 152 (12.18%) patients respectively. Likewise, Kappa and lambda light chains were found in 45.36% and 41.44 % of cases respectively. Based on the classification of Salmon and Durie, patients were diagnosed at stage III at consultation. Melphalan / Prednisone combination was the commonest treatment used for management. Conclusion: Individuals of sub-Saharan countries suffering from MM are young, diagnosed at an advanced stage of the disease and the choice of treatment depends strongly on financial income.

Keywords:
black africans

diagnosis and therapeutic features

Multiple myeloma

Tracks:
Treatment of Newly Diagnosed Myeloma Non-Transplant

SP-056

Treatment of Newly Diagnosed Multiple Myeloma: A Real-world Study in A Western Single Center of China

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Abstract:
Introduction Multiple myeloma (MM) is the second most common hematological malignancy. And there is no standardized treatments that can cure MM. Thus, in this real-world study, we compared the efficacy and safety among bortezomib-containing regimens(BCR), bortezomib-not-containing regimens(BNR) and autologous stem cells transplantation(ASCT) and analyzed prognostic factors in the treatment of newly diagnosed multiple myeloma(NDMM) in West China Hospital. Methods 256 NDMM patients from 2014 to 2018 in our hospital were included in this study. BCR(n=168)

included bortezomib-dexamethasone(BD), bortezomib-cyclophosphamide-dexamethasone(BCD), bortezomib-thalidomide-dexamethasone(BTD), bortezomib-anthracyclines-dexamethasone(BAD), bortezomib-lenalidomide-dexamethasone(BRD). BNR(n=64) included melphalan-prednisone(MP), cyclophosphamide-dexamethasone(CD), thalidomide-dexamethasone(TD), cyclophosphamide–thalidomide-dexamethasone(CTD), vincristine-anthracyclines-dexamethasone(VAD). And this study also compared the efficacy and safety of BD, BXD (including BCD, BTD, BAD) and BRD. Results The ORR, VGPR and CR rate were 59.4%, 21.9% and 10.9% respectively in the BNR group, were 81.0%, 48.8% and 22.0% respectively in the BCR group, were 100.0%, 70.8%, 91.7% respectively in the ASCT group(P<0.05). In high-risk cytogenetics subgroup, the ORR of BCR was higher than BNR(82.5% vs 42.9%, P=0.042). The ORR of BRD was higher than that of BD (71.4% vs 96.1%, P=0.001). The ORR and VGPR rates of the intravenous injection were higher than subcutaneous injection (76.7% vs 94.9%, P=0.018; 40.3% vs 76.9%, P<0.001). Three groups didn't reach the median OS, and the 5-year OS rates were 63.0%, 74.6% and 93.8%, respectively. The median PFS of BD, BXD and BRD subgroups were 28.4, 39.1 and 32.8 months, respectively(P=0.825). The 5-year OS rates were 72.5%, 72.1% and 77.2%, respectively (P=0.725). Toxicities included anemia, granulocytopenia, thrombocytopenia, pneumonia, peripheral neuropathy, herpes zoster, diarrhea, et al. The incidence of grade 3-4 peripheral neuropathy was 4.8% in the bortezomib group, while no one happend in the other two groups. Multivariate analysis showed that the independent factors on PFS were initial infection, extramedullary disease, chemotherapy duration of 4 cycles and ≥VGPR. Initial infection and ≥VGPR were independent factors on OS. Conclusions Both short-term and long-term efficacy of BCR in the treatment of NDMM patients was significantly better than that of BNR, but inferior to ASCT. BCR can overcome the poor efficacy of patients with end-stage disease, renal failure, and high-risk cytogenetics in NDMM patients. The short-term efficacy of BRD was better than that of BD. Subcutaneous injection may gain worse efficacy. The BCR group was prone to severe peripheral neuropathy. Initial infections, extramedullary infiltration, chemotherapy duration of 4 cycles, and reaching at least a VGPR were independent factors on survival of NDMM patients.

Keywords:
Autologous hematopoietic stem cell transplantation

bortezomib

Newly diagnosed multiple myeloma

Tracks:
Treatment of Newly Diagnosed Myeloma Non-Transplant

SP-057

Low Body Mass Index is a Predictor of Early Mortality in Patients with Newly Diagnosed Multiple Myeloma

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Abstract:
Background Multiple myeloma (MM) is a common hematologic neoplasm in Taiwan. Some patients with MM have low body mass index (BMI) associated with their underlying conditions. We aimed to investigate the clinical impact of low BMI on newly diagnosed MM patients. Methods We enrolled patients with newly diagnosed MM at Taipei Veterans General Hospital in Taiwan between January 1, 2002 and October 31, 2018. Patients without histopathologic evidence were excluded. The primary endpoint of the study was all-cause mortality. A Cox proportional hazards model was used to examine risk factors for mortality among

MM patients. The factors with p < 0.1 in the univariate analysis were included in the multivariate analysis. Results During the 10-year follow-up period, a total of 379 newly diagnosed MM patients were recruited into this study. The median age of the patients was 68 years (range 23–95 years) and 61% were men. Thirty patients (7.9%) had low BMI (< 18.5) at diagnosis. The median overall survival time was 1.3 years (95% CI 0.3–5.7) for patients with low BMI while it was 3.1 years (95% CI 1.7–5.7) for the remaining patients. In the univariate analysis, BMI <18.5 (hazards ratio [HR] 2.22), age ≥ 60 years (HR 1.89), male sex (HR 1.57), ECOG ≥ 2 (HR 2.07), heart failure (HR 1.70), pulmonary diseases (HR 2.29), hemoglobin < 10 g/dl (HR 1.55), platelet < 100,000/μ (HR 2.85), serum creatinine ≥ 2 mg/dl (HR 1.61), and lactate dehydrogenase (LDH) ≥ 250 U/L (HR 2.63) were associated with mortality. After mutually adjusting for variables found in univariate analysis, low BMI (adjusted HR 2.03, 95% CI 1.08–3.80, p = 0.028), ECOG ≥ 2 (adjusted HR 2.19, 95% CI 1.38–3.48, p = 0.001), and high LDH (adjusted HR 1.90, 95% CI 1.22–2.96, p = 0.005) were significantly associated with death in MM patients. Conclusion We found that MM patients with low BMI had a higher risk of mortality. Identifying high-risk patients may help clinicians initiate appropriate management. Further validation of our findings in other cohorts is warranted.

Keywords:
body mass index

early mortality

underweight

Tracks:
Treatment of Newly Diagnosed Myeloma Non-Transplant

SP-058

Multiple Myeloma Incidence and Mortality Around the Globe; Interrelations Between GDP/Capita, Access to Cancer Drugs, Patient Visits to the IMF Website and Mortality-to-Incidence Ratio as Proxy for Survival

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Abstract:
Introduction Data on the interrelations of multiple myeloma (MM) incidence and mortality with economic resources such as GDP, access to drugs and with patient empowerment in different countries are not available. Here, we aimed to analyze possible relationships of these factors with MM epidemiology and outcome. Methods Incidence and mortality data were obtained from the International Agency for Research on Cancer (IARC). Data on the Cross Domestic Product (GDP)/capita were accessed from the International Monetary Fund and data on population per country from United Nations Population Division estimates. Since survival data are not available for most countries, the mortality-to-incidence ratio (M/I ratio) was used as proxy for MM outcome. As a measurement of patients' information about MM, we included data on the number of visits to the website of the International Myeloma Foundation (IMF) for 52 countries. Information on access to cancer drugs for 17 countries was obtained from IQVIA Institute. Correlation analyses were conducted with R using corresponding coefficients (Pearson's r and Spearman's ρ). Results The age-standardized incidence of MM was found to correlate with the GDP/capita (r=0.54, p<0.0001) and was highest in New Zealand (5.3 incidences/100.000 inhabitants), followed by Australia (5.0), UK (4.3) Israel, and Norway (both 4.2). The lowest incidence was recorded for South Korea (0.54), Malaysia (0.75), Philippines (0.86), and China (0.92). The M/I ratio showed a marked variation. Poor outcome reflected by a low M/I ratio was observed for Egypt (1.10), followed by the Philippines (1.12), Thailand (1.15), South Korea, and Indonesia (both 1.17). The best outcome expressed by a high M/I ratio was observed for New Zealand (2.79), followed by Iceland (2.62),

Serbia (2.60), UK (2.53), and Belgium (2.41). Correlation analysis revealed a significant association between GDP/capita and M/I ratio (ρ=0.47, p=0.0005). Likewise, a significant correlation was found between the number of visits to the IMF website/100.000 inhabitants and M/I ratio (ρ=0.64, p<0.0001), and between visits and GDP/capita (ρ=0.83, p<0.0001). The strongest correlation was noted between the access to cancer drugs and GDP/capita (r=0.86, p<0.0001). Conclusion The incidence of MM was found to be significantly higher in economically developed countries, possibly due to life style, environmental and genetic factors, and advanced diagnostic measures. The M/I ratio as proxy for survival showed significant correlations with GDP/capita, access to cancer drugs, and visits to the IMF website. The latter finding indicates that more affluent societies create a more favorable environment for patient empowerment and self-education, which may also impact on outcome. Taken together, these findings highlight the importance of economic resources, of well-developed health care systems, access to novel drugs, and patient education for improving survival of patients with MM.

Keywords:
Economic Factors and Myeloma Epidemiology and Outcome

Global Incidence and Mortality

Multiple myeloma

Tracks:
Treatment of Newly Diagnosed Myeloma Non-Transplant

SP-059

Association Between Costs of Care in Oncology Care Model (OCM)-Defined Episodes and Overall Survival in Multiple Myeloma

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Abstract:
Introduction The OCM was introduced in 2016 with the goal of improving quality and reducing costs associated with cancer care. Under this framework, practices are incentivized to reduce spending on chemotherapy-centered episodes. A previous study using SEER-Medicare data (2007–2013) suggested that reducing OCM episode costs in multiple myeloma (MM) may adversely affect patient survival. The present study aimed to evaluate the association between OCM-defined episode costs as well as MM-specific drug costs and overall survival (OS) in MM patients, using more recent data (2010–2015) and included 100% Medicare patients. Methods MM patients and ≥1 OCM-defined qualifying episode, with available data for ≥6 months prior to and following the first diagnosis for MM, were selected from the 100% Medicare patient population between 2010 and 2015. OCM episodes were defined as the 6 months following a triggering MM treatment claim. Each identified patient and episode was attributed to a practice following the OCM algorithm. Regression models were developed to evaluate the impact of the patient and episode characteristics on total episode costs, as well as subcomponents (MM-drug costs, other medical costs). Based on the regression outputs, standardized costs were calculated for each practice. Two Cox proportional hazards models were constructed to evaluate the association between standardized costs and OS while adjusting for key patient covariates (i.e. age, gender, comorbidity index, race, disability entitlement): Model 1 evaluated standardized total episode costs; and Model 2 evaluated standardized MM-drug costs and other medical costs separately. Results 13,105 MM patients (49.6% male) were included in the analysis. Mean age at MM diagnosis was 74.5 years (33.0–100.0). Eligible patients

contributed to a total of 32,202 OCM episodes during study follow-up. The mean (standard deviation [SD]) MM-drug costs, other medical costs, and total costs for OCM episodes were USD 43,797 (24,955), USD 23,399 (27,865), and USD 67,196 (33,292), respectively. After standardization, average (SD) MM-drug costs, other medical costs, and total costs were USD 41,932 (4,982), USD 22,337 (5,429), USD 66,342 (7,013), respectively. Model 1 indicated higher standardized total costs were associated with lower risk of death (hazard ratio [HR] 0.946; P<0.05). Model 2 suggested that MM-drug costs were the primary driver for improved survival. The hazard of death showed a significant decrease of 7% per USD 10,000 increase in standardized MM-drug costs (HR 0.935; P<0.05). This association was not significant for other standardized costs, e.g. other medical costs. Conclusions Within an OCM-defined episode, spending on MM-drugs more significantly contributed to the observed survival benefit versus spending on other medical resource use. Careful evaluation is warranted for healthcare providers when attempting to reduce spending in response to new payment models.

Keywords:
Costs

Multiple myeloma

Overall survival

Tracks:
Treatment of Newly Diagnosed Myeloma Non-Transplant

SP-060

Quality of Life Assessment in Older Patients with Newly-Diagnosed Multiple Myeloma

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Abstract:
Introduction Multiple myeloma is a malignant plasma cell disease, which typically affects older patients, with a median age at diagnosis of 70 years. Following initial diagnosis and prognostication, selected 'fit' older adults may be eligible for high dose therapy with autologous stem cell transplant (SCT), whereas those less 'fit' will be deemed transplant ineligible (Non-SCT). Although there is a paucity of randomized controlled trial data, observational studies continue to support the role of SCT in older patients. However, the quality of life (QoL) impact of SCT versus a non-SCT approach in older patients remains largely unexplored. Methods Consecutive patients with newly diagnosed MM aged 65 and older were enrolled in a prospective cohort study at 2 institutions. Patients underwent a QoL assessment using the validated tool Functional Assessment of Cancer Therapy Scale (FACT-G) and the Gynecologic Oncology Group-Neurotoxicity (FACTt/GOG-Ntx) scale. Patients completed these assessments at baseline and 6-month follow up. Minimally important differences (MID) as defined (3-7 for FACT-G and 2-3 for FACT-GOG Ntx) in the literature were used to compare groups (Cella et al. 2002 and Lavoie et al. 2013). Results Forty patients were enrolled in the study between the years 2012-2014. Mean age was 71.6 years and 25 (62.5%) were male. Initial assessment categorized 19 patients as SCT eligible and 21 patients as ineligible for SCT. At baseline, the non-SCT cohort were older, had an inferior QoL as measured by both FACT-G and FACT-GOG Ntx (mean score 73.4 ± 14.8 SD and 109.0 ± 18.4 SD respectively) compared to the SCT cohort (mean score 80.5 ± 15.4 SD and 116.2 ± 19.3 SD respectively). At the 6-month interval, 20 non-SCT patients who had completed the QoL assessments and 16 SCT patients who had undergone SCT were re-assessed. The proportion of patients attaining a MID improvements of ≥5 points in FACT-G were 9/16 (56.2%) in the SCT versus 8/20 (40.0%) in the non-SCT cohort. The proportion of patients attaining MID improvements of ≥2 in FACT-GOG Ntx were

11/20 (55.0%) in the SCT and 10/16 (62.5%) in the non-SCT cohorts. Conclusion Our study suggests that for patients aged 65 or older with newly diagnosed multiple myeloma an improved QoL as measured by clinical minimally important difference for FACT-G and FACT-GOG Ntx scale may occur at 6 months following treatment although there is a large variation. Larger studies using multi-institutional collaborative approaches are needed to further understand the effect of SCT vs a non-SCT approach on important patient outcomes such as QoL in older patients with myeloma.

Keywords:
Elderly

Quality of Life

Tracks:
Treatment of Newly Diagnosed Myeloma Non-Transplant

SP-061

Significantly improved relative survival of patients with myeloma in Queensland with treatment advances

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Abstract:
Objective: To evaluate the relative survival (RS) of myeloma patients in Queensland to determine if outcomes have improved with treatment advances and to evaluate RS according to place of residence and socioeconomic status. Design: We performed a retrospective population-based study from the cancer database OAsys (Oncology Analysis System), an online reporting tool for cancer incidence and outcomes in Queensland. Participants: Patients ≥18 years of age diagnosed with myeloma in Queensland from 1982-2014. Main outcomes: Five-year RS was the primary endpoint. The study period was divided into three eras based on treatment advances: era 1 1982-1995 chemotherapy alone; era 2 1996-2007 autologous stem cell transplantation; era 3 2008-2014 novel agents (proteasome inhibitors and IMIDs). Results: 6025 patients (57% males) were diagnosed with myeloma between 1982-2014. RS improved significantly across treatment eras: era1 30% vs era 2 43% vs era 3 53% (P<0.001 era 2 vs era 1; P<0.001 era 3 vs era 2). RS improved across all age groups, including patients ≥ 80 years. Five-year overall survival improved across each treatment era (1 25% vs 2 36% vs 3 47%; P<0.001 for each comparison). Patients with disadvantaged socioeconomic status had an inferior RS compared to affluent patients (39% vs 46%; P<0.001). Rural patients had an inferior RS compared to urban patients (40% vs 45%; P<0.001). Conclusion: RS improved significantly for myeloma patients across all age groups with treatment advances in Australia. Patients with myeloma from rural and/or a disadvantaged socioeconomic group had an inferior RS.

Keywords:
EPIDEMIOLOGY

Multiple myeloma

survival

Tracks:
Treatment of Newly Diagnosed Myeloma Non-Transplant

SP-062

Receiving four or less cycles of therapy predicts poor survival in newly diagnosed transplant ineligible patients with myeloma who are treated with bortezomib-based induction

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Abstract:
Background: Major improvements in the treatment of elderly patients with myeloma have occurred through prospective clinical trials, however, trials are often not representative of patients seen in everyday practice. Anecdotal evidence suggests that many elderly patients treated with bortezomib-based therapy are unable to receive regimens delivered in clinical trials. We examined the impact of and predictors of suboptimal bortezomib delivery to elderly patients in a real world registry setting. Methods: Transplant ineligible patients treated with bortezomib-based regimens and at least one year's follow-up were selected from the Australasian Myeloma and Related Diseases Registry. Overall survival (OS) was calculated using the method of Kaplan and Meier. The impact of baseline characteristics, response and number of bortezomib cycles on overall survival was assessed in a 12 month landmark analysis using Cox regression analysis. Differences between groups were assessed using the chi-squared or Fisher's exact test. Results: 289 transplant ineligible patients were identified: median age 74yrs (range, 47-92yrs); 41% female; ISS stage I 20%, stage II 44%, stage III 35%; and high-risk FISH 19% (155 had available data). A variety of bortezomib doses were given, most commonly 1.3mg/m2 weekly s/c in 52%. 32% received 4 or fewer cycles, 33% 5-8 cycles and 34% >8 cycles. In a multivariate landmark analysis, worse overall survival was predicted by more advanced ISS stage (HR 3.05, 95%CI 1.35-6.89 for ISS II vs I, HR 3.1, 95% CI 1.34-7.17 for ISS III vs I), thrombocytopenia (HR 0.99, 95%CI, 0.99-1.00), and 4 or fewer cycles of therapy (HR 0.45, 95%CI, 0.24-0.82 for 1-4 cycles vs 5-8 cycles, HR 0.57, 95%CI 0.34-0.98 for 1-4 cycles vs >8 cycles). Patients who received 4 or fewer cycles did not have more advanced disease as judged by ISS stage or high-risk FISH. 1-4 cycles of therapy were associated with an inferior response rate (CR 8% vs 16% vs 25%, p=0.032; ORR 73% vs 85% vs 96%, p<0.01) and greater likelihood of therapy cessation due to toxicity or death (53% vs 28% vs 5% for 1-4, 5-8 and >8 cycles, respectively, p<0.01). Those who only received 1-4 cycles had a trend to being older (age > 80yrs in 26% vs 16% vs 12%, p=0.1) and having worse performance status (ECOG PS >1 in 34% vs 28% vs 18% in 1-4, 5-8 and >8 cycles, respectively, p=0.13). Conclusions: In a landmark analysis, receiving 4 or fewer cycles of bortezomib-based therapy independently predicted inferior overall survival in patients with newly diagnosed transplant ineligible myeloma. Receiving 4 or fewer cycles was not the result of more advanced disease but due to early cessation from toxicity with patients tending to be older and having worse performance status. Prospective studies assessing frailty-adapted dosing strategies are required in elderly myeloma patients treated with bortezomib to maximize the chance of adequate therapy delivery.

Keywords:
bortezomib

survival

Transplant-ineligible

Tracks:
Treatment of Newly Diagnosed Myeloma Non-Transplant

SP-063

Improved Treatment Outcome of Transplant Ineligible Multiple Myeloma in the Era of Novel Agents: Experience from Tertiary Care Centre in North India

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Abstract:
Background: The outcome for multiple myeloma (MM) transplant ineligible patients who are conventionally treated with melphalan based regimens is dismal. Novel agents' viz. the proteasome inhibitor (PI) bortezomib and immunomodulatory drugs (IMiD) like thalidomide and lenalidomide have significantly improved the outcome in transplant eligible patients. However, the data on these agents in transplant ineligible patients is conflicting, because of the increased incidence of treatment toxicity. Therefore, the aim of this study was to analyse the outcome of novel agents (bortezomib and IMiD based regimens) in transplant ineligible > 65 years of age MM patients. Methods: A retrospective analysis was done on 140 newly diagnosed >65 years of age, transplant ineligible MM patients treated between January 2013-December 2016. The patients received either 9-12 cycles of bortezomib containing triplet regimen followed by maintenance therapy with IMiD or a continuous therapy with doublet regimen comprising of Lenalidomide/thalidomide+ Dexamethasone till disease progression. Treatment regimen allocation was based on treating physician's choice, performance status, comorbidities and affordability. Results: The median age of patients was 67 years (range 65-87 yrs) with a male to female ratio 1.85:1. Of the 140 patients, 69 (49.2%) received Bortezomib based (Bortezomib+ Cyclophosphamide/Thalidomide/Lenalidomide + Dexamethasone) while 71 (50.7%) received non-Bortezomib (Thalidomide/Lenalidomide+ Dexamethasone) based chemotherapy. The Overall Response Rate (≥ partial response) was 95.7% in the Bortezomib group and 85.9% in the IMiD arm (P=0.047). The CR was significantly higher in the Bortezomib (21.8%) as compared to non Bortezomib arm (9.9%) (P= 0.012). The median PFS & OS of the entire cohort was 25 months (95% CI: 18.56-31.44) and 44 months (95% CI: 36.33-51.66), respectively. In the subgroup analysis, the PFS & OS were significantly higher in bortezomib group (PFS: 47 months; 95% CI: 36.08-57.92; OS: 53.71; 95% CI:47.89-59.53) as compared to IMiD group (PFS: 14 months; 95% CI: 2.24-9.60, P value =0.001; OS: 34.86; 95% CI:29.33-40.38, P value=0.02). The incidence of thrombocytopenia (>Grade 2), diarrhoea (>Grade 2) and peripheral neuropathy (>Grade 2) were significantly higher in the Bortezomib group as compared to non Bortezomib group (P=0.02 for peripheral neuropathy, P=0.04 for thrombocytopenia, P=0.05 for diarrhoea). Conclusion: Our data highlights that Bortezomib based regimens in comparison to non-Bortezomib based regimens result in significantly better treatment outcome (CR, PFS, and OS) in >65 years transplant ineligible MM patients. Though a clinically significant higher incidence of peripheral neuropathy, thrombocytopenia and diarrhoea were observed in the Bortezomib group that led to frequent treatment interruptions, but could be managed well with drugs/ modification of dose of Bortezomib and better supportive care.

Keywords:
bortezomib

immunomodulatory drugs

Transplant-ineligible

Tracks:
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SP-064

UPSTAGING ISS AND R-ISS BY PLATELET COUNT: REAL-LIFE ANALYSIS OF 321 MM PATIENTS

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Abstract:
Multiple Myeloma (MM) has to be considered a heterogeneous disease with different outcomes. International Staging System (ISS) and Revised-ISS (R-ISS) are widely and successfully used to stratify MM patients. However, it is somewhat evident a further heterogeneity across the groups defined by these scores. Risk stratification by gene mutations is an attractive method but it requires validation and it is difficult to use routinely. Some studies found platelet count prognostic for PFS and OS. Here we investigated whether a simple and reliable parameter as baseline platelet count could improve the power of ISS and R-ISS staging systems. We analyzed 321 real-life patients with MM recorded in our database, all receiving novel agents (29% IMiDs-based, 35% PI-based and 36% IMiDs+PI-based regimens). Median age was 68 years (range 42-93); 44% of patients were transplant eligible and 28% older than 75 years. PS (ECOG) was ≥ 2 in 24% and there was renal impairment in 18% of patients. ISS stage was 1, 2 and 3 in 41%, 35% and 24%, respectively. Out of 315 evaluable patients, R-ISS stage was low, intermediate and high in 29%, 55%, 14%, respectively. Platelet count was less than normal (150.000/μl) in 55 patients (17%). Overall, PFS was 46 vs 30 months (p=0.002) and OS 96 vs 53 months (p=0.005) in patients with normal (NPC) and low platelet count (LPC), respectively. For each ISS and R-ISS stages, we split patients with NPC or LPC building 2 new staging systems named P-ISS and P-R-ISS. We found a PFS of 55.5 months in ISS1 group (P-ISS1: 58.5 vs 44.5 months; p=0.084), 42.5 months in ISS2 (P-ISS2: 41.5 vs 34.5 months; p=0.035) and 34.5 in ISS3 (P-ISS 3: 34.5 vs 13 months; p=0.004). Median OS in ISS1 group was 124.5 months (P-ISS1: 128.5 vs 99.5 months; p=0.074), 73.5 months in ISS2 (P-ISS2: 81 vs 52 months; p=0.009) and 48.5 months in ISS3 (P-ISS3: 46.5 vs 28 months; p=0.003). Regarding R-ISS, PFS was 58.5 months in R-ISS-LR group (P-R-ISS-LR: 59 vs 55 months; p=0.138), 44.5 months in R-ISS-IR (P-R-ISS-IR: 46 vs 40 months; p=0.182) and 20.5 in R-ISS-HR (P-R-ISS-HR: 31 vs 11 months; p=0.042). Median OS in R-ISS-LR was 144 months (P-R-ISS-LR: 150 vs 99.5 months; p=0.088), 75 months in R-ISS-IR (P-R-ISS-IR: 78 vs 58 months; p=0.041) and 41 months in R-ISS-HR (P-R-ISS-HR: 52 vs 21 months; p=0.034). Taking into account that in any strata of both ISS and R-ISS stages LPC upgraded the risk and that the differences between ISS and R-ISS are negligible, we merged the strata with similar PFS and OS. Accordingly, we were able to build a score recognizing 4 groups of patients, LR-NPC, LR-LPC+IR-NPC, IR-LPC+HR-NPC and HR-LPC, with significantly different PFS (60 vs 46 vs 34.5 vs 13 months; p=0.014) and OS (128.5 vs 82.5 vs 49.5 vs 28 months; p=0.002). In conclusion, LPC seems to confirm its negative impact on PFS and OS segregating patients with the worst outcome in any risk category of ISS and R-ISS. These data claim confirmation in a larger prospective MM population.

Keywords:
ISS

Platelet count

Staging

Tracks:
Treatment of Newly Diagnosed Myeloma Non-Transplant

SP-065

Impact on efficacy of the dose and schedule of bortezomib in Transplant-Ineligible Newly Diagnosed Multiple Myeloma.

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Abstract:
BACKGROUND Melphalan, prednisone and bortezomib (MPV) is a current standard in the treatment of transplant ineligible newly diagnosed multiple myeloma (TI NDMM) and has been used as a control arm in several recent phase 3 clinical trials. Bortezomib related peripheral neuropathy (PN) is a limiting factor to apply the original MPV dose and schedule and reduced intensity schedules have been used both in clinical practice and in clinical trials. However, the feasibility of full-dose MPV and the impact on efficacy of dose intensity in real world have not been described. METHODS Prospective registry of consecutive TI NDMM patients treated at a single institution. Patients were intended to treatment with full dose (VISTA schedule) MPV using the subcutaneous formulation of bortezomib. Early dose reduction was performed at early emergence of PN. Main objectives were time to appearance of PN, time to first interruption and dose reduction, time to treatment discontinuation, cumulative dose of bortezomib received and dose intensity. Prognostic factors for PN development and impact of dose intensity on outcome were explored. RESULTS Between 2010 and 2017, 52 unselected consecutive TI NDMM patients were treated with MPV, median age 71 years (range 62-84), 54% males. Potential risk factors included baseline neuropathy (14%), DM (15%), severe renal insufficiency (13%) or smoking habit (21%). MM baseline characteristics included 47% of pts ISS 3 and 14% R-ISS 3. Median duration of MPV treatment was 49 weeks (range 4-56, expected full treatment 54) and median dose intensity was 1.04 mg/m2/week (range 0.46-1.95, expected full treatment 1.25). Over 25% of patients completed the full dose 54 week scheduled treatment. PN of any grade was detected at a median of 49 weeks from treatment onset. Only 3 pts (6%) developed grade 3 PN. Median time to first dose reduction was 17 weeks and median time to first interruption was 19 weeks), Overall response rate was 82%, CR rate 23%. Median PFS was 2.72 years (95%CI 1.71-3.24) and and median OS was 4.05 years (95%CI 3.69-6.56), no association was observed between outcome measures and bortezomib cumulative dose or dose-intensity. CONCLUSIONS This cohort of unselected TI NDMM patients treated with full dose MPV, show that treatment is feasible for most patients. Early dose reduction limited >2 grade PN to 6% of pts. We were not able to prove an impact of cumulative dose or dose intensity on outcomes, nor could we detect risk factors associated with early development of PN.

Keywords:
bortezomib

Newly diagnosed multiple myeloma

peripheral neuropathy

Tracks:
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SP-066

NEWLY-DIAGNOSED, NON-TRANSPLANT ELIGIBLE MULTIPLE MYELOMA PATIENTS: DETERMINANTS OF CHOICE OF FIRST-LINE TREATMENT IN A SINGLE-CENTER.

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Abstract:
The incorporation of novel agents (bortezomib, thalidomide and lenalidomide) in the treatment of newly diagnosed, non-transplant eligible symptomatic multiple myeloma (MM) patients (pts) improves their clinical outcomes. During the last decade, the Italian Regulatory Drug Agency AIFA approved as 1° line treatments the following: thalidomide-melphalan-prednisone (TMP), bortezomib-melphalan-prednisone (VMP) and lenalidomide-dexamethasone (Rd). Since December 2016 all of these treatments became available in Italy. Although algorithms have been proposed to

help choosing among them, such a choice may still be difficult in the single patient. To evaluate the determinants of choice of the most appropriate 1° line treatment, we performed a retrospective study to analyze the characteristics of 79 newly diagnosed, non-transplant eligible MM pts, who started their treatment at the Onco-Hematology Unit of ASST-Papa Giovanni XXII, Bergamo, Italy from December 2016 to February 2019. Three pts were diagnosed with solitary plasmacytoma and treated with radiotherapy only; 9 were deemed too fragile for age (median, 80 years; range (r), 77-89) and/or frailty score (defined according to Palumbo et al. Blood. 2015;125:2068-7) (median, 5; r 1-5) to receive other than palliative therapy; 7 were enrolled in clinical trials. The study, therefore, is focused on the remaining 60 pts who received 1° line systemic treatment according to AIFA rules. 60 pts - 31 males and 29 females, aged 59-88 years (median, 78 years) – were analyzed. At diagnosis, the characteristics of MM were as follows: isotype (A, n=15; D, n=1; G, n=37; light chain, n=7; kappa, n=32; lambda, n=28), Durie & Salmon stage (I, n=8; II, n=11; III, n=41; A, n=50; B, n=10), ISS (1, n=14; 2, n=17; 3, n=23; not available, n=6). As 1° line treatment, 31 pts received Rd and the other 29 bortezomib-based therapy (VMP, n=7; bortezomib and dexamethasone (Vd), n=22). No patient received TMP. Clinical and biological characteristics of the 60 pts are grouped according to the type of 1° line treatment (VMP/Vd vs Rd): median age (76 years (r 59-86) vs 78 years (r 73-88)), frailty score (median 2 in both group), B stage (34% vs 0%), ISS 3 (48% vs 29%), presence of extramedullary disease (4% in both group), median creatinine clearance (40 vs 58 ml/min) and median beta 2 serum microglobulin (4.65 vs 4.40 mg/dl). At a median follow-up of 9.9 months (r 0.7-30.1), Progression Free Survival (PFS) and Overall Survival (OS) are comparable (PFS 8.4 (r 0.7-26.3) vs 9.3 months (0.7-26.6) and OS 10.5 (r 0.7-26.3) vs 9.3 months (r 0.7-23.1)). Early death (defined as death occurring within 90 days from starting treatment) occurred more often in VMP/Vd group (21% vs 16%). The choice between Rd and a 2 or 3-drug bortezomib-based 1° line treatment was mostly driven by renal function, as none of the pts with kidney failure received Rd. For the same reason, among pts receiving bortezomib-based therapy, we often choose to skip melphal.

Keywords:
bortezomib

Lenalidomide

Transplant-ineligible

Tracks:
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SP-067

Prognostic impact of rapid involved light chain reduction in first line therapy with Bendamustine, Prednisone and Bortezomib (BPV) in myeloma patients

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Abstract:
Introduction: Light chain involvement is observed in almost every newly diagnosed multiple myeloma (MM). While 15-20% of MM patients suffer of a light chain only myeloma, 70-80% of IgA and IgG myeloma present an additional abnormal free light chain ratio (FLCR), too. Due to a shorter half life period a rapid reduction of the involved light chain (iFLC) could be of prognostic value in order to personalize and optimize treatment options. Methods: The retrospective analysis included 85 patients with newly diagnosed MM treated with bendamustine, prednisone and bortezomib (BPV) at the Leipzig University Hospital between January 2013 and October 2018. Data was collected on day 1, 7, 15 and 21 of each BPV cycle. Results: A median number of two (range 1-5) BPV cycles were given to the patients. The majority of patients (n=74; 87%) responded with sCR (n=5), nCR (n= 0), VGPR (n=24) and PR (n= 35). After at least one BPV cycle 60 patients discontinued therapy after median two

cycles to receive autologous stem cell transplantation as consolidation therapy. After a median observation time of 33 months PFS and OS at 36 months were 50% and 81% respectively. 65 out of 85 patients (76%) had iFLC level above the upper standard level and an abnormal FLCR of involved to uninvolved free light chain (FLC) ≥8: 33 out of 41 IgG MM, 19 out of 21 IgA MM and 23 light chain MM. In a subgroup analyses of these patients we evaluated the prognostic importance of an early reduction of the iFLC during the first two BPV cycles. 34 patients presented a reduction ≥50% of the iFLC level on day 7 of the first cycle BPV and had a significantly better median PFS of 39 months. The other 31 patients showed in contrast only a median PFS of 21 months ($p<0.03$). In OS both groups differed with a median of 68 vs 49 months ($p=0.185$). In the further course of treatment 32 patients showed a reduction of ≥80% of the iFLC after the first cycle BPV and 32 patients had an iFLC reduction of ≥90% after completing the second cycle which did not show significant impact on the prognosis. We analyzed the prognostic influence of chromosomal aberrations in 78 patients. The presence of t(4;14) in 13 patients had a significant adverse impact on PFS ($p<0.05$) and OS ($p=0.005$) whereas del(17p13) in 12 and +1q21 in 20 was not associated with a worse clinical outcome. Conclusion: Our results indicate that a rapid decrease of the iFLC on day 7 is a feasible prognostic parameter for newly diagnosed MM patients under BPV treatment while analysis regarding the reduction of the iFLC at a later point during treatment have not proven to be of predictive value.

Keywords:
BPV therapy

Free Light Chains

prognostic impact

Tracks:
Treatment of Newly Diagnosed Myeloma Non-Transplant

SP-068

Outcome of elderly patients with newly diagnosed multiple myeloma depending on the eligibility for clinical trials: a single institution experience.

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Abstract:
Introduction/Background Patient participation in clinical trials forms the backbone of cancer clinical research. Clinical trials are the key step in advancing new treatments and improving outcomes in in incurable diseases such as multiple myeloma (MM). Despite this, the vast majority of patients with MM do not participate in clinical trials, although the results obtained from them determine the future therapeutic approaches. Methods To determine the reasons they were or weren't recruited into prospective clinical trials and evaluate their outcome in one group or the other, we retrospectively reviewed from our database all consecutive patients with newly diagnosed MM, non-candidate to autologous stem cell transplantation, who received first line treatment at our institution from 2003 to 2017. We thoroughly reviewed their characteristics and their outcome after first line treatment only. We analyzed the reasons why they were or not included in a trial and compared the outcome of those included in a clinical trial versus those who did not meet the eligibility criteria and who received standard therapy. Patients who didn't have a clinical trial available at the time of diagnosis were excluded from the analysis. Results Between January 2003 and December 2017 we analyzed 211 patients

diagnosed and treated at our institution; 105 entered a clinical trial and 106 did not meet the eligibility criteria. Patients included in clinical trials were significantly younger (median 71 vs. 78 p<0.001) and had better ECOG (0/1 78.4% vs. 35.6 p<0.001). No differences regarding immunological subtype or bone marrow plasma cells infiltration were found. Durie Salmon stage and ISS were slightly lower in the clinical trial group although not statistically significant. The ORR was 79 vs.46 p<0.001 and the CR rate was 17% vs 3% p<0.001 both significantly higher in the clinical trial group. Patients included in clinical trial had a significantly longer OS than those who were not (median 61 vs.32 p<0.001). The causes for not entering in a clinical trial were as: 1) Didn't fulfill inclusion criteria due to comorbidities (26.7%), other previous malignancies (16.2%) or renal insufficiency (13.3%); 2) Didn't have measurable disease (1.9%); 3) The urgency to start treatment didn't allow the delay of a screening period (8.6%); 4) Very advanced age (10.5%), cognitive impairment (1.9%) or performance status (4.85%); 5) Patient refusal (10.5%). Finally 1.9% were screen failures and 3.8% did not participate for unknown reasons. Conclusion Patients included in clinical trials have a significantly higher response rate and OS than those who do not meet the eligibility criteria. Only half of the elderly patients at our institution fulfill the inclusion criteria to enter a clinical trial. This questions the extrapolation of the results of clinical studies to broader populations.

Keywords:
clinical trials

Elderly patients

Multiple myeloma

Tracks:
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SP-069

PRESCRIPTION PATTERNS AND OUTCOMES OF FIRST-LINE THERAPY FOR NON-TRANSPLANT ELIGIBLE MULTIPLE MYELOMA REAL-LIFE PATIENTS ACCORDING TO AGE: A RETROSPECTIVE ANALYSIS OF THE 2012-2016 PERIOD

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Abstract:
Background Multiple myeloma (MM) affects elderly individuals with two-thirds of patients aged >65 years at diagnosis, 35% ≥75 and 10% ≥80. In

general, routine clinical practice is based on the results of large, multicenter, randomized clinical trials. However, despite efforts from cooperative groups, patients enrolled in trials are generally younger and presumably healthier than the typical older patient with MM. Aims To describe prescription patterns for first-line treatment of non-transplant eligible MM patients in the setting of real-life practice and to analyze treatment outcome according to patients' age. Methods Retrospective analysis of newly diagnosed MM patients not eligible for transplantation, who started anti-myeloma treatment between 2012-2016 in 20 Spanish hospitals. Variables collected included patients' characteristics at diagnosis (ECOG, laboratory parameters, ISS, and cytogenetics/fluorescent in situ hybridization), characteristics of first-line treatment, overall survival (OS), progression-free survival (PFS), and overall response rate (ORR), defined as partial response or better. Results The retrospective cohort included 421 patients with a median age of 76 years (41-90); 203 (49%), 106 (26%), and 104 (25%) were ≤75, 76-80, and >80 years old, respectively; 28 (12%) had ECOG >2. ISS staging was I, II, III in 57 (18%), 93 (30%), and 160 (52%) patients, respectively; 73 (25%) patients had high-risk cytogenetics. The most frequently prescribed regimen was VMP (n=208), followed by other bortezomib-based regimens (n=130), melphalan (n=44), lenalidomide (n=19), and other (n=20). Patients aged >80 years accounted for 16-21% of those receiving bortezomib and lenalidomide and 61% of those receiving melphalan. Of all patients receiving no-VMP bortezomib-based regiments, 56% had a severely decreased glomerular filtrate; the corresponding percentages in VMP, lenalidomide, and melphalan regimens were 13%, 5%, and 10%, respectively. Median treatment duration was 6 months (95%CI 5-7) and the ORR was 74% (for patients ≤75, 75-80, and >80 years old: 76%, 80%, and 62%; P=0.025). Overall, 188 (45%) patients required a dose adjustment and 225 (81%) started second-line treatment. Median OS and PFS were 32 (95% CI 29-37) and 15 months (95% CI 14-17), respectively. OS and PFS of patients ≤75, 75-80, and >80 years old were 44 and 16 months, 28 and 17 months, and 23 and 12 months (P<0.01 for age-group differences in both OS and PFS). Conclusion In real-life practice, there is high variability in treatment regimens, being bortezomib-based the most frequently prescribed regimens in the study period. Besides the clinical characteristics of MM patients, age influenced survival in our cohort of real-life patients, suggesting that treatment choice for elderly patients should be based on a specific pre-treatment assessment of risks and benefits.

Keywords:
Elderly

Multiple myeloma

Real-World Data

Tracks:
Treatment of Newly Diagnosed Myeloma Non-Transplant

SP-070

PROGNOSTIC RELEVANCE OF THE PROPORTION OF RESIDUAL POLYCLONAL PLASMA CELLS IN THE DIAGNOSTIC BONE MARROW OF NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS MANAGED WITHOUT AUTOLOGOUS STEM CELL TRANSPLANTATION

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Abstract:
Background: Multiple myeloma (MM) is a malignant neoplasm of abnormal clonal plasma cells with heterogeneous clinical outcome. The proportion of clonal against polyclonal plasma cells (PPC) reflects the burden of disease, microenvironment status and underlying biology. Recently, the prognostic value of residual PPC at diagnosis has been demonstrated in newly diagnosed multiple myeloma (NDMM) treated with autologous stem cell transplant (ASCT) and relapsed MM. However, it has not been studied in NDMM managed without ASCT. We present a study highlighting the prognostic relevance of the proportion of residual PPC in bone marrow aspirate (BM) NDMM managed without ASCT due to limited resources. Methods: We prospectively studied the proportion of residual PPC in total PC (TPC) and TPC in all viable cells in BM samples from newly-diagnosed MM patients treated with VCD (Bortezomib/Cyclophosphamide/Dexamethasone)-protocol using 9-10 color flow cytometric immunophenotyping (FCI). Results: We studied FCI in BM and PFS in 123 patients of NDMM (age: median-59 years, range- 34 to 78 years and M: F-1.8). Median-values (range) of M-protein levels and FLC ratio were 3.95 g/dl (0-12 g/dl) and 15.1 (0.0064-495.8) respectively. The patients were ISS stage I -47.9%, ISS-II – 29.4% and ISS-III – 22.7%. High-risk cytogenetics (HRCG) was detected in 18/104 (17.3%) and LDH levels were high in 31/83 (37.4%) patients. Median (range) of TPC and PPC were 6.2% (0.2-69 %) and 98.4% (5-100 %) respectively. On initial response evaluation, patients with CR, VGPR, PR, MR, SD and PD were 17.9%, 35.8%, 39%, 4.1%, 0.8%, and 2.4%. Median (range) follow-up was 19.2 (6-52) months. A cut-off of 10% PPC was determined using ROC analysis and ≥10% PPC were found in 15.4% of the patients. On Kaplan-Meier survival (KMS) analysis, the median PFS in MM with <10% PPC was 22.5 versus 48.4 months in MM with ≥10% PPC (P=0.0004). Similarly, the median PFS in MM with <2.5% TPC was 22.9 versus 41.1 months in MM with ≥2.5% TPCs (P= 0.004). We also studied association of ≥5% PPC with PFS and KMS analysis, the median PFS in MM with <5% PPC was 22.5 versus 33.8 months in MM with ≥5% PPC (P= 0.01). The patients with CR showed better median PFS (22.9 months versus not reached; p=005). On Cox regression analysis, the hazard ratio for <10% PPC was found to be "4.7". On multivariate analysis, NDMM<10% PPC was found to be an independent prognostic factor and the only statistically significant factor (p=0.011). MM with ≥10% PPC were also associated with better baseline clinical characteristics including a lower frequency of HRCG. Conclusion: Presence of ≥10% residual polyclonal PCs in diagnostic bone marrow samples is the clinically most relevant and independent prognostic factor in NDMM patients managed without ASCT. It identifies a category of good prognostic MM that may not require ASCT or can be managed less aggressively in resource-limited settings.

Keywords:
Multiple myeloma

Progression-free survival

residual polyclonal plasma cells

Tracks:
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TREATMENT OF PREVIOUSLY TREATED MYELOMA

SP-071

A Patient-Physician Tool to Improve CoMMunication in Relapsed Refractory Multiple Myeloma (RRMM)

Authors:

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Abstract:
Multiple myeloma (MM) patients and their physicians often have conflicting treatment goals. Patient-centered communication (PCC) and shared decision making (SDM) can encourage collaborative dialogue and help the physician better understand and incorporate patient needs, preferences, and goals in treatment planning. Here, we describe the development of a tool to aid physicians in improving PCC and SDM in treatment selection for RRMM using literature review, multi-disciplinary advisory boards, and a national survey of physicians and patients. Articles and conference abstracts focusing on PCC in MM in the US published between 2007 – 2017 (n = 18) were identified and analyzed for factors affecting PCC. A 30-minute online survey was conducted among patients (n = 200) and physicians (n = 200) in US academic and community settings to assess preferences about communication, level of physician engagement, and treatment goals. Two advisory boards were assembled with 10-12 members, including physicians, nurses, a MM patient, and experts in advocacy, behavioral sciences, and communication. The literature review identified three main barriers to PCC – poor information exchange, misaligned treatment goals, and ambiguity on treatment decision-making roles. Studies from the review showed most patients prefer to be involved in treatment decisions but feel physicians ultimately make the decision. Lack of physician availability was a limiting factor for effective PCC in elderly MM patients. Survey findings were consistent with literature review findings. Patients identified a desire for SDM and discussing treatment options amid gaps in physician understanding of patient goals, preferences, and comprehension. Physicians reported an openness to more effective resources for discussing treatment options with patients. Advisory board members named limited time with patients and a dynamic and varied treatment landscape as barriers to effective PCC. Advisors suggested that a tool to improve PCC be relevant over time, applicable to various patient types and enable patient understanding of treatment options in a time-efficient manner. Based on these findings, a physician-focused tool was developed to be used when interacting with patients. It is meant to be an EMR-compatible, adjustable resource that provides discussion prompts and can be used digitally or printed. Key topics covered include: 1) Establishing patient engagement and communication preferences 2) Discussing the approach to therapy recommendations 3) Communicating strategy and starting therapy for RRMM Effective PCC and SDM can aid RRMM patients navigate a complex treatment landscape. Our development process using literature review, multi-disciplinary advisory boards, and a national survey between physicians and patients produced a tool for physicians to improve PCC and SDM with RRMM patients. Large scale prospective use of this tool may reveal its value and usability and identify future improvements.

Keywords:
patient centered communication

Shared decision making

Therapeutic-decision-making

Tracks:
Treatment of Previously Treated Myeloma

SP-072

Relapsed/refractory multiple myeloma (R/R MM): a real-world overview of oral vs. IV/SC treatment cost and time burden in a Portuguese hospital

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Abstract:
Objective Estimation of the administration burden of different R/R MM therapeutic options in a Portuguese center: duplets lenalidomide/dexamethasone (Rd), pomalidomide/dexamethasone (Pd), carfilzomib/dexamethasone (Kd), and the triplets ixazomib/lenalidomide/dexamethasone (IRd), carfilzomib/lenalidomide/dexamethasone (KRd), daratumumab/lenalidomide/dexamethasone (DRd) and bortezomib/lenalidomide/dexamethasone (VRd). Methods Questionnaires were applied to 3 HCPs involved in the management of MM patient at a Portuguese center in order to estimate, based on the drug's technical information and the center organization, the times spent by the haematologist (in consultations), the pharmacist (in education to the patient, preparation and dispensing of drugs), and the nurse (education of the patient and administration of drugs). From that, it was possible to estimate the time spent by the patient (number and length of visits to the center for medical appointments, drug administration, and drug dispensing) in the different R/R MM regimens. Results Considering a 2-year analysis of R/R MM treatment, IV/SC treatments (DVd, DRd, KRd, Kd) require on average 15 times more time from the patient than oral treatments (Rd, Pd, IRd), including travel to and from center and time spent in different center services. IV/SC treatments also imply considerably higher time and costs related to healthcare providers: this is particularly relevant on pharmacists' time (14 times more than oral treatments) and on nurses' time which are entirely absent in oral treatments; as for hematologists, all treatments involve similar time allocation. IV/SC treatments represent an average increase in administration cost of 5250€ versus oral treatments, mainly due to higher cost on healthcare provider honoraria and use of consumable devices (absent in oral treatments). Considering the average time per cycle, exclusively oral treatments (Rd, Pd, IRd) reduce patient time in travel to and from center from 1h to 17 min, time spent in outpatient unit from 13h to none, and pharmacy burden time from 2 h 24 min to 10 min. When comparing Rd-based triplets, assuming 2 years of treatment, IRd reduces patient time by 94% vs. KRd and by 89% vs. DRd, pharmacy time (preparation and dispense) by 93% vs. KRd and by 86% vs. DRd and travel time to and from center by 77% vs. KRd and 55% vs. DRd. IRd does not consume nurse time and pharmacist devices usage. Conclusion Considering the evolving landscape of R/R MM treatment, with guidelines recommending triplet instead of duplets, several aspects are taken in consideration when selecting a treatment. Although most triplets imply a considerable administration burden, IRd, being a fully oral regimen, is the only R/R MM approved triplet that does not increase the burden in relation to duplets. (This analysis was carried out with funding from Takeda Portugal.)

Keywords:
ixazomib

Relapsed Refractory MM

relapsed/refractory multiple myeloma

Tracks:
Treatment of Previously Treated Myeloma

SP-073

Real World Data on the Safety and Efficacy of Pomalidomide as a Single Agent and in Combination with Corticosteroids in Relapsed and Refractory Multiple Myeloma

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Abstract:
Background: Pomalidomide (pom), an immunomodulatory agent, in combination with low-

dose dexamethasone (dex), is approved for the treatment of multiple myeloma (MM) refractory to lenalidomide (R) and bortezomib (V). Herein we report on the efficacy and safety of pom with/without dex in the real world setting. Methods: This was a retrospective cohort analysis of adults with RRMM treated with pom with/without dex at the Cleveland Clinic from February 2013 until January 2018. Our primary objective was efficacy assessment (overall response rate (ORR)), defined as partial response (PR) or better, progression free survival (PFS) and overall survival (OS). Our secondary objective was safety assessment. Results: A total of 74 patients with RRMM received pom (4 mg daily, 21 days/28) plus dex (20-40 mg weekly 21 days/28) (n=49) or single-agent pom (n=25). Median age at diagnosis was 63 years (36-87). The median number of prior lines of therapy was 3 (range 1-11). Thirty-six percent of the patients had undergone an autologous hematopoietic cell transplant. Patients who were refractory to R or V constituted 64% and 41%, respectively. The ORR was 26% (19/74). Four percent (3/74) had complete response (CR) and 4% (3/74) very good partial response (VGPR). Fifty-one percent had stable disease and 17% had progressive disease. After a median follow up of 39.6 months (4.8-69.6), median PFS was 14.4 months (95% CI 9.6-25.2) and OS was 76.8 months (95% CI 10.8, NA(not calculable)). Adverse effects were noted in 31% of patients with hematologic toxicity being the most common. Neutropenia occurred in 11% of patients (7% grade 3-4), anemia (grade 2 or 3) in 9%, and thrombocytopenia in 11% (7% grade 3 or 4). Conclusion: To the best of our knowledge, our study constitutes the first real-world US experience using pom with/without dex in RRMM. Our cohort demonstrated a similar ORR to that reported in clinical trials. However, PFS was notably longer (14.4 vs 4 and 4.2 months, respectively) as was OS (76.8 vs 12.7 and 16.5 months, respectively) but with a longer median follow up in our analysis (39.6 vs 10 and 14.2 months). Safety was concordant with published clinical trials. Our study has several limitations including small sample size and retrospective design. In conclusion, this study confirms the clinical efficacy and safety of pom with/without dex in a real-world setting for patients with RRMM. References: 1.Miguel JS, et al.Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial.Lancet Oncol. 2013;14(11):1055-1066. 2.Richardson PG, et al. Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. Blood. 2014; 123 (12):1826-183

Keywords:
Pomalidomide

real-world evidence

Relapsed Refractory MM

Tracks:
Treatment of Previously Treated Myeloma

SP-074

Progressive Multifocal Leukoencephalopathy in a Patient with Multiple Myeloma

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Abstract:
Introduction: Progressive multifocal leukoencephalopathy (PML) is an aggressive, demyelinating and fatal brain infection caused by reactivation of the John Cunningham virus (JCV). Mostly immunocompromised individuals having acquired immune deficiency syndrome or hematological malignancies are affected. Multiple myeloma (MM) and its treatments including immunomodulatory drugs (IMiDs) can predispose patients to PML. Neurological changes and

characteristic magnetic resonance imaging (MRI) features associated with the evidence of JCV in the brain establish PML diagnosis. In this case report we present a 69-year-old man with MM who developed PML during treatment with IMiDs. Case Report: At the age of 66 the patient presented with renal disease and was diagnosed with κ light chain MM in April 2015. His medical history included coronary artery disease. He was initially treated with bortezomib-dexamethasone. After 5 cycles peripheral neuropathy occurred and he achieved partial remission. Lenalidomide was started and continued for one year. In April 2017 he received intravenous immunoglobulin (IVIg) replacement therapy for recurrent respiratory infections. After one month he experienced a seizure episode at home but no further examinations were carried out at that time. Pomalidomide was started in June 2017 due to disease progression. After 5 months cyclophosphamide was added for insufficient response and he had stable disease. In January 2019 he presented with seizure and disorientation. He was lethargic and had echolalia. A non-contrast computed tomography of the brain demonstrated hypodense areas in the white matter of both frontal lobes more prominent on the left side. Diffusion weighted MRI revealed high signal intensity in the same areas without restricted diffusion. Gadolinium enhanced MRI of the brain identified hyperintense non-enhancing lesions in the white matter of the same areas. Pomalidomide and cyclophosphamide were stopped. PET/CT demonstrated a large defective area in the left frontal and temporal lobes, with less FDG avidity compared to the cortex. Analysis of the cerebrospinal fluid (CSF) by polymerase chain reaction (PCR) revealed JCV deoxyribonucleic acid (DNA) with 309.000 copies/ml. Five months following drug cessation his neurological status and quality of life improved. A new MRI is pending. Discussion: Broader use of IMiDs may increase incidence of PML among patients with MM. Given the time course of the events we speculate that the patient had begun to develop PML while on lenalidomide. The patient had also hypogammaglobulinemia which has been reported to cause PML. It is impossible to know to what degree each drug contributes to the condition. Drug cessation is the mainstay of therapy and can improve survival leading to restoration of the immune system. Clinicians must maintain a high index of suspicion for PML in patients with MM developing neurological symptoms. Early detection of PML is key to improved outcome.

Keywords:
immunomodulatory drugs

Multiple myeloma

Progressive multifocal leukoencephalopathy

Tracks:
Treatment of Previously Treated Myeloma

SP-075

Ex-Vivo 3D-Cultures of Patient-Derived Primary MM cells Retrospectively Predicts Treatment Clinical Outcomes in MM Patients

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Abstract:
Background: The understanding of biological mechanisms of MM led to the development of novel therapies; novel agents such as bortezomib, carfilzomib, lenalidomide, pomalidomide and daratumumab which have dramatically changed the landscape of treatment for MM. However, for patients who have failed all of these treatments have poor prognosis. However, currently there is no validated way to select the optimal treatment for each patient, leading to a trial-and-error approach to treating the disease. Therefore, there is an urgent need to develop models to improve our ability to predict drug efficacy in these patients in order to improve patient outcomes. We have developed a patient-derived 3D Tissue Engineered Bone Marrow (3DTEBM) ex vivo cultures, in which we use BM

aspirates from MM patients to develop 3D cultures which include MM cells as well as all the accessory cells, growth factors and cytokines naturally found in the MM BM microenvironment, and induce activation of macrophages. The 3DTEBM recreates the structural and biological features of the MM niche in patients, which allows proliferation of primary MM cells ex vivo, and showed better representation of drug resistance to common MM drugs. Methods: We used whole-BM, viably frozen tissue banked samples from 20 MM patients with clear clinical response patterns of complete remission, and either very good partial response (sensitive) or progressive disease (non-sensitive). The BM aspirates were used to develop a 3DTEBM that represents each individual patient. The patient-derived 3DTEBM cultures were treated ex vivo with the same therapeutic regimen that the patient received in the clinic for 3 days. The treatment ex vivo was based on combinations at different concentrations which mimic the steady state concentrations (Css) of each drug. The efficacy of the treatment ex vivo was evaluated by digestion of the 3DTEBM matrix, extraction of the cells, and analysis for prevalence of MM cells in the treatment groups compared to the non-treated controls. Patients were defined "sensitive" if the effect reached 50% killing in the range of 10xCss. The ex vivo sensitivity data was then correlated with the clinical response outcomes. Results: We found that the 3DTEBM was predictive in approximately 80% of the cases (in about 85% of the combination therapy cases, and in about 70% of the single therapy cases). Broken down by individual drug, it was predictive in 80% of the cases treated with Bortezomib, 78% Lenalidomide, 84% Dexamethasone, 100% Daratumumab, 50% Carfilzomib, 50% Pomalidomide, and 100% Doxorubicin. Conclusions: The 3DTEBM is a more pathophysiologically relevant model which predicts clinical efficacy of drugs in multiple myeloma patients, retrospectively. This data provides the bases for future studies which will examine the ability of the 3DTEBM model to predict treatment efficacy, prospectively, for development of personalized treatment plans in individual multiple myeloma patients.

Keywords:
Drug Screen

Ex-Vivo

Personalized Medicine

Tracks:
Treatment of Previously Treated Myeloma

SP-076

ELOTUZUMAB PLUS POMALIDOMIDE OR LENALIDOMIDE IS ABLE TO ACHIEVE DURABLE ≥VGPR RESPONSES AMONG IMMUNOMODULATORY / PROTEASOME INHIBITOR REFRACTORY MYELOMA PATIENTS: A REPORT ON MULTICENTER EXPERIENCE FROM TURKEY

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Abstract:
Introduction: With introduction of monoclonal antibodies (moab) to the treatment armamentarium, deep responses have been made possible even among patients refractory to proteasome inhibitors (PI) and immunomodulatory drugs (IMID). Here in this multicenter retrospective study we aimed to analyze the efficacy and safety of elotuzumab in different combinations . Patients & Methods: 50 patients(median age: 63 range: 43-85) treated, at 18 sites, with at least 2 prior lines of therapy(with PI and IMID), or refractory to both PI and IMIDs, were included in an early access program(n:42) or in a clinical study(n:8) to receive 10 mg/kg of intravenous elotuzumab weekly during the first two cycles and then on alternate weeks until progression, combined with either lenalidomide(n=23) or pomalidomide(n=20) or bortezomib(n:5) or carfilzomib(n:2) and dexamethasone. The primary endpoints were overall response rate(ORR) or overall survival(OS). Results: The first patient was enrolled in September 2012, and two patients are still on treatment. Follow-up is ongoing. Patients had received a median of 4(range 2-10) previous lines of therapy. 33(66%) patients had undergone autologous stem cell transplantation prior to elotuzumab.. Median duration of elotuzumab treatment was 3.8 months(range 1.2-81.2). The median number of treatment cycles was 4(1 - 81) in the lenalidomide group and 3 (1 - 21) in the pomalidomide group. Anemia, fatigue and diarrhea(lenalidomide group); fatigue, anemia, neuropathy, infection and thrombocytopenia (pomalidomide group) were the most common adverse events, none of which led to treatment discontinuation. The ≥VGPR response rate was similar between IMID groups(lenalidomide: 30% vs. pomalidomide: 20%). Median progression-free survival(PFS) was 5.5 months with 7.5 months among patients receiving lenalidomide compared 6.5 months to those on pomalidomide (p=NS). 31(62%) patients died due to progression (n=14) and infections(n=10). Although ISS was equally distributed between pomalidomide and lenalidomide patients, there were more pomalidomide treated patients among those with >3 lines of therapy. Among the heavily treated patients(>3 lines), the median PFS and OS were 2.9 months and 11.7 months with lenalidomide compared with 6.5 months and 17 months with pomalidomide(p=NS). Median PFS for ISS I/II patients were 6.5 months vs. 3.6 months for ISS III. The median 12-month OS rates were 54.9% and 61.4% for the lenalidomide and pomalidomide groups, respectively (p=NS). Conclusion: Our experience with Elotuzumab plus an IMID combination is a highly tolerable regimen with durable ≥VGPR responses among heavily pretreated patients. A median PFS of 5.5 months among patients who have received a median of 4 lines of therapy is a highly promising option. Furthermore responses appear to be better, among patients with low risk MM, but the size of the study prevent us from drawing definitive conclusions about IMID type.

Keywords:
elotuzumab

immunomodulatory drugs

Multiple myeloma

Tracks:
Treatment of Previously Treated Myeloma

SP-077

The addition of a HIV protease inhibitor to carfilzomib therapy in myeloma overcomes ABCB1-mediated drug resistance: a proof of concept

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Abstract:
Background/Aim. Relapsed/refractory myeloma with resistance to carfilzomib (CFZ) portends a poor prognosis. CFZ-resistant MM cells show strong up regulation of ABCB1/P-gp, in contrast to BTZ resistant MM. In vitro studies have shown drug inhibition of the ABCB1 efflux pump increases CFZ levels and restores drug sensitivity. Local data has shown the median survival from progression on CFZ to be two months. Therefore, the addition of an ABCB1 inhibitor to CFZ at acquisition of resistance, in heavily treated myeloma patients, may offer a further line of treatment and potentially prolonged survival in the absence of imminently available alternatives. Kaletra (lopinavir/ritonavir) is a registered, well-tolerated, HIV protease inhibitor combination that has been shown to restore CFZ sensitivity in vitro. Methods. We performed a retrospective analysis of 12 patients identified from our database who, at the time of biochemical progression on CFZ-triplet therapy (KCd (n=11) or KTd (n=1) were offered and received the addition of Kaletra 800mg (lopinavir/ritonavir,) administered orally at least 30mins prior to each CFZ infusion. Maximal response, time of response, duration of response, and overall survival were calculated. Results. 12 patients, of median age 71 (range 54-83), developed biochemical disease progression after a median 11 cycles of CFZ. They had received a median 5 lines of previous treatment. All patients had received CFZ, bortezomib and lenalidomide, and 8/12 had a prior ASCT. The median time from diagnosis was 6.8 years. 11 of 12 patients achieved at least a minor response to the addition of Kaletra with median maximal response (% reduction in paraprotein or SFLC) of 48% (range 15-89 %,) seen after a median 41 days (range 11-56). CFZ triplet-Kaletra treatment was continued for a median two cycles; up to six cycles in two patients, and two ongoing. Median overall survival from time of progression on CFZ is 4.5 months; two patients successfully bridged to daratumumab upon its availability with ongoing disease control. Treatments were well tolerated with mild loose bowel motions on the day of administration requiring dose reduction to 400mg in two patients the only additional side-effect of treatment noted. Discussion. These results demonstrate an in vivo proof of concept; the addition of an ABCB1-inhibitor can reinduce clinically meaningful responses to CFZ when resistance on treatment develops. Treatment options are limited in CFZ-refractory myeloma patients – this simple approach may support survival until the availability of novel or trial therapy. Our experience backs up the preclinical data and supports further works to determine the optimal timing of inhibitor administration in treatment cycles and structures, the importance of ABCB1 with respect to the triplet therapy partners, and other supplementary dynamic mechanisms of CFZ-resistance.

Keywords:
carfilzomib

relapsed/refractory multiple myeloma

resistance

Tracks:
Treatment of Previously Treated Myeloma

SP-078

Phase II Trial of Ixazomib and Dexamethasone Versus Ixazomib, Dexamethasone and Lenalidomide, Randomized with NFKB2 Rearrangement. (Proteasome Inhibitor NFKB2 Rearrangement Driven Trial, PINR)

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Abstract:
Introduction: Proteasome inhibitors (PI) and immunomodulatory drugs have become the backbone of therapy for multiple myeloma (MM). The oral boron-containing selective and reversible proteasome inhibitor ixazomib has been shown to induce deep and durable responses (Kumar RK et la, Blood 2016. 128(20):2415-2422). Triplets containing ixazomib, has been shown to be more efficacious than doublet regimens in the relapse setting (Moreau P, et al. N Engl J Med 2016. 374:1621-1634).However, to date, there is not companion diagnostics capable of predicting PI response. We have recently discovered that MM patients resistant to PI lack of the ankyrin (ANK) and death domain (DD) present in the 3'-end of NFKB2. Loss of NFKB2 3'end frequently resulted from a structural rearrangements. We found that NFKB2-ANK and -DD are crucial at initiating bortezomib's apoptotic signal by facilitating caspase-8 activation (unpublished data). Based on this findings, we designed this study to examine the efficacy of NFKB2 break apart FISH to predict the response to ixazomib and dexamethasone (Id) vs. ixazomib, lenalidomide and dexamethasone (IRd) in early relapse MM patients. Methods: In this phase 2 biomarker-driven open-label trial, relapsed patients with <4 lines of therapy were randomized to ixazomib 4 mg weekly 3 of 4 weeks and 40 mg weekly dexamethasone vs. Id plus 25 mg of lenalidomide daily days 21/28, based on the status of NFKB2 rearrangement in plasma cells. Patients were screened for NFKB2 rearrangement detected by NFKB2 break apart FISH. Patients without NFKB2 rearrangement received Id and patients with NFKB2 rearrangement were subsequently randomized in a 1:1 fashion to receive Id or IRd. The primary endpoint is to compare the response rate of Id or IRd at 4 cycles according to the rearrangement status of NFKB2 Results: At the moment of the interim analysis, 46 patients have achieved 4 cycles of treatment. All treatment groups (NFKB2 FISH [-] Id, n=23, NFKB2 FISH [+] Id, n=13 and IRd, n=10) received a median of 2 prior lines of therapy. A higher ORR was observed in NFKB2 FISH negative treated with Id compared with NFKB2 FISH positive (50% CI:32%-68% vs. 23% CI:6.6%-49%, P=0.1), including significantly higher rates of ≥very good partial response, ≥ partial response, ≥ minimal response (17%, 29%, 12.5% vs. 0%, 23%, 0%, respectively). ORR for IRd arm is for now 50% CI:22%-77%. The most common (≥10%) grade 2/4 include pneumonia 23%, diarrhea 17% (Id NFKB2 FISH negative) and thrombocytopenia 60% and diarrhea (20%), (IRd NFKB2 FISH positive). Treatment discontinuations only occurred in 3 Id treated patient (13%). Conclusion: Interim analysis demonstrates a trend higher efficacy of ixazomib with dexamethasone in MM patients with negative NFKB2 break-apart FISH compared to those with a positive test. Efficacy and toxicity of the triplet regimen are comparable to what is seen in the Tourmaline 1 trial. This study is registered clinicaltrials.gov# NCT02765854

Keywords:
Biomarker

NFkB-pathway

Relapsed Refractory MM

Tracks:
Treatment of Previously Treated Myeloma

SP-079

A 'real-world' study of panobinostat, bortezomib and dexamethasone in a very heavily pre-treated population of myeloma patients

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Abstract:

Introduction: The combination of panobinostat, bortezomib and dexamethasone (PAN-Vd) is approved for the treatment of patients with relapsed myeloma who have received ≥2 prior lines of therapy, including bortezomib and an immunomodulatory agent. Approval was based on subgroup analysis of the PANORAMA1 trial which compared PAN-Vd to placebo-Vd in patients with 1-3 prior lines of therapy. There is no published experience in more heavily pre-treated patients and in UK clinical practice this regimen is often positioned as a 5th+ line therapy. Methods: After local ethical approval we retrospectively assessed patients treated with PAN-Vd at the Royal Marsden Hospital, London, between April 2016 and March 2019. Bortezomib was given at 1.3 mg/m2 weekly, D1,8,15,22; panobinostat 20mg D1,3,5,15,17,18; dexamethasone 20-40mg D1,8,15,22. Response was assessed using IMWG criteria. PFS and OS were calculated from C1D1 and medians compared using the Logrank test. Cytogenetic high-risk (HR) included t(4;14), t(14;16), t(14;20), del(17p) and gain(1q). Results: 46 patients received PAN-Vd, with a median age of 68 years (range 51-79) and a median 5 prior lines of therapy (range 2-8). The majority of patients (70%, 32/46) were International Staging System (ISS) 3. 17/25 (68%) had HR disease. The overall response rate, (≥PR), was 45% (20/44) with 14% (6/44) achieving VGPR. The median PFS of the whole group was 3.5 months (median follow-up 22 months) and the OS was 7.8 months (median follow-up 17 months). Patients achieving ≥PR had a significantly longer PFS and a longer OS (median PFS 5.3 months, OS 10) than those with <PR (PFS 2.2 months, OS 5.3). 7 patients received ≥10 cycles of PAN-Vd. The presence of HR disease in patients with such heavily treated disease did not affect outcomes. Patients who were not previously refractory to proteasome inhibitor therapy had a similar PFS but longer OS than those refractory (OS 9.0 months vs 3.7 months). The main adverse events were haematological. Given the extensive pre-treatment of this patient cohort 70% (32/46) had grade 2/3 anaemia and 30% (14/46) had grade 3/4 thrombocytopenia prior to PAN-Vd. This increased to 80% (37/46) and 74% (34/46) respectively during treatment. 85% (39/46) required a transfusion of platelets and/or red cells. Conclusions: Compared to those in PANORAMA 1, patients in our cohort were older, more often ISS3 and more heavily pre-treated. This created difficulties for treatment delivery, with transfusions required in the majority of patients. In this context the median PFS for PAN-Vd was 3.5 months, demonstrating the difficulty of treating multiply relapsed patients. These results are similar to heavily pre-treated patients receiving pomalidomide and dexamethasone (Pd) in the NIMBUS trial (5 median prior lines) in which the PFS with Pd was 4.0 months vs 1.9 months with high-dose dexamethasone. PAN-Vd was efficacious and offers an alternative to Pd in the multiply relapsed setting.

Keywords:
bortezomib

Panobinostat

Relapsed Refractory MM

Tracks:
Treatment of Previously Treated Myeloma

SP-080

Development and Evaluation of Methods for Early Relapse Detection in Multiple Myeloma Patients Treated with Bortezomib

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Abstract:

Background: Current treatment guidelines recommend waiting for IMWG progression criteria to be met before proceeding to the next line of therapy (Rajkumar et al, Blood 2011;117, NCCN Guidelines – Multiple Myeloma V2.2019 – Nov 16, 2019 NCCN.org). Assuming relapsed disease is more difficult to treat than disease that is still in remission, a tool that can accurately anticipate relapse 3-6 months before it occurs would be valuable for patient care. Methods: Using dosing and serum M-protein time course data from 130 patients from the COMMPASS observational study (NCT01454297-IA9), we developed an individualized adaptive mathematical model of myeloma induction and relapse in patients taking any combination of bortezomib, lenalidomide, and dexamethasone. We tested the accuracy of this adaptive model to anticipate serum M-protein relapse 3-6 months in advance in a separate 'validation' set of 130 COMMPASS patients. For comparison, we also tested the ability of the M-protein 'velocity' calculated over the two most recent assessments to predict relapse over the same time window. We derived receiver operating characteristic (ROC) curves for both predictors to compare their sensitivity and specificity for relapse detection. The prespecified goal for using either tool in clinical practice was 80% sensitivity and specificity. Results: ROC analysis showed that, at the target true positive rate (TPR) of 80%, the adaptive model-based method has a false positive rate (FPR) of 36%, while the M-protein velocity method has a FPR of 91%. At a FPR of 20%, however, the TPR of the adaptive method was 50% while the TPR for the M-protein velocity was slightly higher at ~61%. Conclusion: While they were both better than random guessing, neither the current version of the adaptive model-based tool nor the M-protein velocity method could achieve the prespecified criteria of 80% sensitivity and specificity in predicting M-protein relapse 3-6 months in advance. ROC analysis suggests the two approaches have complementary operating characteristics. We hope to augment the model-based tool with Bayesian priors informed by baseline disease markers as well as incorporating minimal residual disease data as available.

Keywords:
bortezomib

M-protein

Minimal residual disease

Tracks:
Treatment of Previously Treated Myeloma

SP-081

ICARIA-MM study: efficacy analysis according to prior lines of treatment

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Abstract:

Background: Despite the introduction of targeted therapies and combination regimens, patients (pts) with multiple myeloma (MM) continue to experience multiple relapses and/or become refractory to treatment. Outcomes for pts generally worsen with successive lines of therapy. The randomized, open-label, active-controlled, multicenter phase 3 ICARIA-MM study (NCT02990338) compared treatment with the anti-CD38 monoclonal antibody isatuximab (Isa) in combination with pomalidomide and dexamethasone (Pd) vs Pd. Pts had relapsed/refractory MM (RRMM) after ≥2 prior lines of therapy, including lenalidomide (Len) and a proteasome inhibitor (PI). Methods: Pts were randomized (1:1) to receive Isa-Pd or Pd. Isa (10 mg/kg IV) was given on days 1, 8, 15, and 22 (cycle 1), and days 1 and 15 in subsequent 28-day cycles. Pts received standard doses of Pd in each cycle. The primary endpoint was progression free survival (PFS), assessed by an independent response committee. Subgroup analyses by refractory status, defined as progression ≤60 days post treatment, were conducted for pts refractory to Len, PI, or both (double-refractory). Results: Overall, 307 pts were randomized to Isa-Pd (n=154) or Pd (n=153). In the Isa-Pd and Pd arms, 102 (66%) and 101 (66%) pts had received 2–3 prior lines of therapy, and 52 (34%) and 52 (34%) had received >3 prior lines, respectively. All pts had received Len and a PI. After a median 11.6 months of follow-up, median PFS in the intent to treat population was 11.5 months with Isa-Pd and 6.5 months with Pd (hazard ratio [HR] 0.60 [95% confidence interval (CI) 0.44–0.81]). Median PFS among Len-refractory pts with Isa-Pd (n=144) was 11.4 months (95% CI, 8.2–13.3) vs 5.6 months (95% CI, 3.8–7.9) with Pd (n=140); HR 0.59 (95% CI, 0.43–0.82). PFS was similarly higher with Isa-Pd (n=93) vs Pd (n=88) for pts refractory to Len at last line (11.6 vs 5.7 months; HR 0.50 [95% CI, 0.34–0.76]). Median PFS in PI-refractory pts with Isa-Pd (n=118) was 11.4 months (95% CI, 7.6–14.8) vs 5.6 months (95% CI, 3.7–8.0) with Pd (n=115); HR 0.58 (95% CI, 0.41–0.82). In double-refractory pts, median PFS was 11.2 months (95% CI, 7.4–14.8) with Isa-Pd (n=111) and 4.8 months (95% CI, 3.2–7.9) with Pd (n=107); HR 0.58 (9% CI, 0.40–0.84). PFS was also higher with Isa-Pd vs Pd for pts who had received 2–3 prior lines of therapy (12.3 vs 7.8 months; HR 0.59 [0.40–0.88]) and >3 prior lines of therapy (9.4 vs 4.3 months; HR 0.59 [0.36–0.98]). ORR in pts receiving Isa-Pd vs Pd was: 59.0% (95% CI 0.51–0.67) and 31.4% (95% CI, 0.24–0.40) in Len-refractory pts; 60.2% (95% CI, 0.51–0.69) vs 32.2% (95% CI, 0.24–0.42) in PI-refractory pts; and 58.6% (95% CI, 0.49–0.68) and 29.9% (95% CI, 0.21–0.40) in double-refractory pts. Conclusion: Addition of Isa to Pd improved PFS and ORR regardless of number of prior lines of therapy and in pts refractory to Len, refractory to Len at last line, and double-refractory, consistent with the benefit observed in the overall population.

Keywords:
CD38

Multiple myeloma

Relapsed/Refractory

Tracks:
Treatment of Previously Treated Myeloma

SP-082

A Randomized Phase 2 Study of Subcutaneous Daratumumab Plus Carfilzomib/Dexamethasone Versus Carfilzomib/Dexamethasone Alone in Patients with Multiple Myeloma who have been Previously Treated with Intravenous Daratumumab to Evaluate Retreatment (LYNX)

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Abstract:
Trial in Progress Background: Daratumumab, a human anti-CD38 IgGκ monoclonal antibody, is approved in many countries for use as monotherapy in relapsed/refractory multiple myeloma (RRMM), and in combination with standard-of-care regimens in RRMM and transplant-ineligible newly diagnosed multiple myeloma. The randomized phase 2 LYNX (MMY2065) study will evaluate the efficacy and safety of retreatment with daratumumab. Methods: In this ongoing, multicenter, open-label, randomized phase 2 study, approximately 230 patients with prior exposure to daratumumab will be randomized 1:1 to receive daratumumab plus carfilzomib and dexamethasone (D-Kd) or carfilzomib and dexamethasone (Kd) alone. Patients must have received 1 to 2 prior lines of therapy (at least one of which included intravenous daratumumab) with the daratumumab-based therapy completed ≥3 months prior to randomization. Eligible patients must have achieved a partial response or better (assessed via International Myeloma Working Group criteria) to daratumumab-based therapy, with a duration of response of ≥4 months. Patients must not have discontinued daratumumab due to a daratumumab-related adverse event or received prior treatment with carfilzomib. All patients will receive 20 mg/m^2 carfilzomib IV on Day 1 of Cycle 1, escalated to 70 mg/m^2 on Days 8 and 15; carfilzomib 70 mg/m^2 will be administered on Days 1, 8, and 15 of each 28-day cycle thereafter. Dexamethasone 40 mg will be administered (IV or PO) QW for Cycles 1-9 and then on Days 1, 8 and 15 from Cycle 10 onwards. Patients in the D-Kd group will also receive subcutaneous daratumumab (1,800 mg co-formulated with recombinant human hyaluronidase PH20 [rHuPH20; Halozyme]) QW in Cycles 1-2, Q2W in Cycles 3-6, and Q4W thereafter. The primary endpoint is the rate of patients achieving a very good partial response or better. Secondary endpoints include overall response rate, rate of patients achieving complete response or better, progression-free survival, overall survival, overall MRD-negativity rate, time to next treatment, pharmacokinetics, and safety. ClinicalTrials.gov identifier: NCT03871829.

Keywords:

CD38

daratumumab

retreatment

Tracks:
Treatment of Previously Treated Myeloma

SP-083

Results of the Daratumumab Monotherapy Early Access Treatment Protocol (EAP) in Patients from Brazil With Relapsed or Refractory Multiple Myeloma

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Abstract:
All authors contributed equally. Background: Daratumumab (DARA) is approved as monotherapy for relapsed or refractory multiple myeloma (RRMM) and in combination with standard-of-care regimens for RRMM and newly diagnosed MM. This open-label, multicenter EAP provided RRMM patients with early access to DARA monotherapy

and collected safety and efficacy data. We report results for patients enrolled at 6 sites in Brazil. Methods: Eligible patients had RRMM and ≥3 prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD), or were double refractory to both PI and IMiD. Patients received DARA 16 mg/kg IV weekly for 8 weeks, Q2W for 16 weeks, and Q4W until disease progression, unacceptable toxicity, or lack of clinical benefit. Grade 3/4 treatment-emergent adverse events (TEAEs), serious TEAEs (SAEs), infusion-related reactions (IRRs), best response per investigator assessment, and progression-free survival (PFS) data were summarized. Results: Forty-nine patients (median [range] age: 65 [50-81] years) were enrolled and received ≥1 dose of DARA. ECOG scores at baseline were 2 for 8.3%, 1 for 52.1%, and 0 for 39.6% of patients. The median duration of treatment was 6.41 months (range: 0.26-11.76), with a median number of 17 infusions (range: 2-23). Median durations of infusion were 7.2, 4.3, and 3.5 hours for the first, second, and all subsequent infusions, respectively. Grade 3/4 TEAEs were reported in 19 (38.8%) patients, the most common (>10%) being neutropenia and pneumonia (each 10.2%). SAEs were reported in 19 (38.8%) patients and the most common (>5%) SAE was pneumonia (10.2%). Primary reasons for treatment discontinuation included progressive disease (46.9%), adverse event (6.1%), loss to follow-up (4.1%), and subject withdrawal (4.1%). Seven (14.3%) patients discontinued treatment due to TEAEs (3 [6.1%] drug-related). Seven (14.3%) patients had a fatal TEAE (2 [4.1%] drug-related). Four (8.2%) patients discontinued treatment due to a fatal TEAE. IRRs occurred in 25 (51.0%) patients, including 2 (4.1%) with grade 3/4 IRRs. Among patients reporting IRRs, 23 (92%), 0, and 2 (8.0%) occurred during the first, second, and all subsequent infusions, respectively. The most common (>5%) any grade IRRs were dyspnea (22.4%), cough and pyrexia (each 8.2%), and throat irritation and chills (each 6.1%). Twenty (40.8%) patients achieved a partial response or better; 9 (18.4%) achieved a very good partial response or better. The estimated median PFS was 8.25 months (95% confidence interval [CI], 5.55-17.54) and the estimated 12-month median PFS rate was 41.7% (95% CI, 26.9-55.9). Conclusions: These EAP results among patients from Brazil are consistent with the known safety and efficacy profiles of DARA monotherapy in patients with RRMM treated with ≥3 prior therapies including a PI and an IMiD or who were refractory to both PI and IMiD. ClinicalTrials.gov NCT02477891.

Keywords:
daratumumab

drug access

Multiple myeloma

Tracks:
Treatment of Previously Treated Myeloma

SP-084

Greater Treatment Satisfaction in Patients Receiving Subcutaneous (SC) Versus Intravenous (IV) Daratumumab (DARA) for Relapsed or Refractory Multiple Myeloma (RRMM): COLUMBA

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Abstract:
Background: DARA IV is approved as monotherapy and in multiple combinations with standard-of-care regimens for MM. A previous phase 1b trial of a SC formulation of DARA with recombinant human hyaluronidase PH20 (rHuPH20; ENHANZE® drug delivery technology, Halozyme, Inc.) demonstrated similar efficacy to DARA IV and was well tolerated by patients. The phase 3 COLUMBA study evaluated safety and efficacy of DARA SC vs IV in RRMM patients. Median duration of administration was substantially shorter for DARA SC (5 min across all injections) than DARA IV (421, 255, and 205 min for first, second, and subsequent infusions). DARA SC patients experienced significantly fewer infusion-related reactions than IV patients (12.7% vs 34.5%, respectively). Here we present patient-reported outcomes evaluating satisfaction with treatment from the COLUMBA study. Methods: DARA SC or IV were administered in 28-day cycles: QW Cycles 1-2, Q2W Cycles 3-6, and Q4W thereafter until disease progression or unacceptable toxicity. Patient-reported satisfaction with treatment was a secondary endpoint. Patients completed a modified Cancer Therapy Satisfaction Questionnaire (CTSQ; paper administration) at weekly (Cycles 1-2, starting on Day 8 of Cycle 1) and monthly (Cycles 3+) time points and at the end of treatment. The modified CTSQ contained the Satisfaction with Therapy domain (7 items) and single items taken from the Thoughts about Cancer Therapy domain. Domain scores were calculated only for Satisfaction with Therapy (≥5 items must have been completed) and were reported as mean responses using descriptive statistics. Scores were determined for each cohort for Cycles 1-10 (C1-C10) in the intent-to-treat population; few patients reached later cycles at the time of analysis. A meaningful difference in score was 5.9 points. Results: CTSQ analysis included 263 and 259 patients in the SC and IV groups, respectively. Compliance rates in both groups were high (>88%) through Cycle 10. Mean values in the Satisfaction with Therapy domain were meaningfully higher for DARA SC vs IV patients at several time points and maintained during the course of treatment (77 vs 71 at C1D8; 89 vs 78 at C10D1). Through C10, more DARA SC than IV patients reported positive responses to the following 3 most relevant domain items: "Satisfied with Form of Cancer Therapy (IV/SC)", "Taking Cancer Therapy as Difficult as Expected", and "Were Side Effects as Expected". DARA SC patients reported more favorable scores than IV patients for the remaining 4 items ("Satisfied with Most Recent Cancer Therapy", "How Worthwhile Was Cancer Therapy", "Benefits Meet Expectations", and "Would You Take This Cancer Therapy Again"). Conclusions: DARA SC patients were more satisfied with their cancer therapy and had more positive perceptions of their treatment than DARA IV patients, possibly due to the reduced treatment burden associated with shorter administration time and fewer infusion-related reactions.

Keywords:
CD38

daratumumab

Multiple myeloma

Tracks:
Treatment of Previously Treated Myeloma

SP-085

Therapeutic Antibody as Interference for identification of endogenous monoclonal proteins-Three Clinical Cases

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Abstract:
Background:For the evaluation and follow up of patients with multiple myeloma (MM), the detection, quantification and typing of monoclonal components (M-spike) by protein electrophoresis (SPE) and immunofixation (IFE) are critical. In the last years, new monoclonal antibody (m-Ab)-based immunotherapies against relapsed/refractory MM were developed. Among them, anti-CD38 m-Ab Daratumumab. Since Daratumumab is an IgG kappa m-Ab, it can interfere with the interpretation of SPE and IFE, therefore, It's crucial to identify endogenous M-spikes from Daratumumab. Hydrashift2/4-Daratumumab is a commercial kit from Sebia designed to overcome this possible interference by forming a complex anti-Daratumumab-Daratumumab and shifting Daratumumab band to the alpha zone in IFE gel. The aim of this study was to assess the interference of Daratumumab with SPE and IFE tests Methods:3 patients who received one intravenous infusion with intervals as follows: 1-week(P1W), 2-week(P2W) and 1-month(P1M). IgG, IgM, IgA (NV: 700-1600, 40-230 and 70-400 mg/dL, respectively), Kappa/Lambda ratio (K/L) (NV: 0.25-1.65), SPE, IFE and Hydrashift2/4 were evaluated at baseline, post-Daratumumab, 7d and 14d after administration. Results:P1W=IgG:501 and 500; IgM:26 and 24; IgA:25 and 23 mg/dL with K/L: 0.07 and 0.06 at baseline and post-Daratumumab were observed respectively. SPE showed one single band in the gamma zone corresponding to two monoclonal IgGK and IgGL (weak) bands in IFE before and after treatment. However, following Hydrashift2/4 the IgGL diagnosis was confirmed due to the shifting of the IgGK band at baseline and post-Daratumumab. P2W=IgG:398, 466 and 388;IgM:8, 9 and 7;IgA:79, 86 and 74 mg/dL at baseline, post-Daratumumab and 7d respectively with a K/L of 1.32 (baseline) and 1.34 (7d). SPE showed a strong IgGK band post-Daratumumab infusion compared to a weak IgGK band at baseline and after 7 days. Hydrashift2/4 led to no evidences of any band at any time confirming the results that no monoclonal band was observed in this patient. P1M=IgG:526, 559, 513 and 517;IgM:23, 22, 19 and 25;IgA:26, 25, 23 and 21 mg/dL at baseline, post-Daratumumab, 14 and 30 days respectively. No evidences of any M-spike were observed in SPE. However, IFE showed:IgGL at baseline, IgGK and IgGL post-Daratumumab and again IgGL at 14d and 30d. The use of Hydrashift2/4 kit ratified monoclonal IgGL at baseline, post-Daratumumab, 14d and 30d. Conclusion:It's essential for the lab to know the Daratumumab protocol therapy (dosage and administration intervals) to avoid misinterpretations of SPE and IFE results. Based on this study, it is recommendable to draw blood just before the next infusion to decrease the possibility of seeing the therapeutic m-Ab in IFE. The use of Hydrashift2/4-Daratumumab kit could help to successfully distinguish Daratumumab from endogenous M-spike, however, we still need to be aware of the possible interference from others many therapeutic m-Ab which are used in the clinic.

Keywords:
daratumumab

immunofixation

monoclonal spike

Tracks:
Treatment of Previously Treated Myeloma

SP-086

A Phase 1 Trial of Ruxolitinib, Lenalidomide and Methylprednisolone for Patients with Relapsed/Refractory Multiple Myeloma (MM)

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Abstract:
Introduction Preclinical studies from our laboratory have demonstrated that ruxolitinib (RUX) in combination with lenalidomide (LEN) and dexamethasone shows marked anti-myeloma effects both in vitro and in vivo. Furthermore, MUC1 is responsible for LEN resistance in MM cells, and RUX blocks its expression in MM cells. Thus, RUX may restore sensitivity to LEN. Therefore, a Phase 1 trial was conducted to determine the safety and efficacy of RUX in combination with LEN and methylprednisolone (MP) for relapsed/refractory (RR) MM patients (pts) who had previously been treated with LEN/steroids and a proteasome inhibitor (PI) and showed progressive disease at study entry. Methods A traditional 3+3 dose escalation design was used to enroll subjects in four cohorts with planned total enrollment to be 49 pts. Subjects received RUX twice daily continuously, LEN daily on d1 21 of a 28-d cycle and MP orally every other day. In DL0, pts received RUX 5 mg, LEN 5 mg, and MP 40 mg. In DL+1 and +2, both doses of LEN and MP remained unchanged and RUX was escalated to 10 and 15 mg, respectively. DL+3 escalated LEN to 10 mg with MP unchanged and RUX at 15 mg. Primary endpoints were safety, clinical benefit rate (CBR) and overall response rate (ORR). Results As of September 1, 2018, 36 pts were enrolled, and 32 were evaluable for efficacy. The median age was 66 years (range, 46 81), and 21 (58%) were male. Pts received a median of 6 prior treatments including LEN and steroids to which they were all refractory and a proteasome inhibitor. No DLTs occurred, and DL+3 was expanded. Among evaluable pts, the CBR and ORR were 47% and 41%, respectively (1 CR, 2 VGPR, 10 PR and 2 MR), and 14 and 3 pts showed SD and PD. All 15 responding pts were refractory to LEN. G3 AEs included anemia (17%), neutropenia (14%), sepsis (14%), lymphopenia (11%), thrombocytopenia (11%), and pneumonia (11%). The most common SAEs included sepsis (14%) and pneumonia (11%). Conclusions This Phase 1 trial demonstrates for the first time that a JAK inhibitor, RUX, can overcome refractoriness to LEN and steroids for RR MM pts. These promising results are leading to expansion of the current clinical trial to 78 pts, and represents a novel therapeutic approach for treating MM.

Keywords:
JAK1 inhibitor

JAK2 inhibitor

Relapsed Refractory MM

Tracks:
Treatment of Previously Treated Myeloma

SP-087

A Phase 2 Trial of the Efficacy and Safety of Elotuzumab in Combination with Pomalidomide, Carfilzomib and Dexamethasone for High Risk Relapsed/ Refractory Multiple Myeloma Patients

Authors:
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Abstract:
Background: Despite the recent introduction of novel anti-multiple myeloma (MM) agents, high risk MM continues to have poor prognosis and remains a therapeutic challenge. Elotuzumab (ELO) is a humanized monoclonal antibody that recognizes

SLAMF7, a molecule highly expressed on MM cells. The addition of ELO to lenalidomide (LEN) and dexamethasone (DEX) improved overall response rates and progression-free survival among patients (pts) with relapsed/refractory (RR) MM. The FDA has also approved ELO in combination with pomalidomide (POM) and low-dose DEX for the treatment of pts with RRMM following 2 or more prior therapies. However, more conclusive data is needed for an ELO containing combination's efficacy for high risk MM pts. Carfilzomib (CFZ) is a potent second-generation PI that has shown to be efficacious for treatment of refractory MM pts as well as high risk pts with cytogenetic abnormalities. Thus, we are evaluating the efficacy and safety of ELO in combination with POM, DEX and CFZ for high-risk RRMM pts. Methods: This is a Phase 2, multicenter, open label, nonrandomized study evaluating the efficacy and safety of ELO, POM, CFZ, and DEX combination therapy for high-risk RRMM pts. This study will enroll previously treated MM pts that currently show evidence of progressive disease and have high-risk MM. High-risk MM was defined as showing del(17p-p53), t(14;16) or t(14;20), plasma cell leukemia, extramedullary MM, doubling of MM markers in the past 3 months, refractoriness to LEN and PI containing regimen, or renal failure related to MM. All drugs will be administered on a 28-day cycle with a maximum of 8 cycles. ELO will be administered intravenously (IV) at 10 mg/kg on days 1,8,15, and 22 during cycles 1 and 2. On cycle 3 and beyond, ELO will be given at 20 mg/kg on day 1. POM capsules will be given per Orem (PO) at 3 mg daily, on days 1-21 during all cycles. CFZ will be given as an IV infusion at 20 mg/m2 day 1, cycle 1 and 56 mg /m2 on days 8 and 15 of cycle 1, and days 1, 8 and 15 on cycle 2 and beyond. Pts will be pre-medicated with 28 mg PO of DEX and given 8 mg DEX IV on the days of ELO infusion. Clinical trial: NCT0310427. Results: 13 of planned 39 pts have been enrolled. The median age was 63 years, and 10 (77%) were male. Pts received a median of 6 prior treatments. Among 12 evaluable pts, the clinical benefit and overall response rates were 50% and 42%, respectively (2 CR, 1 VGPR, 2 PR and 1 MR), and 2 and 4 pts showed SD and PD. For 5 responding pts, the median duration of response was 4.6 months with the median follow up time of 5.3 months. Most common ≥ G3 AEs included hypophosphatemia (15%), leukopenia (15%) and sepsis (15%). Most common SAEs included sepsis (15%) and acute encephalopathy (15%); 1 pt expired while on the study. Conclusions: Preliminary results from this Ph 2 trial demonstrate that ELO in combination with POM, DEX and CFZ appears to be an effective therapy for high-risk RRMM pts.

Keywords:
elotuzumab

High-risk cytogenetics

Multiple myeloma

Tracks:
Treatment of Previously Treated Myeloma

SP-088

The Impact of Lenalidomide Maintenance on Second Line Chemotherapy in Transplant Eligible Patients with Multiple Myeloma in the Canadian Setting

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Abstract:
Introduction Post-transplant lenalidomide (L) maintenance (LM) is used routinely in frontline treatment of patients with multiple myeloma. However, it's impact on response to L-containing therapy in first relapse is unclear. This is of critical importance given the efficacy of L-containing therapy in relapsed disease. We sought to address this question using the Myeloma Canada Research Network Canadian Multiple Myeloma Database (MCRN CMM-DB), a centralized research platform encompassing data from 13 Canadian cancer centers. Methods The study population included patients treated with upfront ASCT and bortezomib-based induction who had experienced at least one relapse and had 2 years of follow-up. Our primary endpoint was second progression free survival (2nd PFS) defined as time from initiation of second line chemotherapy to second relapse, death or last follow-up. We also examined overall survival from time of initiation of second line chemotherapy to death or last follow-up (2nd OS) and depth of response to 2nd line treatment. Results 575 patients were included. 297 (52%) patients were treated with LM of which 136 (24%, group 1) received L at relapse and 161 (28%, group 2) did not. 278 (48%) patients did not receive LM of which 209 (36%, group 3) received L at relapse and 69 (12%, group 4) did not. There was no significant difference in ISS stage ($p = 0.17$) or presence of high-risk cytogenetics ($p = 0.24$) where tested. The median 2nd PFS for patients in groups 1, 2, 3 and 4 respectively were 10.2 months (95% CI: 7.1-13.9), 14 months, 18 months and 12 months. 2nd PFS from group 3 was statistically significant compared to groups 1 ($p = 0.04$), group 2 ($p = 0.047$) and group 3 (0.0495). No other significant differences were observed. At the time of analysis 217 patients (38%) had died. The OS from 2nd line therapy in groups 1, 2, 3, and 4 respectively were 55.3 months (95% CI: 49 – NYR), 38 months, 49 months and 27 months. A statistically significant difference in OS from relapse was noted between groups 1 and 2 ($p = 0.004$) and groups 1 and 4 ($p = 0.02$). Rates of favorable response (VGPR and higher) were not significantly different across the groups at 84%, 87%, 78% and 80% in groups 1, 2, 3, and 4 respectively ($p = 0.23$). Conclusion There remains a paucity of data examining L-based second line therapy for patients relapsing on LM. In patients who did not receive LM there is a superior 2nd PFS when L is used at first relapse. With the widespread use of LM however, this cohort is diminishing. Outcomes of patients treated with LM are more relevant to current practice. For such patients, our real-world data demonstrated no statistically significant worsening of 2nd PFS in those who receive L at relapse. Additionally, in this cohort a superior 2nd OS was also seen. As such, the widespread us of LM in the management of frontline MM should not deter clinicians from choosing L-based therapy at first relapse

Keywords:
Lenalidomide

relapsed

survival

Tracks:
Treatment of Previously Treated Myeloma

SP-089

3-weekly Daratumumab-IMiD-dexamethasone is highly efficacious and cost-effective in relapsed/refractory multiple myeloma

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Abstract:
Background Daratumumab (dara) with immunomodulatory agents (IMiD) and dexamethasone (dex) is highly effective in relapsed multiple myeloma (MM). The recommended schedule of dara is weekly for 8 doses, followed by 2-weekly for 8 doses, and then every 4-weekly thereafter. Given the high cost and the long half-life as an antibody, a 3-weekly dosing of dara was used together with IMiD/dexamethasone. Method Dara at 16mg/kg was used every 3-weekly with lenalidomide or pomalidomide. Patient achieving best response received single agent IMiD maintenance until disease progression. Fourteen relapsed MM patients were enrolled. One had received weekly dara from a private oncologist, hence was excluded from analysis. Thirteen patients at a median age of 63 years (range: 50-84 years) were studied. The median number of previous therapies was 2 (range: 1-5), with nine patients (69.2%) having undergone autologous stem cell transplantation. Three patients (23.1%) were refractory to bortezomib, seven patients (53.8%) to lenalidomide, and eight patients (61.5%) to last treatment. At relapse, two (15.4%) had high LDH, eight (61.5%) impaired renal function, and three (23.1%) extramedullary disease. Treatment was dara-lenalidomide-dex in six (46.2%), and dara-pomalidomide-dex in seven (53.8%). Results Responses after four cycles included CR in 5 patients (38.5%), VGPR in five patients (38.5%), and PR in three patients (23%). After a median of four dara infusions (range: 3-10), the best responses included CR in seven patients (53.8%), nCR in two patients (15.4%), VGPR in two patients (15.4%), and PR in two patients (15.4%). Median time to VGPR was 4 weeks. One patient had PET-CT before and after dara with PET-CR post-dara. Two had MRD test that showed MRD-negativity at serological CR. At 10 months, the OS was 90%, and PFS 54.7%. Three patients progressed, one of whom died of ruptured hepatic plasmacytoma. The most frequent toxicity was haematological especially neutropenia (all grades: 92.3%, Grade ¾: 76.9%), infusion reaction (38.5%, all grade ½), neuropathy (38.5%, all grade ½), gastrointestinal (all grades: 38.5%, grade ¾: 7.7%), and sepsis (all grades: 30.8%; grade ¾: 23.1%). Neutropenia was effectively prevented with prophylactic G-CSF. Conclusion A 3-weekly dara-IMiD-dex regimen is highly efficacious, inducing deep and rapid responses, hence cost-effective for less affluent countries. In view of prevalent grade 3/4 neutropenia despite less frequent dara, 3-weekly dara might be more suitable for Asian patients.

Keywords:
3-weekly daratumumab

cost-effectiveness

dara-IMiD-dex

Tracks:
Treatment of Previously Treated Myeloma

SP-090

Treatment Patterns and Clinical Outcomes Across Consecutive Treatment Lines in Multiple Myeloma Patients: Single-Center Real World Experience.

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Abstract:
Background: Multiple myeloma follows a relapsing-remitting course; therefore multiple lines of therapy are usually required. Treatment options are now more numerous and effective than ever before. We aimed to explore patterns of treatment, in particular the characteristics of patients reaching advanced treatment lines, in a real world setting. Methods: In a single-center, retrospective study, we analyzed treatment patterns, treatment duration and clinical outcomes of multiple myeloma patient in our

Myeloma clinical database. Patient and disease characteristics, treatment regimen, clinical endpoints focusing on time to next treatment (TTNT) and overall survival (OS), were documented. The treatment response categories were defined according to the IMWG criteria. Results: Complete data on treatment schedules were available on 307 patients diagnosed between 2008-2019. The median age at myeloma diagnosis was 66.9 (range: 32-91); 119 patients were ≥ 70, 188 patients <70. Intermediate/High risk cytogenetics was reported among 77 (36%) of the 214 evaluable patients. 139 (45%) patients received an upfront autologous transplant (ASCT) and 31 (10%) receive a second transplant. 167 patients (54%) received 2nd line, 91 (30%), 50 (16%), 30 (10%), 36 (12%) got 3rd, 4th, 5th, and ≥6th lines of therapy, respectively. Median time to next treatment was 16.5, 7.8, 3.6, 6.5 and up to 4 months at 1st, 2nd, 3rd, 4th, and ≥5 lines, respectively. Most frequent treatment regimen was PI ± chemotherapy (mostly VCD) in 1st line (59%), IMiD (43%) or IMiD/mAb (DARA-Len) (31%) in 2nd line; IMid ± mAB (11%) or PI ± chemotherapy (7%) in 3rd line. A longer time from 1st to 2nd treatment start was observed in patients who underwent ASCT (20 vs 8.5 mo, p=0.001), younger patients (22.3 vs 10.6, age <70 vs ≥70, p<0.001) and patients with at least VGPR after induction (22.8 vs 10.3 mo, p=0.001). Among patient subgroup who responded to induction (n=244), time to 2nd line was 23.7mo in patient patients who underwent ASCT in 1st line vs 13.2 mo among non-transplanted (p<0.001). Depth of response to induction was inversely related to the likelihood of proceeding to 2nd line: 46% vs 61% (p=0.047) in patients achieving PR vs ≥VGPR, respectively. Conclusion: Real life TTNT is shorter than progression free survival reported in randomized trials in first and second lines, and gets progressively shorter as treatment lines advance. Despite the availability of multiple regimens, few patients received treatment beyond the 3rd line. These findings suggest that improving effectiveness in induction and early treatment lines may have a major effect on patient's overall outcomes.

Keywords:
real-world evidence

response to therapeutic

RRMM

Tracks:
Treatment of Previously Treated Myeloma

SP-091

Therapy With Steroid-Containing Regimens in Myeloma Patients Can Result in Significantly Low Serum Cortisol Levels

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Abstract:
Background The vast majority of treatment regimens used in the treatment of myeloma contain significant amount of steroid (usually dexamethasone or prednisolone). Total steroid exposure, even on weekly steroid dosing, can be extremely high when patients are treated for many months, sometimes years, in continuous regimens. We hypothesised that such patients might have low cortisol levels and thus evaluated a random sample of our clinical cohort with long term steroid exposure. Methods Over a 4 week period, all patients attending clinic who had had been exposed to a continuous treatment regimen had a random cortisol measured (between 1-4pm). Those who showed a possible suppression of cortisol production (random level <300) went on to have secondary 9am cortisol levels with ACTH if low cortisol level confirmed. Results Patient population is shown in table 1 with patient characteristics. Of note, 92% had received a regimen containing bortezomib and steroids (median 4.5 cycles, range 3-11) and 92% had received a regimen containing

Lenalidomide and dexamethasone (median of 21 cycles, range 0-65).60% had prior autologous transplant. The median random cortisol level was 251nmol/L (mean 257.6nmol/L, range 37-541nmol/L with laboratory normal range 172-497nmol/L between 10.00 and 12.00). 5 patients (16% had cortisol levels <150nmol/L) of which repeat morning cortisol of <150nmol/L have been confirmed in 3, awaiting result in a 4th. The 5th patient did not re-attend for repeat testing. 14 (56%) of patients had random cortisol levels of 151-300nmol/L, none of whom had a level below the normal range on repeat testing. Further investigations of those with repeatedly low random cortisol levels are ongoing and will be reported subsequently. 1 other patient was found to have repeatedly low levels of cortisol (<100nmol/L) secondary to long term prednisolone for severe eczema. There was only a very weak correlation between cortisol levels and number of cycles of Lenalidomide and Dexamethasone (r=0.033) or total number of cycles of steroid containing regimens (r=0.174) Conclusion In this random sample of patients exposed to steroid containing regimens, 12% had repeatedly low random cortisol levels, suggestive of steroid suppression of the adrenal axis. Further work is ongoing to determine the nature of this. A random cortisol level of <150nmol/L identified those patients with repeatedly low levels. All patients on long term steroid-containing regimens should be evaluated- there is no correlation between the number of cycles of steroid-containing therapy and the likelihood of a low serum cortisol. Table 1 Patient Characteristics Age 55-85 Median 68.5 Male:Female 15:9 Lines of treatment 1-6 Median 3 Prior Bortezomib and Steroid 23 (92%) 0-11 cycles, median 4.5 Prior Lenalidomide and Steroid 23 (92%) 0-65 cycles, median 21 Prior Autograft 15 (60%) Total Number of Steroid Containing Cycles 4-72 cycles, median 34

Keywords:
cortisol

Steroids

treatment toxicity

Tracks:

Treatment of Previously Treated Myeloma

SP-092

KD-PACE salvage therapy for aggressive relapsed multiple myeloma

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Abstract:
Introduction: The non-cross-resistant combination VDT-PACE (bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide and etoposide) incorporating novel and traditional anti-MM drugs has been evaluated for relapsed and/or refractory myeloma (RRMM) or aggressive clinical situations such as plasma cell leukemia (PCL) or extramedullary myeloma (EMM). However, in the modern era, many patients are already refractory to bortezomib when this therapy is utilized. Outcomes from incorporation of carfilzomib (KD-PACE) instead of bortezomib as salvage therapy for relapsed aggressive MM are described. Methods: Consecutive patients between 9/2015-9/2018 receiving KD-PACE for RRMM were retrospectively identified at two institutions. Carfilzomib was dosed at 20 mg/m2 days 1 and 2 then 27 mg/m2 thereafter. All patients had to have cardiac ejection fraction >35%, KPS ≥ 80 and an expected OS of least 3 mo. Responses to therapy were defined per IMWG criteria. Progression free survival (PFS) and overall survival (OS) were assessed by Kaplan Meier. Toxicities were evaluated according to CTCAE v5.0. Results: Fifty-two consecutive patients receiving KD-PACE were identified. Median age was 57 years (range 32-65 years) and 67% were male. At time of KD-PACE, patients had MM alone (71%), PCL (19%) or EMM (10%). The majority had high-risk cytogenetics (54%; defined as FISH positive for t(14;16), t(14;20), t(4;14), deletion 17p or +1q) and had received a median of 3 prior lines of therapy

(range 1-7). Most (85%) patients received 1-2 cycles of KD-PACE in salvage for immediate disease control followed by other options. Addition of IMiDs to KD-PACE included pomalidomide (31%), thalidomide (25%) and lenalidomide (7.7%). Grade 3/4 toxicities included neutropenia (93%), thrombocytopenia (87%), anemia (37%). Febrile neutropenia occurred in 35%. Cardiovascular toxicities included heart failure (6%), venous thromboembolism (2%), bradycardia (2%) and atrial fibrillation, supraventricular tachycardia and pericarditis (all 1% each). Overall response rate (≥ PR) was 77% including CR (12%), VGPR (23%) and PR (42%). Median PFS was 4.6 mo (95% CI 3.2-7.5 mo) and median OS 11.2 mo (95% CI 6.1-14.5 mo). Therapy was stopped due to transition to transplantation (autologous hematopoietic cell transplant 29%; allogeneic hematopoietic cell transplant 27%), progression (15%), poor performance status (11%), clinical trial (12%) or for maintenance therapy (6%). Conclusions: Hematologic toxicities were as anticipated for this regimen and no treatment related deaths occurred. The treatment was clinically successful in 68% as a transition to transplantation or a clinic trial. KD-PACE can be considered a viable bridging treatment option for disease control in multiply relapsed patients with rapidly progressive MM.

Keywords:
carfilzomib

relapsed/refractory multiple myeloma

transplantation

Tracks:
Treatment of Previously Treated Myeloma

SP-093

MIROIR: 4-Year Interim Analysis of a Multicenter, Non-Interventional Study in France of Pomalidomide in Relapsed or Refractory Multiple Myeloma

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Abstract:
BACKGROUND Pomalidomide (POM) + low-dose dexamethasone (LoDEX) significantly prolonged progression-free survival (PFS) vs high-dose DEX (median, 4.0 vs 1.9 mos; P < .0001) in a phase 3 study of patients (pts) with relapsed or refractory multiple myeloma (RRMM; San Miguel J, et al. Lancet Oncol. 2013). However, real-world data on the use of POM are limited. The MIROIR study was designed to evaluate POM treatment (Tx) in routine clinical practice in France. Here, we present results from a pre-specified 4-yr interim analysis of MIROIR. METHODS MIROIR is a multicenter, observational, non-interventional study. Adult pts with MM who initiated POM Tx in France between October 1, 2014, and September 30, 2018, were included. All pts were required to have been enrolled

in the POM registry. Data were collected from medical records of consenting pts. Pts were followed for up to 24 mos after POM Tx initiation. The primary endpoint is PFS at 6 mos. Key secondary endpoints include time to next Tx (TTNT), overall survival (OS), and safety. This study is ongoing (NCT02902900). RESULTS As of February 1, 2019, 2099 pts (median follow-up, 23.3 mos) have been enrolled in the study. Median age was 70.0 yrs, and 655 pts (31.2%) were ≥ 75 yrs; 1134 pts (54.0%) were male. Median time from first-line Tx to POM initiation was 51.4 mos. Median prior lines of therapy was 3; 1 pt received POM in the first line. Nearly all pts received prior lenalidomide (LEN; 97.0%) and bortezomib (96.7%). In the overall population, the 6-mo PFS rate was 51.7% and median PFS was 6.2 mos. In pts with ≤ 2 (n = 914), 3 (n = 644), and ≥ 4 prior Tx lines (n = 541), median PFS was 7.8, 6.0, and 5.3 mos, respectively. Median PFS was 6.5 mos in pts whose last Tx was LEN (n = 1177) and 6.1 mos in pts whose last Tx was another agent (n = 922). In pts who were < 75 yrs (n = 1444) and ≥ 75 yrs (n = 655), median PFS was 6.4 and 6.1 mos, respectively. Median TTNT was 10.4 mos. The 1-yr OS rate was 70.6%, and median OS was 24.6 mos. Among 1164 pts (55.5%) with ≥ 1 adverse event (AE), the most common AEs were neutropenia (24.9%), thrombocytopenia (8.5%), and asthenia (7.5%). POM dose was reduced due to an AE in 20.7% of pts; POM Tx was interrupted or discontinued due to an AE in 36.2% and 15.2% of pts, respectively. CONCLUSION These real-world findings align with what has previously been reported with POM in RRMM clinical trials. Median PFS in pts with ≤ 2 prior Tx lines was numerically longer than in pts who had more Tx lines, supporting earlier Tx with POM. The similar median PFS in pts whose last prior Tx was LEN and those who received other agents demonstrates that the efficacy of POM is not diminished by immediately prior LEN exposure, indicating that there is no need to switch agent class after LEN. No new safety signals were observed.

Keywords:
Pomalidomide

real-world evidence

Relapsed Refractory MM

Tracks:
Treatment of Previously Treated Myeloma

SP-094

Effect of isatuximab plus pomalidomide/dexamethasone on renal impairment in relapsed/refractory multiple myeloma: ICARIA-MM study subgroup analysis

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Abstract:
Background: Renal impairment (RI) is a common feature in multiple myeloma (MM) and an adverse predictor of survival. Anti-myeloma treatments that

can also improve renal function in patients (pts) with MM are required. ICARIA-MM was a randomized, open-label, active-controlled, multicenter phase 3 study that investigated the anti-CD38 monoclonal antibody isatuximab (Isa) in combination with pomalidomide and dexamethasone (Pd) in pts with relapsed/refractory MM (RRMM) and ≥2 prior lines of therapy (NCT02990338). Median progression free survival (PFS) was significantly improved with Isa-Pd versus Pd (11.5 vs 6.5 months; hazard ratio [HR] 0.60 [95% confidence interval (CI) 0.44–0.81]). This subgroup analysis of ICARIA-MM examined efficacy and renal response in pts with RI. Methods: Pts had a baseline estimated glomerular filtration rate (eGFR) of ≥30 mL/min/1.73m², (Modification of Diet in Renal Disease). Isa (10 mg/kg IV) was given on days 1, 8, 15, and 22 (cycle 1), and days 1 and 15 in subsequent 28-day cycles. All pts received standard doses of Pd in each cycle. The primary endpoint was PFS, assessed by an independent response committee. RI was defined as eGFR <60 mL/min/1.73 m² (eGFR <60) at baseline. Complete renal response was defined as improvement in eGFR from <50 mL/min/1.73m² at baseline to ≥60 mL/min/1.73m² (eGFR ≥60; no RI) in at least 1 post-baseline assessment (International Myeloma Working Group recommendations), and was classified as durable if lasting ≥60 days. Results: 307 pts were randomized to Isa-Pd (n=154) and Pd (n=153) of whom 55 (35.7%) and 49 (32.0%) pts had RI, respectively. Median PFS for pts with eGFR <60 was 9.5 months with Isa-Pd and 3.7 months with Pd (HR 0.50; 95% CI, 0.30–0.85). In pts with eGFR ≥60, median PFS was 12.7 months with Isa-Pd (n=87) and 7.9 months with Pd (n=96; HR 0.58; 95% CI, 0.38–0.88). In pts with eGFR <60, median OS was not reached in the Isa-Pd arm compared with 11.6 months in the Pd arm (HR 0.53; 95% CI, 0.30–0.96).The overall response rate (ORR) for pts with eGFR <60 and eGFR ≥60 was higher with Isa-Pd (56% and 68%) than Pd (25% and 43%); 32.7% and 4.1% of pts with eGFR <60 had a very good partial response or better with Isa-Pd and Pd. Complete renal response occurred in 71.9% pts in the Isa-Pd arm (23/32) and 38.1% (8/21) pts in the Pd arm and these were durable in 31.3% and 19.0% pts, respectively. In pts with eGFR <60, grade ≥3 and serious TEAEs were higher with Isa-Pd (90.7% and 77.8%) than Pd (78.7% and 59.6%); incidence of Grade 5 TEAEs (Isa-Pd, 9.3%; Pd, 12.8%) and TEAEs leading to treatment discontinuation (Isa-Pd, 11.1%; Pd, 14.9%) were similar. The number of pts developing end stage renal disease (eGFR <15 mL/min/1.73m²) on treatment was lower with Isa-Pd than Pd (2.9% vs 7.9%). Conclusion: The addition of Isa to Pd increased the number of pts with reversal of RI, sustained renal responses and improved PFS and ORR consistent with the benefit observed in the overall study population.

Keywords:
CD38

Multiple myeloma

Renal impairment

Tracks:
Treatment of Previously Treated Myeloma

SP-095

Consolidation following DPACE therapy improves outcomes in relapsed/refractory myeloma patients in the era of novel agents

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Abstract:
Background and aims: Historical indications for DPACE-based therapies include salvage treatment of aggressive myeloma (MM) resistant to conventional therapies, plasma cell leukaemia (PCL), and initial presentation with extra-medullary disease. We performed a retrospective study of

DPACE-treated MM patients from different UK Centres in order to describe its use and establish the best place for its indication. Method: 59 patients between 2009 and 2017 were eligible for inclusion. Data was collected from chemotherapy databases and patient records. The primary outcome is a descriptive analysis of the cohort. Secondary outcomes include response rates, time to next treatment (TTNT) for: total cohort, BMT post-DPACE vs. No BMT, and according to number of prior therapies (≤2 vs. >2); overall survival (OS) and treatment-related mortality (TRM) for the cohort . Results: Male/female ratio was 1.5:1. Age (years) distribution was (<50: 28.8%, 51-64: 59.3%, ≥ 65: 11.9%). Myeloma subtypes were: Ig: 76.3%, LC: 15.2%, non-secretory: 5.1%, PCL: 3.4%). ISS was: I: 25.4%, II: 27.1%, III: 30.5%, unknown: 17%). 45.8% of patients had relapsed disease post BMT, 47.5% received DPACE prior to BMT. Eleven patients (18.6%) received 2 BMT (pre and post DPACE). The nature of prior therapies was: IMiD: 6.8%, PI: 10.2%, IMiD and PI: 72.9%, chemotherapy only: 1.7%, none: 8.5%). Median number of cycles (range) was 2 (1-4). Median follow up was 46.7 months. Response rates were: CR: 23.7%, VGPR: 11.9%, PR: 30.5%, MR/SD: 10.1%, PD: 8.5%, unknown: 15.3%. Out of 53 (for TTNT) and 57 (for OS) evaluable patients, median TTNT and median OS for the total cohort were 14.2 and 15.1 months, respectively. Median TTNT (BMT post-DPACE vs. no BMT) was 12.8 months vs. 2.7 months, p=0.118). Median TTNT according to number of prior therapies was (>2: 5.1 months vs. ≤2: 24.6 months, p=0.34). The majority of patients who received >2 lines of therapy received a prior BMT (15/17: 88.2%) and only a small group (i.e. 3/17: 17.63%) consolidated DPACE with a BMT (the second transplant in all 3 patients). In those who received <2 prior therapies, 26/36 (72.2%) received BMT post-DPACE. The comparatively longer median TTNT can be attributed to both the lower number of prior therapies as well as the higher rate of BMT post-DPACE. TRM rate was 10.5% (6/57) Conclusion: This cohort study demonstrated that DPACE can be beneficial if consolidated with a BMT, particularly in those with a small number of prior therapies, and is of limited benefit in transplant non-eligible patients or those heavily pre-treated. In the latter group, it would be logical to schedule subsequent therapy shortly after DPACE completion to improve outcomes

Keywords:
bone marrow transplantation

consolidation

myeloma

Tracks:
Treatment of Previously Treated Myeloma

SP-096

Angiotensin II receptor blockers might reduce a cardiotoxicity induced by carfilzomib: retrospective analysis of 17 cases

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Abstract:
Carfilzomib, the first irreversible proteasome inhibitor, is used for treating multiple myeloma (MM). An increased incidence of cardiac toxicity due to carfilzomib has been reported. One proposed mechanism of cardiac adverse events is vascular endothelial effects leading to vascular dysfunction. Angiotensin II receptor blockers (ARB) are a key drug of treatment for heart failure and have efficacy for improving endothelial function. The purpose of this study is to demonstrate that adding ARB to carfilzomib contributes to reducing heart strain. METHODS: We conducted a single center retrospective analysis at The Cancer Institute Hospital of the Japanese Foundation for Cancer Research from 1 May 2017 to 1 May 2019. Patients with MM who were treated with carfilzomib-containing regimens were selected regardless of prior treatments and divided into two groups based

on a use of ARB during treatment: carfilzomib-containing regimen alone (carfilzomib alone group) and carfilzomib-containing regimen plus ARB (ARB group). Carfilzomib-containing regimens are defined as Kd (carfilzomib dexamethasone), KRd (carfilzomib lenalidomide dexamethasone), and KPd (carfilzomib pomalidomide dexamethasone). We defined brain natriuretic peptide (BNP) as a surrogate marker of cardiac toxicity. The primary objective was to assess the BNP reduction rate before and after treatment. BNP levels were analyzed with Welch's t-test. RESULTS: 17 patients were enrolled in this analysis. The median duration of carfilzomib-containing regimen was 162 days and the median age at beginning of carfilzomib was 63 (range 33–78). Most patients had performance status < 2 (88.2%) and were the International Staging System 1 (47.1%) and 2 (47.1%). While 13 were treated with carfilzomib alone, 4 were treated with carfilzomib-containing regimen plus ARB. In the ARB group, all patients had already on ARB before the starting carfilzomib because of hypertension. Performance status, renal function, chromosome abnormalities (del17p, t(4;14), t(11;14), t(14;16)), amyloidosis, comorbid hyperuricemia and diabetes mellitus, history of smoking, and the number of prior treatments were well balanced between the two groups, however hypertension was not: 3/13 (23.1%) of the carfilzomib alone group versus 4/4 (100%) of the ARB group (P=0.015 by Fisher's exact test). The median number of prior treatments was 3 (range 1-12) in the carfilzomib alone group and 2.5 (range 1-4) in the ARB group. Significant difference was found in BNP reduction rate between the two groups (mean reduction rate 75.0% vs. -62.4%: P= 0.0128 by Welch's t test). CONCLUSION: The present result suggest that combined use of carfilzomib and ARB preserve heart function in patients with multiple myeloma, although sample size is relatively small. Further prospective studies are required to assess the efficacy of combined use.

Keywords:
Angiotensin II receptor blocker

Cardiovascular adverse event

carfilzomib

Tracks:
Treatment of Previously Treated Myeloma

SP-097

European Post-Authorization Safety Study of Patients With Relapsed or Refractory Multiple Myeloma Treated With Pomalidomide in a Real-World Setting

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Abstract:
BACKGROUND In the European Union (EU), pomalidomide (POM) is approved in combination with dexamethasone (August 2013) for the treatment (Tx) of relapsed or refractory multiple myeloma (RRMM) patients (pts) who have received at least 2 prior Tx regimens, including lenalidomide and bortezomib. RRMM pts are at an increased risk for adverse events (AEs) due to prior exposure to multiple lines of Tx and high disease burden. The POM EU post-authorization safety study (PASS; NCT02164955) is an observational, non-interventional registry designed to characterize the safety profile of POM-based Tx in RRMM pts in a real-world setting. METHODS RRMM pts initiating

POM-based Tx were enrolled at physician's discretion. AEs of special interest, including neutropenia, thrombocytopenia, peripheral neuropathy (PN), venous thromboembolism (VTE), and second primary malignancies (SPMs), were recorded. The study is closed for recruitment. RESULTS As of April 16, 2019, the safety population comprised 728 pts across 112 institutions in 8 European countries. Median age was 71 yrs, with 223 pts (30.6%) aged ≥ 75 yrs; 53.8% of pts were male. Median time from MM diagnosis was 4.8 yrs. Median number of prior regimens was 3, and 72.3% of pts had received at least 3 prior regimens. ECOG PS was assessed in 442 pts; 359 of these pts (81.2%) had ECOG PS ≤ 1. Median Tx duration was 20.0 wks. Tx was still ongoing in 131 pts (18.0%). The most common causes of Tx discontinuation were progressive disease (43.1%), AEs (17.2%), and death (10.2%). Concomitant cyclophosphamide was administered to 118 pts (16.2%). As this study was primarily designed to evaluate safety, response data are limited. Of 561 pts with recorded response, best response was complete response in 2 pts, partial response in 86 pts, and stable disease in 222 pts. The most common grade 3/4 hematologic AEs were neutropenia (24.3%), anemia (10.6%), and thrombocytopenia (8.9%). Overall, 51.5% of pts had infections, including pneumonia (14.1%) and other respiratory tract infections (16.2%). PN, VTE, and pulmonary embolism were reported in 6.2%, 1.9%, and 0.8% of pts, respectively. In pts aged ≤ 75 yrs vs those aged > 75 yrs, there were similar rates of hematologic AEs, including neutropenia (37.8% vs 34.5%) and thrombocytopenia (16.8% vs 17.0%), as well as pneumonia (14.9% vs 12.6%). The following SPMs were observed: 13 non-melanoma skin cancers (10 basal cell carcinomas, 2 squamous cell carcinomas, 1 Bowen's disease), 11 solid tumors (4 colorectal cancers, 3 carcinomas of unknown primary, 2 transitional cell carcinomas, 1 breast cancer, 1 soft tissue carcinoma), and 2 hematologic SPMs (1 each of acute myeloid leukemia and myelodysplastic syndrome). CONCLUSIONS Data from this ongoing, prospective, non-interventional PASS in RRMM pts continue to demonstrate that the safety profile of POM-based Tx in a real-world setting is consistent with what has been reported in clinical trials.

Keywords:
Pomalidomide

real-world evidence

relapsed/refractory multiple myeloma

Tracks:
Treatment of Previously Treated Myeloma

SP-098

Carfilzomib, bendamustine, dexamethasone in patients with advanced multiple myeloma: The EMN09 Phase I/II study of the European Myeloma Network

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Abstract:
Introduction: Despite recently introduced immunotherapeutic strategies the selection of an efficient, well-tolerated and affordable treatment option for advanced patients with relapsed/refractory multiple myeloma (RRMM) remains challenging. Since bendamustine (B) and the proteasome inhibitor carfilzomib (K) seem safe even in compromised patients and act synergistically a combination termed KBd including dexamethasone (d) was evaluated. This multicenter phase 1/2 trial was conducted within the European Myeloma Network as EMN09 study. Patients and Methods: Sixty-three patients with RRMM with ≥2 lines of prior therapy were included. The phase 1 was designed to determine the maximum tolerated dose (MTD) of K with B set at 70 mg/m2. After 8 cycles responding patients continued maintenance with Kd until progression. Results: Based on the safety profile of the phase 1 the phase 2 dose of K remained at 27 mg/m2. In the heavily pretreated patient population with a range 2 to 9 prior lines of therapy 52% of patients achieved at least PR and 30% had a VGPR or CR. With 38% patients maintaining SD a clinical benefit rate of 90% was obtained. The median PFS was 11.6 months and the median OS 24.0 months. One-year PFS was higher for patients with standard-risk compared to those with high-risk genetics. Hematological grade ≥3 adverse events (AE) were lymphopenia (29%), neutropenia (25%) and thrombocytopenia (22%). Frequent non-hematological G ≥3 AEs were pneumonia and thromboembolic events (10%). Severe cardiac AEs were reported in 6% and hypertension in 2% of patients. Conclusion: KBd is with a PFS of 11.6 months an effective treatment option and in RRMM patients well-tolerated even when given rather late in the course of their disease. This cost- effective KBd combination can be applied safely in an outpatient setting. However, infection prophylaxis and attention to patients with cardiovascular predisposition are required.

Keywords:
carfilzomib

Chemotherapy

Tracks:
Treatment of Previously Treated Myeloma

SP-099

DEMOGRAPHIC CHARACTERISTICS AND TREATMENT PATTERNS OF RELAPSE / REFRACTORY MULTIPLE MYELOMA PTS: CHARISMMA STUDY AND INSIGHT MM REGISTRY IN SPAIN

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Abstract:
Introduction In Spain, the evidence related to the treatment of MM population according to patient's characteristics is scarce. There are no demographic studies that elucidate the impact of patient and disease characteristics on treatment selection strategies. Based on that, interim results of two studies in Spanish population have been analysed independently Methods CharisMMa (NCT03188536) is an observational, cross-sectional study in RRMM pts,involving 30 public hospitals around Spain. An interim analysis was conducted in the 169 pts enrolled up to June 2018. Information was collected 2.15 (SD: 1.76) months after the last relapse. INSIGHT MM (NCT02761187)is the

largest global, prospective, observational MM study to date which is currently enrolling~4200 adult pts with newly diagnosed (NDMM) or RRMM multiple myeloma from Europe, the United States,Asia,and Latin America.An interim analysis was conducted in November 2018 including 119 RRMM pts treated in Spain with a median follow up of 9.56 (P25: 5.82, P75: 15.21)months Results In the charisMMa study, the median age at relapse was 69 (57,75),being 55.2% men.The majority of them live in urban areas (71.8%)and with their families (88%). Pts have been treated with a median of 2 (1,3)previous lines.More than half of them (56.7%) had received stem cell transplant (SCT)(97.8% autologous). ISS was I (36.3%), II (35.6%) and III (28.1%), and 74% of pts were treated when presented CRAB symptoms. The most common were bone lesions (65.6%).39.3% were considered intermediate or high-risk cytogenetics pts.67.5% of the pts suffered from comorbidities including cardiovascular (48.1%),diabetes (23.1%) and neuropathy (22.1%). Pts were mainly treated with doublets both in second (59.7%) and 3+lines(Table 1).Pts are living 23.9 (40.4)km far from their hospital In INSIGHT MM, the median age at relapse was 71 (63,76), 55.5% are male and 85% are living with at least one adult. At enrolment, pts had received a median of 1 prior line of therapy (59%) and 29% had received 2 prior lines. SCT was utilized in 37% of pts as part of their 1st line of therapy and in 31% pts as part of 2nd line. ISS stage was I (16.8%),II (21.8%)and III (37.6%).The most common symptom presented was bone involvement with 53% of pts having at least 1 bone lesion.High-risk cytogenetics was documented in 11% of pts. Most frequently reported comorbidity was diabetes without end-organ damage (15%) followed by moderate/severe renal disease (9%)and cardiovascular disease (15%). Pts are treated mainly with triplets in second (57.8%)and third line (65.6%) and doublets in fourth line.Pts are living 29.3 (42) km far from their hospital Conclusions Based on the preliminary results and due to the wide inclusion criteria from the two studies in the Spanish population, there is a common heterogeneity in the MM patient´s characteristics. Further results from final analysis of both studies will be proprovided to analyse treatment patterns at relapse

Keywords:
Clinical Characteristics

Multiple myeloma

real-world evidence

Tracks:
Treatment of Previously Treated Myeloma

SP-100

Weekly 20/56mg/m² Carfilzomib, Lenalidomide and Dexamethasone until progression in Early Relapsed Refractory Multiple Myeloma

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Abstract:
Background: Triplet-based Carfilzomib (K), Lenalidomide and Dexamethasone combination (KRd) has led to approval in early RRMM based on ASPIRE International phase 3 study. However, K was used on a twice a week basis at 27mg/m2 and limited to 18 months exposure. We have reported already that KRd on a weekly basis at 56 mg/m2 was active similar to ASPIRE KRd and safe. We report herein the long-term exposure data on KRd weekly given until progression. We aimed to evaluate the efficacy of KRd given on a prolong duration beyond 18months, and to validate the safety profile of continuous exposure to K. Methods: 28 patients were prospectively recruited. Carfilzomib 20/56mg/m2 was administered on days 1,8,15,

Lenalidomide 25mg/day was given 21/28 days and Dexamethasone was administered weekly on 28 days cycles until progression. Results: With a median follow-up at start of KRd of 30 months, 50% of patients relapsed and 39% died. 24/28 patients received 1 prior line of treatment. 8/28 patients are still on treatment with duration > 24 month and 6/28 with duration > 30 months. The median number of cycles was 15. ORR and CBR was 85.7% and 89.3%, whom 46% ≥ CR ; with a median DOR of 13 months and 43% having more than 18 months. 6 patients had negative MRD at 10-6 and normalized PET CT. Median of OS is not reached, and the 30 month-expected OS from the start of KRd was 56%. The median PFS and EFS was at 29 months, and the 30 month-expected PFS and EFS was 45%. PFS and EFS being superimposable speaks to that there was no safety concern related to prolonged exposure to K. Only 4 patients stopped KRd for safety issues. Hematologic and non-hematologic adverse events ≥ grade 3 were reported in 16/28 and 10/28 patients. Adverse events ≥ grade 3 seen in ≥10% of patients were neutropenia, thrombocytopenia, vomiting and pyrexia. Of note, 5 patients (18%) were ≥ 65 years old and showed similar data compared to the cohort. Conclusions: KRd weekly is effective and safe to early in RRMM patients, provides improved safety profile to patients allowing treating patients until progression. Further studies are warranted to confirm this data on a larger early RRMM population and validate the concept of long duration of treatment using Carfilzomib combination.

Keywords:
carfilzomib-lenalidomide-dexamethasone

Multiple myeloma

Relapsed Refractory MM

Tracks:
Treatment of Previously Treated Myeloma

SP-101

Pomalidomide 3rd line versus 4th line for in Early Relapsed Refractory Multiple Myeloma

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Abstract:
Background. Pomalidomide in association with dexamethasone is approved for RRMM in 3rd line and beyond based on the multicenter international phase 3MM-003 study that demonstrated greater efficacy for Pomalidomide plus dexamethasone over high dose dexamethasone. However, MM-003 mainly recruited RRMM with 5 prior lines +, and very few data are available regarding real life Pomalidomide-based treatment in 3rd and 4th line RRMM. The aim of this study was to study efficacy and safety of Pomalidomide-based treatment in 3rd and 4th line RRMM. Methods. This study is a retrospective, multicenter study based on 108 consecutive RRMM treated with Pomalidomide-based treatment in 3rd and 4th line. All assessment made according to IMWG. Results. Median age was 62.5 (range, 30-86), with 36% older than 65 years, sex ratio M/F 1.25 and ISS disease stage 2 or 3 in 58%. 100% patients received previous treatment with Bortezomib and Lenalidomide and 34,2% had previously an autologous stem cell transplantation. 52 patients (48%) had pomalidomide-based therapy as 3rd, and 56 (52%) as 4th line. 74% of patients received a double-based therapy (Pomalidomide plus Dexamethasone) and 26% received a triple based therapy (Pomalidomide, Cyclophosphamide and Dexamethasone). Overall ORR was 55%, with 25% more than VGPR including 3 complete response with Pomalidomide-based as 3rd line. ORR was 53% with 16% ≥ VGPR including 1 CR for Pomalidomide-based as 4th line. With a median follow-up of 24 months, 58% and 48% at relapsed

and died, respectively, in 3rd line, and similarly, 74% and 50% in 4th line. The median TTP was 7 (CI95% 1.4;12.6) and 9 (6.1;11.9) months in 3rd and 4th line, and the median OS 17 (7.8;26.1) and 23 (12.6;33.4) months, respectively. 22% and 30% have discontinued and reduced pomalidomide-based treatment respectively. No patient died related to adverse events. AEs leading to pomalidomide-based modification in schema included hematological AEs in 40% and non-hematological AEs in 12% of patients. Overall, the most common adverse events grade 3 or 4 were neutropenia (22%), anemia (11%), thrombocytopenia (7%) and infectious disease (5%). Conclusion. Pomalidomide-based therapy demonstrates efficacy in the real life with a manageable safety profile. Further study ill look into triplet versus doublet pomalidomide-based regimen, with a benefit expected for the former. Further prospective studies are warranted to confirm this data on a larger MM population.

Keywords:
Multiple myeloma

Pomalidomide

Relapsed Refractory MM

Tracks:
Treatment of Previously Treated Myeloma

SP-102

Initial Results of MCRN 009: Phase 2 Study of an Accelerated Infusion Rate of Daratumumab in Patients with Relapsed/Refractory Multiple Myeloma (MM).

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Abstract:
Background: Daratumumab is a first-in-class CD 38-directed monoclonal antibody approved by Health Canada for relapsed/refractory (R/R) and front-line MM. Data pooled from 3 R/R studies indicated that infusion-related reactions (IRRs) occurred in 48% of patients. Daratumumab is currently administered per product monograph via an infusion rate escalation protocol with the 1st infusion lasting ≥6.5 hr, the 2nd infusion for 4.5 hr and all subsequent infusions over 3.5 hr, which makes administration difficult in an ambulatory setting. In the pooled analysis, 95.8% of IRRs were seen with the 1st infusion. One published study reported that IRRs were not increased by accelerating the daratumumab infusion time to 90 min beginning in week 3. We hypothesized that earlier accelerated infusions after an initial half-dose of daratumumab on cycle 1, day 1 (C1D1) with standardized pre- and post-medications would not increase the incidence of IRRs. Methods: This is a multi-center phase 2 open label study of a daratumumab accelerated infusion regimen with a fixed pre- and post-medication regimen (Table 1) in patients with R/R MM. The 1st dose of daratumumab (8mg/kg) is given over 4 hr on C1D1. All subsequent doses (16mg/kg) are administered over 90 min with 20% of the dose given over the 1st 30 minutes and the remaining 80% of dose given over 60 minutes (Infusion Rates for Daratumumab Administration will be presented). The primary endpoint is the number of Grade ≥ 3 IRRs per accelerated infusion. The IRR 95% CI will be calculated assuming all infusions are all independent (even within the same subject). Results: Safety data on the first 14 patients are presented. Median age was 72. Two patients have discontinued the study (disease progression in cycle 2). Fifty-nine accelerated infusions have been given. IRR's

occurred in 42.9% (6) of the patients, all occurring on C1D1 (1 grade 1 and 5 grade 2) with no grade 3 or 4 IRRs. All infusions received pre- and post-medications as per protocol. Conclusion: Based on data for the first 14 patients on this study, an accelerated daratumumab infusion over 90 min starting on cycle 1 day 8 is well tolerated without an increase in anticipated number or grade of IRRs. This study is ongoing but early results suggest this new accelerated infusion protocol could become an alternative administration schedule for daratumumab, as it is more convenient and decreases resource utilization. Table 1: Pre- and Post-Medication Regimen • Montelukast 10 mg po day -2, -1 and day 0, pre-daratumumab administration • Cetirizine 10 mg po day -2, -1 and day 0, pre-daratumumab administration • Dexamethasone 20 mg on day of and day after daratumumab administration • Acetaminophen 975-1000 mg po 1 hr pre-daratumumab administration • Diphenhydramine 50mg IV 1 hr pre-daratumumab infusion

Keywords:
daratumumab

Myeloma Canada Research Network

relapsed/refractory multiple myeloma

Tracks:
Treatment of Previously Treated Myeloma

SP-103

Marital Status and Survival in Patients with Multiple Myeloma: The Role of Marriage in the Management of Multiple Myeloma

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Abstract:
Background Multiple myeloma (MM) is plasma cell neoplasm characterized by notable inter-patient and intra-clonal heterogeneity that is gradually decoded over the last decades. Despite the deeper and better understanding of its biology and the development of novel therapeutic strategies that have prolonged overall survival, MM still remain largely incurable. This warrants a better understanding of socio-demographic factors that may influence disease course and outcomes across MM patient. Positive influence of marital status is extensively examined and established for many solid and liquid cancers. However, limited literature is available showing its influence on MM patients. Methods Surveillance, Epidemiology and End Results programme (SEER) data was used to identify total 29,507 MM patients diagnosed in 2011 through 2015. We used mixed effects Cox proportional hazards multiple regression to analyze16,519 patients who had symptomatic MM and their clinical and follow-up information available. The outcome variable was the survival time from diagnosis to death due to myeloma. Results On mixed effects Cox regression for myeloma-specific mortality, there was a significant interaction between marital status and sex at the nominal significance level (α) of 0.01. Holding demographic covariates eg. age, income, education, race, and residence at a fixed value, the hazard ratio (HR) of myeloma-specific mortality for married male patients over the HR for married female patients was about 15% lower. In addition, younger age, high income, or African-American patients when compared with white patients were less likely to die of myeloma.Further analysis indicated that patients who were never married, widowed or divorced, when compared with those married, were at significantly greater risk of myeloma-specific mortality after being adjusted for the demographic covariates ($p < 0.01$). Conclusion Findings from our analysis support the positive effect of marriage on the outcome of MM patients.It is conceivable that patients who are unmarried (divorced, widowed, and

never married) have a more fragile support network to cope with the challenges of MM treatment. The effect of strengthening psychosocial support should be investigated as a potential supplementary treatment for MM patients.

Keywords:
marital status

Multiple myeloma

survival

Tracks:
Treatment of Previously Treated Myeloma

SP-104

Retrospective analysis on 20 relapsed or refractory cases of multiple myeloma treated by panobinostat with subcutaneous bortezomib

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Abstract:
(Introduction) Panobinostat is an oral pan-deacetylase inhibitor that synergizes with bortezomib to inhibit both the aggresome and proteasome pathways in multiple myeloma (MM). The combination of panobinostat, bortezomib, and dexamethasone (PVD) was able to recapture responses in some heavily treated patients with MM (reported as PANORAMA 2 trial), however, some adverse events (AEs) such as diarrhea, fatigue, thrombocytopenia were frequently observed. These AEs may be related to the route and schedule of the administration of bortezomib (in PANORAMA 2 trial, bortezomib was administered intravenously and twice weekly). We present here 20 cases of relapsed or refractory MM (RRMM) treated by PVD using subcutaneously, once weekly bortezomib. (Objectives) We retrospectively analyzed 20 cases of RRMM treated by PVD in our hospital since August 2015, when panobinostat was approved by the government in Japan. (Methods) Panobinostat 20 mg on day 1, 3, 5, 8, 10, 12 daily was orally administered, bortezomib was administered subcutaneously once per week (day 1 and 8), and dexamethasone was administered at a dose of 20 mg orally on day 1, 2, 8, 9, until disease progression was observed. For the prophylaxis of herpes zoster, acyclovir 200 mg daily was added. (Results) Characteristics of the patients were as follows; male/female =9/11 cases, age (mean) 67.5 years (53-84). Bortezomib refractory cases were 19 (95.0%). Best responses observed in each cases were as follows; PR=5, SD=7, PD=8, clinical benefit rate (CBR:VGPR+PR＋SD)=12/20 (60.0%). Median progression-free survival (PFS) and overall survival (OS) were 128 days and 418 days respectively in all the cases, 128 days and 357 days in the cases received at least 2 lines of therapies (14 cases). AEs were as follows; severe (grade 3 to 4) thrombocytopenia (8 cases), fatigue (7 cases) and diarrhea (4 cases, all the cases were considered in grade 1). (Conclusion) Although the patient numbers were relatively small in the present study, CBR and PFS were considered comparable to PANORAMA 2 study (34.5% and 5.4 months, respectively). Relatively low incidence of diarrhea may be linked to once-weekly and subcutaneously administration of bortezomib. Recently, relatively low rates of AEs were also reported in PANEX trial (Hansen VL, et al. Clinical Lymphoma, Myeloma & Leukemia 2018). Further studies are warranted to optimize the treatment schedule of PVD to reduce the toxicities.

Keywords:
bortezomib

Panobinostat

Tracks:
Treatment of Previously Treated Myeloma

SP-105

The efficacy and safety profiles of carfilzomib based therapy in real world practice for patients with relapsed or refractory multiple myeloma

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Abstract:
Introduction The introduction of novel agents such as proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies has made significant progress in the treatment of multiple myeloma. In particular, the use of carfilzomib, an irreversible proteasome inhibitor, has played an important role in the treatment of patients with relapsed or refractory multiple myeloma. However, as use of carfilzomib increases, reports of adverse events such as cardiac toxicity are increasing. In this study, we compared the efficacy and safety of two most widely used carfilzomib based regimens: carfilzomib and dexamethasone (KD) and carfilzomib, lenalidomide, and dexamethasone (KRD) in real world practice. Methods We retrospectively analyzed 58 patients with relapsed or refractory multiple myeloma who were treated with carfilzomib based chemotherapy in Korea University hospital. KRD group received carfilzomib 20mg/m² on days 1 and 2 of cycle 1 and 27mg/m² thereafter on days 1, 2, 8, 9, 15, and 16, while KD group received carfilzomib 20 mg/m² on days 1 and 2 of cycle 1 and 56 mg/m² thereafter on same days. KRD group received lenalidomide on days 1 through 21, and both groups received dexamethasone 20 mg on days 1, 2, 8, 9, 15, 16, 22, and 23. Results A total of 41 and 17 patients were treated with KRD and KD regimen. The baseline characteristics were not significantly different between two groups. The overall response rate was 86.2% in all patients, 87.9% in the KRD group and 82.3% in the KD group, respectively. KRD group showed relatively higher CR, VGPR rate than KD group (29.3%, 29.3% vs. 17.6%, 29.4%). However, progression free survival and overall survival were not statistically significant between two groups (P=0.299 and 0.615). In other words, although patients in the KD group administered carfilzomib at a later phase of disease, the efficacy of KD regimen was not inferior to that of KRD regimen. Most patients (6 out of 8) who did not achieve partial response had multiple extramedullary plasmacytomas, thus carfilzomib also has limited effects on extramedullary lesions like other drugs. In our study, the incidence of adverse events was significantly higher than those reported in previous large scaled randomized trials such as ASPIRE and ENDEAVOR. The frequency of grade 3 or higher neutropenia was higher in the KRD group than in KD (53.7% vs. 17.6%, P=0.012), however, there was no difference in the incidence of infection (34.1% vs. 29.4%, P=0.727). Uncontrolled hypertension was more frequent in the KD group than KRD group (29.4% vs. 4.9%, P=0.009). Conclusions Carfilzomib-based therapy was effective in patients with relapsed or refractory multiple myeloma in real world practice. The efficacy of KRD and KD regimen was not significantly different. However, some cardiac toxicity such as uncontrolled hypertension was higher in the KD group. Therefore, careful monitoring of adverse events should be needed when choosing the KD regimen in elderly.

Keywords:
carfilzomib

real-world

Relapsed Refractory MM

Tracks:
Treatment of Previously Treated Myeloma

SP-106

A single-center retrospective cohort analysis of venetoclax in relapsed/refractory multiple myeloma.

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Abstract:
Background: Despite recent advances, treatment of relapsed multiple myeloma (MM) remains a challenge. Pre-clinical and clinical studies suggest that bcl-2 inhibition can induce MM cell death and may synergize with bortezomib. Methods: We performed a single-center, retrospective chart review of all patients with relapsed MM who were treated with venetoclax, a BCL-2 inhibitor. Results: 31 patients were identified. Median number of lines of prior therapy was 7 (range 2-13). 5/31 patients had documented high risk cytogenetics, defined as the presence of a 17p deletion, t(14;16), or t(14;20). Of the 24 patients with cytogenetics/FISH available, 8 had t(11;14). 22/31 patients were refractory to bortezomib. 29/31 patients had progressed after carfilzomib, 27/31 after pomalidomide, and 30/31 after anti-CD38 antibody therapy. In all but one case, patients were treated with venetoclax in combination with bortezomib. Patients were started at 400 mg daily for 7 days then increased to the median dose of 800mg daily (3/31 received < 800mg/daily as a final dose). Overall patients received median of 73 days of treatment (range 12-801) with 1 remaining on therapy. By IMWG criteria responses were: 1/31 complete response (CR), 5/31 very good partial response (VGPR) and 5/31 partial response (PR) for an overall response rate of 35% (11/31). 1/31 had a minor response (MR), 2/31 achieved stable disease (SD), and 17/31 (55%) had progressive disease (PD). Out of the 8 patients who had t(11;14), there were 2 VGPR, 2 PR, 2 SD, and 2 PD giving a response rate of 50% (4/8). Median time to best response was 58 days (range 15-305) and median duration of response was 220 days (range 15-801) with 1 patient remaining on drug. At time of data collection, 4/31 patients had not progressed and 6/31 remain alive with 4 patients lost to follow-up for over 6 months. The most common toxicities were gastrointestinal (bloating, nausea, vomiting, diarrhea) which were seen in 9/31 patients with one patient discontinuing due to side effects. There was no evidence of tumor lysis and there were no treatment-related deaths. Conclusions: Venetoclax is an active and well-tolerated agent in relapsed multiple myeloma. Further efforts to study this therapy include multivariate analysis to correlate cytogenetics/FISH with response and prospective phase II/III trials using venetoclax in combination with proteasome inhibitors and steroids.

Keywords:
real-world evidence

relapsed/refractory multiple myeloma

Venetoclax

Tracks:
Treatment of Previously Treated Myeloma

SP-107

Flow-Mediated Dilatation (FMD) and Aortic Blood Pressure May Predict Cardiovascular Adverse Events During Carfilzomib Therapy: A Prospective Study in Relapsed/Refractory Multiple Myeloma Patients

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Abstract:
Background: Carfilzomib (CFZ) is a proteasome inhibitor associated with cardiovascular (CV) adverse events (AEs) such as hypertension (HTN), cardiac dysfunction and thrombotic events such as venous thromboemolism and thrombotic microangiopathy (TMA). Endothelial dysfunction is a major mediating mechanism in these complications and may be affected by proteasome inhibition caused by CFZ. Methods: We prospectively evaluated markers of vascular function as potential predictors of CFZ-associated CV complications and assessed associations with CFZ-mediated inhibition of proteasome activity in 46 relapsed/refractory myeloma (MM) patients treated with Kd [CFZ 20/56 mg/m2 and dexamethasone](NCT03543579). At baseline and at pre-specified time-points during Kd therapy, cardiac echo and hemodynamic and vascular function parameters were non-invasively assessed [aortic blood pressure and arterial wave reflections using pulse wave analysis, aortic stiffness using pulse wave velocity and endothelial function using flow-mediated dilatation of the brachial artery (FMD)] while proteasome activity (PrA) was measured in PBMCs. The incidence of CV events [hypertension, acute coronary syndrome (ACS) and heart failure(HF)] was defined as the primary end-point and of both CV events and extra-coronary thrombotic events (pulmonary embolism (PE) and TMA) was defined as the secondary end-point. Results: Median follow up is 12 months. The prevalence of risk factors for CV toxicity was high (median 3 factors). CV AEs were recorded in 23 (50%) patients [HTN(Gr3/4): 29%, HF: 10%, ACS (Gr3): 4%, PA (Gr3): 2%, TMA: 10%]. Median time to first CV event was 1.9 months. Kd was discontinued in 3(6.25%) and dose was reduced in 2 patients (4.2%) due to cardiotoxicity; no CFZ dose reduction or discontinuation was needed for HTN. Low FMD [adjusted HR=3.68] and high aortic systolic BP [adjusted HR=4.57] (but not peripheral systolic BP), were the strongest independent predictors of the CV events, even after adjustment for baseline risk factors. Low FMD (adjusted HR=4.01) was also an independent predictor of the secondary end-point. Increased baseline aortic, but not peripheral, SBP was the strongest independent predictor of grade ≥3 HTN [adjusted HR=11.23] after adjustment for risk factors for CV toxicity. FMD decreased acutely within 2 hours from 1st CFZ dose (from 5.2% to 3.6%, p=0.008), and partially recovered before and after 2nd CFZ infusion; the decrease of FMD was more pronounced among patients who had lower recovery rate of PBMCs PrA at 24h post 1st CFZ (5.12% to 2.97%, p=0.002) but, was less pronounced in those who had higher PrA recovery rate (5.25% to 4.5%, p=0.197), indicating that PrA could be implicated in CFZ induced endothelial dysfunction. Conclusions: Impaired FMD and increased aortic SBP at baseline were strong predictors of CV AEs during CFZ therapy and could serve as clinical markers to identify patients at high risk for CFZ-associated CV toxicity.

Keywords:
Cardiotoxicity

carfilzomib

proteasome

Tracks:
Treatment of Previously Treated Myeloma

SP-108

A Phase 1/2 Trial of Low-Dose Continuous Azacitidine in Combination with Lenalidomide and Low-Dose Dexamethasone in Relapsed/Refractory Multiple Myeloma

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Abstract:
Background: Epigenetic changes contribute to evolution of therapy resistant myeloma clones. The DNA methyltransferase inhibitor azacitidine (AZA) may restore sensitivity to lenalidomide (len, R) and dexamethasone (dex, d) through re-activation of genes required for apoptosis and adaptive immune responses. We report the final results of a phase 1/2 study evaluating AZA in combination with Rd in relapsed/refractory MM (RRMM). Methods: Patients (pts) received len 25 mg (10 mg if GFR 30-59 ml/min) on days 1-21 and dex 40mg weekly every 28 days with escalating doses of AZA SC (5 cohorts: 30mg/m2 weekly and biweekly, 40 mg/m2 weekly and biweekly and 50mg/m2 biweekly). Dose limiting toxicities (DLT) were assessed during cycle 1. Response was assessed according to IMWG 2011 response criteria. The primary endpoint was safety. Secondary endpoints included overall response rate (ORR), progression-free survival (PFS) and overall survival (OS). Correlative studies included analysis of plasma activity of the AZA inactivating enzyme cytidine deaminase (CDA) measured by HPLC at Zymo Research Corp., CA before treatment, weekly x4 then every 28 days. Results: Between July 2010 and April 2016, 51 pts with RRMM were screened and 43 enrolled (phase 1: 26, phase 2: 17). Median age was 62.5 years (39-88). Females were 56% (24). Median number of prior lines of therapy was 5 (1-11). MM was refractory to len in 77% (33). Two DLTs were observed, one neutropenic fever at 40mg/m2 SC twice a week in 1/6 pts and one possibly related GGT elevation in 1/6 pts with GFR 30-59 ml/min treated at 50mg/m2 SC twice a week, that did not cause DLTs in 6/6 pts with GFR>60. AZA 50mg/m2 SC twice a week was chosen for the extension study. Grade 3/4 toxicities occurred in 31 pts (72%): neutropenia (17), anemia (7), lymphopenia (5), thrombocytopenia (4) and infection (5). At a median follow up of 39 months (m), ORR (≥ partial response (PR)) was 28% (12/43) and clinical benefit rate (CBR, ≥minimal response (MR)) was 35% (15/43). Six pts (14%) each achieved PR and very good partial response, respectively and 3 pts (7%) achieved MR. Median time to response was 29 days (27-71) and median duration of response was 125 days (30-1058). Median PFS was 3.3 m (95% CI: 2.1-3.9 m) and median OS was 18.6 m (95% CI: 9.5-23.4 m). Median plasma CDA activity (pCDA) at screening was 1233 mU/mL (range 753; 3411, STD 573 mU/mL) and varied by a median of 17% on treatment in individual pts. Achieving at least an MR inversely correlated with pCDA measured at screening and on treatment ($p < 0.03$, $p < 0.01$, respectively, Wilcoxon rank sum test). Pts with screening pCDA < 1000 mU/mL had a 50% CBR vs. 21% if > 1000mU/mL. Conclusion: AZA was well tolerated up to a target of 50mg/m2 SC twice a week in combination with Rd in RRMM (GFR > 30mL/min). pCDA varied among pts and inversely correlated with CBR, thus it may have value in patient selection for AZA therapy.

Keywords:
epigenetic

Relapsed Refractory MM

Tracks:
Treatment of Previously Treated Myeloma

SP-109

Practical considerations and role of Daratumumab retreatment for relapsed refractory Multiple Myeloma

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Abstract:
Background: Daratumumab is a first-in-class anti-CD38 monoclonal antibody approved for multiple myeloma. Because of the incidence and severity of infusion-related reactions with initial doses, daratumumab is administered over 6.5 hours for the first dose. With the need for pre-medication and monitoring, patients are scheduled for a 10-hour infusion visit. In an attempt to improve patient experience as well as optimize clinic space, additional pre-medications have been added with the initial doses and rapid infusion rate has been introduced for subsequent doses. A further opportunity exists in infusion strategies when daratumumab is re-initiated. In this retrospective chart review, we aim to characterize re-initiation of daratumumab after a break in treatment by examining previous daratumumab history, our infusion strategies upon re-initiation, infusion-related reactions, and treatment responses. Methods: Between April 1, 2016 and April 1, 2019, patients who received commercial daratumumab were identified and the electronic medical record was reviewed for a treatment break of greater than 8 weeks between daratumumab doses. Results: Over the three-year period, 125 patients received 1384 daratumumab doses. Daratumumab re-initiation after a treatment break occurred in 19 (1.4%) patients. Among these, 8 (42%) were due to disease progression, whereupon patients received other therapies before starting another daratumumab-based regimen; 11 (58%) were due to delay in the same therapy. On re-initiation, daratumumab was infused as a first dose (in 1000 mL over ~7 hours) in 3 patients, while 16 patients received daratumumab as a non-first dose (in 500 mL; 6 (37.5%) administered as rapid rate over 90 minutes, 10 (62.5%) as a second dose over ~4 hours). The treatment break ranged from 54 - 931 days and the number of daratumumab doses received prior to re-initiation ranged from 2 – 25 doses. Pre-medications were given according to institutional standards. None of the 19 patients had any documented infusion-related reactions upon re-initiation. Of 8 instances where a different daratumumab-based regimen was re-initiated upon progression, the number of subsequent therapies following the initial daratumumab regimen ranged from 1 – 7. The duration of therapy upon re-initiation was 1 – 14 doses. In this heavily pre-treated population, the response rates were variable, but generally low. The majority of patients (4 out of 7) had some response in the initial daratumumab-based regimen. Upon retreatment, however, the response was much lower. Conclusions: Our experience suggests that daratumumab may be safely administered as either rapid-rate infusion or as a second-dose when it is re-initiated after a treatment break. Response rates with daratumumab retreatment are low and would require further study in a prospective manner in a larger population.

Keywords:
daratumumab

real-world evidence

retreatment

Tracks:
Treatment of Previously Treated Myeloma

SP-110

REAL WORLD USE OF IXAZOMIB WITH LENALIDOMIDE AND DEXAMETHASONE FOR PATIENTS WITH RELAPSED MULTIPLE MYELOMA

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Abstract:
Background: Ixazomib (Ixa) is an oral proteasome inhibitor (PI) approved with lenalidomide and dexamethasone (IRD) for patients with relapsed multiple myeloma (MM) based on the Tourmaline-MM1 trial. This demonstrated a median progression free survival (PFS) of 20.6 months (m) vs RD of 14.7m. However real world outcomes differ from clinical trials due to strict eligibility criteria, implicit participant selection and centre effects. Hence the importance to demonstrate clinical benefit in the real world with a more heterogeneous patient group and more flexibility with dosing. Aims: To characterise real world outcomes of IRD by overall response rate (ORR), progression free survival (PFS), time to next treatment (TNT), overall survival (OS) and adverse events (AE). Methods: This was a retrospective review of 85 patients treated sequentially with IRD (Ixa 4mg D1, 8, 15 with lenalidomide (per label) days 1-21 and dexamethasone 40mg weekly or as tolerated every 28 days until disease progression or intolerance. Efficacy was assessed by IMWG criteria and haematological toxicity by CTCAE 4.03. Results: Patients were a median age of 65 years (32-84); ISS I, 44 (52%), II 12 (14%), III 13 (15%) and had a median of 2 (1-4) prior lines of therapy. All were exposed to at least 1 proteasome inhibitor (PI) (81 bortezomib, 13 carfilzomib) and 13 (15.2%) were refractory. 11 (13%) had prior lenalidomide (none refractory) and 65 (76.5%) had prior ASCT. 19 (22.4%) had adverse cytogenetics including 15 (11.7%) with del 17p. After a median follow-up of 24.2 months, the ORR was 77.6% (≥VGPR 22 (25.9%), PR 44 (51.8%)) and the median overall PFS was 16.6m (95% CI 10.2-not reached (NR)). The median TNT was 19.0m (95% CI 13.1-NR), but 8.6m for those >75 years vs 20.0 months for those <75 (p=0.9). Patients that were refractory to PI had an inferior TNT (6.2m vs 20.2m, p=0.04). As PI refractory patients were excluded from the Tourmaline trial, we looked at the following PI sensitive sub-groups: 1-3 prior lines (PFS 16.6m, TNT 20.2m); 2-3 prior lines (PFS 16.6m, TNT 22.4m). Those with del 17p had an inferior TNT of 12.4 vs 23.3m (p=0.01). The median overall survival was not reached; however was 23.3m for those with del 17p and 17.9m for PI refractory patients. The 2 year OS was 57%. 50 patients discontinued treatment, 36 due to progressive disease and 6 due to AEs. Ixa was well tolerated with 4 discontinuations due to AEs. ≥grade 3 haematological AEs were noted in 63.5% (neutropenia 24.7%, thrombocytopenia 22.4%, anaemia 16.5%). Subsequent treatment was daratumumab (30.8%), V(T)D panobinostat (20.5%), pomalidomide (18.0%) or a clinical trial (18.0%). 2 patients were palliated. Conclusions: This real world data demonstrated similar overall outcomes compared to the Tourmaline MM1 trial. However patients with del 17p and those refractory to PI had an inferior TNT and OS. This data supports the continued use of IRD in routine practice.

Keywords:
myeloma

Real-World Data

relapsed

Tracks:
Treatment of Previously Treated Myeloma

SP-111

The comparison of Carfilzomib, and dexamethasone versus pomalidomide-based combination chemotherapy after a 2nd-line therapy in relapsed and refractory multiple myeloma patients

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Abstract:
Background: New class of drugs are emerging in heavily pretreated patients in clinical trials, carfilzomib, and dexamethasone (Kd) and pomalidomide and dexamethasone with or without cyclophosphamide (Pd or PCd) are still important options for treatment of relapsed and/or refractory multiple myeloma (RRMM). However, direct comparison of the efficacy of carfilzomib and pomalidomide has not been evaluated. The aim of this study was to compare the efficacy and safety profile of Kd and pom-based regimens in RRMM patients after 2nd line chemotherapy in the real world clinical setting. Patient and method: Two-hundred and twenty-five patients from 14 hospitals participating in the Korean multiple myeloma working party (KMMWP) were retrospectively analyzed by review of medical records. Multiple myeloma patients who relapsed or were refractory to 2 or more lines of chemotherapy regimens and who had been treated with Kd (Kd group, N=44) or pomalidomide-based chemotherapy (Pom group, N=181) were included. When patients who had been administered with both carfilzomib and pomalidomide-combination chemotherapies sequentially, the drug used in advance was analyzed. The pomalidomide group included patients who had undergone Pd (N=108) and PCd (N=73). Results: There were no significant differences in international staging system (ISS) and revised ISS between the three groups. The median lines of previous chemotherapy in Kd, Pd and PCd groups were 3 (range, 2-7), 4 (range, 2-14) and 3 (range, 2-7), respectively. Median treatment cycles of Kd, Pd and PCd were 3 (range, 1-11), 3 (range, 1-37), and 4 (range, 1-22). Overall response (partial response or better) rate in the Kd, Pd and PCd group were 38.6% (including 13.6% of very good partial response, VGPR or better) and 35.2% (including 12.1% of VGPR or better), and 43.8% (including 16.5% of VGPR or better), respectively (P=0.582). The median follow-up duration was 6.23 months (range, 0.30-47.03months). The median progression-free survival (PFS) in Kd versus Pd versus PCd cohort were 5.27 months (95% CI, 2.41-8.13) versus 4.97 months (95% CI, 4.28-5.66) versus 9.33 months (95% CI, 5.71-12.96), respectively (P=0.032) and the median overall survival (OS) were 11.50 months (95% CI, 4.18-18.82) versus 10.20 months (95% CI, 5.89-14.51) versus 24.67 months (95% CI, 12.47-36.86), respectively (P=0.294). The most common adverse events were hematologic toxicities in Kd and Pom cohort. The most common non-hematologic toxicity was fatigue. Heart failure occurred in 9.1% versus 0.9% and 1.4% in Kd, Pd and PCd group. Conclusion: After 2 or more lines of chemotherapy in RRMM, the combination regimens of Kd vs. Pd vs. PCd showed similar response rates. In terms of progression-free survival, Kd and Pd were similar but PCd treated patients showed better PFS compared with Pd and Kd.

Keywords:
carfilzomib

Pomalidomide

relapsed/refractory multiple myeloma

Tracks:

Treatment of Previously Treated Myeloma

SP-112

Real World Data on the Efficacy and Safety of Ixazomib Based Therapy in Multiple Myeloma: An Observational Study from China

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Abstract:
Introduction: Ixazomib was the first oral bioavailable proteasome inhibitor (PI) approved by China Food and Drug Administration (CFDA) for the treatment on multiple myeloma (MM) in 2018 April. Based on the results of the Tourmaline-MM1 trial, Ixazomib in combination with lenalidomide and dexamethasone (IRd regimen) has shown to be safe and efficacious for refractory/relapsed MM (RRMM). However, real-life experience on ixazomib for MM out of clinical trial remained limited in China. Here, we conducted a single-center real life-based observational study to evaluate the efficacy and safety of ixazomib in Chinese patients with MM. The primary endpoint was overall response rate (ORR) and secondary endpoints included the time to response (TOR) and safety. Patients: We retrospectively analyzed 27 patients treated with at least 2 cycles of ixazomib based therapy from July 1, 2018 to April 4, 2019 in Zhongshan Hospital Fudan University, China. All patients were diagnosed as MM according to IMWG criteria (light chain amyloidosis excluded), with 15 RRMM and 12 newly diagnosed MM (NDMM). Patients received ixazomib 4mg (day 1, 8, 15) in a 28-days cycle. Ixazomib based therapies included single agent therapy and doublet- or triplet-drug regimens combined with other agents (lenalidomide, thalidomide and dexamethasone alone, etc.). Median age of the 15 patients with RRMM was 68 years (range: 40-84), and R-ISS I/II/III was 53%/20%/27%. The median number of previous therapies was 2 (range:1-4), with 46% patients received ixazomib in 2nd line, 27% in 3rd line and 27% in 4th line or more. Overall, 93% of patients had previous bortezomib exposure and 73% had immuno-modulators (IMiDs) exposure prior to ixazomib therapy. More specifically, 73% of RRMM patients were refractory to bortezomib and 40% were refractory to lenalidomide. Median age of 12 NDMM was 63.5 years (range: 35-84), and R-ISS I/II/III was 66%/17%/17%. Results: The median follow up from first ixazomib dose was 5.1 months (range: 2.1-9.6 months). The ORR in RRMM were 53.3%, with 2 patients obtaining complete response(CR), 1 very good partial response(VGPR), 5 partial response(PR). The median time to response (TOR) was 1.76 months in RRMM. The ORR was 54.5% (6/11) in bortezomib-refractory patients, with 1 CR, 1 VGPR and 4 PR. 60% (3/5) of patients who were refractory to both PIs and lenalidomide had PD during follow up. The ORR in 9 evaluable previously untreated MM patients was 100.0%, with 2 CR,3VGPRand 4 PR. The median TOR was 1.26 months in NDMM. Grade 3-4 adverse events (AEs) were reported in 29.6% patients. Common hematological AEs included mild lymphopenia, anemia, thrombocytopenia, and neutropenia. Other common AEs were mild fatigue and gastro-intestinal response. No grade 3-4 peripheral neuropathy was recorded. Conclusions : Our real-life data demonstrated ixazomib based therapy were generally well tolerated and effective in both RRMM and NDMM.

Keywords:
Proteasome Inhibitor

Real-World Data

relapsed/refractory multiple myeloma

Tracks:
Treatment of Previously Treated Myeloma

SP-113

Carfilzomib (K) in relapsed and refractory multiple myeloma (RRMM): frailty subgroup

analysis from phase 3 ASPIRE and ENDEAVOR

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Abstract:
Background: K-based regimens improved progression-free survival (PFS) and overall survival (OS) in RRMM patients (pts) in ASPIRE (K [27 mg/m2]-lenalidomide-dexamethasone [KRd] vs Rd) and ENDEAVOR (K [56 mg/m2]-dexamethasone [Kd56] vs bortezomib-dexamethasone [Vd]), regardless of age. Frailty scores have been developed based on age, comorbidities, and functional status (Palumbo Blood 2015; Facon Blood 2015). We assessed post hoc patient outcomes by frailty status. Methods: PFS, OS, and safety were assessed by treatment arm and frailty score (based on age, medical history-derived Charlson Comorbidity Index, and ECOG performance status); frailty scores were 0=fit, 1=intermediate (int), and ≥2=frail. Results: Pt frailty status was balanced between treatment arms in ASPIRE and ENDEAVOR. Median PFS and OS were longer for K-based regimens vs controls across frailty subgroups. In ASPIRE, numbers of fit, int, and frail pts were similar between KRd and Rd (n=115, 114; 149, 138; 93, 103, respectively). KRd vs Rd resulted in median PFS for fit, int, and frail pts of 31.4 vs 18.9 mos (hazard ratio [HR]=0.70; 95% confidence interval [CI]:0.49–1.01), 29.6 vs 18.5 mos (HR=0.70; 95% CI:0.50–0.96), and 24.1 vs 15.9 mos (HR=0.78; 95% CI:0.54–1.12), respectively. Median OS for KRd vs Rd was 55.6 vs 43.3 mos for fit pts (HR=0.71; 95% CI:0.51-0.99), 48.3 vs 47.9 mos for int pts (HR=0.94; 95% CI:0.70-1.27), and 36.4 vs 26.2 mos for frail pts (HR=0.79; 95% CI:0.57-1.08), respectively. Grade ≥3 adverse event (AE) rates for KRd and Rd were 89% and 84% for fit pts, 88% and 79% for int pts, and 94% and 94% for frail pts; AE-related discontinuation rates were 33% and 30%, 36% and 23%, and 37% and 43%, respectively. In ENDEAVOR, numbers of fit, int, and frail pts were similar between Kd56 and Vd (n=110, 121;168, 169; 168, 162, respectively). Kd56 vs Vd resulted in median PFS for fit, int, and frail pts of not estimable (NE) vs 12.1 mos (HR=0.51; 95% CI:0.33–0.79), 16.8 vs 9.9 mos (HR=0.54; 95% CI:0.39–0.75), and 18.7 vs 6.6 mos (HR=0.50; 95% CI:0.36–0.68), respectively. Median OS for Kd56 vs Vd was NE vs 42.2 mos for fit pts (HR=0.65; 95% CI:0.40-1.06), NE vs 41.9 mos for int pts (HR=0.89; 95% CI:0.64-1.24), and 33.6 vs 21.8 mos for frail pts (HR=0.75; 95% CI:0.56-1.00), respectively. Grade ≥3 AE rates for Kd56 and Vd were 83% and 64% for fit pts, 81% and 71% for int pts, and 85% and 79% for frail pts; AE-related discontinuation rates were 26% and 29%, 27% and 22%, and 33% and 30%, respectively. Conclusions: KRd and Kd56 consistently improved outcomes vs Rd and Vd, respectively, in all frailty subgroups as described above. These findings support the favorable benefit-risk profile of KRd and Kd56 regardless of frailty score.

Keywords:
carfilzomib

frailty

Relapsed Refractory MM

Tracks:
Treatment of Previously Treated Myeloma

SP-114

Trial in Progress: Once-Weekly vs Twice-Weekly Dosing of Carfilzomib-Lenalidomide-

Dexamethasone in Patients w/ Relapsed or Refractory Multiple Myeloma

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Abstract:
Introduction: Carfilzomib (K), an irreversible proteasome inhibitor, is approved for the treatment of patients (pts) with relapsed or refractory multiple myeloma (RRMM). In the randomized phase 3 ASPIRE trial, twice-weekly K (27 mg/m2) in combination with lenalidomide-dexamethasone (Rd) (KRd27) led to significant improvement over Rd in progression-free survival (PFS) (median PFS, 26.3 mos for KRd27 vs 17.6 mos for Rd; hazard ratio [HR], 0.69) and overall survival (OS) (median OS, 48.3 mos for KRd27 vs 40.4 mos for Rd; HR, 0.79). However, the demands of twice-weekly dosing of K may be burdensome for pts and caregivers, compromising adherence to the correct K-dosing schedule. The randomized phase 3 A.R.R.O.W. trial demonstrated that once-weekly Kd70 significantly reduced the risk of progression by 30% compared with twice-weekly Kd27 and increased the overall response rate (ORR) to 62.9% from 40.8% in twice-weekly Kd27 with comparable overall safety between the two groups. The U.S. has approved this more convenient once-weekly K (70 mg/m2) in combination with dexamethasone (Kd70) for the treatment of RRMM pts (Moreau Lancet Oncol 2018). Given the favorable outcomes of the once-weekly Kd70, a more convenient once-weekly dosing of K at 56 or 70 mg/m2 was explored in combination with Rd (KRd56 or KRd70) for pts with RRMM in a phase 1b study (Biran Am J Hematol 2019), which demonstrated efficacy and acceptable safety for once-weekly KRd56. Based on the results of the phase 1b trial, a randomized, open-label, non-inferiority phase 3 A.R.R.O.W.2 trial has been initiated to evaluate the clinical outcomes of once-weekly KRd56 vs twice-weekly KRd27 dosing using the ASPIRE trial as a historical reference. Design: In A.R.R.O.W.2 trial, pts with RRMM and 1 to 3 prior lines of therapy will be randomized 1:1 to once-weekly or twice-weekly dosing of KRd. Approximately 460 pts will be enrolled in 14 countries. Pts will receive KRd up to twelve 28-day cycles (C) or until discontinuation of treatment, disease progression, or death. No crossover between the once-weekly and twice-weekly arms is permitted. In the once-weekly group, K will be administered intravenously (IV) for 30 mins on days (D) 1, 8, and 15 (20 mg/m2: C1D1; 56 mg/m2 thereafter). In the twice-weekly group, K will be administered IV for 10 mins on D1, 2, 8, 9, 15 and 16 (20 mg/m2: C1D1 and C1D2; 27 mg/m2 thereafter). Pts in both arms will take 25 mg of R orally on D1 to D21, and 40 mg of d orally or intravenously on D1, 8, and 15 of each cycle with d on D22 for C1 to C9 only. The primary endpoint is ORR. The secondary endpoints include one-year PFS, patient-reported convenience with K-dosing schedule, minimal residual disease negativity rate for patients with complete response or better, and safety. The first subject was enrolled on May 8, 2019.

Keywords:
carfilzomib-lenalidomide-dexamethasone

once-weekly dosing

RRMM

Tracks:
Treatment of Previously Treated Myeloma

SP-115

A Phase 3 Study of Carfilzomib and Dexamethasone (Kd) in Patients With Relapsed and Refractory Multiple Myeloma (MM) in China

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Abstract:
Introduction: Carfilzomib (K) is an irreversible proteasome inhibitor (PI) that received accelerated approval in the U.S. in 2012, after a phase 2 trial demonstrated a 23.7% ORR in patients (pts) with relapsed and refractory MM treated with K monotherapy at 27 mg/m2 (Siegel Blood 2012). Full approval was granted after the randomized phase 3 ASPIRE and ENDEAVOR trials showed that pts with relapsed or refractory MM receiving K-based regimens had significant improvement in progression-free survival (PFS) and overall survival (OS) when compared with those receiving standard therapies (Siegel JCO 2018; Dimopoulos Lancet Oncol 2017). These studies did not enroll pts in China. A phase 3 study of twice-weekly K (27 mg/m2)-dexamethasone (Kd27) was conducted in China in pts with relapsed and refractory MM. The primary endpoint was overall response rate (ORR) with a prespecified threshold that the primary endpoint would be met if the lower limit of the 95% confidence interval (CI) was greater than 18%. Patients and Methods: In this multicenter, open-label, single-arm study, 123 pts in China that were refractory to the last prior regimen and previously received an alkylator or anthracycline, bortezomib and immunomodulatory drug (IMiD) with at least 2 prior regimens were dosed. Pts received Kd27 in 28-day cycles (C) until unacceptable toxicity, disease progression, or discontinuation. K was administered intravenously on days (D) 1, 2, 8, 9, 15 and 16 (20 mg/m2: C1D1 and C1D2; 27 mg/m2 thereafter) and 20 mg of d was taken orally on D1, 2, 8, 9, 15, 16, 22, and 23. The primary endpoint was ORR. The lower and upper bounds of the 2-sided 95% exact binomial CI were derived for ORR. The median duration of overall response (DOR), PFS, and OS were estimated using the Kaplan-Meier (KM) method, while the CIs were estimated by the method of Brookmeyer and Crowley. Results: Pts had a median age of 60 yrs and had received a median of 4 prior regimens. 75.6% were refractory to PI (bortezomib or ixazomib) and 74.0% were refractory to both PI and IMiD. The ORR was 35.8% with a 95% CI between 27.3% and 44.9%, surpassing the prespecified threshold. The median PFS was 5.6 mos (95% CI, 4.6-6.5), median DOR was not estimable (NE). The median OS was 16.6 mos (95% CI, 12.2-NE). Selected treatment-emergent adverse events (TEAEs) of interest were peripheral neuropathy (8.9%), acute renal failure (7.3%), cardiac failure (0.8%), ischemic heart disease (1.6%), and hypertension (48.8%). The grade ≥3 TEAE rate was 76.4%. The TEAE rate leading to K discontinuation was 5.7%. Conclusions: K provided a meaningful response rate in a heavily pretreated population of Chinese patients with refractory myeloma. The 242 study met its primary objective with regard to ORR endpoint. The results indicate that Kd27 has a

favorable benefit-risk profile in Chinese adults with relapsed and refractory MM.

Keywords:
carfilzomib

China

relapsed/refractory multiple myeloma

Tracks:
Treatment of Previously Treated Myeloma

SP-116

MULTIPLE MYELOMA (MM) IN FIRST RELAPSE PATIENTS: ROLE OF THE SECOND AUTOLOGOUS STEM-CELL TRASPLANT (ASCT): EXPERIENCE OF TWO CENTERS

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Abstract:
INTRODUCTION: the 2nd ASCT is considered as a salvage therapy in the 2016 IMWG guidelines for patients with MM in the 1st relapse, provided that the duration of the response to the 1st ASTC is ≥ 18 months. Currently, the increasing effectiveness of the available therapies as 2nd line treatment for MM, could challenge the role of the 2nd ASCT in this setting. OBJECTIVE: to evaluate the results of the 2nd ASCT as a salvage therapy in patients with MM at their 1st relapse. MATERIAL AND METHOD: this is a retrospective observational study involving patients with MM treated with a 2nd ASCT in 1st relapse from January 2000 to April 2019 (last transplant included was performed in February 2018), in the Mútua de Terrassa University Hospital and at the San Llàtzer University Hospital. Melfalan at a dose of 200 mg/m2 was the induction therapy prior to ASCT in all patients. Non of the patients received maintenance therapy after the 1st ASCT and only 5 patients received it after the 2nd ASCT. Patient information has been collected retrospectively by consulting the medical records. The demographic variables, date of diagnosis, type of MM, previous response to the first and second ASCT, date of first and second ASCT, date of progression, date of last visit and mortality have been included in the database. A survival analysis was performed with the Kaplan-Meier method to calculate progression-free survival (PFS) from the 1st ASCT until the relapse and from the 2nd ASCT till relapse or death, as well as the overall survival from the diagnosis. RESULTS: a total of of 21 double ASCT were included. The median follow-up since the diagnosis is 105.7 months. The median PFS after the 1st ASCT was 42 months and the median PFS after the 2nd ASCT was 23.8 months. At the time of the study, 66.3% of the patients are still alive (Graph 3). CONCLUSIONS: in our series, the 2nd ASCT as a salvage therapy in 1st relapse, allows to achieve a treatment-free time and a prolonged PFS. If we consider the rates of PFS obtained in 1st relapse in the pivotal studies with the new therapeutic combinations (CASTOR DVd, 27m, POLLUX DRd 22.6m, ENDEAVOR Kd56 15.6m, ASPIRE KRd 26.3m), the 2nd ASCT is still a good treatment option, probably improved if therapy maintenance post-ASCT with lenalidomide is added.

Keywords:
relapse

Stem Cell Transplant

Tracks:
Treatment of Previously Treated Myeloma

SP-117

Assessing the Effect of Pomalidomide or Carfilzomib Treatment on Patient-Reported Outcomes Among Patients With Relapsed/Refractory Multiple Myeloma

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Abstract:
Introduction Healthcare resource utilization (HCRU) and patient opinion play a role in treatment decisions for multiple myeloma (MM). This study aimed to characterize the impact of pomalidomide (POM) or carfilzomib (CARF) MM treatments on patient-reported outcomes (PROs). Methods This was a cross-sectional survey of US MM patients recruited by the ENDEAVOUR and BELONG studies, aged ≥18 years who were currently receiving either POM or CARF, without lenalidomide or thalidomide. Patients completed a web-based self-administered survey; their experiences were assessed using the Work Productivity and Activity Impairment (WPAI) questionnaire, Functional Assessment of Cancer Therapy-Multiple Myeloma (FACT-MM) scale, and patient-centric questions relating to MM. Patient characteristics, treatment history, HCRU, and PROs were summarized and compared between patients receiving POM and CARF. Multivariable analyses estimated the association between POM or CARF use and outcomes of the WPAI; the number of oncologist/hematologist visits and hospitalizations; out-of-pocket (OOP) costs for oncologist/hematologist visits and hospitalizations; financial burden regarding all MM-related OOP expenses; and the impact of MM on family. Analyses were adjusted for patient characteristics that differed significantly between the 2 groups. Results Of the 211 respondents, 51.7% reported currently receiving a POM regimen and 48.3% a CARF regimen. Patient characteristics were similar between treatment cohorts with an average (standard deviation [SD]) age of 61.0 years (7.60), majority male (55.9%), most having health insurance coverage (99.5%), and a low mean number of comorbidities (0.4 [SD 0.6], adjusted Charlson Comorbidity Index). The POM group vs the CARF group were more likely to be white (49.5% vs 40.2%), college educated (54.1% vs 38.2%), and have been diagnosed with MM longer (4.8 vs 3.6 years). The POM group also reported a longer duration of treatment than the CARF (35.2 vs 17.0 weeks). In univariate analysis of the WPAI, the POM group reported significantly lower activity impairment vs CARF (62.0% vs 73.9%, P=0.001) and higher FACT-MM scores (97.2 vs 88.3). In multivariable analysis, these differences were no longer significant. After adjusting for patient characteristics, the POM group reported fewer oncologist/hematologist visits (3.8 vs 5.5, P<0.001), fewer hospitalizations (0.12 vs 0.19, P=0.138), and lower OOP costs for hospitalizations (USD 10.1 vs USD 43.7, P=0.027). This group were less likely to report extremely high/high financial burden regarding all MM-related OOP expenses (21% vs 35%, P=0.047), and were less likely to strongly agree/agree that MM impacts their family (92% vs 98%, P=0.042). Conclusions Findings suggest that a POM treatment regimen was associated with less HCRU, financial burden, and family impact vs a CARF regimen. These findings should be considered while making treatment decisions for patients with relapsed/refractory MM.

Keywords:
Multiple myeloma

Patient Reported Measures

Pomalidomide

Tracks:
Treatment of Previously Treated Myeloma

SP-118

Examining Treatment Patterns, Patient Characteristics, and Outcomes Associated With Pomalidomide in Multiple Myeloma Following Lenalidomide Therapy

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Abstract:
Introduction Despite an array of therapeutic options, multiple myeloma (MM) remains an incurable malignancy for most patients. A substantial unmet need exists in the treatment of MM, particularly for patients requiring multiple lines of therapy (LoT). This analysis describes clinical outcomes and treatment patterns among patients with MM initiating their first therapy after treatment with lenalidomide (LEN). Methods This retrospective study examined MM patients and their second or subsequent LoT using Flatiron anonymized electronic health record data from Jan 1, 2011 to Mar 31, 2018. Patients with MM who immediately following a LEN-containing therapy initiated pomalidomide (POM), were compared with those who initiated a non-POM regimen. A Cox proportional hazards model was used to assess the relationship between treatment groups and the outcome of 'time to an event'. Primary endpoints were duration of treatment (DoT) and a proxy for disease progression (defined as time to next treatment [TTNT] or the end of data). These analyses adjusted for baseline patient demographic and clinical factors, such as age, gender, race, US region, insurance type, index year baseline doublet/triplet treatment, baseline progression, practice type, and baseline clinical characteristics (ECOG score, FISH status, creatinine clearance). Results The POM cohort (N=317; mean age 66.4 years, standard deviation [SD] 10.7) was similar demographically to the non-POM cohort (N=1,037, mean age 67.2 years, SD 11.0). Of the POM cohort, 64% of patients were receiving their second LoT and 36% were receiving their third LoT or higher; 78% of the non-POM group were receiving their second LoT. A majority (78.8%) of the non-POM cohort had no evidence of POM therapy at any subsequent time during the study period. The POM cohort had a longer observed DoT (the primary endpoint) versus the non-POM cohort (222 days, SD 230.1 vs 161 days, SD 207.0). Of patients treated with POM, 22.9% received doublet therapy, whereas 35.0% received triplet therapy compared with 50.9% and 12.4% of non-POM-treated patients, respectively. POM patients had lower rates of subsequent therapy versus non-POM-treated patients (45.1% vs 51.8%, P=0.038) and similar TTNT rates (285 days vs 264 days, P=0.33). Multivariable analysis indicated a greater risk of treatment discontinuation for non-POM-treated patients (hazard ratio [HR] 2.5; 95% CI 1.69–3.57, P<0.0001) and a greater risk of post-index disease progression (HR 1.32; 95% CI 1.10–1.58, P=0.0036). Conclusions Patients with MM who switched from LEN to POM were more likely to be at a later LoT versus non-POM treated patients. Despite this, after statistical matching on clinical and demographic characteristics, POM-treated patients experienced longer duration of index LoT and a lower likelihood of disease progression. The majority of non-POM patients did not go on to receive POM in a later LoT, indicating potential underuse in relapsed MM.

Keywords:
Multiple myeloma

Pomalidomide

treatment patterns and outcomes

Tracks:
Treatment of Previously Treated Myeloma

SP-119

An SLR of Clinical and Real-World Evidence in Relapsed/Refractory Multiple Myeloma (RRMM) Studies to Inform Clinical Decision-Making in the US

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Abstract:
Introduction Multiple myeloma (MM) is a life-threatening chronically relapsing disease. Lately,

several new agents have been introduced to treat patients with RRMM, leading to a remarkable increase in the number of available treatment regimens. This systematic literature review (SLR) aimed to identify recently published evidence investigating the effectiveness and impact on patient quality of life (QoL) of lenalidomide (LEN) in patients with MM who had received ≥1 prior therapy, in order to inform clinical decision-making. Methods The SLR followed the methods recommended by the Cochrane Collaboration and is reported according to the PRISMA guidelines. On February 26, 2019, studies were identified through a systematic search of biomedical literature databases (EMBASE, MEDLINE, and Cochrane Database of Systematic Reviews) using Population, Intervention, Comparison, Outcomes, and Study design (PICOS)-based inclusion/exclusion criteria. Relevant congress presentations were also searched. Key inclusion criteria were: (a) treatments: LEN, bortezomib (BORT), pomalidomide, panobinostat, ixazomib, elotuzumab, daratumumab, carfilzomib; and (b) study design: randomized controlled trials (RCT; any phase), meta-analyses (MA), indirect treatment comparisons/network meta-analyses (ITC/NMA), real-world evidence (RWE), and QoL. Exclusion criteria were: (a) case series; or (b) RWE and QoL studies with <10 patients. Only studies relevant to the USA were included for RWE and QoL analyses. The search was restricted to studies published in the English language between 2016 and May 10, 2019. Results The SLR search identified 4,928 records. Of these, 25 RCTs, 3 ITC/NMAs, 13 RWE studies, and 3 QoL studies were extracted; no MA studies were selected. Evidence from these selected studies showed triplet regimens containing LEN+dexamethasone (DEX; 6 analyses) or BORT+DEX (3 analyses) were associated with significantly longer progression-free survival (PFS; 9 analyses) or overall survival (OS; 6 analyses) compared with doublet regimens LEN+DEX or BORT+DEX. Studies comparing LEN+DEX-based doublet or triplet regimens versus BORT+DEX-based doublet or triplet regimens showed that the LEN+DEX backbone was superior to the BORT+DEX backbone for PFS (4 analyses) and OS (2 analyses). In the RWE setting, LEN-based regimens were associated with longer PFS, OS, duration of treatment, time to next treatment, and time to treatment discontinuation compared with BORT-based regimens. QoL studies demonstrated that patients treated with LEN-based regimens discontinued treatment less frequently and experienced QoL deterioration in fewer domains compared with patients treated with BORT-based regimens. Conclusions Since 2016, numerous publications of RCTs, follow-ups of RCTs, ITCs, and RWE studies in patients with RRMM are informing the treatment landscape with robust data and supporting the use of LEN+DEX based regimens in patients with RRMM in the USA.

Keywords:
Lenalidomide

Multiple myeloma

relapsed/refractory multiple myeloma

Tracks:
Treatment of Previously Treated Myeloma

SP-120

OPTIMISMM Japanese Subgroup Analysis: Pomalidomide, Bortezomib, and Dexamethasone in Relapsed or Refractory Multiple Myeloma

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Abstract:
BACKGROUND In Japan, pomalidomide (POM) in combination with dexamethasone (DEX) is approved for the treatment (Tx) of relapsed or refractory multiple myeloma. In the phase 3 OPTIMISMM trial (NCT01734928), pomalidomide, bortezomib, and dexamethasone (PVd) significantly improved progression-free survival (PFS) vs bortezomib and dexamethasone (Vd) (median, 11.2 vs 7.1 mos; HR 0.61; P < .0001) in the intent-to-treat population (100% lenalidomide [LEN] pretreated; 70% LEN refractory) who had 1 to 3 prior regimens. Here we report data for patients (pts) enrolled in Japan. METHODS Eligible pts received (1:1) PVd or Vd in 21-day cycles (C): POM 4 mg/day, days 1-14 (PVd arm only); bortezomib (BORT) 1.3 mg/m2, days 1, 4, 8, and 11 in C1-8 and days 1 and 8 in C9+; and DEX 20 mg/day (10 mg/day if age > 75 yrs) on days of and after BORT. RESULTS Of 559 pts enrolled in OPTIMISMM, 17 were from Japan and received PVd (n = 12) or Vd (n = 5); 13 (76%) were LEN refractory (8 PVd; 5 Vd). Median age was 72 yrs, and 58% vs 80% of pts were male. Most pts received 1 prior line of therapy (67% vs 60%) and prior BORT (67% vs 60%). Tx is ongoing in 7 vs 1 pt; most pts (4 vs 3) discontinued due to progressive disease. Median Tx duration was 14.5 vs 4.0 mos. Median PFS was 17.6 with PVd vs 4.4 mos with Vd; median follow-up was 14.8 mos. ORR was 100% vs 60%; median time to response was 0.8 vs 1.5 mos, and median duration of response was 16.8 vs 7.4 mos. Both arms had a 12-month overall survival rate of 100%. Grade 3/4 treatment-emergent adverse events (TEAEs) with PVd vs Vd included infections (5 vs 2 pts), neutropenia (6 vs 0), thrombocytopenia (2 vs 1), and anemia (0 vs 1). No pts discontinued PVd due to TEAEs; 1 discontinued Vd due to bronchitis. TEAE-related dose reductions occurred in 10 pts (83%) in the PVd arm vs 4 (80%) in the Vd arm, mostly due to peripheral sensory neuropathy (4 vs 3 pts). Five pts had their POM dose reduced due to ≥ 1 TEAE, which included thrombocytopenia (2 pts) and dermatitis, rash, diarrhea, pneumonia, dehydration, peripheral neuropathy, and renal impairment (1 each). Dose interruptions due to ≥ 1 TEAE occurred in 11 pts (92%) in the PVd arm vs 4 (80%) in the Vd arm, mostly due to infections (7 vs 2 pts) and sensory neuropathy (3 vs 4). Eleven pts had their POM dose interrupted, primarily due to infections (7 pts), including pneumonia (3), bronchitis (2), and influenza (2). Other reasons for POM dose interruptions included muscle abscess, upper respiratory tract infection, neutropenia, thrombocytopenia, hematuria, renal impairment, dermatitis, rash, diarrhea, humerus fracture, dehydration, and oropharyngeal pain (1 pt each). CONCLUSIONS PVd demonstrated a clinical benefit vs Vd in a highly LEN-refractory (76%) Japanese subgroup, consistent with that in the overall OPTIMISMM population. Of note, PVd led to a 100% ORR. Toxicities were managed with dose reductions and interruptions; no pts discontinued PVd due to TEAEs.

Keywords:
Lenalidomide

Pomalidomide

relapsed/refractory multiple myeloma

Tracks:
Treatment of Previously Treated Myeloma

SP-121

Maintenance Therapy vs Re-treatment at Biochemical Relapse vs Observation in Relapsed/Refractory Multiple Myeloma Patients: Results of a Phase II, Randomized Study

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Institutions:
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Abstract:
Background: Multiple myeloma (MM) is a disease characterized by biochemical relapses (increase of monoclonal paraprotein without organ damage) and clinical relapses (increase of monoclonal protein and organ dysfunction). So far, salvage treatment is indicated only at occurrence of clinical relapse. We performed a randomized, phase II study to evaluate efficacy and safety of bortezomib as continuous treatment until progression or as a re-treatment at biochemical relapse, as compared to observation until clinical relapse in MM patients. Methods: Patients with relapsed/refractory MM who had received 1-3 prior lines of therapy were enrolled within 45 days of completion of the previous salvage cycle. Of note, the last therapy should include bortezomib, and patients should have no evidence of disease progression. In arm A, patients received maintenance treatment with bortezomib (1.3 mg/m2, days 1,15) and dexamethasone (20 mg, days 1,2,15,16); in arm B, patients were treated at biochemical relapse with six 4-week cycles of bortezomib (1.3 mg/m2 on days 1,8,15,22) and weekly dexamethasone (40 mg); in arm C, patients received no treatment until clinical relapse. Time to progression (TTP) was the primary endpoint and it was calculated from the time of enrolment to both biochemical relapse (TTBR) and clinical relapse (TTCR). Results: A total of 60 patients were evaluated, 16 in arm A, 23 in arm B, and 21 in arm C. Median number of prior therapies was 2 (1-3). At enrolment, no significant differences were detected in terms of response to prior bortezomib-salvage treatment between the 3 arms. Median follow-up was 39 months. In patients receiving bortezomib maintenance, median TTBR was 18 months and median TTCR was 22 months; in patients receiving bortezomib-retreatment at biochemical relapse, median TTBR was 8.4 months and median TTCR was 20 months; in the observation arm, median TTBR was 10.5 months and median TTCR was 11 months. Median progression-free survival-2 was longer in patients receiving bortezomib maintenance (45 months) or re-treatment (31 months) as compared with patients in the observation arm (26 months). The incidence of grade 3-4 adverse events was low (<20%), and no significant differences were seen in patients receiving bortezomib as maintenance or re-treatment. Conclusions: In relapsed/refractory MM patients treated with a bortezomib-based regimen, bortezomib maintenance or re-treatment with bortezomib at biochemical relapse were safe strategies and prolonged TTCR as compared with observation. Of note, such advantage did not have any negative impact on the efficacy of subsequent therapies.

Keywords:
bortezomib

Maintenance therapy vs re-treatment

relapsed/refractory multiple myeloma

Tracks:
Treatment of Previously Treated Myeloma

SP-122

Real-world comparison of Ixazomib, lenalidomide and dexamethasone vs lenalidomide and dexamethasone in relapsed and refractory multiple myeloma

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Abstract:
Aims: We have performed a face to face comparison of all-oral triplet ixazomib, lenalidomide and dexamethasone (IRD) versus lenalidomide and dexamethasone (RD) in patients with relapsed and refractory multiple myeloma (RRMM) in the routine clinical practice. The primary endpoint was progression free survival (PFS), secondary end points included response rates and overall survival (OS). Patients and methods: Overall 344 patients with RRMM were treated with either IRD triplet (N=127) or RD (N=217). The two cohorts were well balanced including gender, ECOG performance status, ISS stage,M-protein type, cytogenetics, number of prior therapies. Slight differences in IRD vs RD included age (median 66.0 vs 68.0 years), previous stem cell transplant (62.0% vs 43.3%) and the presence of extramedullary plasmocytoma (14.2% vs 6.7%). Data were acquired from the Czech Registry of Monoclonal Gammopathies. Results: The median follow-up in the IRD vs RD arm was 13.2 vs 9.6 months, respectively. Median PFS for IRD cohort was not reached and for RD was 11.6 months favoring the all-oral triplet, p = 0.002. The hazard ratio for PFS was 0.60 (95% confidence interval [CI] 0.43 – 0.83, p = 0.002). The PFS advantage translated into improved OS for patients treated with IRD, median not reached vs 27.1 months, p = 0.023. The landmark analysis favored IRD vs RD both at 12 months (77.1% vs 71.5%) and 24 months (71.0% vs 53.4%). The IRD arm had better PFS for most subgroups, including age, ISS stage, treatment response or prior therapy. The IRD regimen was most beneficial in younger patients ≤75 years with ISS I, II, and in the first and second relapse. Patients with the presence of extramedullary disease did not benefit from IRD nor RD treatment (median PFS 5.5 vs 11.2 months). The overall response rate (ORR) was 73.0% in the IRD vs 66.2% in the RD group with the complete response (CR) of 11.1% vs 8.8%, and very good partial response (VGPR) 22.2% vs 13.9%. Patients treated with the IRD arm achieved significantly higher ≥VGPR responses vs RD arm (33.3% vs 22.7%, p = 0.042). Both regimens were well tolerated and incidence of grade 3/4 toxicities was comparable. The majority of grade ≥3 AEs included hematological toxicity, followed by infections. Peripheral neuropathy (PN) was slightly more frequent in IRD arm. Diarrhea was significantly more frequent in the IRD arm but only 1 patient had grade ≥3 diarrhea. Conclusions: Our analysis confirmed the benefit of all-oral IRD treatment versus RD doublet. The IRD regimen improved PFS over RD and translated into OS benefit in patients with RRMM in the routine clinical practice. Patients ≤75 years, ISS I, II, and treated with IRD in early lines have benefited most from the all-oral triplet. In a contrary, patients with extramedullary disease did not benefit from either treatment. Supported by: AZV 17-29343A, NV18-03-00500, FNOl 00098892, IGA-LF-2019-001, PROGRES Q40/08, UHHK 00179906

Keywords:
ixazomib

myeloma

relapsed/ refractory

Tracks:
Treatment of Previously Treated Myeloma

SP-123

Unusual Carfilzomib Toxicity: Three Cases of Drug-induced Thrombotic Microangiopathy (TMA) after Treatment with High-dose weekly Carfilzomib, Cyclophosphamide, and Dexamethasone (wCCD)

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Institutions:
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Abstract:
Background: Drug-induced thrombotic microangiopathy (DITMA) is a recognized but uncommon complication of proteasome inhibitors. We present 3 novel cases of TMA observed on the MCRN003/MYX1 phase 2 clinical trial in multiple myeloma (MM) previously treated with 1-3 lines of therapy (NCT02597062). Methods: Protocol treatment consisted of intravenous carfilzomib (20 mg/m2 day 1 cycle 1 then escalated to 70 mg/m2 for all subsequent doses) on days 1, 8, and 15 of a 28 day cycle plus weekly oral dexamethasone (< 70 years 40 mg; ≥ 70 years 20mg) and cyclophosphamide 300 mg/m2, capped at 500 mg. The trial met its primary endpoint with >80% response rate by cycle 4. Results: Of 75 individuals treated on study, 3 cases of TMA occurred. All 3 had preceding hypertension (HTN), normal baseline ADAMTS13 levels, and made a complete recovery following cessation of protocol therapy and appropriate treatment. Case 1: 74 yo male with IgG lambda MM, negative for del17p, t(4;14), and t(14;16) with a history of glaucoma and reflux disease. He started perindopril during cycle 7 for new HTN. During cycle 8 after carfilzomib 70mg/m2, he presented with anemia, thrombocytopenia (plt 24 x10^9/L), increased creatinine (Cr) 162 µmol /L. Blood pressure (BP) was 170/82 mmHg. Bloodwork showed high LDH level (394 U/L), low haptoglobin (0.08 g/L) and schistocytes. A renal biopsy showed diffuse glomerular involvement by a TMA. There was no immune complex deposition; immunofluorescence showed trace, non-specific glomerular staining for IgM, kappa, C3. He was treated with high-dose prednisone. Case 2: 54 yo female with lambda light chain MM, negative for del17p, t(4;14), and t(14;16). One day after her 2nd dose of carfilzomib 70mg/m2, she presented with fever (39.3 C°) and cough. Her BP was 142/88 mmHg. Bloodwork revealed hemoglobin (Hb) 63g/L, plt 3 x10^9/L, elevated Cr (304 µmol/L), schistocytes, increased LDH (1536 U/L), low haptoglobin, high bilirubin (83 µmol/L), normal INR and aPTT. She was treated with daily plasma exchange and high-dose prednisone. After 3 days, her hemolysis improved; at 2 weeks her CBC and Cr returned to baseline. Case 3: 55 yo male with IgA kappa MM, negative for del17p, t(4;14), and t(14;16) with history of type 2 diabetes mellitus and HTN. After receiving carfilzomib 70mg/m2 in cycle 6, he presented with a headache, myalgias and night sweats. His BP was 120/77 mmHg. Bloodwork showed thrombocytopenia (plt 10 x10^9/L), anemia (Hgb 81g/L), schistocytes, elevated LDH (669 U/L), normal Cr, normal INR and aPTT. He was treated with plasma exchange for 4 days with improvement in hemolytic parameters, which normalized by 6 weeks. Discussion: High-dose wCCD is an effective, convenient and generally well-tolerated regimen. The unexpectedly high rate (4%) of TMA seen merits further exploration to better understand the etiology of PI-related DITMA and the risk factors that lead to its onset.

Keywords:
carfilzomib

Drug-induced toxicity

Thrombotic microangiopathy

Tracks:
Treatment of Previously Treated Myeloma

SP-124

Relapse after allogeneic hematopoietic cell transplantation for multiple myeloma (MM): Single center experience

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Institutions:
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Abstract:
Background: Over the past decade, outcomes for patients with multiple myeloma(MM) have significantly improved with the availability of novel therapies, including proteasome inhibitors, immunomodulatory agents, and more recently, monoclonal antibodies. The data on survival outcomes in MM patients experiencing disease relapse following an allogeneic hematopoietic cell transplantation (alloHCT) are limited. Methods: We retrospectively examined the outcomes of a single-center cohort of MM patients (n=53) who experienced relapse or progression after alloHCT performed between 2002 and 2016. Univariate analysis of post-relapse survival outcomes consisted of constructing the Kaplan-Meier curves of post-relapse survival with different covariates. Results: Median age of patients was 62, 51% were female among the total of 53 patients. The majority of patients had an HLA-identical sibling donor (n=40, 76%). Three patients had haplo-identical related donor and 10 had matched unrelated donor. Majority (n=48, 91%) received reduced intensity conditioning (RIC) and peripheral blood (PB) grafts (n=49, 93%). All patients received calcineurin inhibitor-based GVHD prophylaxis. Twenty-five patients (47%) had received maintenance therapy after alloHCT, before developing relapsed or progressive MM. More than three-fourths of patients had received proteasome inhibitors (84%), IMiD (80%) before undergoing alloHCT. Maintenance therapies post-transplant included bortezomib (n=6), lenalidomide (n=10), pomalidomide (n=6), ixazomib (n=5) and carfilzomib (n=1). Thirty one patients (59%) included in the study had biochemical relapse and 23 (44%) had clinical relapse, one patient had both. After relapse/progression post-alloHCT, patients received a median of two lines of additional therapy (range, 0-8). Proteasome inhibitors were used for salvage post-relapse/progression in 78% (n=38) patients and IMiDs in 86% (n=42) patients. Daratumumab was used for salvage therapy in 49% (n=24), elotuzumab in 8% (n=4), checkpoint (PD-1) inhibitors in 16% (n=8) and DLI in 38% (n=20). After a median follow up of 2.4 years from the time of relapse, median post-relapse survival was 3 years (95% CI, 1.2-8.1 years). Those receiving RIC (median, 3.4 years) had a significantly improved post-relapse survival than MAC (median, 0.7 year, p=0.04) alloHCT recipients (Fig. 2). Those with disease status of ≥VGPR had a median post-relapse survival of 5.7 years, compared to 1.0 year for those with ≤PR (p=0.001) . The most common cause of death after relapse was progressive MM (n=22) in about two-thirds of the cases, other treatment-related causes (infections, n=6; GVHD, n=1; organ failure, n=1; other, n=2) were responsible for the remaining third. Conclusion: Long-term myeloma control and survival is attainable in those relapsing/progressing after alloHCT and suggest that the synergism between novel therapies and the allogeneic immune platform is the key to improved survival in this patient population.

Keywords:
Allogeneic hematopoietic stem cell transplantation

Multiple myeloma

post relapse survival

Tracks:
Treatment of Previously Treated Myeloma

SP-125

Efficacy of intensive salvage regimen (VTD-PACE and DCEP regimen) in the era of novel agents.

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Abstract:
[Introduction] Although many novel drugs have been developed, treatment for relapsed and refractory multiple myeloma (RRMM) has been challenging, especially in patients who became resistant to various drugs. We retrospectively evaluated the efficacy of intensive salvage regimen (VTD-PACE and DCEP regimen) for RRMM. [Methods] We reviewed medical records of patients who were treated with VTD-PACE or DCEP regimen during June 1, 2014 to May 24, 2019 in Japanese Red Cross Medical Center. We used the International Myeloma Working Group (IMWG) criteria for disease response and Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for assessing adverse events. [Results] Forty-six RRMM patients were treated with VTD-PACE or DCEP regimen. The median follow-up time since initiation of the salvage therapy was 7.9 months. The median age was 57-year-old[32-74]. Patients with ISS stage I, II, and III were 8(17.4%), 12(26.1%), and 21(45.7%). Patients with R-ISS stage I, II, and III were 5(10.9%), 15(32.6%), and 19(41.3%). High-risk cytogenetics, defined as the presence of deletion 17, t(4;14) and t(14;16) by FISH analysis, were identified in 22(47.8%) patients. The median time from diagnosis to initiation of the therapy was 21.8 months [2.0-169.5]. Twenty-two and 24 patients received VTD-PACE and DCEP regimen, respectively. The median previous treatment lines were 3 [1-9] (VTD-PACE 4[1-9], DCEP 2[1-7]). Forty-five (97.8%), 44(95.7%) and 12(26.1%) patients received proteasome-inhibitors, IMiDs and monoclonal antibodies prior to the therapy, respectively. The median cycle of treatment was 2[1-3] (VTD-PACE 2[1-4], DCEP 1[1-3]). Overall response (Partial Response or better) was 56.5% (VTD-PACE 63.6%, DCEP 50%). The median time of progression free survival was 4.8 months and the median time of overall survival was 15.8months. Grade 3 or higher adverse events (AEs) were observed in all patients. Most frequent grade 3 or higher AE was lymphocytopenia (95.7%), followed by neutropenia (89.1%), anemia (73.9%) and thrombocytopenia (73.9%). Febrile neutropenia was observed in 30(65.2%) patients. Two patients died during treatment due to worsening of the disease and grade 5 TLS, respectively, otherwise well tolerated. [Conclusion] VTD-PACE and DCEP regimen were effective even in heavily pretreated RRMM in the era of novel agents. Responses better than PR could be achieved relatively in a short time and would be one of the options for salvage bridging therapy including transplantation.

Keywords:
DCEP

relapsed/refractory multiple myeloma

VTD-PACE

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Carfilzomib, Thalidomide and Dexamethasone (KTd) is safe and effective in RRMM: interim analysis of the single arm, multicentre phase II ALLG MM018/AMN002 study

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Abstract:
Background: Combination of proteasome inhibitors (PI) and immunomodulatory drugs (IMiD) have synergistic antimyeloma activity. Carfilzomib when combined with lenalidomide and dexamethasone (KRd), is superior to Rd in relapsed/refractory multiple myeloma (RRMM). Thalidomide, a first generation IMiD, is less costly than lenalidomide. We anticipate that carfilzomib, thalidomide and dexamethasone (KTd) will be synergistic and more affordable combination for RRMM for the APAC region. ALLG MM018/AMN002 is an open-label phase II study of KTd for patients with RRMM. Method: Patients (pts) with RRMM, measurable disease and 1-3 prior lines of therapy were eligible for enrolment. Induction therapy (12 months) was followed by maintenance (6m) unless disease progression or adverse events (AEs) resulted in treatment cessation. Induction consisted of carfilzomib 20/27mg/m2 (n=20; safety run-in cohort) or 20/56mg/m2 on days 1, 2, 8, 9, 15, 16 of a 28-day cycle; thalidomide [100mg PO nocte] and dexamethasone [40mg (20mg for those >75 years) PO weekly]. Maintenance consisted of IV carfilzomib [56mg/m2 on D1, 2, 15 & 16 in a 28-day cycle] and PO dexamethasone [40mg (20mg for those >75 years) D1, 15]. The primary endpoint is progression-free survival (PFS). Secondary endpoints were overall survival (OS), overall response rate (ORR), duration of response (DOR) and safety. Results: From March 2017 to April 2019, 71 pts [ALLG=50; AMN=21; M 55%; mean age 66.4 years (range 41.9-84.5 yrs.), Caucasian 65%, East Asian 13%, South East Asian 22%] were recruited. 66 were evaluable for survival with a median follow-up of 12 months (95% CI 0.9-22.1). Median PFS was 19.3 months (95% CI 18.9- not yet reached) and 12-month PFS was 71.3% (95% CI 57.9 to 81.1%). Median OS was not reached with a 12-month OS of 94.6% (95% CI 84.2 to 98.3%). Best overall response rate in 64 evaluable pts was 77.5% (>/=MR 83.1%, >/=PR 77.5%, >/=VGPR 63.4%, >/=CR 24%). Median time to loss of response was 19.1 months (95% CI 17.5 to NR). 63 patients (70%) experienced >/= grade 3/4 AEs; dyspnoea (9.6% of all grade 3/4 AEs), peripheral neuropathy (8.7%), infection (other than upper respiratory tract (URTI); 7.0%), URTI (5.2%) & hypertension (4.3%). 86% of patients experienced AEs (all grade) related to carfilzomib, with 63% requiring dose reduction/delay and 3 pts discontinuing carfilzomib therapy. To-date, 11 pts on study have died in total, due to progressive disease (7), haemorrhage (2), cardiac ischaemic event (1) and accident (1). There is no difference in safety profile, including cardiac toxicity, between the ALLG and AMN cohorts. Conclusion: This interim analysis with a median of 12 months of follow-up demonstrates that KTd is effective and safe in the RRMM setting with a median PFS of 19.3 months, 12-month OS of 94.6% and favourable response rates including ≥VGPR in 63% of patients. Safety profile of carfilzomib and thalidomide is similar to previous reports. Patient accrual is ongoing.

Keywords:
Carfilzomib Thalidomide Dexamethasone

KTd

Relapsed Refractory MM

Tracks:
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Factors associated with the probability to skip subsequent lines of therapy: analysis of 321 Multiple Myeloma (MM) patients in a single tertiary centre

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Abstract:
Background: Management of MM rapidly changes throughout the years depending on drugs approval and study protocols availability by the Centers. Nevertheless, there are limited data on the number of lines given to MM patients and the factors related to skip subsequent lines of therapy. Methods: We analyzed patients with MM recorded in our database from 2005 to 2018 to estimate, in patients relapsed from a prior line, Kaplan-Meier probability to skip a subsequent line of therapy, to identify factors affecting this probability by Cox regression analysis and to build a risk model. Results: Median age of 321 examined patients was 68 years (range 42-93) and 42.5% were older than 70 years; more than 2 comorbidities (CCI) were detected in 22.5% of patients; 44% were transplant eligible (TE). R-ISS stage was low, intermediate and high in 29%, 56%, 15%, respectively. All patients received novel agents in first line (29% IMiDs-based, 35% PI-based and 36% IMiDs+PI-based regimens). With a median follow-up of 48 months, median PFS and OS were 45 (57 vs 33 months,in TE and not TE)) and 85.5 months (125 vs 57 months, in TE and not TE), respectively. Among 183 patients who relapsed, 154 (84%) received a second line consisting in PI-based (36%), IMiDs-based (34%), monoclonal antibodies (MoAb)-based (19%) and IMiDs+PI regimens (11%), with 23% of patients who were enrolled in clinical trials. Out of 86 patients with a second relapse, 69 (79%) received a third line treatment, 28% within a clinical trial (PI-based 32%, IMiDs-based 54%, MoAb-based 7%, IMiDs+PI 7%). A fourth line of treatment (25% within a clinical trial; PI-based 20%, IMiDs-based 40%, MoAb-based 8%, others 32%) was administered to 38 (72%) of 53 with a third relapse; among 37 patients with a fourth relapse, 23 (62%) received a further line of therapy (36% within clinical trials) consisting on IMiDs-based (52%) or MoAb-based (17%) and other regimens (31%). Throughout the disease course, probabilities to skip 2nd, 3rd, 4th, and 5th line of therapy were 27%, 30%, 41% and 43%, respectively. Among variables considered as factors affecting this probability (age, Hb, Platelet count, PS, RI, comorbidities, R-ISS, prior severe adverse events), univariate analysis selected age and comorbidities and prior severe adverse events. In multivariate analysis only age and comorbidities retain significance. A scoring system was derived by assigning a score to the significant variables according to their HR (age 66-75 years or comorbidities ≤ 2: 1 point; age >75 or comorbidities >2: 2 points, others: 0 point). Patients with 0-1, 2 or 3-4 risk factors had 5%, 20% and 80% probability to skip 2nd line therapy, respectively ($p< 0.001$) Conclusions: in contrast with other surveys, most of our patients received many lines of therapy. However, our simple score is able to identify patients with the lowest and, especially, the highest probability to skip 2nd line therapy, giving the chance to tailor first line therapy.

Keywords:
lines of therapy

predictive factors

second line therapy

Tracks:
Treatment of Previously Treated Myeloma

SP-128

Analysis of risk factors for lenalidomide-associated skin rash and desensitization protocol using prednisolone administration in patients with multiple myeloma

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Abstract:
It is widely known that skin rash is a common adverse event during lenalidomide treatment in patients with multiple myeloma(MM), resulting in treatment interruption and deterioration of the patient's quality of life. We conducted a retrospective investigation of the medical records of 112 patients with MM treated with lenalidomide-containing therapies between May 2010 and November 2017, with the aim of identifying the risk factors for lenalidomide-associated skin rash. The median age of patients was 74 years of age (range: 50–92 years of age). In total, 44 (38.4%) patients had skin rash: 18, 19, and 7 patients with Grade 1, 2, and 3, respectively. The incidence was 44.4% and 37.2% in patients with newly diagnosed and relapsed/refractory MM, respectively. In a univariate analysis, the risk of skin rash was significantly higher in older patients (p=0.041), impaired renal function (p =0.017), and Bence Jones Protein (BJP)-type MM (p =0.026). Multivariate logistic regression analysis demonstrated that BJP-type MM and older age (≥70 years of age) were significant risk factors for lenalidomide-associated skin rash. We applied a desensitization protocol using prednisolone administration (5–20 mg/day) when the rash reached Grade 2 or higher. Eight patients that had previously experienced skin rash (7 with Grade 2 or higher after lenalidomide treatment, and 1 with Grade 3 or higher after pomalidomide treatment) restarted treatment. The minimum dose of IMiDs was gradually increased as follows: initially, 2.5 or 5 mg of lenalidomide or 1 mg of pomalidomide once per week, followed by the same dose twice per week, then three times per week, and then daily. No reappearance of skin rash was observed; all patients were able to tolerate continuous treatment. Currently, IMiDs, especially lenalidomide, are key drugs for the treatment of MM. Thus, patients with these risk factors should be carefully monitored for the appearance of skin rash during lenalidomide treatment; in addition, the protocol to mitigate the adverse event may play an important role in the improvement of MM treatment.

Keywords:
adverse event

desensitization

immunomodulatory drugs

Tracks:
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Retrospective Review of hyperammonemic encephalopathy due to multiple myeloma: clinical features and response to treatment

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Abstract:
Background: Hyperammonemic encephalopathy due to multiple myeloma (HEMM) is rare. The clinical presentation can range from mild confusion to coma. Data on clinical features and treatment outcomes of HEMM is scarce. In this case series, we sought to describe the clinical features and treatment outcomes of patients with HEMM. Methods: Retrospective review of 9 patients with HEMM from a single institution. Results: Clinical features: Two of 9 patients with HEMM had newly diagnosed multiple myeloma (NDMM) while 7 had relapsed refractory myeloma (RRMM) with features of aggressive and highly proliferative disease: high risk cytogenetics (7/9), early relapse after ASCT (6/6 within 24months; 3/6 within 6 months of ASCT), extramedullary disease (5/7 RRMM), high LDH (7/7 RRMM). Five of 9 patients had IgA subtype of MM. Time from MM diagnosis to HEMM ranged from 0

to 120 months (median 28 months). Treatment outcomes: Ammonia level (NH3) did not improve with lactulose. In 5 RRMM patients treated with high dose cyclophosphamide (HDCy) (600mg/m2 IV days 1-4), NH3 normalized within 10 days. In 2 NDMM patients, NH3 normalized within 3 days of starting bortezomib based regimen. Two of 7 patients with RRMM were not candidates for chemotherapy and died in 5 and 11 days. All 7 patients with RRMM were refractory to PIs, IMIDs and MA with 2-6 prior lines of therapy; 6 underwent ASCT. Among 5 RRMM patients treated with HDCy, 3 achieved PR by IMWG criteria and 1 patient with nonsecretory extramedullary plasmacytoma had partial response. One patient with RRMM normalized NH3 on day 10 after HDCy, but died on day 15 from other complications of RRMM before MM response could be assessed. Survival: Patients with RRMM and HEMM in our series had poor outcome (4/7 died within one month). Three patients with RRMM who survived episode of HEMM relapsed within 3 months. Two of them received subsequent lines of treatment: one survived 9.2 months from HEMM diagnosis and one is alive at a follow up of 4.5 months. One NDMM patient with HEMM presented in coma; his NH3 normalized in 3 days after starting CyBord. This patient remains in CR since initial treatment of MM at a 5 year follow up. Conclusions: Prognosis of patients with HEMM depends mainly on the treatability of underlying MM; in NDMM long term remission can occur. Patients with HEMM and RRMM have features of aggressive and highly proliferative disease and overall poor prognosis. In our series, response to high dose cyclophosphamide in RRMM with HEMM was observed in 80%. High dose cyclophosphamide can serve as a bridge to the next line treatment in patients with RRMM presenting with HEMM.

Keywords:
Hyperammonemic encephalopathy

relapsed/ refractory

Tracks:
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Patient characteristics and treatment patterns in multiple myeloma by treatment administration route and disease status: EASEMENT observational study

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Abstract:
Background: EASEMENT is being conducted in real-world settings in Canada, Italy, and the UK with aims of understanding the burden of multiple myeloma (MM) and describing the perspectives of patients (pts), caregivers, and physicians on currently available treatment options. Here we report pt characteristics and treatment patterns in newly diagnosed (NDMM) and relapsed/refractory (RRMM) pts receiving injectable or oral therapies. Methods: This multicenter cross-sectional study is enrolling up to 400 MM pts (excluding clinical trial participants) who have received ≥1 cycle of their current line of therapy at date of inclusion (index date); similar numbers of NDMM and RRMM pts and pts receiving injectable and oral therapies are being enrolled. The study is also enrolling pts' informal (i.e. non-professional) caregivers, if attending at the index date. Primary objective: to describe pt and caregiver quality of life (QoL) and pt preferences/satisfaction according to MM status and type of treatment. MM history, treatment patterns, and resource use are being collected via retrospective medical chart review. Pts/caregivers complete questionnaires on QoL, treatment preference/satisfaction, activities of daily living, and non-healthcare direct costs at the index date. Results: As of 22 March 2019, 130 pts (51 NDMM, 78

RRMM) and 44 caregivers had been enrolled. Median age of pts was 71 yrs (range 35–88), 66%/34% were male/female, 23%/49% were living alone/with caregiver, 76% were retired, and 31% had ECOG performance status ≥2. NDMM pts were more likely than RRMM pts to be living with a caregiver (59% vs 42%, p=0.037). NDMM pts: 37 (73%) vs 14 (27%) were receiving injectable vs oral treatment (median age 68 [range 35–86] vs 74.5 [48–85] yrs, p=0.044; 68% vs 36% were living with a caregiver, p=0.064); 18 (35%), 9 (18%), 19 (37%), and 3 (6%) were receiving proteasome inhibitor (PI)-based (no immunomodulatory drug [IMiD]), IMiD-based (no PI), PI/IMiD-based, or other therapies, respectively. RRMM pts: 23 (29%) vs 55 (71%) were receiving injectable vs oral treatment (78% vs 84% were retired, p=0.044), including 10 vs 9 at 2nd line, 4 vs 27 at 3rd line, and 9 vs 17 at ≥4th line; 11 (14%), 35 (45%), 22 (28%), and 7 (9%) pts were receiving PI-based, IMiD-based, PI/IMiD-based, and other therapies, respectively. At data cut-off, 7 pts (5%) had discontinued treatment. Conclusions: Preliminary data from EASEMENT show emerging differences between NDMM and RRMM pts and pts receiving injectable and oral therapies, and differential use of injectable/oral therapies by line of therapy; these differences appear to be driven by common treatment options in participating countries. Data on comorbidities, pt characteristics/treatment patterns by individual line of therapy, and specific therapeutic regimens will be presented. Subsequent reports from EASEMENT will provide valuable insights into treatment burden, pt/caregiver QoL, and treatment preferences/satisfaction.

Keywords:
burden

oral therapy

real-world

Tracks:
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Health-Related Quality of Life With Pomalidomide + Dexamethasone + Daratumumab After Lenalidomide in Relapsed or Refractory Multiple Myeloma Patients

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Abstract:
BACKGROUND Treatment of relapsed/refractory multiple myeloma (RRMM) is complex and requires evaluation of disease and patient factors to maximize efficacy and minimize toxicity. As therapeutic advances have improved survival in multiple myeloma, maintaining quality of life has become an important aspect of treatment. Results from cohort B of the ongoing phase 2 MM-014 trial (NCT01946477) have demonstrated that pomalidomide (POM) + dexamethasone (DEX) +

daratumumab (DARA) is safe and effective in patients with RRMM after first- or second-line lenalidomide (LEN)-based treatment. This analysis evaluated the impact of POM + DEX + DARA on health-related quality of life (HRQoL) in patients in cohort B of MM-014. METHODS Patients with RRMM and 1 to 2 prior lines of treatment, LEN-based treatment as their most recent regimen, and progressive disease during or after their last treatment line were eligible for inclusion in cohort B. In 28-day cycles, patients received POM 4 mg/day on days 1-21 + DEX 40 mg/day (20 mg/day for patients aged > 75 years) on days 1, 8, 15, and 22, and DARA 16 mg/kg intravenously on DEX dosing days of cycles 1 and 2, then on days 1 and 15 of cycles 3-6, and then on day 1 of cycle 7 and beyond. Thromboprophylaxis was mandatory. The primary endpoint was overall response rate. HRQoL, an exploratory endpoint for cohort B, was assessed using EQ-5D. RESULTS As of October 15, 2018, 108 patients were evaluable for HRQoL. Baseline characteristics were similar to those of the intent-to-treat population (N = 112). EQ-5D completion rates for each cycle (1-6) were ≥ 88%. Mean change from baseline in the EQ-5D index and visual analogue scale (VAS) health score was stable through 6 treatment cycles. At cycle 6, 28.8% and 39.0% of patients achieved a minimum clinically important improvement in the EQ-5D index (≥ 0.1) and VAS health score (≥ 6), respectively. EQ-5D index values trended toward improvement in the usual activities, pain/discomfort, and anxiety/depression domains, with 15%, 26%, and 13% of patients having partial or complete resolution in each domain, respectively. Additionally, EQ-5D values were stable in most patients in each domain (mobility, 84%; self-care, 94%; usual activities, 71%; pain/discomfort, 61%; anxiety/depression, 81%). CONCLUSION HRQoL was maintained or trended toward improvement in patients with RRMM who received POM + DEX + DARA after first- or second-line LEN-based treatment. The results of this HRQoL analysis support the earlier use of POM-based treatment in patients with RRMM immediately following LEN-based treatment failure.

Keywords:
Pomalidomide

Quality of Life

relapsed/refractory multiple myeloma

Tracks:
Treatment of Previously Treated Myeloma

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Quality of life of treatment for relapsed/refractory multiple myeloma: a systematic review

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Abstract:
Background: Multiple Myeloma (MM) is an incurable cancer where most patients experience relapse and require additional therapy. Its incidence is increasing with 159,985 newly cases (2018) worldwide. The severity of relapsed/refractory multiple myeloma (RRMM) impairs with Health-Related Quality of Life (HRQoL). As many new anti-myeloma drugs and drug combinations are being investigated, HRQoL is becoming an important tool for health economic evaluations of new interventions. Methods: A systematic literature review (SLR) was conducted, following best practice guidelines (such as Cochrane), assessing the clinical and HRQoL for patients with RRMM. Randomized controlled trials (RCTs) were searched for in MEDLINE, Embase, and the Cochrane Central Library. English-language publications published between 2008 and 2018 were evaluated. Results: In total, 86 articles were included, of which seven reported HRQoL evidence in patients with RRMM. All seven trials were large Phase III studies, multicenter and included patients with RRMM with at least one prior line of treatment. Two double-blind RCTs and five open label studies were identified covering interventions from three different drug

classes. The EORTC-QLQ-C30 was used in all studies, followed by EORTC-QLQ-MY20 (n=4) and EQ-5D (n=1). Overall, HRQoL was generally maintained or slightly improved. For proteasome inhibitors (PIs) combined with immunomodulatory agents (IMiDs), HRQoL was sustained while QLQ-C30 GHS mean scores were relatively stable over time. Whereas carfilzomib was associated with superior HRQoL scores in QLQ-C30 GHS, ixazomib showed no statistically significant differences compared to control group. For panobinostat (HDAC-inhibitor) combined with bortezomib + dexamethasone, QLQ-MY20 showed an initial improvement in most domains and subsequent stabilization for both arms. Majority of the EORTC functional and symptom domains showed improvements for pomalidomide (IMiD) combined with low-dose DEX. Differences in QLQ-30 GHS favored BTZ over high-dose DEX in most EORTC domains. In addition, five publications reported minimal important difference (MID) for HRQoL. In general, improvements were largely sustained for PIs (as mono or combination therapy) meeting the predefined MID. IMiDs, however, reported statistically significant clinical meaningful improvements. Conclusion: Surprisingly, only a small number of RCTs reported on HRQoL outcomes in patients with RRMM. The available evidence did not allow for any comparisons between interventions due to heterogeneity across studies and differences in methodology. While there is a need for further HRQoL evidence beyond RCTs, future RCTs should include HRQoL to enable better understanding and meaningfully interpretation of the impact different therapies may have on patient's quality of life.

Keywords:
Health related quality of life

Multiple myeloma

Quality of Life

Tracks:
Treatment of Previously Treated Myeloma

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Venetoclax for the Treatment of Multiple Myeloma: Outcomes Outside of Clinical Trials

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Abstract:
Background Venetoclax is a B cell lymphoma 2 (BCL-2) inhibitor that has shown activity as a single agent and in combination with other therapies in patients with multiple myeloma, particularly those harboring t (11;14) associated with high BCL-2 expression. We aimed to identify the efficacy of venetoclax in patients with multiple myeloma treated outside clinical trial. Methods We conducted a retrospective review of all patients with multiple myeloma treated with venetoclax between December 2016 and March of 2019 at the Mayo Clinic outside of a clinical trial setting. Results 56 patients treated with venetoclax for relapsed or refractory multiple myeloma were identified. 75% (n=42) of patients had t(11;14) detected on cytogenetic studies and 36% (n=20) had presence of high risk abnormalities. Median number of prior therapies was 6 (range 1-15). 79% (n=44) had received prior autologous transplant and 61% (n=34) were penta-refractory or exposed. Venetoclax was used as monotherapy or in combination with dexamethasone in 55% (n=31) of patients and a triplet/quadruplet [with a proteasome inhibitor (PI), immunomodulatory drug (IMiD) or daratumumab] in 45% (n=25). Antimicrobial prophylaxis was utilized in 86% (n=48) patients consisting of antiviral, anti-pneumocystis, anti-bacterial and anti-fungal therapy in 86%, 43%, 21% and 4% respectively. After median follow-up of 11.3

months (95% CI 7.2-14.8) 32% (n=18) of patients remain on venetoclax therapy. Overall response rate in the 52 patients evaluable for response was 44% (21% CR, 8% VGPR, and 15% PR). Patients with t(11;14) had a numerically higher response rate than those without (49% vs 31%, p=0.34). Data on BCL2 expression by immunohistochemistry was available in 30 patients [strong 18 (60%), variable 7 (23%) and weak in 5 (17%)]. Response was higher in patients with strong BCL2 expression (ORR 59% for strong vs 8% for not strong expression, p=0.0080). Median time to best response was 2 months (range 1-9 months). The median PFS is 5.6 months (95% CI 4.8-9.9) and median OS is not reached (95% CI 12-NR). Presence of t (11;14) was associated with improved PFS and OS (median PFS 5.7 months vs 4.2 months, p=0.01 and median OS not reached vs 10.8 months, p=0.008). High risk cytogenetic abnormalities were associated with a shorter PFS and OS (median PFS 3 months vs 14 months, p<0.0001 and median OS of 9.4 months vs not reached, p=0.0003). At last follow up 14 (25%) patients have died. All had progressive disease at the time of death and 3 patients were diagnosed with sepsis secondary to pneumonia (all 3 were receiving acyclovir and bactrim prophylaxis with one patient also on penicillin prophylaxis). Of the 14 patients who died 7 (50%) had received venetoclax as their last line of anti-myeloma therapy. Conclusion Venetoclax is an effective oral agent in relapsed and/or refractory myeloma, and can produce deep and durable responses in heavily pretreated patients.

Keywords:
BCL-2

Relapsed Refractory MM

Venetoclax

Tracks:
Treatment of Previously Treated Myeloma

SP-134

A phase 2 study of carfilzomib plus elotuzumab plus dexamethasone for myeloma patients relapsed after 1-3 prior treatment lines

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Abstract:
Introduction: Bortezomib (B), with elotuzumab and dexamethasone (d) showed superiority to Bd with PFS of 9.7 vs. 6.9 months, respectively, without excessive toxicity (Jakubowiak et al. Blood 2016;127:2833-40). In our pilot study we investigate the safety, feasibility and initial efficacy of carfilzomib (K), elotuzumab (E) and dexamethasone (D) combination (KED) in relapsed or refractory

MM (RRMM) patients. Patients and methods: 15 RRMM patients after 1-3 prior lines were included. The primary endpoint was overall response rate (ORR). In patients achieving at least very good partial remission (VGPR) the quality of response was assessed according to the 8-colour EuroFlow protocol with 10-5. Carfilzomib was given once weekly 20 mg/m2 on C1D1 and thereafter 70 mg/m2 in 28 day cycles on days 1,8,15 in cycles 1-8 and on days 1,15 thereafter combined with weekly elotuzumab 10 mg/kg on days 1,8,15 in cycles 1-2, thereafter on days 1,15; dexamethasone 40 mg on days 1,8,15,22 on cycles 1-8, thereafter on days 1,15. Treatment will continue until progression or excessive toxicity. Patient samples collected prior to treatment will be comprehensively profiled by whole exome and RNA sequencing and evaluated for ex vivo response to the agents. Together, the study addresses clinical response, ex vivo-in vivo translation, identifies molecular biomarkers for the KED combination. Patients will also complete questionnaires on health-related quality of life (QoL) at day 1,15. Results: Median number of prior lines was 2 (1-3). After a median of 7 (1-20) cycles ORR is 87 %. Until now 7 patients achieved VGPR (median flow-MRD 0,002%), 6 patients PR, 2 MR. Four patients have progressed. Initial molecular characterization highlighted diverse subclonal backgrounds among the treated patients, but interestingly, the best responding VGPR patients displayed mutations to RAS genes in the dominant clones (NRAS 828, 2662; KRAS 733). We noticed two grade 2 infusion reactions during first infusion. One patient was withdrawn due to thrombotic microangiopathy. One patient developed autoimmune hemolytic anemia (AIHA), without red cell antibodies. She recovered and continued Kd without reappearance of AIHA. Regarding QoL, patients reported mild diarrhea and dyspnoea at day 15 compared to day 1, but the symptoms always returned to the starting point before the next cycle and did not lead to dose reduction or treatment discontinuation. Conclusion: Here we evaluate the carfilzomib, elotuzumab and dexamethasone combination in RRMM with comprehensive molecular annotations. We noticed two remarkable serious adverse events; previously not reported AIHA and one thrombotic microangiopathy. Preliminary results of this KED combination showed efficacy in patients with clonal RAS mutations and ORR of 87 % after the median of 2 prior treatment lines using weekly carfilzomib of 70 mg/m2. QoL assessment revealed mild diarrhea and dyspnoe on day + 15 which were recovered by the beginning.

Keywords:
carfilzomib

elotuzumab

relapsed/refractory multiple myeloma

Tracks:
Treatment of Previously Treated Myeloma

SP-135

Progressive multifocal leukoencephalopathy after daratumumab in a patient post allo-HCT successfully treated with JC-virus specific donor lymphocytes

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Abstract:
Introduction Progressive multifocal leukoencephalopathy (PML) is a life-threatening

demyelinating CNS disorder caused by reactivation of JC virus (JCV). Due to profound T-cell depletion and potent immunosuppressive factors, allogeneic hematopoietic cell transplantation (allo-HCT) recipients are at risk for JCV reactivation. Likewise, an increased risk for infectious complications has been reported for patients treated with the anti-CD38 monoclonal antibody daratumumab, potentially attributable to the depletion of NK cells. Here, we report a case of a heavily pretreated myeloma patient, post allo-HCT, who experienced PML during daratumumab therapy. Remarkably, PML was successfully treated using multiple agents, including the administration of JC virus (JCV) specific donor lymphocytes. Case report A 59-year old myeloma patient with an 11-year history of anti-myeloma therapy and 6.5 years post allo-HCT was treated with daratumumab, pomalidomide, bortezomib, cyclophosphamide and dexamethasone for 20 cycles. The patient developed seizures and a cerebral MRI revealed a lesion in the posterior white matter. Cerebrospinal fluid (CSF) analysis confirmed JCV reactivation with 500 copies/dL. The constellation of clinical and radiological manifestations with JCV positive CSF met the criteria for PML. PML is almost universally fatal when occurring after allo-HCT. We stopped daratumumab therapy and initiated treatment with cidofovir and mirtazapine as these drugs have shown some PML activity in anecdotal reports. Furthermore, we administered donor lymphocytes to facilitate immune reconstitution. In an attempt to optimize therapy specifically for this patient, we collected lymphocytes from an HLA-identical, anti-JCV-antibody positive family donor. JCV specific T-cells were isolated using CCS technology with the Prodigy device. For antigen-specific T-cell activation, five overlapping JC-virus peptide libraries were used. The final product contained 20,000 antigen-specific T-cells. These T-cells were administered without complication roughly two months after PML was diagnosed. Following these therapies, the patient went in to full remission of PML with JCV negative CSF and almost complete radiologic resolution. We successfully resumed myeloma therapy with elotuzumab, carfilzomib, lenalidomide, and dexamethasone. Now, 9 months after initial manifestation, the patient has residual hearing impairment and minor loss of vision, but remains in remission for both PML and myeloma. Conclusions To the best of our knowledge, this is the first report on PML occurring after daratumumab therapy in a patient post allo-HCT. This case highlights the severe immunosuppression characteristic of late stage myeloma through a novel sequelae of this immunosuppression. We also report a promising and successful treatment of PML after allo-HCT, using a multimodal approach including the adoptive transfer of JCV specific donor lymphocytes.

Keywords:
Allogenic stem cell transplant

daratumumab

PML

Tracks:
Treatment of Previously Treated Myeloma

SP-136

The elevation of eosinophils could prolong the time to the next treatment in patients with RRMM who are treated with lenalidomide

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Abstract:
Lenalidomide (LEN) directly targets myeloma cells and stimulates an immunological response. Eosinophils (Eo) have a variety of immunological functions and play roles in the development of allergic diseases and asthma. Eo level elevations have been shown to represent immunological activity in patients with myeloma who are treated with LEN. The purpose of this study was to

investigate the clinical significance of Eo level elevation in patients with relapsed or refractory multiple myeloma (RRMM) who were treated with LEN. We reviewed the medical records of patients with RRMM who were treated with LEN-containing regimens at the Jikei Kashiwa Hospital, between November 2010 and June 2018. The included patients were followed-up until March 2019, and the median follow-up period was 24.4 months. Fifty-nine patients with RRMM who were treated with LEN were analyzed, and median patient age was 73 years. An elevation of Eo was defined as an increase in Eo count of 250 /microL or more during the first cycle, compared to the level on day one of the first cycle. As salvage chemotherapy, 39, 8, 4, 3, 3, and 2 patients received LEN plus dexamethasone (Rd), elotuzumab plus Rd (ERd), daratumumab plus Rd (DRd), ixazomib plus Rd, bortezomib plus Rd, and LEN, melphalan, plus prednisone, respectively. The median time from diagnosis to the start of LEN was 25.9 months. The median number of prior regimens was two. The percentage of patients with the Eo elevation was 22.0%. There were no a significant relationships among Eo elevation and age, sex, M protein type, international staging system (ISS), serum lactate dehydrogenase level, serum C-protein level, number of prior chemotherapies, prior bortezomib, dose of lenalidomide, and dose of corticosteroid. The overall response rate (ORR) in the groups with Eo level elevation and non-elevation were 84.6% and 63.0%, respectively (P = 0.189). The elevation of Eo was not related to any grade of skin rash (P = 0.713). The median time to next treatment (TTNT) of the Eo elevation group was significantly longer than that of the Eo non-elevation group (40.3 vs 8.4 months, P = 0.017). In addition, the median TTNT in the Eo elevation group with partial response (PR) or better was significantly longer that of the Eo non-elevation group with a PR or better (40.3 vs 11.9 months, P = 0.021). In the multivariate analysis, the Eo elevation was a significant good prognostic factor for TTNT (hazard ratio 0.401, P = 0.043). The overall survival was similar between the Eo elevation and non-elevation groups (P = 0.334). From our findings, we conclude that Eo level elevations are common and can prolong TTNT in patients with RRMM who are treated with LEN.

Keywords:
eosinophils

Lenalidomide

Tracks:
Treatment of Previously Treated Myeloma

SP-137

The clinical course of multiple myeloma in the era of novel agents: a retrospective, single-center, real-world study

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Abstract:
In this retrospective, single-center real-world study we reviewed the clinical course of every patient with multiple myeloma (MM) treated throughout a 11-year period (2006-2016) at a primary referral center (Vejle Hospital). 303 patients with a median age of 69 years received a median (range) of four (1-18) lines of therapy. Anti-myeloma treatment was initiated in 149 patients between 2006 and 2010 (2006-2010 cohort) and 154 patients between 2011-2016 (2011-2016 cohort). The median age at diagnosis was 69 years. 241 (80%), 190 (63%), 153 (50%), 123 (41%), 96 (32%), 67 (22%), 46 (15%), 31 (10%) and 23 (8%) patients received lines 2 to 10, respectively. Lenalidomide-dexamethasone (n=156), bortezomib-dexamethasone (n=107) and bortezomib-lenalidomide-dexamethasone (n=84) were the most commonly used regimens. Response was evaluated in 1200 lines of therapy. The partial response or better rate was 78%, 58%, 55%, 44%, 32%, 29%, 36%, 30%, 29% and 30% in lines 1 to

10, respectively. The median (95% confidence interval, CI) progression-free survival (PFS) was 18 (15; 22), 10 (8; 13) eight (7; 10), six (4; 8), four (3; 5), three (2; 4), three (2; 5), two (2; 6), three (1;8) and four (1; 6) months in lines 1 to 10, respectively. The median (95% CI) overall survival (OS) was 4.1 (3.7, 4.8) years. Compared with the 2006-2010 cohort, patients in the 2011-2016 cohort had significantly longer OS; 5.3 (4.7, not reached, NR) versus 3.4 (2.7, 4.0) years, p<0.0001. The most remarkable survival improvement was seen in patients not treated with high dose therapy and autologous stem cell transplantation (HDT-ASCT); 4.7 (3.2, 5.9) versus 2.6 (2.0, 3.3) years, p=0.0052. Patients in the 2011-2016 cohort were on treatment during a greater part of their life and had higher exposure to HDT-ASCT, lenalidomide, pomalidomide, daratumumab and carfilzomib.

Keywords:
lines of therapy

real-world evidence

survival

Tracks:
Treatment of Previously Treated Myeloma

SP-138

REAL-WORLD USE OF CARFILZOMIB THERAPY AMONG PATIENTS WITH EXISTING CARDIOVASCULAR MEDICAL HISTORY: AN ANALYSIS OF A PROSPECTIVE OBSERVATIONAL STUDY

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Abstract:
Background: Patients (pts) with multiple myeloma (MM) are at higher risk for cardiovascular events (CVAEs) due to patient, disease factors or toxicity associated with anti-MM treatment, including carfilzomib (CFZ). Methods: As of 22 Oct 2018, the study (NCT03091127) included 271 relapsed MM pts who received CFZ and dexamethasone alone (Kd) or CFZ, lenalidomide and dexamethasone (KRd) in routine care. Pts with CV history (CV+ group) at CFZ initiation were identified with ≥1 of the following: cardiovascular disorder, renal disorders, diabetes, or hypercholesterolemia. Results: The CV+ group comprised 45% KRd pts (80/178) and 55% Kd pts (51/93) and was older (median age) than pts without CV history (CV-) in KRd (66 vs 62 years) and Kd pts (71 vs 68 years) at CFZ initiation. KRd pts received 1 prior line of therapy (median), regardless of CV history. Kd was used earlier in CV+ vs CV- pts (median of 3 vs 4 prior lines). The percentage of echocardiography at baseline was similar between CV+ vs CV-: 45% vs 41% of KRd pts; and 41% vs 38% of Kd pts, respectively. The average % of the label dose received by KRd pts was similar in the CV+ (94%) and CV- (96%) groups. Kd CV+ pts received an average 77% of the label dose vs 69% in CV- pts. For KRd, CFZ dose delays (53% vs 39%) or reductions (18% vs 11%) were more common in CV+ vs CV- pts. In contrast, fewer Kd CV+ pts had dose delays (33% vs 57%) or reductions (14% vs 24%). More pts with CV+ vs CV- initiated/increased antihypertensive treatment, for both KRd (19% vs 4%) and Kd (22% vs 14%). The Kaplan-Meier median estimate of treatment duration was comparable between CV+ or CV- pts for both KRd (15.8 vs 17.2 months) and Kd (7.4 vs 7.7 months). Overall response rate (ORR) to KRd was similar for CV+ (82%) and CV- (79%) evaluable pts, with 59% of very good partial response or better (VGPR+) and 18% complete response or better (CR+) for CV+ compared with 63% and 26% of CV- pts,

respectively. ORR to Kd was comparable in evaluable pts with CV+ (61%) and CV- (64%), with similar VGPR+ (37% vs 36%) and better CR+ (11% vs 4%) for CV+ vs CV- pts, respectively. More AEs of grade 3 or above (Gr3+) were reported in CV+ (KRd 36%; Kd 43%) than CV- pts (KRd and Kd: 33%). In KRd pts, 9 Gr3+ CVAEs (3 cardiac AEs [4%] including 1 heart failure [HF]; 6 hypertensions [HT, 8%]) occurred in the CV+ group but did not lead to CFZ discontinuation. In Kd pts, Gr3+ CVAEs did not differ by CV+ or CV- history (cardiac AEs: 6% vs 5%; HT: 0% vs 2% [n=1]), including 1 HF in each group. More fatal events were reported in CV+ (n=4) than CV- (n=1) pts, in each cohort. Conclusion: While CV+ groups were older, more comorbid and experienced more Gr3+ AEs than CV- groups, occurrence of G3+ HT or HF were very low. Regardless of CV history, pts received similar CFZ dosing, treatment duration and achieved high response rates. These data indicate pts with CV history could benefit from CFZ-based therapy to the same extent as other pts.

Keywords:
Cardiovascular adverse event

carfilzomib

real-world evidence

Tracks:
Treatment of Previously Treated Myeloma

SP-139

REAL-WORLD EVIDENCE OF THE USE OF CARFILZOMIB AND DEXAMETHASONE ACCORDING TO AGE SUBGROUP: AN INTERIM ANALYSIS FROM A PROSPECTIVE OBSERVATIONAL STUDY

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Abstract:
Background: Prior results from an observational study of relapsed multiple myeloma showed that patients (pts) receiving carfilzomib (CFZ) and dexamethasone alone (Kd) were older than those receiving CFZ, lenalidomide (Len) and dexamethasone (KRd) (median age at CFZ initiation: 70 vs 64 years, respectively). Here, we further characterize the cohort of Kd pts by age. Methods: Adult pts enrolled in study NCT03091127 received ≥1 prior line of therapy, ≥1 CFZ dose in routine care, and were followed until 30 days after last CFZ dose or up to 18 months (mos) from initiation. In a planned interim analysis, 93 of 293 pts (31.7%) received Kd in 10 participating countries in EU and Israel. Pt characteristics, efficacy and safety outcomes are reported for Kd pts grouped by age at CFZ initiation (<65 vs ≥65 years). Results: Two-thirds (67/93) were elderly (≥65 years) at Kd initiation. Pt characteristics did not differ by age: nearly half of Kd pts at CFZ initiation had an ISS stage III and almost all pts had an ECOG status 0-2, where reported. Elderly pts had more comorbidities than younger pts (96% vs 73%). More elderly pts had history of vascular disorders (52% vs 15%) mainly hypertension (39% vs 15%), cardiac disorders (22% vs 15%), and lipid metabolism (10% vs 4.0%) reported. Regardless of age, Kd pts received a median of 3 (range: 1, 9) prior lines of therapy. Len-refractory pts represented 73% of the elderly and 58% of the younger subgroup. The overall response rate (ORR) was similar for elderly vs younger pts (61% vs 65%). Among elderly pts, 33% achieved a very good partial response or better (VGPR+), including 9% of complete response or better (CR+). In younger pts, 45% had a VGPR+, including 5% of CR+. The average proportion of total CFZ dose received relative to EU label (74%

overall) and proportion of CFZ dose reductions (18% overall) were similar for each subgroup. About half (45%) of the elderly and 23% of the younger pts reported adverse events of grade 3 and above (AE Gr3+), mainly infections or blood disorders. All AEs Gr3+ of cardiac (7.5%), vascular (1.5%) or respiratory disorders (7.5%), including 5 fatal events (1 related to CFZ), occurred in the elderly subgroup. At the time of analysis, 43% of elderly and 42% of younger pts were still on treatment. The Kaplan-Meier estimate of median (95% confidence interval) treatment duration was shorter for the elderly vs younger subgroup: 7.7 mos (5.5, 9.6) vs 9.5 mos (4.0, 17.7), respectively. Conclusion: This real-world Kd cohort was older than the ENDEAVOR trial population (median 70 vs 64 years) and received Kd in later lines (median number: 3 vs 2). The elderly subgroup presented with comorbidities in nearly all pts, and experienced more AEs Gr3+ than younger pts. Despite this, they received similar CFZ administration to younger pts and achieved a similar response rate. Consistent with the findings from ENDEAVOR, Kd appears to be a valuable treatment option regardless of age.

Keywords:
carfilzomib

Elderly

real-world evidence

Tracks:
Treatment of Previously Treated Myeloma

SP-140

Isatuximab short duration fixed volume infusion combination therapy for relapsed/refractory multiple myeloma (RRMM): phase 1b feasibility/safety study

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Abstract:
Background: Isatuximab (Isa) is an anti-CD38 monoclonal antibody with multiple antitumor mechanisms. Part A of a phase 1b, open-label, multicenter study (NCT02283775) in patients (pts) with RRMM identified the recommended dose of Isa, in combination with pomalidomide and dexamethasone (Pd), as 10 mg/kg; infusion volume was weight-based, in mg/hour (h) (Blood. 2019 doi: 10.1182/blood-2019-02-895193). Here we report results from Part B of the study, evaluating the feasibility and safety of a fixed volume infusion in mL/h of Isa 10 mg/kg plus Pd in pts with RRMM. Methods: Pts with RRMM had received ≥2 prior lines including lenalidomide and a proteasome inhibitor (PI). Isa was administered in a 250 mL fixed infusion volume. First infusion: initiated at 25 mL/h and increased gradually to 150 mL/h if there were no infusion reactions (IR). Second infusion: initiated at 50 mL/h, increased gradually to 300 mL/h if no IR. Third and subsequent infusions: fixed infusion rate of 200 mL/h until the total volume was infused. Patients received Pd at standard doses in each cycle. Prophylactic medications consisted of dexamethasone, diphenhydramine, ranitidine and acetaminophen. No mandatory post-infusion corticosteroid prophylaxis was given. Primary endpoint: incidence of Grade ≥3 IRs during the first 6 infusions. Results: Of 47 pts (all treated), 30 (63.8%) remained on treatment at the cut-off date of 26 Feb 2019. Median age was 65 years (range 45–85). All pts were previously treated with a PI and

lenalidomide. Median number of cycles was 4 with 45 (95.7%) pts starting ≥2 cycles (minimum 5 infusions) and 31 (66.0%) pts starting ≥4 cycles (minimum 9 infusions). Overall median duration of exposure was 18.1 weeks (range 1–45). Median relative dose intensities for Isa-Pd were 94.1%, 84.7% and 87.5%, respectively. Median duration of infusion decreased from 3.73 h at the first infusion to 1.85 h at the second infusion and 1.25 h for third and further infusions. IRs (any grade) were reported in 19/47 (40.4%) pts. All IRs were Grade 2 and occurred during the first infusion only, with pts recovering the same day following infusion interruption and/or symptomatic medication. There were no IRs with delayed onset. Four (8.5%) pts discontinued due to treatment-emergent adverse events (2 sepsis; 1 acute myocardial infarction; 1 sudden death). Grade ≥3 infections, and Grade ≥3 laboratory-measured neutropenia and thrombocytopenia were reported in 19.1%, 71.7% and 28.3% pts, respectively. Conclusions: Isa 10 mg/kg administered in a 250 mL fixed infusion volume (mL/h) had a considerably shorter infusion time from the third infusion (median 1.25 h) versus reported infusion schedules in Part A (mg/h; median 2.90 h). All IRs occurred during the first infusion. The general safety profile of the simplified infusion continued to be manageable and consistent with previous observations for Isa-Pd.

Keywords:
CD38

monoclonal antibody

Multiple myeloma

Tracks:
Treatment of Previously Treated Myeloma

SP-141

Comparing clinical trial data against a real world dataset – progression-free survival on Len/Dex and Bor/Dex following 1-3 prior lines of treatment

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Abstract:
Background: Much of the existing published data on myeloma outcomes is derived from randomised controlled trials where patient selection and management is dictated by trial protocol. A need remains to collect and analyse 'real world' data from patients treated outside of clinical trials to check that these results are being replicated. Here we present survival data collected as part of a retrospective multi-centre audit of relapsed myeloma patients in the UK. All patients were treated with lenalidomide (Len) or bortezomib (Bor) in the decade in which these drugs became available for relapsed myeloma in the UK, 2007 to 2017 (with 75% of patients receiving treatment in 2013-15). Rev became available for relapsed patients from 2007 on clinical trials, and for non-trial patients in 2009. Vel received NICE approval for relapsed patients in 2008. Method: Several clinical trials of the last decade used Len/Dex (Aspire and Tourmaline) or Bor/Dex (Panorama and Endeavor) as their control groups. These were taken as comparators for progression-free survival (PFS) with a dataset extracted from existing clinical records as part of an ongoing myeloma outcomes audit. All patients were being treated following 1st, 2nd, or 3rd relapse. 53 patients received Len/Dex and 27 patients received Bor/Dex in the audit dataset. 389 patients received Len/Dex on Aspire (commencing 2010-14) and 360 on Tourmaline (commencing 2012-14). 381 patients received Bor/Dex on Panorama (commencing 2009-13) and 465 on Endeavor (commencing 2012-14).

Results: PFS compares favourably between the audit and clinical trial datasets for both Len/Dex and Bor/Dex patients. The median PFS for audit Len/Dex patients was 17 months, while it was 17.6 months on Aspire and 14.7 months on Tourmaline. The median PFS for audit Bor/Dex patients was 15 months, while on Endeavor it was 9.4 months. Stratified results illuminate this comparison further. We present additional comparisons by line of treatment, by prior exposure to immunomodulatory drugs (ImiDs) or proteasome inhibitors (PIs), and by prior autologous stem cell transplant status. Bor/Dex median survival times are longer in the audit dataset than in any of the clinical trial results regardless of stratification, while Len/Dex median survival times tend to be longer, though with a few notable outliers. These initial comparisons suggest a general parity or better between clinical trial control groups and real world patients. While the smaller sample size (and the presence of a small proportion of patients who received autografts, which may favour increased survival times) may introduce some bias, this is difficult to determine – especially as median age, another factor in survival rates, tends to favour the clinical trial groups. These findings are significant as a test for the clinical trial results, indicating that in this case contemporaneous 'real world' outcomes may be better than is often assumed.

Keywords:
clinical trials

real-world evidence

relapsed

Tracks:
Treatment of Previously Treated Myeloma

SP-142

Pomalidomide and Dexamethasone Treatment for ≥ 1 Year in Renally Impaired Patients With Relapsed or Refractory Multiple Myeloma

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Abstract:
BACKGROUND The immunomodulatory agent pomalidomide (POM) plus dexamethasone (DEX) is approved in the United States and European Union for patients with relapsed or refractory multiple myeloma (RRMM), including those with renal impairment (RI). MM-013, a phase 2, noncomparative trial (NCT02045017; EudraCT No. 2013-001903-36), has shown a benefit with POM + DEX in patients with severe RI, including those requiring hemodialysis, and moderate RI (Dimopoulos M, et al. J Clin Oncol. 2018;36:2035-2043). Here, we report the efficacy and safety of POM + DEX treatment (Tx) for ≥ 1 year.

Methods:
METHODS Three cohorts were enrolled: (A) moderate RI (estimated glomerular filtration rate [eGFR] of 30 to < 45 mL/min/1.73 m2), (B) severe RI (eGFR < 30 mL/min/1.73 m2), and (C) severe RI requiring hemodialysis. In 28-day cycles, patients received POM (4 mg/day on days 1 to 21) and DEX (40 mg/day [20 mg/day if age > 75 yrs] on days 1, 8, 15, and 22). All patients must have received ≥ 1 prior Tx including lenalidomide and progressed during or after their last antimyeloma therapy before

entering the study. Overall response rate (ORR) was the primary endpoint.

Results:
RESULTS At the Jan 4, 2019, cutoff, 17 of 81 patients (21.0%) enrolled had received POM + DEX Tx for ≥ 1 year: 10 in cohort A, 6 in cohort B, and 1 in cohort C, of whom 2, 2, and 1 patient, respectively were still on Tx. Median age was 68 yrs (range, 55-86 yrs) and 64.7% of patients were male. In cohorts A, B, and C, the median number of prior lines of Tx was 3, 2, and 4, respectively. Median Tx duration was 19.8, 19.9, and 32.3 mos. A total of 12 patients (70.6%) discontinued Tx due to progressive disease (7 patients), adverse events (AEs; 3 patients), death (1 patient), and withdrawal from Tx (1 patient). Median dose intensity was 4.1, 3.7, and 4.9 mg, and median Modification of Diet in Renal Disease eGFR was 40.6, 18.0, and 4.0 mL/min/1.73m2. ORR was 100%, 66.7%, and 100% in cohorts A, B, and C, respectively. Median time to response was 1.4, 1.9, and 2.9 mos. Median duration of response was 14.7 mos in cohort A and not estimable (NE) for the 2 other cohorts, as 1 patient progressed in cohort B and the patient in cohort C was still on Tx at the time of analysis. Renal response was achieved in cohorts A (30.0%) and B (50.0%) and was stable for the 1 patient in cohort C. Overall, median progression-free survival was 25.8 mos (95% CI, 14.5 mos-NE). In cohorts A, B, and C, the most frequent grade 3/4 AEs were neutropenia (6, 1, and 1 patient, respectively), anemia (3, 3, and 1 patient), and infections (6, 2, and 1 patient). In cohort A, 1 patient discontinued POM due to ≥ 1 AE. AE-related POM dose reductions occurred in 3 and 2 patients in cohorts A and B, respectively. AE-related POM dose interruptions occurred in 7, 6, and 1 patient in cohorts A, B, and C, respectively.

Conclusion:
CONCLUSION This analysis confirms that POM + DEX Tx of ≥ 1 year is efficacious in renally impaired patients with RRMM, with no new safety signals noted.

Keywords:
Pomalidomide

relapsed/refractory multiple myeloma

Renal impairment

Tracks:
Treatment of Previously Treated Myeloma

SP-143

Multi-agent therapy with pomalidomide, bortezomib, doxorubicin, dexamethasone and daratumumab (Pom-PAD-Dara) in relapsed/ refractory multiple myeloma

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Abstract:
Background Even in the era of novel immunotherapies for multiple myeloma (MM), treatment of late stage relapsed/refractory(RR) patients remains challenging. Especially in patients being resistant to two classes of IMiDs, and two classes of proteasome inhibitors, and to the monoclonal antibody daratumumab (referred to as penta-refractory), effective treatments are highly warranted. Here, we report on our experience with the five-drug combination pomalidomide, bortezomib, doxorubicin, dexamethasone, and daratumumab (Pom-PAD-Dara). The aim of our study was to analyze the efficacy and safety of this regimen in patients with RRMM. Methods We retrospectively analyzed the outcome data of 56 patients with RRMM who received Pom-PAD-Dara at our institution between September 2016 and April

2019. Results Median age at initiation of Pom-PAD-Dara was 61 years (range 43-81) and the majority of the patients were male (N=43, 77%). We detected high-risk baseline cytogenetics in 19 patients (34%). Serologic, radiographic and extramedullary relapse/progression was present in 52 (93%), 25 (45%) and 18 (32%) of patients, respectively. Patients were heavily pre-treated with a median of four (range 1-10) prior lines of therapy, includingautologous and allogenic stem cell transplant (SCT) in 37 (66%) and five (11%) patients, respectively. The majority of the patients (N=42, 75%) was refractory to the last line of therapy. 10 (18%) of the patients were penta-refractory. Patients received a median of three cycles (range 1-14) of Pom-PAD-Dara. The overall response rate was 78%, and we observed partial remission (PR), very good partial remission (VGPR), and complete remission (CR) in 27 (48%), 13 (23%), and 4 (7%) patients, respectively. Median progression free survival (PFS) was five months (95% CI 4-6) and the median overall survival was not reached at 24 months. Nine of the 10 patients with penta-refractory disease responded to Pom-PAD-Dara. The subgroup did not reach median PFS and OS at 9 and 10 months, respectively. One patient died during therapy due to lung infection (respiratory syncytial virus pneumonia). In another patient, treatment with bortezomib had to be withdrawndue to grade 3 peripheral polyneuropathy. We had to replace doxorubicin with cyclophosphamide due to heart failure in a third patient. Conclusion Pom-PAD-Dara represents a promising multidrug regimen in heavily pretreated RRMM patients with high overall response rate and an acceptable safety profile.

Keywords:
Multiple myeloma

Relapsed Refractory MM

Tracks:
Treatment of Previously Treated Myeloma

MYELOMA TRANSPLANT AND MAINTENANCE STRATEGIES

SP-144

Prolonged Lenalidomide Maintenace Therapy Improves the Quality and Deep of Response in Multiple Myeloma

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Abstract:
Introduction: Lenalidomide has been approved as maintenance treatment in newly diagnosed multiple myeloma (NDMM) patients. However, the impact of prolonged therapy with Lenalidomide on residual disease response is not completely characterized. This study is focused on the results derived from the use of Lenalidomide maintenance in actual clinical practice. Methods: We performed a retrospective analysis on 139 patients with NDMM who had available minimal residual disease (MRD) data from 5 health centers. Patients included received maintenance treatment with Lenalidomide during first-line therapy. We gathered all available data regarding clinical and biological parameters, treatment received and response monitoring. MRD was assessed by flow cytometry or next-generation sequencing with sensitivity from 10-4 to 10-5. Statistical analyses were performed with SPSS v21.0 (SPSS, Inc., IBM, Armonk, NY). Results: The median age was 60 years (31–83 years). The induction schemes were heterogeneous (triplet, including a proteasome inhibitor and an immunomodulatory drug 63.3%, VCD/VMP 23%,

others 13.7%) and 83.5% of the patients (n=116) received an autologous stem cell transplant. Median duration of Lenalidomide maintenance was 22 months. For the entire cohort of 139 patients, median progression-free survival (PFS) was 61 months and 5-year overall survival was 82.6%. Overall, 19.4% of patients (n=27) relapsed during maintenance treatment. Additionally, 38.1% of patients (n=53) deepened their response during this period (Figure 1); and 29.4% (n=25) from those whose MRD was positive before the maintenance achieved a MRD- over the course of maintenance. Globally, achievement of MRD- at any time was associated with improved PFS (median PFS 83 vs. 53 months, p=0.03), without differences in PFS between patients who reached MRD- before or during the maintenance (p=0.34). From 65 patients who had available serial MRD assessments during maintenance, those with improving MRD values but without achieving MRD negativity showed a survival benefit relative to those with stable MRD values (median PFS 88 vs. 45 months, p=0.04) (Figure 2). Excluding relapses during maintenance, patients who receive maintenance for ≥24 months achieved longer PFS (4-year PFS 90.1% vs. 59.7%, p<0.001). In multivariate analysis, only achievement of MRD- (HR 0.36; CI95 0.16-0.79) and absence of active disease by PET-CT (HR 0.12; CI95 0.03-0.39) showed a significant impact on PFS. We were able to perform a safety analysis on 61 patients. A therapy-related adverse event grade >2 was noticed in 50.8% of them, being neutropenia, fatigue and diarrhea the most common in this subset. A second primary neoplasm was detected in 8.2% (n=5) and a thrombotic event was reported in 11.5% (n=7) during the maintenance. Conclusion: Lenalidomide maintenance in NDMM helps to deepen the response obtained after induction, improving the PFS outcomes. Safety results are similar to those reported in previous studies.

Keywords:
Lenalidomide

maintenance

Minimal residual disease

Tracks:

Myeloma Transplant and Maintenance Strategies

SP-145

Impact of cytogenetics at relapse on prognosis and benefit from salvage autologous stem cell transplantation in the GMMG phase III trial ReLApsE

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Abstract:
In relapsed or refractory multiple myeloma (RRMM) treatment stratification is an important clinical issue. We previously reported subgroup analyses from the ReLApsE trial showing a benefit from a salvage transplant and lenalidomide maintenance versus continuous lenalidomide/dexamethasone (Rd) primarily in patients with standard-risk (SR) cytogenetics and low risk according to the revised international staging system (R-ISS).1 In the present analysis we further dissected the prognostic and predictive value associated with recurrent cytogenetic aberrations (t(4;14), t(14;16), del 17p, gain 1q, t(11;14), hyperdiploidy) assessed by iFISH. Prognostic significance regarding progression-free and overall survival (PFS, OS) was tested by Cox regression in the ITT population (any available FISH n=205/277; 74%). Heterogeneity of treatment effect was assessed by Cox regression with interaction term between treatment and subgroup factor in the previously reported landmark-cohort2 focusing on patients that actually received the assigned salvage transplant (any available FISH n=156/217; 72%). Patients with high-risk (HR) cytogenetics defined as t(4;14), del 17p, gain 1q >3 copies and/or t(14;16) (n=70/189; 37%) had significantly inferior PFS (HR 1.94; p<0.001) and OS (2.24; p=0.003) compared to patients with SR cytogenetics (n=119/189; 63%). The combined presence of two HR aberrations (n=13/186; 7%) was associated with even worse PFS (HR 2.96; p<0.001) and OS (HR 3.42; p=0.004). In univariate analysis of individual cytogenetic aberrations, gain 1q >3 copies (n=23/202; 11%) had the strongest negative prognostic impact on PFS (HR 2.64; p<0.001) and OS (HR 3.04; p<0.001). Association of t(4;14) (n=29/193; 15%) with PFS (HR 1.44) and OS (HR 1.51) failed to reach statistical significance (p=0.11 and 0.22). Similarly, del 17p (n=29/205; 14%) did not reach statistical significance for PFS (HR 1.47; p=0.09) or OS (HR 1.66; p=0.12). Conversely, hyperdiploidy (n=90/170; 53%) was associated with superior PFS (HR 0.69; p=0.044) and trended towards superior OS (HR 0.58; p=0.051). Multivariate Cox proportional hazard models for PFS/OS revealed a significant adverse impact of gain 1q >3 copies (HR 3.33/4.53; both p<0.001) and del 17p (HR 1.75/2.42; p=0.02/0.01) but not of t(4;14) (HR 1.04/1.14; p=0.88/0.72). Of the individual cytogenetic aberrations included in the HR definition, only del 17p showed a significant subgroup effect regarding OS (interaction p=0.017). Patients without del 17p significantly benefitted from the salvage transplant arm (HR 0.41; p=0.02) while those with del 17p did not (HR 2.49; p=0.22). In conclusion, gain 1q >3 copies and del 17p independently conferred inferior survival in RRMM. The absence of del 17p predicted an OS benefit from the salvage transplant arm, thereby driving the benefit of SR patients in the transplant arm reported previously. 1Goldschmidt H et al., Blood 2018; 132:253 2Baertsch MA et al., Blood 2018; 132:254

Keywords:
autologous transplantation

cytogenetics

Lenalidomide

Tracks:
Myeloma Transplant and Maintenance Strategies

SP-146

Racial disparities in multiple myeloma patients with durable stringent complete response

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Abstract:
Background: Multiple myeloma (MM) is one of the rare malignancies in which African Americans have a higher disease-specific and relative survival than Caucasians. Although MM is incurable disease, many patients achieve durable stringent complete remission (sCR). We hypothesize that African American have a longer duration of sCR compared to non-African American and intend to describe the clinical and pathological features of both groups. Methods: This is a single institution retrospective cohort study. Consecutive patients with MM seen in the MM clinic from 1/2016 until 7/2016 with sCR of 24 months or more were identified. Data collected included demographics, laboratory and cytogenetic data, duration of sCR, time to remission, type and duration of maintenance, and patterns of relapse. Results: 56 patients with a sCR of greater than 24 months were identified. African American represented 37.5 % (n=21) of patients. Median duration of sCR for AA was 76.5 months [46.8-115] and 61 months [44.5, 85] for non-AA (p=0.3). We did not observe a statistically significant difference between the cytogenetics of both groups. Median time to achieving sCR was not significantly associated with duration of sCR in both groups. The pattern of relapse in both groups was positive immunofixation, followed by increase in light chain ratio in patients with light chain disease, and increase in BMPC. In AA, maintenance duration was statistically significant associated with duration of sCR (r=0.58, p=0.012) as well as in both groups combined (r=0.41, p= 0.0029). Conclusions: African American MM patients with durable sCR appear to derive the most benefit from longer duration of maintenance therapy.

Keywords:
Racial disparities

Tracks:
Myeloma Transplant and Maintenance Strategies

SP-147

INTRAVENOUS BUSULFAN-MELPHALAN VS MELPHALAN AS PREPARATIVE REGIMEN FOR NEWLY DIAGNOSED MULTIPLE MYELOMA: LONG-TERM FOLLOW-UP OF A CASE-CONTROL STUDY

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Abstract:
Background: Autologous stem cell transplantation (ASCT) is considered the standard consolidation therapy for younger patients with newly diagnosed multiple myeloma (MM). We have previously reported the results of a matched case-control study comparing the outcome of a series of patients with newly diagnosed MM undergoing ASCT after intravenous (iv) busulfan (BU) and melphalan (BUMEL) or melphalan 200 mg/m2 (MEL200) as preparative regimen (Blanes et al, BBMT 2013). Here we update the progression free survival (PFS) and overall survival (OS) data from this case-control study. Methods: Between June 2005 and September 2009, 51 patients with newly diagnosed MM underwent ASCT after BUMEL in five Spanish centers. These patients were compared with a control group of 102 pair mates included in the Grupo Español de Mieloma trial GEM2000. Induction therapy in both groups of patients was based in polychemotherapy without the use of new drugs. Case matching was performed according to age, clinical stage at diagnosis, and response to induction therapy. Conditioning regimen consisted of iv BU at a dose of 3.2 mg/kg once a day on days -5 to -3 followed by MEL at a dose of -140 mg/m2 on day -2

in the BUMEL group versus MEL200 in the control group. Maintenance therapy after transplant consisted of interferon and steroids in the majority of patients. Results: The cut-off date for this update was June 30, 2018. After a median follow-up of 56 and 63 months in the BUMEL and MEL200 groups respectively, 35 patients had relapsed in the BUMEL group and 82 patients in the control group. Median PFS was 33 (95% CI, 25.4-48.3) months in the BUMEL and 24 (95% CI, 20.1-32.7) months in the MEL200 group (P = 0.04). In this update, 12 patients in the BUMEL group maintain their response: 2 are in partial response, 3 in very good partial response, and the remaining 7 in complete response CR (two with negative status for minimal residual disease). Interestingly, ten of these patients remain in response more than 9 years after transplantation. Ten-year OS was 41 (95% CI, 30-58) months in the BUMEL and 29 (95%, CI 18-47) months in the control group (p= not significant). Transplant-related mortality was similar in both groups of patients (4% in the BUMEL and 2% in the MEL200 group). Regarding toxicity, BUMEL was associated with a higher incidence of mucositis and liver toxicity than the melphalan-only approach but no patient in our series developed sinusoidal occlusive syndrome and the hepatic toxicity observed was only grade I/II. Finally, no long-term side effects have been reported to date among BUMEL recipients. Conclusions: This long-term follow-up analysis confirms that a therapeutic strategy including BUMEL as conditioning regimen before ASCT in patients with newly diagnosed MM is highly active and safe in these patients.

Keywords:
autologous stem cell transplant

Intravenous busulfan

Multiple myeloma

Tracks:
Myeloma Transplant and Maintenance Strategies

SP-148

Evolving Risk Factors for Mortality, Progression, Myeloid Dysplasia and Survival in Large 2-Decade Single-Centre Autologous Transplant Cohort of Myeloma, Amyloidosis and related Plasma Cell Dyscrasia

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Abstract:
Autologous Stem Cell Transplant (ASCT) with High-Dose Melphalan conditioning has been a unchallenged standard for intensive consolidation therapy in younger fitter Multiple Myeloma (MM) since late 1990, & was ratified as increasing PFS & OS, through RCT by various collaborative groups, as well as meta-analysis.However induction regimens have evolved from anthracycline-based infusions (e.g. [C]VAD & DTPACE]), through thal- & now len- alidomide-based IMid regimens (CTD/DTPACE/CRD), alongside advent of proteasome-inhibitors (esp. bortezomib [VCD/VTD/PAD/VDTPACE], but latterly carfilzomib [KD/KCD/KCRD]). Second ASCT initially only supported by registry data, but now RCT data (Cook et al. 2016/2018) prompted re-expansion 2nd ASCT. Reharvest was formerly more difficult, but now chemokine-antagonism via Plerixafor can expedite even pre-treated patients (but long-term outcomes, incl. 2ry MDS rates & PFS for such 2nd-ASCT less well-described). Emergent concerns re. 2nd 1ry malignancy (SPM), esp. with prior IMid-alkylator combination & maintenance, incl. myelodysplasia (MDS), esp. with len-maintenance &/or borderline cell-dose, merit a longitudinal evaluation of risk/benefit ASCT in MM, esp. given advent new therapy combinations with greater efficacy/less morbidity. A large (n=897) UK single-centre serial cohort of consecutive MM patients undergoing ASCT from 1987 to 2019 was analysed to determine determinants of early transplant-related- & non-relapse mortality (TRM & NRM), myeloid engraftment & subsequent dysplasia

(MDS), progression-free & overall survival (PFS/OS), and after univariable assessment, retrograde multi-step logistic regression analysis is being performed to identify core patient, disease and transplant-related factors affecting outcomes. MM ASCT activity gradually increasing over time period to 57 per annum 2017-18. Age: median 59 (range 34-75), with 152 (16.9%) over 65yr & 41 (4.6%) over 69yr; 37.5%F: 62.5%M. 1st ASCT in 789, 2nd in 108, 3rd in 1 subject. Bone Marrow (BM) sole graft in 13; both BM & Peripheral Blood Stem Cells (PBSC) in 5; PBSCH sole graft in 98%: Main PBSC mobilisation CyclophosphamideGCSF; Plerixafor only for CycloGCSF-failure. Mean PBSC CD34+ dose (2017-19) = 3.08x10~6/kg (Range 1.8-8.2). 12.7% in CR1-2, 56.9% >=VGPR1-2, 89.4% >=PR1-2 & 4.5% had PD at ASCT (mainly pre-2002). High-dose (200mg/m2) Melphalan-conditioning (Mel) in 86.4%, but until 2000: 117 had Mel/TotalBodyIrradiation - 12Gy fractionated (13%), 2 TBI alone, 2 Mel/Busulfan & 1 Cyclo/TBI. Early TRM very low overall (0.67% at day 30), mainly multi-organ failure due to neutropaenic sepsis. Day 100 NRM falling over time, from 0.9% (0.2-3.1) in 2009-2014, to 0.0% (0.0-8.7) from 2015 onwards. Neutrophil engraftment median day 14 (10-18); Platelet engraftment median day 20 (16-36). One year NRM 1.3% (0.4-2.2) in 2009-2014, and 0.0% (0.0-8.7%) from 2015 onwards, displaying no late NRM. Regression analysis to follow re. determinants TRM, MDS, PFS & OS.

Keywords:
autologous transplantation

modified risk stratification

therapy-related

Tracks:
Myeloma Transplant and Maintenance Strategies

SP-149

Outcomes of newly diagnosed multiple myeloma with deferred ASCT after achieving ≥VGPR following PAD induction in the Phase 2 PADIMAC study

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Abstract:
BACKGROUND With increasing use of multi-drug induction regimens able to achieve deep responses, deciding who should proceed to ASCT and when this should occur continues to be debated. We present the outcomes for patients allocated to deferred ASCT pathway based on depth of response. METHODS PADIMAC is a single arm Phase 2 study, treating newly diagnosed MM patients with Bortezomib, Adriamycin and Dexamethasone (PAD). Patients with ≥PR proceeded to PBSCH, those with <PR came off study. Post-PBSCH,

patients in ≥VGPR were allocated to no further treatment (watch and wait, W&W), those in PR proceeded to ASCT. Cytogenetics were performed at diagnosis, high risk disease defined as del(17p), t(4;14) or t(14;16). MRD (multi-parameter flow cytometry, 10-4) was assessed at PBSCH and day 100 (d100, post-ASCT/harvest); disease response assessed by IMWG. This analysis details outcomes of ≥VGPR W&W patients who relapsed, the impact of receiving salvage ASCT and of MRD status at PBSCH. RESULTS Of 153 patients recruited, 126 proceeded to PBSCH, 63 achieved ≥VGPR and were allocated to W&W. For these patients, with median follow-up 60.0 m from PBSCH, median PFS was 18.2m (95%CI 11.4-24.1), with 2-year PFS, PFS2 and OS rates 38.7% (95%CI 26.7-50.5), 75.7% (95%CI 63.0-84.6) and 91.9% (95%CI 81.6-96.5) respectively. 51 (81.0%) have relapsed, of whom 19 have died (17 due to MM, 2 from infection), 49 received further treatment. 28/49 (57.1%) proceeded to salvage ASCT with 21/28 (75.0%) achieving ≥VGPR. Re-induction regimens included bortezomib (n=11), lenalidomide (n=7) and thalidomide (n=6). 21/49 (42.9%) did not proceed to ASCT due to frailty (n=5), PD/death (n=2) or other/unknown (n=14); 12 had bortezomib, 5 lenalidomide and 4 thalidomide-containing salvage regimens. Salvage ASCT patients had progressed earlier (11.8m (6.4-15.7) vs. 18.9m (7.6-30.7)) but had longer 2nd-PFS (25.1m (17.7-35.9) vs. 13.6m (95%CI not estimable)), resulting in similar PFS2 (HR=0.94, 0.47-1.87, p=0.87) and OS (HR=1.48, 0.60-3.64, p=0.40). ASCT patients were younger (median 54 vs. 60y), there was no difference in gender, performance status, ISS stage, isotype, cytogenetics, or MRD status at PBSCH or d100. Patients who were MRD negative at d100 (n=18) had longer PFS2 (HR=0.38, 0.15-0.94, p=0.04), with trend towards longer OS (HR=0.34, 0.10-1.20, p=0.09) than those who were MRD positive (n=32). 12/56 (21.4%) with baseline cytogenetics were high risk; there was no evidence of difference in outcomes between risk groups. CONCLUSION This cohort is unique because patients achieving ≥VGPR received no further treatment post-PAD, and were managed as W&W until relapse. Majority of patients received further treatment post-relapse. Patients who had salvage ASCT had relapsed earlier than patients that did not, however, with no evidence of a difference in long term outcomes. MRD negative at d100 was associated with better outcomes, which may further guide selection of patients for deferred ASCT.

Keywords:
autologous stem cell transplant

Deferred

Outcome

Tracks:
Myeloma Transplant and Maintenance Strategies

SP-150

Allogeneic hematopoietic stem cell transplantation in patients with multiple myeloma. Impact of disease characteristics, disease status at transplant, and prior number of lines of therapy. Results of retrospective, multicentre Spanish study.

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Abstract:
Introduction: Despite several recent therapeutic advances, multiple myeloma (MM) is still considered an incurable disease. Allogenic transplantation (allo-SCT) is a potential curative treatment for these patients. However, the high morbidity and mortality associated with the procedure makes necessary to identify which are the best candidates and the most adequate timing to perform it. Aim: To analyze the impact of disease characteristics at diagnosis and at the time of allo-SCT in overall survival (OS) and progression-free survival (PFS) in patients with MM treated with proteasome inhibitors (PI) and/or immunomodulatory drugs (IMiDs). Patients and methods: Retrospective, multicentre study of 178 consecutive patients with MM undergoing allo-SCT in 22 Spanish centers from January 2010 to October 2017. Responses were defined according to IMWG criteria. OS and PFS were evaluated with the Kaplan–Meier method. Regression covariates for PFS, and OS were analyzed by the Cox proportional hazards regression model using SPSS 22.0. Every patient had received prior treatment with PI (98%) and/or IMiDs (78%) and 20% of patients had high-risk cytogenetics [del 17p, t(4;14), t(14;16)] at diagnosis. Median (range) number of lines of therapy prior to allo-SCT was 3 (1-8) and 20% of patients were in CR (13% MRD-negative) at the time of transplant. Results: Every patient grafted. The cumulative incidence of acute graft-versus-host disease (GVHD) grade III-IV was 19.8% and extensive chronic GVHD 18%. After a median follow-up of 51.4 months (range, 4.3-100.6) median OS was 22 months (95%CI, 14.3-29.7) with 2- and 5-years OS of 47.7% and 29.8%, respectively. Median PFS was 9.5 months (95%CI, 6.5-12.4). At the time of the analysis, 120 (67.4%) patients had died, most of them because of MM progression (n=47, 26.4%) or due to transplant-related complications (n=62, 34.8%): bacterial (n=23), and/or viral (n=24), and/or fungal (n=6) infections in patients with grade III-IV GVHD. Multivariate analysis identified age at transplant (HR 1,037 95%CI 1.008-1,066; p=0.012), ≥3 prior lines of treatment (HR 1.654 95%CI 1.11-2.46; p=0.013), and grade III-IV acute GVHD (HR 3.754 95%CI 2.32-6.056; p<0,001) as variables influencing OS. Age at transplant (HR 1.047 95%CI 1.013-1.083; p=0.007), grade III-IV acute GVHD (HR 3.832 95%CI 1.969-7.456; p<0.001) and disease status other than CR (HR 5.119 95%CC 2.002-13.091; p=0.001) significantly influenced PFS. Conclusions: In this cohort of patients, allo-SCT achieves significant 2- and 5-years OS and PFS. Age at transplant, active disease, and development of acute grade III-IV GVHD negatively influenced PFS, while age, acute grade III-IV GVHD, and the number of prior lines of therapy negatively affected OS. Our data suggest that allo-SCT should be performed in initial phases of the disease, particularly in younger patients in CR. Additionally, intensifying GVHD prophylaxis should also be considered to improve results in these patients.

Keywords:
allograft

relapsed

Tracks:
Myeloma Transplant and Maintenance Strategies

SP-151

Health-related quality of life is maintained with ixazomib maintenance in post-transplant newly diagnosed multiple myeloma: the TOURMALINE-MM3 trial

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Abstract:
Background: Health-related quality of life (HRQoL) is important to consider in maintenance therapy post autologous stem cell transplant (ASCT) in newly diagnosed multiple myeloma (NDMM) as patients have minimal disease burden post ASCT. The phase 3, double-blind TOURMALINE-MM3 study demonstrated improved progression-free survival with ixazomib maintenance vs placebo post ASCT (Dimopoulos et al, Lancet 2019) and is the first study to evaluate the impact of post-ASCT maintenance on HRQoL in NDMM. Methods: Patients were randomized (3:2) to oral ixazomib or matching placebo. HRQoL was assessed by EORTC QLQ-C30 and MM-specific symptoms by EORTC QLQ-MY20 at screening, the start of every cycle (cycles 1-26) for QLQ-C30 or every 3 cycles (cycles 1-25) for QLQ-MY20, the end of treatment, every 4 weeks until the start of next line of therapy after progression, and twice thereafter. Higher scores in both instruments indicate better HRQoL for global/functional domains and greater symptomatology for symptom scales (score range, 1-100). Change from study entry in subscale scores was analyzed at 30 four-week intervals using a linear mixed-effects model among patients who reported HRQoL outcomes at study entry and completed ≥1 post-study entry assessment. Results: Characteristics at study entry were well balanced between the ixazomib (n=386) and placebo (n=251) groups (median age 58 years; 97% ECOG performance status 0-1; 79% ≥very good partial response post ASCT). At study entry, least squares (LS) mean scores for ixazomib vs placebo on QLQ-C30 were: Global Health Status/QoL, 69.8 vs 69.1; Physical Functioning, 82.1 vs 82.0; Pain, 25.3 vs 25.7; Nausea/Vomiting, 2.3 vs 2.0; Diarrhea, 5.9 vs 6.0; and on QLQ-MY20 were: Disease Symptoms, 20.3 vs 19.2; Peripheral Neuropathy, 25.0 vs 25.6. Compliance with assessments, averaged across cycles, was high in the treatment phase (≥94%) and similar between groups. Subscale score changes were generally similar between groups and below a threshold of 10, the recommended minimal important difference (MID) for QLQ-C30 in MM (Cocks et al., JCO 2011). LS mean (95% CI) score changes at interval 24 (week 96) for ixazomib vs placebo on QLQ-C30 included: Global Health Status/QoL, –0.4 (–3.4, 2.7) vs 1.8 (–1.7, 5.2); Physical Functioning, 0.7 (–1.8, 3.1) vs 3.0 (0.3, 5.8); Pain, 4.1 (0.5, 7.7) vs –1.4 (–5.5, 2.7); and on QLQ-MY20 were: Disease Symptoms, 5.1 (2.4, 7.9) vs 0.8 (–2.3, 3.8); Peripheral Neuropathy, –0.7 (–5.1, 3.7) vs –6.2 (–11.1, –1.3). QLQ-C30 Nausea/Vomiting (5.0 [3.0, 7.0] vs 1.0 [–1.3, 3.3]) and Diarrhea (4.0 [1.1, 6.8] vs 0.5 [–2.8, 3.8]) subscales, while consistently worse for ixazomib vs placebo, but treatment differences did not exceed 10. Conclusions: HRQoL was maintained during treatment in both arms; active treatment with ixazomib did not have an adverse impact on HRQoL. Nausea/Vomiting and Diarrhea subscales were in line with the ixazomib toxicity profile.

Keywords:
ixazomib

maintenance

Quality of Life

Tracks:
Myeloma Transplant and Maintenance Strategies

SP-152

A Prospective, Multicenter Phase II Study of Consolidation with Cyclophosphamide, Bortezomib and Dexamethasone (CVD) in Patients with Multiple Myeloma after Autologous Stem Cell Transplantation; The KMM130 Study

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Abstract:
Background: The three-drug combination of cyclophosphamide, bortezomib and dexamethasone (CVD) has shown significant efficacy and manageable toxicity as induction therapy in patients with multiple myeloma (MM). The Korean Multiple Myeloma Working Party (KMMWP) decided to evaluate the efficacy and toxicity of CVD as consolidation therapy following autologous stem cell transplantation (ASCT). Method: In this phase II study, 46 patients achieving very good partial response (VGPR) or partial response (PR) after ASCT were initially enrolled. Of whom, 42 patients completed three courses of CVD consisting of cyclophosphamide 300mg/m2 orally on days 1, 8, 15 and bortezomib 1.3mg/m2 subcutaneously on days 1, 8, 15 and 22, along with dexamethasone 20mg per mouth on days 1-2, 8-9, 15-16 and 22-23. Results: Median age at the enrollment was 55 and twenty seven (64.3%) were male. About a quarter (23.8%) of patients were classified as International Staging System (ISS) III at diagnosis, 31.0% as ISS-I in comparison. Sixteen (38.1%) patients received both thalidomide and bortezomib for induction while 20 (47.6%) and 6 (14.3%) were treated based on thalidomide and bortezomib, respectively. High dose melphalan (200mg/m2) was done as conditioning regimen for ASCT for 33 (78.6%) cases whereas 8 (19.0%) patients received busulfan with thiotepa. Busulfan with melphalan was done for only one patient. At the enrollment, 36 (85.7%) patients showed VGPR and 6 (14.3%) presented PR. Thirteen (30.9%) patients newly achieved complete response (CR) at the end of consolidation, of whom 3 (7.1%) fulfilled the criteria of stringent CR (sCR). To evaluate the best response after completion of CVD, 19 (45.2%) revealed CR in which 9 (21.4%) cases with sCR were included. Thirty four (81.0%) patients achieved their best responses right after completion of CVD. The most common toxicities with CVD were neurologic, infection and hematologic including grade 1-2 neuropathy (19.0%), grade 1-2 infection (14.3%), grade 3-4 neutropenia (11.9%) and thrombocytopenia (7.2%). There was no treatment-related mortality. During the median follow up of 22.5 months after the enrollment, 2-year overall survival (OS) and progression-free survival (PFS) were 92.0% and 56.4%, respectively. We also assessed the effect of CVD consolidation to the level of N-terminal cross-linking telopeptide of type-I collagen (NTX) which has been considered as a marker of bone degradation. Serum level of NTX decreased significantly from 26.9 to 17.7 nM bone collagen equivalent/mM Creatinine (n=26, p=0.011) after

completion of CVD. Conclusion: Consolidation therapy with CVD following ASCT could improve response with reasonable toxicity.

Keywords:
consolidation

CVD

Multiple myeloma

Tracks:
Myeloma Transplant and Maintenance Strategies

SP-153

Severe obesity does not worsen transplantation outcome in multiple myeloma

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Abstract:
Background Obesity and severe obesity are increasingly prevalent in the United States. Epidemiological studies have shown an association between obesity and mortality in multiple myeloma (MM) (Br J Haematol 2014;166:667-676). Autologous peripheral blood stem cell transplantation (autoPBSCT) remains a crucial element in the treatment of MM. There is limited data analyzing the relationship between severe obesity and transplant outcomes in MM patients in the era of modern therapy, routine post-transplant maintenance, and genetic-based risk stratification. In addition, there is concern that this population is underdosed as many institutions adjust melphalan dosing for body weight, which could potentially lead to earlier relapse. Methods Consecutive patients undergoing autoPBSCT for MM from 2010-2017 at our institution were retrospectively reviewed and followed from time of first transplant until death. Surviving patients and those lost to follow-up were censored at last point of contact. Patients were categorized by body mass index (BMI), Revised International Staging System (R-ISS) score, and Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI). Cox proportional hazard regression models and associated log-rank tests were used to assess whether BMI and R-ISS score were associated with risk of death. Post-transplant hospital length of stay (LOS) was evaluated using generalized linear models with response following a gamma distribution. Results Patients were classified as non-obese (BMI < 30 kg/m2; n=178, 56.7%), obese (30 kg/m2 ≤ BMI < 35 kg/m2; n=72, 22.9%), or severely obese (BMI ≥ 35 kg/m2; n=64, 20.4%), totaling 314 patients (59.2% male). BMI was not found to be associated with risk of progression (p=0.884) or death following transplant (p=0.17), even after accounting for age, sex, lag time between diagnosis and transplant, use of maintenance therapy, and R-ISS score. The distribution of HCT-CI values (p=0.082) and Karnofsky performance status (p=0.939) did not significantly differ among BMI groups. As expected, R-ISS score (p=0.006) and HCT-CI (p=0.014) were each associated with risk of death after transplant. No association was found between mean LOS and BMI (p=0.875). Conclusions Obesity and severe obesity were not associated with an increased risk of mortality for MM patients receiving autoPBSCT. Although severe obesity is a health hazard, this should not be used to exclude patients from transplant.

Keywords:
Obesity

Outcome

transplant

Tracks:
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SP-154

Comparison of Granulocyte colony stimulating factor support versus antibiotic prophylaxis in autologous stem cell transplantation in multiple myeloma

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Abstract:
Infections are the major cause of morbidity and mortality after high-dose therapy with melphalan followed by autologous blood stem cell transplantation (HDT/ABSCT) in multiple myeloma (MM). Therefore, there is a need for effective anti-infective strategies like antibiotic prophylaxis (AB-P) or Granulocyte colony stimulating factor (G-CSF) support. Given the increasing prevalence of multidrug resistant (MDR) bacteria, AB-P with ciprofloxacin or cotrimoxazole twice a day was stopped in January 2017 at our transplantation center and replaced by G-CSF support and Pneumocystis jirovecii pneumonia (PCP) prophylaxis with cotrimoxazole thrice a week in March 2017. The aim of this retrospective cohort study was to compare AB-P (I) with G-CSF support and PCP prophylaxis (II) and neither AB-P nor G-CSF nor PCP prophylaxis (III) during HDT/ABSCT in MM. We analyzed 353 HDT/ABSCT in MM at our center between March 2016 and July 2018 stratified by three anti-infective strategies: (I) AB-P (n=151), (II) G-CSF support and PCP prophylaxis (n=150) and (III) no prophylaxis (n=52). The groups were compared regarding time until leukocyte and platelet recovery, mucositis, febrile neutropenia, infections, detection of MDR bacteria, need of antimicrobial therapy, transfer to intensive care unit, death, duration of hospitalization and hospital readmission after discharge. Patients receiving G-CSF support and PCP prophylaxis had a significantly shorter time until leukocyte recovery (6 versus 9 days) and duration of hospitalization (17 versus 19 days) compared to patients receiving AB-P. Time until platelet recovery, rates of mucositis, febrile neutropenia and infections, need of antimicrobial therapy, transfer to intensive care unit and death showed no significant differences between the two groups. However, patients receiving AB-P had a significantly higher rate of newly detected MDR bacteria, especially vancomycin resistant Enterococcus faecium (22 versus 4). The risk of hospital readmission was higher in the G-CSF support group (16 versus 8), but the rate of infection-related hospital readmission was similar between the two groups (9 versus 7). Patients receiving no prophylaxis showed a higher rate of febrile neutropenia, an increased need of antimicrobial therapy, especially carbapenems, and a longer duration of hospitalization compared to patients in the AB-P or G-CSF support group. In total, there were four PCP detections in our cohort, two in the G-CSF support group and two in the group without any prophylaxis. In conclusion, AB-P and G-CSF plus PCP prophylaxis have similar efficacy in preventing infections after HDT/ABSCT. Furthermore, G-CSF support enables a shorter duration of hospitalization and a lower risk of acquiring MDR bacteria. Therefore, G-CSF support and PCP prophylaxis during HDT/ABSCT in MM should be recommended. Neither AB-P nor G-CSF nor PCP prophylaxis should be omitted due to higher rates of febrile neutropenia and associated infections.

Keywords:
antibiotic prophylaxis

autologous blood stem cell transplantation

G-CSF support

Tracks:
Myeloma Transplant and Maintenance Strategies

SP-155

Management of adverse events (AEs) observed in the TOURMALINE-MM3 study of post-transplant ixazomib maintenance in multiple myeloma (MM)

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Abstract:
Background: The phase 3, double-blind, placebo-controlled TOURMALINE-MM3 study (NCT02181413) demonstrated improved progression-free survival with ixazomib maintenance vs placebo in MM patients (pts) post-autologous stem cell transplant (ASCT) (Dimopoulos et al, Lancet 2019). Ixazomib maintenance was well tolerated with a low rate of discontinuation due to AEs. We report additional safety data from TOURMALINE-MM3 to inform AE management recommendations. Methods: Pts were randomized 3:2 to ixazomib (n=395) or placebo (n=261) on day 1, 8, and 15 of 28-day cycles for ~2 years or until progressive disease/toxicity. The initial 3 mg ixazomib dose was escalated to 4 mg in cycle 5, if tolerated in cycles 1–4. Safety was a secondary endpoint assessed in all treated pts; AEs were graded using Common Terminology Criteria for AEs v4.03. Previously identified AEs of clinical importance, exploratory AEs, and supportive therapies will be described. Results: Peripheral neuropathy (PN) rates were similar with ixazomib vs placebo (19% vs 15%), and typically low grade (Gr) (Gr3: <1% vs 0%; no Gr4). Dose reductions (3% vs 2%) and discontinuations (<1% in both arms) due to PN were uncommon. Most PN events occurred in the first 0–3 (9% in both arms) or 3–6 (3% vs 2%) months. PN symptoms improved (75% vs 74%)/resolved (71% vs 69%) in the majority of pts; pregabalin was the most common prescribed therapy for PN. Median time to PN improvement was similar in both arms (134 vs 130 days). The median time to resolution was longer with ixazomib vs placebo (225 vs 159 days) and PN was ongoing in 9% and 7% of pts at end of treatment. Gastrointestinal (GI) AE incidences were higher for ixazomib vs placebo, although rates of Gr≥3 events were low in both arms: nausea, 39% vs 15% (Gr≥3: <1% vs 0%); vomiting, 27% vs 11% (Gr≥3: 2% vs 0%); diarrhea, 35% vs 24% (Gr≥3: 3% vs <1%), respectively. Dose reductions due to GI AEs were rare (≤2% in both arms), only 1 pt (ixazomib) discontinued due to a GI event (Gr1 diarrhea), and potential complications of GI AEs (dehydration, weight loss, electrolyte imbalances) were infrequent (≤2% in both arms). Antiemetic use as prophylaxis or symptomatic treatment was higher with ixazomib vs placebo (16% vs 2%). For ixazomib vs placebo, 33/55 (60%) vs 12/47 (26%) pts not on antiviral prophylaxis and 6/339 (2%) vs 2/212 (<1%) pts on prophylaxis reported herpes zoster. Acyclovir was the most common prescribed antiviral. No pts discontinued due to herpes zoster; however, prophylaxis should always be administered with ixazomib. Conclusion: Ixazomib is an efficacious and tolerable option for post-ASCT maintenance; most AEs in TOURMALINE-MM3 were low grade, manageable with supportive therapy/dose reduction, reversible, and did not lead to discontinuation. AEs associated with ixazomib maintenance can be managed in the context of routine post-ASCT supportive care due to the limited additional toxicity and lack of requirement for supplementary interventions.

Keywords:
ixazomib

maintenance

safety

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Myeloma Transplant and Maintenance Strategies

SP-156

Multiple Myeloma: Autologous Stem Cell Transplant in an aging population

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Abstract:
Autologous stem cell transplant (ASCT) is the standard-of-care for eligible patients with multiple myeloma. While there is no universally accepted age cutoff for ASCT, limited data are available for older patients particularly those over 75 years old. To further investigate this matter, we performed a retrospective chart review of patients between the ages of 75-78 years old, with newly diagnosed MM patients from the years 2012-2018 that were referred to Washington University School of Medicine. Over that time period, 86 newly diagnosed myeloma patients between the ages of 75-78 were referred to our institution. Twenty-four of these patients underwent ASCT as part of first-line therapy. Of those transplanted, the median age was 76, 96% were white, and 79% were male. 25% had ISS Stage I disease, 21% Stage II, 21% Stage III, and 33% were unknown. The median Charlson Comorbidity Index score, independent of age, was 2 (range 0-5). All patients received novel agents as part of their induction. The median number of cycles prior to transplant was 4 (range 2-12). All patients received melphalan conditioning; 8% received full dose (200mg/m2) while 92% received reduced dose (140mg/m2). Treatment-related mortality was 4% (sepsis). Patient response measured at 3 months after transplant (IMWG) included 25% of patients achieving a complete response, 29% with a very good partial response, 42% had a partial response, and 4% had no response/stable disease. Nearly all (96%) received maintenance, 70% with lenalidomide, 13% with a proteasome inhibitor, and 13% with a combination regimen of lenalidomide and a proteasome inhibitor. The estimated median progression-free survival (PFS) was 41 months (95% confidence intervals 19.6 - 62.5). At the time of analysis, only 17% patients had expired. ASCT for eligible patients age 75-78 results in similar outcomes as compared to historical data on younger patients. Pending analyses include a case-matched study including those who did not undergo ASCT to better examine the impact of ASCT in this population.

Keywords:
autologous stem cell transplant

Elderly patients

Multiple myeloma

Tracks:
Myeloma Transplant and Maintenance Strategies

SP-157

The Quality of Life on Effect and the Cost of Tandem Transplantation in Multiple Myeloma Patients

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Abstract:
[Introduction] Autologous stem cell transplantation (ASCT) plays a significant role in the treatment of multiple myeloma. Although the result of STaMINA trial showed no extra survival benefit of second transplantation or consolidation therapy in addition to single ASCT, there is still an argument about the optimal treatment intensity. In the light of the patient's QOL and the cost, the effect of the post ASCT treatment has not been well discussed. Therefore, we investigated the impact of the single and tandem ASCT on the QALY and the cost. [Methods] We analyzed multiple myeloma patients who were treated with ASCT in National Center for Global Health and Medicine Hospital from January 2010 to the end of March 2017. After the completion of the first ASCT, physicians discussed post-transplantation therapy with patients. Patients who agreed with tandem ASCT proceeded to the second ASCT. In a comparison between single and tandem ASCT, a propensity score matching analysis was performed to minimalize the biases. Overall Survival (OS) and progression-free survival (PFS) was analyzed using the Kaplan-Meier methods, and the log-rank test. Also, QALY, cumulative cost, and incremental cost-effectiveness ratio (ICER) after ASCT were evaluated. Adverse Cytogenetics were defined as hypodiploidy, del (17p), t (4; 14), and t (14; 16). [Result] Fifty-three patients were treated with single ASCT and 32 patients with tandem ASCT. The matched-pair analysis was performed based on the propensity score. Both PFS and OS after the ASCT of the tandem ASCT group were superior to the single ASCT group by Log-rank analysis (p=0.005 and 0.03). The estimated 5-year PFS was 44.8 ±15.3% vs. 12.7±11.2%, and the estimated 5 year-OS was 53.5±15.9% vs. 52.1±13.7%. We compared QALY of tandem ASCT patients with single ASCT patients. The QALY of the tandem ASCT group was significantly better than the single ASCT group by the Mann–Whitney U test (p=0.001). The QALY of the tandem ASCT group was 3.09, and that of the single ASCT group was 1.47. Cost Effectiveness Ratio (CER) of the tandem ASCT was $50,547.1/QALY, and CER of the single ASCT was $89,906.7/QALY. Therefore, the ICER (Incremental cost-effectiveness ratio) of tandem ASCT was -$24, 296.0/QALY ($1=110yen). [Conclusion] Both PFS and OS after the ASCT of the tandem ASCT group were superior to the single ASCT group in multiple myeloma patients. Also, the QALY in patients with tandem ASCT was better than the QALY of single ASCT patients. The CER in patients with tandem ASCT was better than that with single ASCT. Tandem ASCT for multiple myeloma patients may preserve patients' QOL and reduce the cost of treatment after ASCT.

Keywords:
cost-effectiveness

Quality of Life

transplantation

Tracks:
Myeloma Transplant and Maintenance Strategies

SP-158

Reduced-dose melphalan (140 or 100 mg/m2) maintains efficacy and tolerability for multiple myeloma patients with advanced age or renal impairment undergoing autologous transplant

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Abstract:
Background: Melphalan 200 mg/m2 (MEL 200) is standard conditioning for autologous transplant (auto-HCT) in multiple myeloma (MM). Melphalan 140 or 100 mg/m2 (MEL 140/100) is given to patients with advanced age or renal dysfunction. Prior comparisons of MEL 200 versus MEL 140/100 raised concerns about reduced efficacy with MEL 140/100. However, those studies took place prior to the era of induction and post-auto-HCT maintenance with novel agents. We asked whether a diverse, unselected MM cohort treated with novel agents

maintains the full benefit of auto-HCT from MEL 140/100. Methods: We reviewed 55 consecutive auto-HCT episodes for MM and amyloidosis patients treated with proteasome inhibitors (PI) and/or immunomodulators (IMiD) followed by MEL 200 (n = 30), MEL 140 (n = 20), and MEL 100 (n = 5) from 2006 to 2018. Patients with age > 70 or reduced renal function, Karnofsky score, or cardiopulmonary function received MEL 140/100. We analyzed pre-auto-HCT prognostic factors. We examined post-transplant toxicities and disease control. Statistical analyses were performed with SPSS25. Results: Female and non-Caucasian patients were well-represented. Pre-transplant therapy was similar in terms of IMiD and PI exposure. Pre-transplant disease response was similar for both MEL 140/100 and MEL 200 (VGPR+CR 65 vs 67%, p = 0.9). MEL 140/100 trended towards older age (median 65 vs 59, p = 0.09) and worse Karnofsky score (median 85 vs 90, p = 0.10); MEL 140/100 had significantly worse HCT-CI (median 4 vs 1, p < 0.001), ISS stage (stage III 64 vs 22%, p = 0.001), and renal function (GFR<60, 65 vs 6%, p < 0.001). Maintenance therapy after auto-HCT was similar. Engraftment did not differ. Non-hematologic toxicities did not differ except for mucosits (all grades), which trended lower in MEL 140/100 (29 vs 50%, p = 0.13). Post-auto-HCT responses (CR 57 vs 46%, p = 0.46; VGPR 33 vs 32%, p = 0.93) were similar. EFS (33 vs 38 months, p = 0.79) and OS (not reached vs 91 months, p = 0.79) were similar. 8% and 17% of patients from MEL 140/100 and 200 died from MM progression. Subgroup analysis showed that cytogenetics, ISS stage, age, renal function, and pre-auto-HCT therapy did not impact outcome. More mucositis was seen in patients with IMiD+PI induction or high-risk cytogenetics. Conclusion: MM patients with higher ISS and HCT-CI scores tolerated auto-HCT with MEL 140/ 100 conditioning, Post-transplant outcomes were indistinguishable. Conditioning with MEL 140/100 has equivalent safety and efficacy for patients who are not candidates for MEL 200 in the setting of induction and maintenance with novel agents.

Keywords:
autologous stem cell transplant

melphalan

Tolerability

Tracks:
Myeloma Transplant and Maintenance Strategies

SP-159

Maintenance lenalidomide therapy following upfront autologous stem cell transplantation does not impact progression-free survival 2.

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Abstract:
Background: In multiple myeloma (MM), despite the use of novel induction therapies first-line followed by autologous stem cell transplant (ASCT), the majority of patients will relapse, often experiencing multiple relapses before succumbing to their disease. The use of lenalidomide (Len), a second-generation immunomodulatory drug, as maintenance therapy following upfront ASCT has been shown to significantly improve progression-free survival (PFS) and overall survival (OS). 'Progression-free survival 2' (PFS2), defined as time to second objective disease progression or death from any cause, is a valuable endpoint to assess sequential therapies in the case where a salvage therapy may be contributing to improved OS. A retrospective chart review was conducted to investigate the impact of Len-based maintenance on PFS2 following upfront ASCT. The study was approved by the institutional review board. Methods: 91 MM patients who received upfront ASCT with either Len-based maintenance or no maintenance between 2010 and 2016 were included in the analysis. Demographics and clinical parameters were extracted from the electronic medical record. PFS1, PFS2, and OS were calculated from date of ASCT to first relapse, second relapse, and death, respectively. Patients were censored if lost to follow-up prior to

experiencing the relevant event. PFS1, PFS2, and OS of patients receiving Len-based maintenance, defined as Len monotherapy or Len-containing doublet therapies, were compared to those of patients not receiving maintenance. Log-rank tests were used to quantify differences between Kaplan-Meier survival curves. Results: Among the 91 patients included in this analysis, 47 received Len-based maintenance and 44 received no maintenance. Of the total cohort, 42 patients experienced at least 1 relapse post-transplant, with 27 patients relapsing more than once. 49 patients either remain in remission or were lost to follow-up post-transplant. Patients receiving Len-based maintenance had a longer median PFS1 than patients not receiving maintenance (5.45 vs 3.25 years; P=0.058). However, neither median PFS2 (7.46 vs 6.11 years; P=0.58) nor OS (P=0.20) was significantly longer for patients who received Len maintenance compared to those who did not. Median OS was not reached for either group after a median follow-up period of 4.8 years. Conclusions: In this cohort of 91 MM patients who underwent upfront ASCT, the use of Len-based maintenance post-transplant predictably improved PFS1, but not PFS2. The majority of patients not receiving maintenance received Len-based salvage therapies which may explain the similar PFS2 and OS found. Despite this occurrence, a shortened PFS2 was not seen in the Len maintenance group suggesting that Len maintenance does not cause untoward resistance to subsequent therapies. PFS2 should be routinely evaluated in maintenance trials in MM and our findings validated in a larger cohort of upfront ASCT patients receiving Len maintenance.

Keywords:
autologous stem cell transplant

Lenalidomide

Progression-free survival

Tracks:
Myeloma Transplant and Maintenance Strategies

SP-160

Outcomes of Post-Induction Bortezomib Therapy in Patients with Newly diagnosed Multiple Myeloma: A Multi-Center Retrospective Observational Study

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Abstract:
Introduction Post-transplant lenalidomide and ixazomib maintenance and continuous first line therapy (ConTx) were shown to improve long-term outcomes in patients (Pts) with newly diagnosed myeloma (NDMM). However, there is less evidence to support bortezomib (BTZ) maintenance or ConTx and real life data are scarce. BTZ, rather than lenalidomide maintenance and ConTx, were widely used in Israel due to reimbursement limitations. In this multicenter retrospective study we investigated the practice patterns, efficacy, safety and tolerability of BTZ maintenance and ConTx in Pts with NDMM. Methods In this observational, retrospective, multicenter (n=6) study, we reviewed centers' databases to identify all consecutive Pts with MM, diagnosed between 1.1.2010 – 3.7.2019. Pts who received a BTZ-based induction, followed by an autologous transplantation and subsequently BTZ maintenance in transplant eligible (TE), or followed by BTZ ConTx in transplant ineligible (TI) were included in the analysis. Post induction BTZ was administered SC q14 days. Patient and disease characteristics, treatment, safety and tolerability, progression free survival (PFS) and overall survival (OS), were documented. Results A total of 104 Pts

receiving post induction BTZ were identified, 58 (56%) were TE and 46 (44%) were TI. Median follow-up was 45 mo (range 12-113), most (82, 80%) received VCD induction. 21 Pts (24%) had high risk FISH cytogenetics. Overall response to induction was 79%, 73% achieved ≥ VGPR; rates were similar for TI and TE. Median duration of post-induction BTZ was 14 months (range 1-109), 30 (29%) are ongoing treatment at time of analysis. 74 Pts (71%) discontinued: due to progressive disease (57, 55%) or toxicity (17,16%). Non-hematological toxicities of BTZ maintenance/ConTx reported in >5% of the pts included peripheral neuropathy (sensory: 37%, 28% grade 1; motor: 8%), fatigue (31%), pneumonia (10%), insomnia (8%), nausea (8%) and dyspnea (6%). Hematological toxicity included anemia (69%), thrombocytopenia (37%) and neutropenia (47%); 96% of all events were grade 1-2. Three Pts developed second primary malignancy (AML, Ca of lung, and melanoma). PFS was 45 mo [95% CI 37-57] for the entire cohort from induction start (33 mo from q14d start), 40 mo [95% CI 26-54] in the TI and 46 in the TE Pts [95% CI 30-63]; Median OS was 92 months, 2-, 3- and 5- and year OS were 96%, 90% and 76%. In univariate analysis, increased age was associated with worse PFS (HR 1.34 per decade, p=0.05), while gender, % PCs in bone marrow, ISS, Calcium, Hb, the presence of high risk FISH cytogenetics, induction response, and ASCT were not significantly associated with PFS. Conclusions In a multicenter cohort, real-life data suggests that post induction maintenance and ConTx BTZ are reasonably well tolerated in Pts with NDMM. Median PFS of 45 months is encouraging; yet, results should be interpreted in caution d/t methodological limitations in a retrospective study.

Keywords:
bortezomib

continuous treatment

maintenance

Tracks:
Myeloma Transplant and Maintenance Strategies

SP-161

Effectiveness of Maintenance Treatment in Newly Diagnosed Multiple Myeloma (NDMM): Results of an SLR to Inform Clinical Decision-Making in the US

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Abstract:
Introduction Multiple myeloma (MM) is a life-threatening disease with a 5-year survival rate of approximately 50%. The goal of maintenance therapy is to extend response duration and survival. Lately, the introduction of new maintenance regimens has considerably improved outcomes in patients with MM. This systematic literature review (SLR) aimed to identify recently published evidence investigating the effectiveness and impact on patient quality of life (QoL) of lenalidomide (LEN) as maintenance therapy in NDMM, in order to inform clinical decision-making. Methods The SLR followed the methods recommended by the Cochrane Collaboration and is reported according to the PRISMA guidelines. In May 2019, studies were identified through a systematic search of biomedical literature databases (EMBASE, MEDLINE, and Cochrane Database of Systematic Reviews) using Population, Intervention, Comparison, Outcomes, and Study design (PICOS)-based inclusion/exclusion criteria. Relevant congress presentations were also searched. Key inclusion criteria were: (a) treatments: maintenance regimens that included LEN versus any comparator; and (b) study design: randomized controlled trials (RCT; any phase), meta-analyses (MA), indirect treatment comparisons/network meta-analyses (ITC/NMA), real-world evidence (RWE), and QoL. Exclusion criteria were: (a) case series; or (b) RWE and QoL studies with <10 patients. Only studies relevant to the USA were included for RWE and QoL analyses. The search was restricted to studies published in the English language between 2016 and May 10, 2019. Results The search identified 1,242 records. Of

these, 6 RCTs, 4 MAs, 2 ITCs/NMAs, 22 RWE studies, and 5 QoL studies were selected for extraction. Evidence from these selected studies showed LEN maintenance was associated with significantly longer progression-free survival (PFS) compared with no treatment (hazard ratio [HR] 0.46), placebo (HR 0.57), thalidomide (THAL; HR 0.60), or bortezomib (BORT; HR 0.86) (all P<0.05). Also, LEN maintenance was associated with significantly longer overall survival (OS) compared with no treatment (HR 0.74), placebo (HR 0.47), THAL (HR 0.63), or BORT (HR 0.74) (all P<0.05). RWE studies confirmed the positive impact of LEN maintenance on PFS and OS, and showed LEN maintenance was associated with a significantly longer time to next treatment and a reduction in the risk of progression versus no maintenance. LEN maintenance did not have a negative impact on patient QoL. Conclusions Recent clinical and RWE data indicate LEN maintenance was associated with a positive impact on PFS and OS. The superior outcomes of LEN maintenance over no maintenance support its use in patients with NDMM in the USA.

Keywords:
Lenalidomide

maintenance

Multiple myeloma

Tracks:
Myeloma Transplant and Maintenance Strategies

SP-162

Cognitive performance and perceived cognitive function in multiple myeloma patients treated with an autologous stem cell transplant: Results of the Brilliant Study

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Abstract:
Background:Treatment of multiple myeloma (MM) with induction chemotherapy followed by autologous hematopoietic cell transplant (auto HCT) improves event-free survival and overall survival. This prolonged survival has unmasked long-term complications related to therapy that impact quality of life. Studies in other cancers have identified cognitive impairment related to chemotherapy treatment based on exposure or dose. To date, there are no studies evaluating the impact auto HCT may have on cognition in MM patients. We administered standardized and validated measures of cognitive performance and self-reported cognitive problems to determine if there were changes in cognitive performance and cognitive problems following HCT. Methods: Patients with a diagnosis of MM (documented by IMWG criteria) and undergoing consecutive evaluation for auto HCT were consented for this study. Those illiterate or with uncontrolled psychiatric conditions were excluded. Participants underwent a baseline assessment including the Montreal Cognitive Assessment (MoCA), Self-Administered Gerocognitive Exam (SAGE) and the Patient Reported Outcomes Measurement Information System (PROMIS) Cognitive Impairment scale during pre-transplant evaluation and then 85-110 days post-HCT. Alternate forms of the MoCA and SAGE were used at each timepoint to reduce practice effects. Patients who completed all assessments were included in the final evaluation. MoCA and SAGE results were compared and cognition changes calculated using paired T-test statistical analysis. Patient testing tool preference was obtained after their evaluations. Results: 54 patients were consented with 36 evaluable patients (67%). Study included 16 women and 20 men with an average age of 64.6 and 72.2% (n=26) having an achieved education beyond high school level. Average pre-treatment scores of the MoCA, SAGE and PROMIS were 25.2 (SD=3), 17.2 (SD=3.9) and 29.6 (SD=6.5), respectively with no significant difference in scores by gender (p=0.93). The MoCA score at post-HCT evaluation was not different when compared to baseline (25.2 vs 25.8 p=0.68). The

same was seen with SAGE (17.2 vs 17.8, p=0.68) and PROMIS (29.6 vs 30.4, p=0.48) scores. When looking at gender, PROMIS scores among female patients decreased following HCT while increasing among males (mean -2.6 vs 3.6, p=0.007). When assessing SAGE, results in women improved slightly (mean=1.8) after HCT while a mild decrease (mean=-2.6) was seen in males (p=0.02). Patients showed no preference between the SAGE and MoCA. Conclusions:The MoCA and Sage tests showed no impact of HCT on cognition in the early follow-up. Interestingly, changes in cognition were perceived differently by gender. While females felt a decline despite of slightly higher SAGE scores, males felt cognitively better despite of lower SAGE scores after HCT. More studies comparing assessment tools and gender implications could help us understand how cognition is affected when managing MM.

Keywords:
cognition

myeloma

transplant

Tracks:
Myeloma Transplant and Maintenance Strategies

SP-163

IMPROVEMENT OF EARLY MORTALITY AND LONG-TERM SURVIVAL IN PATIENTS WITH MULTIPLE MYELOMA BETWEEN 1970 AND 2015

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Abstract:

Introduction: Multiple myeloma (MM) is the second most frequent hematologic malignant disease. The estimated 5-year overall survival (OS) is around 50%. The prognosis has steadily increased over the last decades. Nevertheless, many studies do not reflect properly the true real-world population. The aims of the study were to analyze the survival improvements and determine the incidence and causes of early mortality (EM) and predictors of long-term survival over the last 45 years in MM patients treated at a single institution. Methods: We reviewed the clinical records of MM patients diagnosed at a single institution between 1970 and 2015. One thousand one hundred sixty-one patients (591 [50.9%] male; median age at diagnosis 64 years) was the final study population. Median follow-up for alive patients was 5.4 years (range, 0.5-34.4 years). Relative survival (RS) and disease-specific incidence mortality were calculated and expressed in incidence rate ratio (IRR). Long-term survival was defined as those who lived more than 10 years after the diagnosis of MM. The population was divided into three periods, which included: group A (1970 to 1985), group B (1986 to 1999) and group C (2000 to 2015). Results: The median OS (mOS) of all patients was 3.6 years (95% CI: 3.2-3.8) from diagnosis. When demographic effects of age, sex, and year of diagnosis were compensated, the RS showed a continuous improvement during the periods analyzed, more pronounced in group C. The 5-year and 10-year RS were 26% and 8% in group A, 36% and 18% in group B, and 56% and 33% in group C, p<0.01. In the stratified analysis by age and sex, group B and C retained its prognostic value in terms of IRR compared with group A. The EM rate (first 60 days after diagnosis) was 5.8%; 16.5% in Group A, 5.5% in Group B, and 2.6% in Group C; p<0.01. The most frequent causes of early mortality were disease-related (46.7%, 63.6% and 66.6%; respectively), and infectious complications (36.7%, 22.7%, and 20.0%; respectively). In the multivariate Cox proportional hazard model in patients who received novel drugs, thrombocytopenia (OR 5.07, p=0.04), hypercalcemia (OR 11.5, p<0.01) and high beta-2 microglobulin (OR 8.81, p<0.01) were significantly associated with EM. Regarding long-term survival, in the multivariate analysis, clinical

variables at diagnosis associated with >10-year survival were age <60 years (OR 2.23, p=0.02), platelet count >190,000/uL (OR 1.98, p=0.04), and performing autologous stem cell transplantation (ASCT) (OR 4.25, p<0.01). Conclusions: This study shows that the survival outcome has significantly improved over the last decades in all age groups. The incidence of EM has decreased over time, being the most frequent causes of MM progression and infectious complications. Thrombocytopenia, hypercalcemia and high beta-2 microglobulin were associated with worst early outcomes and age<60 years, platelet count >190,000/uL and ASCT as predictors of long-term survival.

Keywords:
Long term outcome

myeloma

survival

Tracks:
Myeloma Transplant and Maintenance Strategies

SP-164

Depth of Response and Outcomes by Initial Therapy Prior to Autologous Hematopoietic Stem Cell Transplantation for Multiple Myeloma

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Abstract:
Background: Second generation proteasome inhibition can increase the depth of response in multiple myeloma (MM) patients (pts), which may be important for progression free (PFS) and overall survival (OS) after autologous hematopoietic stem cell transplantation (AHCT). We evaluated response and post-AHCT outcomes in pts treated with lenalidomide and dexamethasone with bortezomib (VRD) or carfilzomib (KRD). Methods: From 2012-2017, MM pts who received their first AHCT within 1 year of starting induction were identified from the database at Memorial Sloan Kettering Cancer Center & MD Anderson Cancer Center. Response was defined by the International Myeloma Working Group criteria. PFS and OS from time of AHCT were estimated by Kaplan-Meier methodology. Results: Among 665 pts who received AHCT, 328 (49%) received VRD and 94 (14%) KRD as induction. Median follow-up from AHCT in survivors was 2.93 years (range 0.06-5.91), with 84% receiving maintenance. Median age at AHCT was 62 (29-79), 59% male and 75% Caucasian. By the International Staging System (ISS) at diagnosis, 47%, 29% and 25% were stage I, 2 and 3, respectively; and 18% had high risk cytogenetics (del17p, t(4;14), t(14;16)). Median follow-up from AHCT in survivors was 3.1 yrs (range 0.06-5.91) for VRD and 1.1 yrs (range 0.24-2.8) for KRD, with 83% and 89% receiving maintenance respectively. Age, race and ISS were similar among those receiving VRD and KRD prior to AHCT. High risk cytogenetics were seen in 19 vs 26% (p=0.18), respectively. Pre-AHCT response was complete remission (CR) in 12% of all pts, 11% of VRD and 20% of KRD pts, while 53% of all patients, 52% of VRD, and 77% of KRD pts achieved ≥ very good partial remission (VGPR) (p<0.001). Median PFS from AHCT for the entire cohort was 3.6 years (95% CI 3.1 – 4.4 yrs) with 1-year and 3-year PFS 86% and 56%, respectively. Median PFS for VRD and KRD was 3.67 years (95% CI 3.01 – 4.35) and not reached (NR) (95% CI 1.8-NR), respectively (p=0.74). By univariable analysis, older age (HR 1.02, p<0.001), cytogenetic risk (HR 2.23, p<0.001), ISS stage 2 (HR 1.75, p <0.001) and 3 (HR 1.58, p=0.004), and stable disease/progression to initial therapy (HR 1.81, p=0.018) were associated with shorter PFS, but receiving VRD vs KRD induction was not (HR 0.83, p=0.53). All significant variables

remained significant in multivariable analysis. Median OS from AHCT for the entire cohort was NR (est 5.9 years, 95% CI 5.4 years - NR), with 1-year and 3-year OS 96% and 86%, respectively, and was not different between VRD and KRD (p=0.73). Age, cytogenetic risk, and ISS stage predicted for shorter OS by multivariable analysis. Conclusion: In this retrospective study, a higher proportion of pts achieved CR and ≥ VGPR with KRD compared to VRD. Post-AHCT outcomes were similar in both groups with shorter follow-up for the KRD pts. Future analysis will explore comparative effectiveness of post-AHCT outcomes with these regimens with longer follow-up.

Keywords:
KRD

Outcome

Stem Cell Transplant

Tracks:
Myeloma Transplant and Maintenance Strategies

SP-165

Interleukin-6 (IL-6) Blockade with Siltuximab Peri-Autologous Hematopoietic Stem Cell Transplantation (AHCT) May Reduce Symptom Burden by Altering the Cytokine Milieu in Older Patients with Multiple Myeloma (MM)

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Abstract:
Background: Elevated inflammatory markers during blood count nadir after AHCT for multiple myeloma (MM), such as IL-6, have been associated with symptom burden post-AHCT (Wang, 2014). As older pts can experience significant toxicities with AHCT, we aimed to mitigate fatigue and additional side effects using siltuximab (anti-IL-6 antibody, EUSA Pharma). Methods: C-reactive protein (CRP) and IL-6 were measured at baseline, day -2, 0, +3, +7, +14, +21, and +30. Siltuximab was given at 11mg/kg on day -7 and day +21 from AHCT. Patient reported outcomes (PROs) were assessed using the MD Anderson Symptom Inventory (MDASI)– MM at baseline, day -2, +7, and +30. IL-6 was quantitated with the Proteinsimple Ella platform. Results: Between 1/2018 – 5/2019, 25 pts were enrolled with a planned interim analysis done after 14 pts (median age 65 (range 60-70), 7 female). Median HCT-CI was 1 (range 0-8, with HCT-CI >2 in 5 pts) and median KPS on day -2 was 80 (range 70-90). Neutrophil engraftment occurred at a median of 9 days (range 8-11; 5 pts (38%) received at least one dose of filgrastim after engraftment. No pt had neutropenic fever and 2 pts developed engraftment syndrome. One pt developed a pneumonia requiring high-flow oxygen. The average MDASI-MM score per question at each time point ranged between 0-3 on a scale of 1-10, which represents an improvement from a historical control group where scores peaked at day 11 after AHCT with average scores up to 8. Two pts had mild first dose siltuximab infusion reactions, one with tingling of lips and one with hives that resolved with Benadryl. Neither had a reaction with the subsequent infusion. CRP levels were elevated at baseline in 85% of pts. Median CRP levels at each time point were 0.12mg/dL (range <0.05 – 0.42), 0.04 (0.04-0.05), 0.04 (0.04-0.11), 0.04 (0.04-0.04), 0.04 (0.04-0.04), 0.04 (0.04-5.04), 0.04 (0.04-2.8), and (0.04 (0.04-0.35), respectively. CRP remained elevated in two of the four pts at day +30 (0.09 and 0.35mg/dL). The pt with pneumonia had the highest CRP (5.04) at day +14. IL-6 levels were lower and with less intra-pt variation across time than in prior studies. Median IL-6 levels at each time point were 2 pg/mL (range 2-16), 759 (412-2598), 918 (349-2885), 1320 (380-2696), 1483 (773 - 128,861), 3688 (1664 - 68,235), 3502 (2346 - 80,070), and 3923 (1013 – 32,699). The pt with pneumonia had the highest IL-6 at day +7 when he was symptomatic, but the level normalized by day +14. Three pts with elevated levels at day +21 had normalization after the 2nd

dose. One pt with low CRP levels through day 21, had rising levels at day 30 and clinically had prolonged cytopenias associated with fatigue through day 40. Conclusion: In this interim analysis, we show for the first time that IL-6 blockade with siltuximab mitigated IL-6 elevation in most pts with improvement in PROs. Having passed the interim analysis for futility, trial enrollment continues and full results will be presented.

Keywords:
siltuximab

Stem Cell Transplant

symptom burden

Tracks:
Myeloma Transplant and Maintenance Strategies

SP-166

Successful Pharmacokinetic (PK)-Directed Dosing of Evomela® (propylene glycol free melphalan, PGF-MEL) for Multiple Myeloma (MM) and AL Amyloidosis (AL) Patients Undergoing Autologous Hematopoietic Stem Cell Transplant (AHCT)

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Abstract:
Background: High-dose melphalan prior to AHCT for MM and AL patients is currently given as a fixed dose based on body surface area leading to inter-patient differences in area under the curve (AUC). Increased exposure (higher AUC) leads to increased toxicity, but longer survival (Shaw et al., BBMT 2012). To optimize therapy, we evaluated the feasibility of PK-directed dosing of PGF-MEL (Acrotech Biopharma), a more stable and possibly less toxic intravenous formulation of melphalan. Methods: Patients were prospectively enrolled on a pilot trial and received 100mg/m2 of PGF-MEL on day -2 prior to AHCT. Serum samples were collected at 5, 15, 30, 40, 75, and 150 min after the dose and AUC PK modeling was used to determine the dose required to achieve a target AUC of 13.5mg/L*h (+/-1). The remainder of the calculated dose was given on day -1 with samples collected at the same timepoints in order to calculate the total AUC. After 5 patients were enrolled, the protocol was amended to increase the maximum allowable dose to the equivalent of 260mg/m2 from 220mg/m2. Patient-reported symptom burden was collected using the MD Anderson Symptom Inventory – MM (MDASI-MM) on day +1, 6, 11, 30, 60, and 90. Results: 15 patients (11 MM, 4 AL), 60% male, median age 62yr (range 48-71), median body surface area 1.9 (range 1.5-2.2), and with median creatinine 0.8mg/dL (range 0.7-1.6) have been treated. Thirteen of 15 patients (87%) achieved the target AUC. The median AUCs on day -2 and day -1 were 6.3 mg/L*h (range 4.2-11.4) and 5.6 (range 3.1 – 8.4) respectively, with a median total AUC of 13.2 (range 9.6-15.2). Three patients received the capped dose of 220mg/m2 prior to the amendment and achieved their predicted AUC; 1 patient received the minimum 140mg/m2 and also achieved the predicted AUC which was higher than the target AUC, as expected. The two patients did not achieve the target AUC were both below 13.5mg/L*h (+/-1). Median time to neutrophil engraftment was 9 days (range 9-12). The median number of red cell and platelet transfusions required were 0 (range 0-3) and 1 (range 0-8), respectively. Engraftment syndrome was seen in 30% of patients and 40% had neutropenic fevers. Twelve had at least 1 day of grade 2 diarrhea (median 2 days, range 0-7). The hematologic response rate post AHCT was 100% including complete remission in 20% and > very good partial response 73%. With median follow-up of 6.4 months (range 2.8-13.1 months), one patient with MM whose AUC was below the target (10.1 units) has relapsed. No patient has died. Conclusion: We show for the first time that PK-directed dosing using PGF-MEL was logistically feasible and allowed for personalization of therapy

to a target AUC. Data for an additional 10 patients, as well as patient-reported outcomes and toxicities will be presented at the meeting.

Keywords:
melphalan

Pharmacokinetics

symptom burden

Tracks:
Myeloma Transplant and Maintenance Strategies

SP-167

Cost of Autologous Hematopoietic Stem Cell Transplantation in Patients of Multiple Myeloma in a Tertiary Care Center in India

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Abstract:
Background &Introduction: Autologous Haematopoietic Stem Cell Transplantation (ASCT) has been an integral part of the management of Multiple Myeloma (MM) patients. During the past few years, several highly effective therapies have become available for treatment of myeloma, raising questions about the role of SCT for its management. Cost plays a major role in the therapeutic decision making in our country. Government tertiary care hospitals cater for MM patient management including ASCT at no out of pocket cost to the patient and all expenses are paid by the exchequer. The cost of transplant in government sector, where patient doesn't have to pay for his treatment has not been studied till date. Methods: Forty patients of MM who underwent ASCT between 01 Jan 2017 and 31 Mar 2019 were prospectively included in this study. All costs pertaining to the transplant were considered. They were divided into fixed costs (constant and mandatory for all patients undergoing ASCT) and variable costs (specific to each patient). The costs of tests, procedures and stay at hospital were derived from cost assessment mentioned by Government regulations (that were inclusive of all indirect costs and manpower estimates). The cost of drugs was based on the last purchase price (LPP) by the hospital. All costs were calculated in INR (1 USD = 70 INR). Statistical analysis was done using Pandas and statsmodel package of Python. Results: The fixed cost for the ASCT was INR 85882/-. The mean (+ SD) variable cost was INR 68429 (±35353, range 23038 to195370). The mean (+ SD) total cost was INR 154311 (±35353, range 108920 to 281252).These costs were much cheaper than the previous analysis done at another government institute (INR 500631) where the patients paid for their own expenses (Malhotra et al, 2007). The fixed cost constituted 55% of the total costs. Of the variable costs, the maximum expenditure was for plerixafor (Rs 12000, 7.77 %), followed by antibiotics (Rs 11235, 7.28 %), and antifungals (Rs 12984, 8.41 %). The mean(+ SD) cost per patient for BMT stay was INR 9840 (+ 4446, range 4800 to 20,400) and contributed to 6.37 % of the total cost. While each additional day of BMT stay costed the exchequer INR 1997/-, BMT stay itself was not significantly associated with the total cost (r=0.4, p=0.106). There was moderate correlation of the patients antibiotic requirement and total cost (r=0.65, p-0.001) that was statistically significant, suggesting major role of infection in the transplant costs. Though there was a moderate correlation between antifungals usage and the total cost (r=.56, p=0.057) it was not statistically significant, probably due to small fraction of patients requiring antifungals. Conclusions: The results signify that all eligible patients should be offered transplant in our settings as the total cost to the exchequer is significantly lower than the current costs at any other institute in the country.

Keywords:
autologous stem cell transplant

Health Economics

treatment costs

Tracks:
Myeloma Transplant and Maintenance Strategies

SP-168

LDH and Renal Function are Prognostic factors for Long-term Outcomes of Multiple Myeloma Patients undergoing Allogeneic Hematopoietic Stem Cell: a Cohort of 100 Recipients

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Abstract:
Allogeneic hematopoietic stem cell transplantation (Allo-SCT) has been the prototype of immunotherapy in hematological malignancies. Other immunomodulatory are now applied in multiple myeloma (MM) care, but Allo-SCT may still be indicated in selected cases. We retrospectively studied long-term outcomes in a cohort of 100 patients who underwent Allo-SCT at our center between 2000 and 2016. Patients' median age was 54 years. The median estimated glomerular filtration rate (eGFR) was 82 ml/min/1.73m2. Patients had received a median of 4 treatment lines before Allo-SCT, with the majority being previously autografted (93%). Stable disease was the predominant disease status at time of Allo-SCT (47%), with only 28% being in at least PR; 25% had progressive disease. The majority of recipients had a matched-sibling donor (61%) followed by matched-unrelated donor (28%), and mismatched donor (11%). Conditioning with fludarabine and melphalan was used in 65% of patients; melphalan was at a dose of 100 mg/m2 in 81% of cases. With a median follow-up of 12.2 years, the median overall survival (OS) and progression-free survival (PFS) were 9.2 months (IQR: 2.5-30.2) and 5.6 months (IQR: 2.03-13.6), respectively. At 5-years following Allo-SCT the probability for OS and PFS were 18.0% (95% CI: 0.3-25.8) and 16.8% (95% CI: 9.4-24.2), respectively. The cumulative incidence of 5-years relapse was high (45.9% [95% CI: 36.0-55.9]) as was as non-relapse mortality (NRM, 36.0% [95% CI: 26.6-45.4]). The cumulative incidence of grade 2-4 acute at 1-years GVHD and chronic GVHD at 5-years following transplantation were 36.4% (95% CI: 26.9-45.8) and 25.3 (95% CI: 16.7-33.8), respectively. In a multivariable Cox regression model, decreasing albumin, increasing LDH, advanced disease and mismatched donors were predictive of both reduced OS and PFS. In the univariate analysis, the 5-years OS/PFS corresponding with disease status were partial or better response (21%/24%), SD (23%/19%), PD (4%/4%), p-value (<0.001/0.002%). The probability of 5-years OS was also greater in patients with LDH below the upper limit of normal (22% vs. 5%, p=0.004). Low albumin and advanced disease were also associated with increased risk for relapse. In the multivariable analysis, the hazard of non-relapse mortality was increased with low albumin, mismatched donor type and declining eGFR. Indeed, in the univariate analysis, patients with an eGFR > 60 ml/min/1.73m2 had a 5-year NRM cumulative incidence of 31% vs. 56% in patients with lower levels (p=0.02). In conclusion, in this retrospective study of 100 MM patients with a median follow-up of 12.2 years, Allo-SCT may provide cure for a small selected group of MM patients. Our analysis demonstrated that aside from disease status, LDH and renal function are powerful determinants in patient prognostication. It will be interesting to explore the role of allogeneic transplantation in the current immunotherapy era and whether similar prognostic factors hold.

Keywords:
Allogenic stem cell transplant

prognostication

Tracks:
Myeloma Transplant and Maintenance Strategies

SP-169

Clinically significant delay in engraftment with day -1 melphalan prior to stem cell infusion in myeloma patients receiving stem cell transplant.

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Abstract:
Background Although single agent melphalan is considered the standard conditioning regimen for autologous transplant in myeloma, the timing of melphalan administration is less standardized with limited evidence on optimal timing of infusion. Methods We conducted a retrospective study comparing post-transplant outcomes between myeloma patients receiving conditioning melphalan on day -2 vs day -1 for autologous stem cell transplant. Between January 2017 and December 2018, 201 patients received melphalan on day -2 and 166 on day -1 prior to stem cell infusion. Results Baseline demographics and disease characteristics including disease status at transplant were well matched between the cohorts. Time from stem cell collection to transplant and CD34 progenitor cell dose was not significantly different when comparing day -2 to day -1. The number of stem cell collections patients underwent was higher in the day -2 cohort (median 2 for day -2 vs 1 for day -1, p=0.02). The median time between end of melphalan infusion and beginning of stem cell infusion for day -1 cohort was 18.6 hours. Rates of hospital admission were higher in the day -1 cohort although this did not meet statistical significance (48% for day -1 vs 42% for day -2, p =0.29). However duration of hospital admission was longer amongst the day -1 cohort (median 7 days for day -1 vs 5 days for day -2, p=0.003). Furthermore rates of fever were significantly higher in the day -1 cohort (69% vs 49%, p=0.0002). Neutrophil and platelet engraftment was achieved in all but one patient who died on day 13 post ASCT from hemorrhagic stroke. 3 patients required a second stem cell infusion prior to engraftment, two in the day -1 cohort and one in the day -2 cohort. Time to platelet engraftment was significantly longer in the day -1 cohort (median days 17 for day -1 vs 15 for day -2, p<0.0001). Although the median time to neutrophil engraftment was similar between the two cohorts, there were a greater proportion of patients with a longer time to neutrophil engraftment. Transfusion requirements in the first 100 days post-transplant were similar between the cohorts (median platelet units transfused 1 unit (range 0-27) for day -1 vs 1 unit (range 0-9) for day -2, p=0.84; median red cell units transfused 0 units (range 0-24) for day -1 vs 0 units (range 0-6) for day -2, p=0.84). Overall response rate was similar between the two cohorts (99% for day -1, vs 100% for day -2). The proportion of patients achieving at least a very good partial response was similar between the two cohorts (79% for day -1, vs 73.5% for day -2, p=0.22). Three patients died within 100 days of transplant, all in the day -2 cohort (100 day mortality 0 for day -1 vs 1.5% for day -2, p=0.25). Conclusion Day -1 melphalan infusions should be abandoned in preference for day -2 protocols, given the clinically significant delay in platelet and neutrophil engraftment and longer duration of hospitalization with day -1 infusions.

Keywords:
engraftment

melphalan

transplant

Tracks:
Myeloma Transplant and Maintenance Strategies

SP-170

The Effect of PET/CT Deauville Criteria on Progression Free Survival and Overall Survival in Multiple Myeloma Patients Following Autologous Stem Cell Transplantation

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Abstract:
Introduction and Objective Multiple myeloma (MM) is a clonal plasma cell malignant neoplasm that accounts for approximately 10% of hematologic malignant disorders. PET/CT is increasingly used as an imaging modality in MM. However, data about the role of PET/CT on prognosis are scarce. The aim of our study was to evaluate the role of Deauville score on PET/CT performed at day 100 after autologous stem cell transplantation, in terms of its guidance on treatment response, overall survival and progression free survival. Materials and Methods A total of 52 patients (26 male and 26 female, median age of 60) between the ages of 39-75, diagnosed with MM who had been treated with autologous stem cell transplantation and had a posttransplantation PET/CT within the first 100 days, were included in the study. Demographic, radiological and laboratory data were obtained retrospectively from the medical records. Deauville score was estimated using liver SUVmax uptake values. Using Deauville score on PET/CT, patients are preliminarily subdivided into two groups as Deauville negative (patient with a score of one, two or three) and Deauville positive (patient with a score of either four or five). Results The types of MM were as follows: 29 (55.8%) IgG, 8 (15.4%) IgA, 13 (25%) light chain disease and 2 (3.8%) of them had non-secretory MM. Ten of the patients (19.2%) had extra-medullary disease at diagnosis. Nine (17,3%) patients had high-risk cytogenetic features (13q-, 17p-, t(4;14), t(14;16), hypodiploidy). Initially 11 (18,2%) patients had ISS III disease. Twenty-six (50%) patients at day 100 after autologous stem cell transplantation were classified as Deauville positive and 26 (50%) as Deauville negative. The progression-free survival was 12(7,7-16,3) months for Deauville positive and 35(14,2-55,8) months for Deauville negative group respectively (p=0,04). The overall survival of Deauville positive group was 71(47,0-95,0) months, while Deauville negative group overall survival couldn't be reached (p=0,14). The third-year progression free survival was %18,5 for Deauville positive and %31,2 for Deauville negative group respectively (p=0,04). The third-year overall survival was %88,6 for Deauville positive group and %93,3 for Deauville negative group (p=0,14). The relationship between overall survival-ISS and progression free survival-ISS were not statistically significant (p=0,45 for overall survival, p=0,528 for progression free survival). Discussion and Conclusion In MM patients, Deauville score calculated by liver cut-off at day 100 after autologous stem cell transplantation was statistically significant for progression free survival, although not statistically significant for overall survival, have a tendency to predict overall survival. We also found that; the Deauville score at the day 100 after autologous stem cell transplantation have greater tendency to predict progression free and overall survival than ISS and ISS-R score of patients.

Keywords:
Deauville score

Multiple myeloma

PET-CT

Tracks:
Myeloma Transplant and Maintenance Strategies

SP-171

Preemptive plerixafor based mobilization strategy in multiple myeloma patients for autologous stem cell transplantation

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Abstract:
Background: Optimum mobilization of CD34+ve cells following G-CSF is critical for engraftment in multiple myeloma (MM) patients undergoing autologous stem cell transplantation (ASCT). Approximately 10% of patients are poor mobilizers. We compared use of pre-emptive plerixafor based on day 4 circulating CD34+ve cells with patients mobilized with G-CSF alone. Patients and methods: We retrospectively studied 84 consecutive multiple myeloma patients who underwent ASCT at our centre between 01 Jan 2017 and 31 May 2019. Patients median age was 52 yrs, ranging from 30 yrs to 72 yrs. 67.86 % were males. All patients received inj G-CSF 10 mcg/kg daily for 5 days, PB CD34 + counts were measured on day 4. Patients with CD34+ve counts <20/microlitre were defined as poor mobilizers and received Inj plerixafor (dose) at 0.24 mg/kg sc, followed by stem cell harvest 12 hours later. Engraftment kinetics of these patients (Group A, n=41) were compared to group which had PB CD34+ counts >20/µl (without plerixafor) (Group B, n=43). All patients who underwent ASCT were myelo-ablated using inj Melphalan 200 mg/m2 followed 24 hours later by infusion of non-cryopreserved stem cells. Results : All patients had received standard induction using novel agents. Median CD34+ cell doses of 3.19 million /kg and 3.01 million /Kg, respectively, p=0.30. Median time for neutrophil engraftment was 10.2 days in group A Vs 9.81 days in group B (p=0.17). Days for platelet engraftment was not different in two groups; Group A requiring :12.7 days vs 11.5 days in G-CSF alone, Gp B (p =0.1094). Median days of antibiotic requirement was also not statistically significant among the two gps viz, Gp A: 7.65 days Vs 7.16 days for Gp B, (p=0.548). Total days of hospitalization from day of transplant (Gp A: 16.02 days Vs 15.6 days in Gp B, p=0.64) were similar in two groups. Median number of RBC and single donor platelets (SDP) required were similar in two groups; Group A: 1.22 and 2.97 Vs and 0.88 Vs 2.74 in Gp B, (p= 0.3 and 0.49 respectively) Conclusion: Our results confirm the capacity of pre-emptive plerixafor based on day 4 PB CD34+ counts to improve mobilization in this poor risk group.

Keywords:
mobilisation

Multiple myeloma

plerixafor

Tracks:
Myeloma Transplant and Maintenance Strategies

SP-172

Natural killer cell alloreactivity is not beneficial in haploidentical bone marrow transplantation with post-transplantation cyclophosphamide for multiple myeloma: results of a prospective phase 2 clinical trial

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Abstract:
INTRODUCTION: Notwithstanding the progress made over the past years in survival of Multiple Myeloma (MM) patients, MM remains incurable. Haploidentical bone marrow transplantation (HaploBMT) is a treatment option with curative potential. HaploBMT already has shown clinical results however, only in a minority of MM patients. We hypothesize that this observation might be due

to differences in natural killer (NK) cell alloreactivity. In this prospective phase II study we investigate if NK cell KIR-ligand mismatched haploBMT with post-transplant cyclophosphamide (PTCY) will improve progression free survival in poor risk MM patients. METHODS: Poor risk MM patients (high-risk cytogenetics, relapse within a year after autologous SCT, or treated with three or more previous lines of therapy), aged < 66 years were enrolled if they were responsive to their last line of therapy. A prerequisite of enrollment was the possibility of an NK cell mismatch and availability of a mismatched family donor. Patients received a haploBMT with a non-myeloablative conditioning regimen and PTCY. RESULTS: In total, 12 poor risk patients were included from 3 hospitals in the Netherlands. We excluded one patient for further analysis due to disease progression just before BMT. Median time to follow-up is 19.8 months (range 5.9-33.8 months). Of the 11 patients evaluable patients, 10 achieved primary engraftment (91%), with a median time to neutrophil and platelet engraftment of 18 days (range 12-30 days) and 30 days (range 20-49 days), respectively. Grade 2-4 acute GVHD (aGVHD) occurred in 2 of 11 patients (none grade 3-4) and cGVHD occurred in 4 of 11 patients. Two of the 11 patients died of treatment-related mortality (18%). Of the 9 - for the primary endpoint evaluable- patients 8 patients relapsed within 1,5 years. Though relapsed, only 5/8 patients had to start anti-myeloma treatment. At day 30, all of the 9 analyzed patients showed NK cell recovery, though with an immature phenotype (NKG2A+, KIR-). At day 60 in both the peripheral blood as well as bone marrow, mature NK cells (KIR+) could be identified. DISCUSSION: The majority of patients showed early disease progression after mismatched haploBMT, comparable to results from haploSCT without mismatch selection. We hypothesize that the late reconstitution of functional mature NK cells is responsible for the lack of response. Though, not yet successful, we show that mismatched haploBMT in MM patients is feasible -in terms of engraftment and late NK cell reconstitution- save and forms a possible platform for future immunotherapeutic strategies.

Keywords:
Haploidentical stemcel transplantation

NK cells

Tracks:
Myeloma Transplant and Maintenance Strategies

SP-173

Clinical Characteristics, Survival Outcomes and prognosis in 82 Immunoglobulin D Multiple Myeloma Patients: A Retrospective Single-Center Study

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Abstract:
Objective: To analyze the clinical characteristics, survival outcomes and prognosis of 82 IgD MM patients that received different therapeutic patterns. Methods : A retrospective single-center study of 82 IgD MM (part of 1635 MM patients, 5.0%) treated between 1995.3 and 2017.12. Results: ①The median age was 51 years (29~72 years), male-to-female ratio was 59:23, with preponderance of lambda light chains (87.7%), high prevalence of BJP (81.8% vs. 66.0%) and low serum M-component (median 10.64 g/L vs. 25.14 g/L). Compared to non-IgD myeloma patients, patients with IgD myeloma had higher frequencies of renal failure (38.3% vs. 21.4%, p=0.000), bone marrow plasmacytosis ≥50% (37.1% vs. 25.8%, p=0.036), high serum LDH (44.6% vs. 11.9%, p=0.000) and extramedullary disease (18.2% vs. 9.7%, p=0.044). In addition, IgD myeloma was more frequently in patients at R-ISS stage III (39.7% vs. 28.5%, p=0.017), cytogenetic abnormalities (31.1% vs. 19.6%) and complex karyotype (26.2% vs. 15.2%). 88% (52/59) of the

patients with IgD myeloma had at least one cytogenetic abnormality demonstrated by FISH. The frequencies of 1q21 amplification (81.4% vs. 57.3, p=0.000) and t (11;14) (47.5% vs. 18.7%, p=0.000) were much higher in IgD patients.②Among 82 IgD MM patients, 31 received bortezomib-based treatment, 33 with non-bortezomib treatment, 18 cases with ASCT. The median OS were 35.3, 37.6 and 72.3 months respectively, the difference of OS between bortezomib-based and non-bortezomib group was not statistically significant (P=0.940), but the median OS of ASCT group was significantly better than the other two groups (p<0.05). After ASCT, 8 cases received maintenance therapy with thalidomide or lenalidomide (ASCT+ tha/len), 10 cases received 2-4 cycles bortezomib-based consolidation or second ASCT then followed by tha/len (ASCT+ bortezomib/ASCT+tha/len), The median OS were 72.3 months and non-reached respectively (p=0.413). Under novel therapies, the median OS of patients with IgD and non-IgD myeloma was 56.1 months and 72.2months, respectively (p = 0.402), median PFS was 30.6 months and 34.0 months, respectively (p=0.157). ③Multivariate analysis found R-ISS stage III and chromosome13 deletions were independent prognostic factor for overall survival. Conclusion: IgD myeloma is a rare subtype of myeloma(5%), affects younger patients and frequently presents with a high tumor burden, high frequency of genetic aberrations and features of advanced disease. Bortezomib alone did not bring more survival benefit in IgD myeloma, but ASCT could improve the outcome of IgD myeloma significantly. After ASCT, more intensive therapy with second ASCT or bortezomib-based consolidation did not bring more benefit compared with tha/len only. Under novel therapeutic patterns, the outcome of patients with IgD MM is similar to other myeloma subtypes. R-ISS stage III and chromosome13 deletions are independent prognostic factor for survival.

Keywords:
Clinical Characteristics

IgD

Outcome

Tracks:
Myeloma Transplant and Maintenance Strategies

SP-174

Interim Analysis of Indian Multicentre Phase II Randomized Study Comparing Three Subcutaneous Bortezomib-based Post Stem Cell Transplantation Consolidation/ Maintenance Regimens for Newly Diagnosed Multiple Myeloma Patients (IMPOSe-Bortecon) Study Number: 4905/2017

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Abstract:
Background & Introduction: Autologous stem cell transplant (ASCT) remains the backbone therapeutic modality with the highest progression-free survival (PFS) and overall survival (OS) benefit even in the era of the novel agents in newly diagnosed multiple myeloma (NDMM). The survival post-transplant can be prolonged using consolidation therapies. The regimen with maximum benefit is still debated, with bortezomib showing PFS benefit even in the high-risk myeloma. Aim & Objective: This randomized phase II trial is aimed at studying the efficacy and safety of post-transplant bortezomib with or without combination chemotherapy in patients with NDMM. The interim analysis intends to assess the remission status including minimal residual disease (MRD) and safety in patients post-ASCT among three regimens. Methods: Multicentric open-label interventional study with randomized allocation, parallel assignment, with intention-to-treat analysis. Recruitment was prospective starting 01 Jan 2017, including all NDMM patients eligible for the study. Remission status was evaluated at D100 and every 6 months for 2y post-ASCT, including MRD analysis by multicolor flow cytometry (MFC) and PET/CT. All patients will be followed for 5y post-ASCT for

PFS and OS. Interim analysis was planned after the recruitment of 06 cycles of consolidation in 50% of the study population. The three arms included (Arm-A) bortezomib alone (V), (Arm-B) bortezomib in combination with cyclophosphamide and dexamethasone (VCD) and (Arm-C) bortezomib in combination with lenalidomide (VR) starting D100 till 2y post-ASCT. Adverse events with CTCAE grade < 2 were defined as non-serious and rest as serious. JMP ver. 13 was used for statistical analysis and $p<0.05$ was considered significant. Results: A total of 78 patients were enrolled till date with equivalent allocation in three arms (24,28,26 respectively). The median age of the study population was 52y (35-66y) with male preponderance (n-48, 61.5%). The remission status was similar in all arms with one progression in Arm A & C each (p-NS). The MRD by MFC, PET positivity and remission status were comparable in all the three intervention arms (p-0.55, p-0.62, and p-0.81 respectively). MRD negative status was achieved in 75%, 61% and 64.7% (p-0.54) in the three arms respectively. All-cause mortality was seen in 2 patients prior to randomization and 1 patient in Arm B. Serious adverse events (SAE) were noted in a significantly higher number of patients in Arm A vis-a-vis Arm B and C (p-0.02) with Arm A recording more neuropathy, whereas Arm C with more neutropenia. Non-SAE were significantly higher in Arm C ($p<0.01$). Conclusion: As per the interim analysis, all the regimens were safe with slightly higher SAE in Arm A, and higher non-SAE in Arm C. There was no significant difference in the MRD by MFC, PET positivity or remission status in any intervention arm.

Keywords:
maintenance

Newly diagnosed multiple myeloma

transplantation

Tracks:
Myeloma Transplant and Maintenance Strategies

OTHER PLASMA CELL DISORDERS AND AMYLOIDOSIS

SP-175

Impact of consolidation therapy post autologous stem cell transplant in patients with light chain amyloidosis

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Abstract:
Introduction: Autologous stem cell transplantation (ASCT) is an effective therapy for eligible patients with immunoglobulin light chain amyloidosis (AL) and is able to induce deep and durable remissions. However, not all patients achieve a deep response after ASCT and the role of consolidation post ASCT in AL amyloidosis is not well defined. Methods: We retrospectively identified patients who had AL amyloidosis and who had ASCT between May 2005-March 2017 at the Mayo Clinic, Rochester, Minnesota. In this study the term consolidation was used to describe any treatment given at or beyond the day 100 evaluation post ASCT to deepen or to maintain the achieved response, without evidence of progression when starting therapy. Patients with and without consolidation therapy were compared in terms of baseline characteristics and outcomes. The type of treatment received, duration, and change in the depth of response were recorded. Progression-free survival (PFS) and overall survival (OS) were also documented. Results: We identified 471 patients, of whom 72 (15%) received consolidation. Patient receiving consolidation had more advanced

disease (Mayo 2012 stage ≥II in 67% vs. 52%, P=0.02) and had lower day 100 response rates (very good partial response (VGPR) or better : 35% vs.84%, P<0.0001), compared to patients not receiving consolidation. Most patients received consolidation therapy with novel agents; immunomodulators (IMiDs, mainly lenalidomide) (29%), proteasome inhibitors (PI, mainly bortezomib) (33%), or a combination of both (28%). Most patients (78%) received steroids in combination with their baseline treatments. After consolidation, rates of VGPR improved from 24% to 28% and rates of complete response (CR) improved from 11% to 40%. Patients with less than VGPR who received consolidation had better PFS than patients who did not receive consolidation (median of 22.4 vs. 8.8 months, P <0.0001). The benefit was greater in those who deepened their response after consolidation (median of 41 vs.8.8 months, P<0.0001). In patients with less than VGPR, there was a trend for better OS in patients with less than VGPR who responded to consolidation (median of 125.8 vs. 74.4 months, P=0.07). In patients who achieved VGPR or better at day 100 post ASCT, consolidation did not improve PFS or OS. Conclusion: Consolidation therapy for patients with AL amyloidosis who are less than VGPR post ASCT results in improved PFS, and should be considered in this population. Patients who achieve VGPR or better post ASCT have better outcomes and are less likely to benefit from consolidation and may be monitored until disease progression.

Keywords:
autologous stem cell transplant

consolidation

Light chain amyloidosis

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-176

Increased mTOR activation in idiopathic multicentric Castleman disease

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Abstract:
Idiopathic multicentric Castleman disease (iMCD) is a rare and deadly hematological disorder characterized by lymphadenopathy and diverse symptoms such as systemic inflammation, cytopenias and multi-organ dysfunction. A recent study led by the co-authors identified the PI3K/Akt/mTOR signaling pathway as a driver of iMCD in 3 patients, who responded to the mTOR inhibitor sirolimus. PI3K/Akt/mTOR is a signaling pathway central to protein synthesis, cellular proliferation, and metabolism and is implicated in multiple hematological disorders. Here, we expanded our investigation of mTOR signaling to 26 iMCD patients. We found that iMCD lymph node tissue had increased mTOR activation in the interfollicular space as compared to sentinel controls by immunohistochemistry (IHC) for pS6, p4EBP1, and p70S6K, known effectors and read-outs of mTOR activation. IHC staining for pS6 also revealed that mTOR activation was significantly increased in iMCD lymph node tissue as compared to Hodgkin lymphoma, systemic lupus erythematosus, and reactive lymph node tissue, suggesting that the level of mTOR activation in iMCD is not just a product of lymphoproliferation. Further, mTOR activation in iMCD lymph node tissue was comparable to autoimmune lymphoproliferative disorder (ALPS), a disease known to be driven by mTOR hyperactivation and treated first-line with mTOR inhibition. Finally, we showed by co-immunofluorescence staining for pS6 and 6 cell markers that mTOR activation in the interfollicular space occurred across multiple cell types, including plasma cells and macrophages. These findings support mTOR activation as a novel therapeutic target for iMCD, which is being

investigated through a trial of sirolimus in anti-IL-6 refractory iMCD patients (NCT03933904).

Keywords:
Castleman disease

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-177

BCMA expression in AL Amyloidosis

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Abstract:
Introduction AL Amyloidosis is a multisystem disorder of clonal plasma cells (PCs) that produce an abnormal light chain which misfolds and deposits in organs causing cellular stress, organ dysfunction and eventually death. Available therapies target PCs to stop the production of amyloidogenic light chains. The burden of clonal PCs in bone marrow (BM) is typically less in AL than in Multiple Myeloma (MM) which is potentially advantageous for immunotherapeutic strategies. B-Cell Maturation Antigen (BCMA) is a transmembrane protein that is involved in the regulation of B cell proliferation and survival as well as maturation/differentiation into PCs. Given the efficacy of therapies targeting BCMA in MM, we evaluated the expression of BCMA on the surface of clonal PCs from patients with AL amyloidosis. Methods Patients with AL amyloidosis who had available unstained BM biopsies at our center between 2012 and 2018 were identified. Specimens were stained for BCMA expression using immunohistochemistry (IHC; clone: D6, catalog: sc-390147, company: Santa-Cruz, monoclonal, dilution 1:400) with a clinical grade assay performed in a CLIA compliant setting. Biopsies were scored for expression, intensity, and site of staining. Results We identified 28 diagnostic and 6 relapsed BM biopsies available for staining. The median age of the population was 63 years (range, 41-73 years); 64% were male and 36% female. Lambda-typic PCs were seen in 75% of patients. By fluorescence in situ hybridization, t(11;14) was present in 36% patients, and gain of chromosome 1q and del 13q were each seen in 32% of patients. No patient had t(4;14) or del 17p. At diagnosis, the median clonal PC burden in BM was 10% (range 2-80%) and 36% had > 10% plasma cells. In clonal PCs, the median BCMA expression was 80% (range 20-100%) with membranous staining in 82% of patients and a Golgi pattern in 11%. The median staining intensity was 2 (range 1-3). Six patients had both diagnosis and relapsed BM tissue available. At diagnosis, the median PC burden was 35% (range 10-80); 83% had > 10% clonal PCs. The median BCMA expression was 65% (range 50-80) and staining was membranous in 50%, Golgi in 17%, and Golgi-membranous in 33%. At relapse, the median clonal PC burden was 13% (range 5-30). Median BCMA expression was 75% (range 50-100) with predominantly membranous staining (83%). The median staining intensity in both diagnostic and relapsed tissue was1. Conclusions This study represents the first description of BCMA expression on the surface of amyloidogenic PCs to our knowledge. BCMA is uniformly expressed by pathologic PCs in AL amyloidosis and remains present at the time of relapse. These data suggest that BCMA directed approaches may represent an effective therapeutic option in AL Amyloidosis and should be explored in the future.

Keywords:
amyloidosis

B-cell maturation antigen

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-178

Identifying regulatory mutational densities within Waldenstrom's Macroglobulinemia by whole genome sequencing

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Abstract:
Introduction Promoters and enhancers are specific regulatory regions within DNA that control the initiation of transcription and modulate transcription efficiency. Because there are no defined, set descriptions where these regions must be positioned on the genome, regulatory studies can be difficult. Our goal is to identify regulatory dysfunction within Waldenstrom's Macroglobulinema (WM) patients. Methods Whole genome sequencing data was analyzed for 54 WM patients to identify mutational density peaks throughout the genome. A R script was written to scan across the whole genome using a 200 nucleotide window around each nucleotide and to calculate the total number of mutations across all samples seen within this window. Regions with total mutation counts >7 (the top 2.5 percentile) were used to identify specific areas with normally high mutational load. Differential gene expression analysis was performed on the affected and unaffected region patient groups and DAVID was used to identify gene functional annotation classification and clustering on the gene expression results. Results Mutations were found in 24.07% (n=13) of WM patients within the intergenic space between genes CCAAT/enhancer-binding protein delta (CEBPD) and DNA-dependent protein kinase catalytic subunit (PRKDC). The top DAVID annotation enrichment for differentially expressed genes associated with mutations in the region included terms: GO:0051436~negative regulation of ubiquitin-protein ligase activity involved in mitotic cell cycle, GO:0000165~MAPK cascade, GO:0038061~NIK/NF-kappaB signaling, GO:0050852~T cell receptor signaling pathway, GO:0090263~positive regulation of canonical Wnt signaling pathway, GO:0000245~spliceosomal complex assembly, GO:0000387~spliceosomal snRNP assembly, and GO:0070374~positive regulation of ERK1 and ERK2 cascade. There is a log2 fold change of 0.481 and -0.549 in transcript per million (TPM) expression levels between affected and unaffected patients for CEBPD and PRKDC, respectively. Conclusions Based on these findings, there is evidence of a targeted regulatory region between CEBPD and PRKDC based on the mutational density. There is a relationship between NFkB and CEBPD that shows a coherent feed-forward type I regulatory circuit controlling NFkB activation and TLR-4 stimulation (Litvak et al. Nat Immunol 2009). PRKDC is a serine/threonine-protein kinase that acts as a molecular sensor for DNA damage and is involved with DNA strand repair and V(D)J recombination. Looking at mutational densities along the whole genome is a promising method for finding regulatory regions of interest.

Keywords:
Bioinformatics

Waldenström macroglobulinemia

Whole genome sequencing

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-179

POEMS SYNDROME: A single centre study of 68 patients and comparison of consolidation Autologous stem cell transplant(ASCT) versus non-ASCT cohorts.

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Abstract:
INTRODUCTION: We here present the updated report of clinical features and treatment outcome of 68 cases seen over a period of 26 years. Data was compared with 14 patients who underwent Autologous stem cell transplant (ASCT).METHODS: Between January 1993 and May 2019, 68 patients were diagnosed to have POEMS syndrome using Mayo Clinic criteria (2011). Major criteria was optional as we do not routinely do VEGF assay. RESULTS: Patients median age at diagnosis was 46.8 years (Range 23-70 years). The male: female ratio was 4.2: 1. Polyneuropathy and monoclonal gammopathy were present in all patients. Other features were : endocrinopathy (in58%), hypogonadism (25%), adrenal axis disorders(17%), hypothyroidism in 47% of patients. 17 patients had Castleman's disease (hyaline vascular). Effusions were noted in 41% patients. Osteosclerotic bone lesions were present in 69% patients. 14/68 (20.6%) patients underwent consolidation with ASCT after a median of 6 cycles of induction. Bortezomib and Dexamethasone (Vd) was the most common regimen. Other regimens included -Meplalan-prednisolone (MP) ,bortezomib-lenalidomide-dexamethasone (VRd) ,Bortezomib-cyclophosphamide-dexamethasone (VCd) ,lenalidomide-dexamethasone(Rd) in 1 patient, each. Post induction 10 patients achieved complete haematological response (CRH), 4 had partial (PRH) while there was clinical improvement in 10 of 14 patients. Median interval from diagnosis to ASCT was 14 months (range=4.0-26.9 months). Median melphalan dose was 140 mg/m2. Four patients had Engraftment syndrome. Post- transplant all 14 achieved CRH. There was no transplant related mortality. Modified Rankin Score (mRS) was used to assess the improvement in disability after treatment. Median baseline score among these 14 patients was 4 that improved to 3 after induction and maintained at 3 after ASCT. Remaining 54 patients received induction followed by maintenance therapy. 40 patients had received one line induction regimen. and two lines were used in 14. Common induction regimens were MP(n=23) followed by VD- (n=22) and Lenalidomide +Dexa (Rd) (4), VCd xa (3),VRd (2) .Response was evaluable in 39 patients. At a median follow up of months 12 achieved CRHand PRH in 15 patients. Clinically improvement (CR+PR) was noted in 27 and stable disease was seen in 12. Median mRS improved from 4 to 3 during this period. The hematological response at last assessment was better in the transplant group compared to non-transplant, although it did not reach to the level of statistical significance . At a median follow up of 64 months (range 12- 96 months), the median overall survival was not reached. On univariate analysis none of the factors appeared statistically significant.CONCLUSION: Clinical presentation of POEMS from our centre is similar to that reported from larger studies. ASCT after initial induction is a feasible, safe option in POEMS syndrome and is associated with improved response rates and most responses durable.

Keywords:
clinical data

myeloma

POEMS syndrome

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-180

Impact of tumor size and minimal marrow involvement on outcomes of patients with solitary plasmacytoma

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Abstract:
Introduction: Solitary plasmacytoma (SP) is a rare plasma cell neoplasm subtype that is characterized by biopsy-confirmed solitary lesion of bone or soft tissue with evidence of clonal plasma cells. Due to its rarity, several clinical questions, including the optimal initial treatment strategy, incidence of systemic progression, and factors affecting survival, remain unclear. We conducted a retrospective study to clarify these aspects of SP. Methods: We analyzed patients who were initially diagnosed with SP and treated at our institution between 2000 and 2017. All SPs were reclassified as SP or SP with minimal marrow involvement according to the 2014 IMWG criteria. Results: In total, 97 patients were diagnosed with plasma cell neoplasms. Among them, those with multiple myeloma (MM), plasma cell leukemia, plasmablastic lymphoma, MGUS, and multiple solitary plasmacytoma (MSP) were excluded. As a result, we identified 21 patients (21%), of whom 16 with SP and 5 with SP with minimal marrow involvement were used as subjects in this study. Ten patients (48%) were male and 11 (52%) were female, with a median age of 60 years (range: 24-84), and 14 patients (67%) had detectable M-protein. The median tumor size was 4.2 cm (range: 0.5-8.0 cm), and 13 patients (62%) had tumors smaller than 5.0 cm and 8 patients (38%) had 5-cm or larger tumors. The most frequently involved site was the vertebra (29%) followed by nasal cavity (14%), sacrum, femur, and clavicle (9.5% each). As initial treatment, 12 patients (57%) received radiotherapy alone, 6 (28%) received surgical resection alone, 2 received chemotherapy, and observation was selected for the remaining one patient. During the median follow-up duration of 57 months (range: 8-215), 11 patients (52%) developed systemic progression to MM (8 patients), MSP (2 patients) and POEMS (1 patient), respectively. The cumulative incidence of systemic progression at 5 years was 40.5% (95%CI: 18.3-61.9%) and median time to systemic progression was 64 months (95%CI: 13.8-NA). Tumor size >5 cm (HR 12.55, 95%CI: 2.753-57.17, p=0.0011) and age >60 years (HR 4.273, 95%CI: 1.447-12.61, p=0.0086) were adverse factors for systemic progression based on the multivariate analysis. The 5-year overall survival (OS) rate for all 21 patients was 75% (95%CI: 45.2-90.1%) and the median OS was not reached. The detectable M-protein and tumor size >5 cm led to a poorer 5-year OS than the absence of M-protein and tumor size <5 cm (57% vs 100% and 64% vs 81%, respectively). In the multivariate analysis, the presence of minimal marrow involvement was an adverse factor affecting OS (HR 19.34, 95%CI 1.883-198.7, p=0.013). Conclusion: Although the total number of patients was relatively small, our detailed clinical data analyses demonstrated a tumor size >5 cm and minimal marrow involvement to negatively affect the outcomes in patients with SP. Novel treatment strategies may be needed for patients with SP having these adverse factors.

Keywords:
PLASMACYTOMA

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-181

Bortezomib, cyclophosphamide, and dexamethasone (CyBorD) as front-line treatment for systemic AL amyloidosis (AL): a real-world experience at a single centre

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Abstract:
Introduction Bortezomib, cyclophosphamide and dexamethasone (CyBorD) as first-line treatment for AL amyloidosis was reported to have excellent clonal responses (Venner et al, 2012; Mikael et al, 2012). We sought to undertake a "real-world" local analysis of CyBorD in this setting. Method We

conducted a single-centre, retrospective, observational study of response rates and overall survival for patients undergoing CyBorD frontline treatment for AL amyloidosis between September 2014 and May 2019. Results Thirty eight patients were identified. Median age was 63.5 years. Based on the Revised Mayo Staging System, there were 6 patients (15.8%) in Stage I, 7 (18.5%) in Stage II, 11 (28.9%) in Stage III, and 14 (36.8%) in Stage IV. Amyloid organ involvement included cardiac in 28 (73.7%), renal in 12 (31.6%), and gastrointestinal in 2 (5.3%). Median follow-up was 24.5 months (range 2-53 months). Overall haematological response (PR or better) was observed in 35 (92.1%) patients, VGPR or better in 26 (68.4%), and CR in 14 (36.8%). A VGPR was achieved in 25 (65.8%) after completing two cycles of CyBorD. Cardiac response (NTproBNP>30% decrease) occurred in 14/28 subjects (50%) and renal response (proteinuria >50% decrease) occurred in 3/12 subjects (25%). Median progression free survival was 17.8 months in 33 out of 38 subjects who did not undergo planned autologous stem cell transplant. Overall survival after 12 months was 90.3%. Median overall survival was 29 months. Median overall survival for Revised Mayo Stage I and II cohorts versus Stage III and IV cohorts were 26 months and 29.6 months (p= 0.067). Ten patients died: 90% had cardiac decompensation; 5 had Stage IV disease; 2 were non-responders. Median NTproBNP at diagnosis was 638pmolL in the deceased cohort versus 393pmol/L in patients still alive. There was no difference between median overall survival for patients who achieved a VGPR by cycle 2 and for those who did not (28.9 vs 28 months) (p=0.59). Conclusion CyBorD was an excellent frontline treatment for AL amyloidosis with impressive clonal and moderate organ responses. Patients with early stages cardiac disease had better outcomes. Although CyBorD did not confer long term PFS, our study suggested the treatment offered brisk clonal responses to stabilize the initial phase of the disease.

Keywords:
NTproBNP

VCD

VGPR

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-182

Ixazomib, lenalidomide and dexamethasone in relapsed AL amyloidosis – a first report

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Abstract:
Background Ixazomib is a next generation oral proteasome inhibitor with proven efficacy in relapsed AL amyloidosis. Whilst the combination of ixazomib, lenalidomide and dexamethasone (IRd) is established in multiple myeloma, its role in AL amyloidosis is undetermined. We present the UK experience of this regimen in the treatment of relapsed refractory AL amyloidosis. Method Forty patients treated with IRd, between 2016 and 2019, were identified from the database at the UK National Amyloidosis Centre. Haematological and disease responses were defined as per the international amyloidosis consensus guidelines. Median progression-free (PFS) and overall survival (OS)

was determined by the Kaplan-Meier method and correlations made using log-rank test. Results Thirty-eight patients were evaluable having received ≥2 cycles of IRd. Two patients received <2 cycles: 1 died, 1 developed grade 3 skin toxicity. The median age was 66 years (range 42-80 years); 60.5% male and cardiac disease stage (Mayo 2004) was: Stage 1 - 8 (21.1%), Stage 2 - 14 (36.8%), Stage 3A - 13 (34.2%) and Stage - 3B, 3 (7.9%). Organs involved were: heart - 28 (73.7%), kidneys - 27 (71.1%), liver - 11 (28.9%), peripheral nerve - 1 (2.6%), autonomic nerve - 6 (15.8%) and soft tissue - 11 (28.9%). Median prior lines of therapy 2 (range 1-4) and all were previously treated with bortezomib. Patients received a median 6 cycles of IRd (range 1-36). At a median follow up of 10.5 months (range 2-35 months), 7 (18.4%) patients died. 12 (31.6%) stopped treatment, 17 (44.7%) continued on IRd and 1 (2.6%) patient was lost to follow up. Haematological responses at 3 months were: complete response (CR) 7 (18.9%), very good partial response (VGPR) 8 (21.6%), partial response (PR) 7 (18.9%). 15 (40.5%) had stable or progressive disease. 25 and 14 patients respectively were assessable for cardiac and renal response at 6 months with responses seen in 5.9% and 14.3% respectively. Median PFS was 16.6 months (95% CI 8.8-19.2 months) with a non-significant trend towards reduced PFS in patients treated with prior lenalidomide. Patients achieving a CR/VGPR had a markedly better PFS of 26.7 months (95% CI 17.6-35.9 months) (p=0.001). Median OS was 27.3 months (95% CI 22.4-32.2 months) and in patients achieving a CR/VGPR was 30.6 months (p=0.106). 12 (31.5%) patients experienced a total of 16 grade 3-4 adverse events: 6 (37.5%) infection, 4 (25%) fluid overload, 3 (8.3%) haematological, 2 (12.5%) cardiac arrhythmia and 1 (6.3%) renal. Conclusion Ixazomib-Lenalidomide-Dexamethasone has activity in relapsed AL amyloidosis with deep responses (VGPR or better) in 40.5% of patients. The patients achieving a CR/VGPR had significantly longer PFS. A third of all patients experienced significant toxicity. This initial data is encouraging and supports formal prospective study of IRd in a larger cohort of patients with AL amyloidosis

Keywords:
amyloidosis

ixazomib

Lenalidomide

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-183

The PROMISE Study: A Nationwide Project for Predicting the Progression of Developing Myeloma in a High-Risk Screened Population

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Abstract:
Background: Monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) are premalignant disorders that progress to overt multiple myeloma (MM) in a subset of individuals for reasons that are poorly understood. The PROMISE Study is a nationwide study that is screening 50,000 individuals at an increased risk for MGUS and SMM, specifically those who are between 45 and 75

with either (1) a family history of a plasma cell dyscrasia or (2) who self-identify as being of African descent. The primary goal of PROMISE is to establish the first screen-detected cohort of patients with MM precursor conditions to identify novel regulators of disease progression and therapeutic options. Methods: Launched in October 2018, the PROMISE Study engages through phone, email, social media, and advocacy groups to educate and assist with consenting, sample collection, and follow-up care. Registration occurs through the study website (www.enroll.promisestudy.org) and enrolled participants are mailed a kit with 3 blood tubes. Participants attend a local clinic for a free blood draw and the resulting samples undergo serum protein electrophoresis and immunoglobulin free light chain testing and research processing. Screening results are communicated to participants who are then asked to complete a baseline questionnaire. Participants who screen positive for MGUS/SMM are asked to sign a Positive Consent Form and Authorization for the Release of PHI to allow the PROMISE team to receive bone marrow and blood samples and medical records from their hematologist. Results: In the first 8 months, 1256 individuals from 50 states have enrolled and 838 (67%) have consented. Accrual continues at a rate of ~200 participants per month. To date, 797 blood draw kits have been mailed to participants and 414 (52%) have been returned for testing. Of those screened, 11 (2.7%) have tested positive for clinical indications of MGUS/SMM and 403 (97.3%) have tested negative. All screened participants have been informed of their results and invited to take the baseline questionnaire, of which 314 (76%) have completed. All 11 (100%) positive participants have scheduled appointments with local oncologists/hematologists and 6 (55%) have sent follow-up medical records and/or bone marrow biopsy and blood samples. Conclusion: The PROMISE Study has created an opportunity for individuals nationwide to take control of their health and contribute to research by establishing a screening study for precursor conditions to MM. This initiative demonstrates the feasibility of obtaining data from a large sample of individuals at risk for MGUS and SMM. As accrual and data collection continue, genomic analysis and epidemiological explorations will be conducted. These studies will not only lead to a better understanding of disease progression in MGUS and SMM patients but may also identify new therapeutic options that will make MM a preventable disease.

Keywords:
Monoclonal Gammopathy of Undetermined Significance

screening

Smoldering Multiple Myeloma

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-184

Minimal residual disease (MRD) in Waldenström macroglobulinaemia (WM): Impact on survival outcomes with rituximab-based therapies.

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Abstract:
Minimal residual disease (MRD) is an independent predictor of survival outcomes in many haematological malignancies, most notably myeloma and CLL. Rituximab-based regimens are widely used as primary therapy in WM with excellent response durations noted in many patients

despite the apparent rarity of complete responses (CR). We have previously demonstrated that rituximab-based therapies can result in depletion of monotypic B-cells but a persistence of CD20- plasma cells. This phenomenon can result in delayed serological responses and may also explain the low incidence of CR. We have therefore developed a flow cytometry assay (based upon the unique immunophenotypic profile of WM B-cells) in order to quantify the extent of B-cell depletion with rituximab-based therapies. This assay has a limit of detection of 0.004%. Aim: To determine the prognostic significance of residual neoplastic B-cells in WM following rituximab-based therapy in the context of the UK R2W clinical trial. Method: 60 treatment-naïve WM patients were enrolled onto the study, which involved 2:1 randomisation to treatment with BCR (Bortezomib; Cyclophosphamide; Rituximab) or FCR (Fludarabine; Cyclophosphamide; Rituximab). Bone marrow aspirate and peripheral blood samples were obtained at baseline, post 3 cycles of treatment and at 3 months following the end of therapy (EOT). Results: WM-phenotype B-cells were confirmed in BM samples in 59/60 patients with a single patient excluded from further analysis following central pathological review. Circulating WM B-cells cells were demonstrable at presentation in 43/55 (78.2%) patients at a median of 0.087x10^9/l (0.014-1.5). The MYD88 L265P mutation was demonstrated in 53 of 57 assessable patients (93%). 44 patients were assessed following 3 cycles and 20/44 (45.5%) were considered MRD-ve while the remaining patients (24/44, 54.5%) had detectable residual disease with a median of 0.99% (0.04-32%) WM B-cells. 53 patients were assessed at the EOT with 29/53 (54.7%) considered MRD-ve. 24/53 (45.3%) had detectable residual disease with a median of 0.26% (0.02-11.2%) WM B-cells. 4 patients with detectable residual disease following three cycles became MRD-ve at the EOT. The presence of residual WM B-cells was associated with an inferior outcome. The 3-year TTF for those with residual WM B-cells following 3 cycles of therapy was 69.2% versus 100% for those considered MRD-ve (p=0.005). At the EOT the 3-year TTF was 58.4% for those with detectable WM B-cells versus 100% for MRD-ve patients (p<0.001). Conclusion: We have developed a sensitive WM-specific MRD flow assay. This allows for a quantitative assessment of BM B-cell depletion following rituximab-based therapies. The presence of residual WM B-cells is associated with inferior survival outcomes and may be a better predictor of response and outcome than conventional IgM responses.

Keywords:
Flow Cytometry

Minimal residual disease

Waldenström macroglobulinemia

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-185

Cell-Free DNA as Alternative to Bone Marrow CD19+ Selection for Diagnostic MYD88 L265P in Waldenstrom's Macroglobulinemia

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Abstract:
Background Mutations in MYD88 are found in over 95% Waldenstrom's Macroglobulinemia (WM) patients, nearly all of which correspond to the c.978T>C mutation resulting in an p.Leu265Pro (L265P) substitution at the protein level. Increasingly, allele specific PCR (AS-PCR) to detect the L265P mutation is being used in clinical pathology for diagnostic and prognostic purposes. Unless B-cell enrichment by CD19+ selection is used, the sensitivity of these tests can suffer. Given the heavy involvement of WM cells in the bone marrow (BM) of most patients, BM aspirates

provide a greater enrichment of WM cells compared with peripheral blood (PB), regardless of CD19+ selection. As CD19+ selection is expensive and impractical for most testing facilities and BM aspirates are far more painful and invasive than PB draws, we evaluated the use cell-free DNA (cfDNA) for diagnostic MYD88 L265P testing and compared it with matched PB and BM aspirate DNA with or without CD19+ selection. Methods Blood was collected in Streck Cell-Free DNA BCT tubes and plasma isolated within 6.5 hours of blood draw. cfDNA extraction was accomplished with the QIAGEN Circulating Nucleic Acid Kit with modifications based on Kang et al ClinBiochem 2016. MYD88 L265P detection by AS-PCR followed established methods from Xu et al, Blood 2013. We collected cfDNA, BM CD19+ cells (BM19+), unselected BM mononuclear cells (BMMC), PB CD19+ cells (PB19+), and PB mononuclear cells (PBMC) from the same visit and ran the L265P AS-PCR assay for each on the same plate to avoid potential batch effect. Relative L265P enrichment was calculated as the difference between the cfDNA and the other comparators using the ddCT method. Results 5 WM patients were screened for the L265P mutation across all 5 fractions (cfDNA, BM19+, BMMC, PB19+, and PBMC). The median age of the patients was 68 (range 60-79) years, BM intertrabecular involvement of 25% (range 5-70%) with 3/5 (60%) of patients having received one prior therapy consisting of bendamustine and/or rituximab. MYD88 L265P was detectable by the current gold standard BM19+ in 3/5 (60%) of patients. BMMC, cfDNA and PB19+ each called 1 false negative while PBMC failed to detect L265P in all cases. The log2 fold change relative enrichment of cfDNA was 1.89 (range -2.48 - 6.45), 1.31 (range -8.9 – 2.71), 1.5 (range 07.75 – 5.65) and -1.8 (range -10.62 - 1.46) compared to PBMC, PB19+, BMMC, and BM19+, respectively. Conclusions Using AS-PCR, cfDNA demonstrated at least a median 2.48 fold relative enrichment of L265P DNA compared to all but the gold standard BM19+. Given these promising preliminary results, we plan to expand this cohort of patients significantly to determine the sensitivity and specificity of cfDNA relative to the other methods. These results indicate the cfDNA may be an affordable and less invasive alternative to the use of BM19+ DNA for diagnostic testing and evaluation of CXCR4 nonsense AS-PCR testing in this population is planned.

Keywords:
cell-free DNA

MYD88

Waldenström macroglobulinemia

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-186

Pilot study of Ixazomib, Lenalidomide, and Dexamethasone for Patients with POEMS Syndrome

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Abstract:
Intro: POEMS syndrome is a rare paraneoplastic syndrome caused by an underlying plasma cell disorder. The combination of a proteasome inhibitor, an IMiD and corticosteroid is known to be highly effective among patients with myeloma. Methods: We conducted a pilot using a 28-day oral regimen of ixazomib (4 mg days 1, 8, 15), lenalidomide (25 mg days 1-21), and dexamethasone (20 mg days 1, 8,

15, 22). Aspirin and acyclovir were used for prophylaxis. Eligibility included a diagnosis of POEMS syndrome, a plasma VEGF 2x normal, a PS < 3. There were two groups [gp] (intended enrollment 15 per gp): Gp 1, 3 cycles for pts destined for high-dose chemotherapy with stem cell transplant; Gp 2, 13 cycles for patients (pts) who had relapsed or refractory disease. Primary endpoint was VEGF complete response (CR=normalization) after 3 cycles. Secondary endpoints included safety, hematologic response, and overall survival at 3 and 12 months. Other domains including PET response, clinical responses including neurologic response were also studied. To date, 13 pts enrolled since 10/31/2016-4 to Gp A and 9 to Gp B. 11 pts were analyzed (2 dropped out before receiving any therapy). Data were frozen as of 1/21/2019. Results: Median age was 55; 73% were male. 81% met primary endpoint of VEGF CR. At 3-months, the following improvements were seen: VEGF, 10/11; hematologic, 1/3; PET 1/3; neurologic impairment score, 4/11. With a median follow-up of 16 months, 1 patient has died of progressive disease and another 2 patients progressed on therapy (one on each arm) with a neurologic progression in 1 and a extravascular leak progression. 38% of patients had grade 3+hematologic AE; 72% had grade 3-4 non-hematologic AE. These included: rash, respiratory infection and hypotension in 2 each; atrial fibrillation, diarrhea, edema, dyspnea, and thromboembolism in 1 each. 4 pts had non-objective worsening of their neuropathy. Conclusions: These preliminary results suggest that Ixa-Len-Dex is an effective and tolerable regimen for patients with POEMS syndrome. By the time of the meeting, the 12 month response data will be available, which will be important for neurologic assessment given the slow rate of remyelination.

Keywords:
immunomodulatory drugs

ixazomib

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-187

Serum BCMA Levels Predict Outcomes for Patients with MGUS and Smoldering Multiple Myeloma (SMM)

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Abstract:

Introduction: BCMA (B-cell maturation antigen) is a TNF receptor family member found on normal B-cells and malignant B-cells including multiple myeloma (MM). It plays a role in in proliferation pathways and antiapoptotic. Levels of serum (s)BMCA are increased in patients (pts) with plasma cell disorders (PCD) and higher with each stage of disease: healthy donor< MGUS. Methods: There were 3 cohorts in this retrospective study: MGUS progressing to MM (n=42); MGUS pts not progressing to MM (MGUS staying MGUS, n=49) were; SMM pts who progressed to MM (SMM progressing to MM, n=32). sBCMA levels were measured using an ELISA-based assay with a polyclonal anti-BCMA antibody from R&D Systems (Minneapolis, MN). The Kruskal-Wallis analysis was used to assess differences. The relationships between sBCMA and both time to progression and overall survival were also assessed using Cox proportional hazard models. Results: The highest values of sBMCA were seen among pts with more advanced PCD. The lowest baseline levels were seen in pts with MGUS who did not progress: MGUS staying MGUS 42 ng/mL; MGUS progressing to MM, 96 ng/mL; and SMM progressing to MM, 175 ng/mL. The change of sBCMA over time was lowest in in the MGUS non-progressors. ROC analysis identified a cutoff of 74.4 ng/mL to be predictive of progression at 5 years. This cut-point was associated with a risk ratio of progression of 5.8 (95%CI 3.2, 11.3) for all comers, a risk ratio of death for all comers of 2.5 (95%CI 1.5, 4.2), and a risk ratio of

death for MGUS pts of 3.3 (95%CI 1.9, 5.7). Discussion: Serum BCMA levels were predictive of diagnosis, progression and death among pts with MGUS or SMM. Limitations of the current study are that only a minority of patients had baseline bone marrow exams or serum FLCs to place sBCMA risk in the context of other previously described risk factors. Serum FLC is now being determined on all patients.

Keywords:

BCMA

Risk stratification

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-188

Blood mass spectrometry Detects Residual Disease Better than Standard Techniques in Immunoglobulin light chain amyloidosis

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Abstract:
INTRODUCTION: In patients (pts) with AL amyloidosis, depth of hematologic response correlates with both organ response and overall survival. Our group has demonstrated that screening with a MALDI-time of flight (TOF) mass spectrometry (MS) is a quick, sensitive, and accurate means to diagnose and monitor the serum of pts with plasma cell disorders. Microflow liquid chromatography coupled with electrospray ionization and Q-TOF MS adds further sensitivity. Our goal was to assess the performance of MS in pts with AL who have been classified as complete response using conventional means. METHODS: Pts were eligible for this study if they: 1) were diagnosed with AL amyloidosis between January 2000 and May 2015; 2) were classified as amyloidosis complete hematologic response by IFE, serum FLC by consensus criteria; 3) had a negative bone marrow by 6-color flow cytometry; and 4) had both a stored research sample prior to starting a line of therapy and a repeat sample while in complete hematologic response. No urine samples were available to test. Paired samples were immunoaffinity purified using nanobodies targeting kappa, lambda, alpha, gamma and mu as previously described. For the MALDI-TOF (Bruker Microflex, LT), a range of 9,000 to 32,000 m/z was acquired. For the ESI-TOF, spectra were also collected on a TripleTOF 5600 quadrupole time-of-flight MS (ABSciex, Vaughan ON, CA) in ESI positive mode. TOF MS scans were acquired from m/z 600−2500 with an acquisition time of 100 ms. RESULTS: Median age was 56 years. 55% were male. No test performed perfectly at baseline with the exception of MASS-FIX due to inclusion requirements. The positive baseline results for other assays were: SIFE, 85%; UIFE, 79%; abnormal FLC ratio, 84%. Five SIFE-negative pts were positive by MASS-FIX and ESI-TOF, another SIFE-negative pt was found to have a monoclonal lambda by ESI-TOF and UIFE, and 4 SIFE-negatives had abnormal FLC ratios. At CR assessment, by definition all had negative SIFE, negative UIFE, normal FLC ratio, and a negative bone marrow by 6-color flow cytometry. By MASS-FIX and ESI-TOF, respectively, 2 and 3 pts (12%) were found to have their original M-protein detected at CR determination. The overall performance of the MS approach should be even better had urine samples been available to test by MS. In the MS-positive group, by 50 months 75% of pts had

progression events in contrast to 13% in the MS-negative group, p=0.003. Respective 10-year OS rates were 62% and 83%, p=NS. CONCLUSION: MS of the blood out-performed SIFE, UIFE, FLC, and 6-color flow cytometry of the bone marrow in detecting residual disease. Additional studies that include urine MS and next generation techniques to detect clonal plasma cells in the bone marrow will further elucidate the full potential of this technique.

Keywords:
Minimal residual disease

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-189

ACQUIRED HEMOPHILIA AND MONOCLONAL GAMMOPATHY OF HEMOSTASIC SIGNIFICANCE

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Abstract:
BACKGROUND Acquired hemophilia A (HAA) is a rare hemorrhagic disease characterized by the appearance of autoantibodies against circulating factor VIII (FVIII). It has been described mainly in two groups: women of childbearing age and in older than 50 years, related to a very heterogeneous group of entities that include: drugs, autoimmune or neoplastic diseases Within the hematological neoplasias, the one that has been most related is the chronic lymphocytic leukemia AIMS We present a very rare case of adquired A-Hemophilia due to an abnormal paraprotein METHODS A 76y man with personal antecedent of MGUS have entered to the Hematology department due to a month-long evolution of hematoma and anemic syndrome. On physical examination, he had scattered bruises all over the body surface, especially in the extremities; with signs of deep bleeding in right upper and lower left limb, which implied limitation for mobility COMPLEMENTARY TEST (relevant): Hemograme:Hb 8.5 g/dL,NC/NC Coagulation study:APTT-R of 2.8,FVIII of 0.7%.The inhibitor titre was 6.2UB/ml Biochemistry:normal (inc creatinine and calcium; and anemia study) A triple monoclonal band (MB) of 2.01 g/dL was observed in electrophoresis (0.56+1.08+0.37). IgA 1668 mg/dL (decreased IgG/IgM) and a serum free light chain (FLC) (lambda/kappa) ratio of 21 24-hour urine: proteinuria of 0.21 g (BJ-lambda) A low-dose whole-body CT was also performed, which ruled out lytic lesions or underlying neoplasms Treatment with Cyclophosphamide (CTX) and Prednisone (PRED) was started The response was good, with inhibitor reduction (5.6 UB), increased factor dosage (13%) and recovery from anemia. This allowed to perform bone marrow aspiration, which was compatible with multiple myeloma (MM), with 13% of plasma cell CTX was temporarily suspended due to an infectious complication. FVIII rise to 136%. FVIII dropped to 18% and the MB rose to 1.2 g/dL (3rd MB:0.6 g/dL). CTX was reintroduced Currently, the patient is asymptomatic, with no recurrence of anemia, with FVIII:90, MB:1.5 g/dL & FLC-r:85. Continue close monitoring (18m) in our consultations w/o MM signs RESULTS The sudden onset of large bruises or extensive bruising in an adult patient with no history of bleeding disorder have to rule out a inhibitor of FVIII.The diagnosis should be based on the basic coagulation tests (lengthened APTT with normal PT), the time correction in the Mixture Test, FVIII dosage and Bethesda titre The treatment of HAA should consist, first of all, in the control of bleeding. Once the hemorrhage is controlled, next objective must be the elimination of the inhibitor by means of immunosuppressants In the limited available evidence, it seems that the best results are obtained with PRED in combination with CTX CONCLUSION The association of HAA and myeloma is extremely rare, with only five cases published The treatment consist on control bleeding

complications and reduce paraprotein with antiMM therapy

Keywords:
Adquired-Hemophilia

monoclonal gammopathies

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-190

Real-Time PET Imaging with Amyloid Fibril-Reactive Antibody CAEL-101 for Personalized AL Amyloidosis Immunotherapy

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Abstract:
Background Mortality of light-chain (AL) amyloidosis remains high due to multi-organ dysfunction caused by persistent, insoluble amyloid fibril deposits. The amyloid fibril-reactive murine monoclonal antibody 11-1F4 directly binds to a conformational epitope on light-chain amyloid fibrils in mice and was successfully used as imaging tool in human (AM J Pathol. 157:1239; Blood. 116: 2241). The chimeric form of 11-1F4 (CAEL-101) demonstrated therapeutic potential in a phase 1a/b study where 67% of patients with cardiac or renal amyloidosis showed organ response (Blood 130:509) and 9/10 cardiac amyloidosis patients showed improvement of the Global Longitudinal Strain (Blood 132:958). Inspired by the promising data, the overall goal of this work is to establish an optimal CAEL-101 PET probe as a potential imaging tool for the diagnosis and stratification of patients with systemic AL amyloidosis. Methods & Results κ or λ subtype AL amyloid extracts derived from patient heart, liver, spleen, and kidney were s.c. injected into BalB/C mice. Animals were then injected with ~100μCi of [124I]CAEL-101 or [89Zr]CAEL-101 and imaged up to 14 days post injection using an Inveon PET. Target : background ratio (TBR) was calculated using SUV mean of amyloidomas and contralateral background. The chimeric mAb [124I]CAEL-101 PET imaged 100% of amyloidomas regardless of the subtype or organ origin (heart, liver, spleen, and kidney). The TBR ratio reached clinic significance on day 1 (TBR 2) in κ and λ amyloidomas but the maximum TBR ratio occurred later in λ amyloidomas. In κ amyloidomas the peak TBR was reached on day 4 (TBR 6) whereas the peak TBR in λ amyloidomas was reached on day 7 (TBR 6). In accordance with that was the observation that κ subtype demonstrated faster clearance of CAEL-101 with no significant TBR on day 7. To further improve the imaging sensitivity of CAEL-101 and to develop it as a translational PET agent, 89Zr was used as an imaging isotope. [89Zr]CAEL-101 retained its immunoreactivity with superior TBR compared to [124I]CAEL-101 (18:1 vs. 6:1). Furthermore, [89Zr]CAEL-101 resulted in a continued increase in TBR up to day 7 in κ amyloidomas. Importantly, we still observed significant amyloidoma PET signal on day 14 post-injection of [89Zr]CAEL-101 suggesting that [89Zr]CAEL-101 has a wide imaging window. Discussion We have demonstrated for the first time the potential of using radiolabeled CAEL-101 as a companion diagnostic to image real-time targeting of human amyloidosis in vivo. By comparing both 124I and 89Zr labeled CAEL-101, we demonstrated that [89Zr]CAEL-101 has significantly better binding characteristics than [124I]CAEL-101 both in terms of TBR and in vivo stability. We hence envision [89Zr]CAEL-101 PET imaging as an effective approach to (1) diagnose systemic amyloidosis, (2) stratify patients for CAEL-101 immunotherapy, and (3) quantify peripheral organ amyloid fibril deposition pre and post anti-amyloid therapy.

Keywords:
amyloidosis

Imaging

immunotherapy

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-191

Primary Plasma Cell Leukemia: a retrospective series from a tertiary care center in India

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Abstract:
Introduction: Plasma cell leukemia (PCL) is rare and aggressive plasma cell dyscrasia which may present primarily (pPCL) or on progression from multiple myeloma. Clinical presentation may be distinct from myeloma with frequent extramedullary involvement. Methods: We retrospectively analyzed our data from January 2013 to March 2018 from patient case records. Diagnosis of pPCL was considered if peripheral blood plasma cells > 10% or > 1000/mm3. Baseline clinical, biochemical data and follow-up data was recorded. Overall survival was calculated from time of diagnosis to time of death. Results: We analyzed data of 14 patient diagnosed as pPCL with above criteria. Majority were males (10/14). Median age was 50 years (20-75 years) with five patients younger than 50 years at diagnosis. Fatigue was most common presenting complaint followed by bony pains, fever, neurologic deficit, dyspnea, and bleeding. ECOG PS was 3-4 in majority (9/14). On evaluation all patients had anemia with mean hemoglobin of 6.4 ± 1.6 gm/dl. Median platelet count was 51500/mm3 and TLC was 9700/mm3. Median peripheral blood plasma cells were 24% (6-45%) with absolute plasma cells count of 2230/mm3 (1062-8086/mm3). Serum albumin < 3.5gm/dl, creatinine >2 mg/dl, and calcium > 11 mg/dl was seen in 85%, 50 % and 43% patients respectively. All patients had high beta 2 microglobulin (10.29 ± 2.54 mcg/ml) and M protein (4.4 ± 2.2 gm/dl). On immunofixation IgG kappa was most commonly detected. Lytic lesions were seen in 10 patients. Extramedullary involvement was seen in eight patients; hepatomegaly in five, plasmacytomas in two, ascitis in two, pleural effusion in one. Bone marrow cytogenetics by FISH was performed in seven patients, four had no myeloma associated abnormality, three patients had del 13q, one patient had concomitant del 17p and t(14;16) while another one had t(4;14). CyBorD was most commonly administered induction therapy in six patients followed by PAD and VRD in three patients each. Post induction eight patients had partial response, two patients had progressive disease and in four patient response evaluation could not be done. Autologous stem cell transplant (ASCT) was performed in three patients, one post 1st line of therapy, while in another two patients post 2nd line therapy. Two patients achieved complete response on day 100 ASCT while one patient had a partial response. All patients received post-transplant consolidation 2 cycles VRD followed by maintenance therapy. At a median follow up of 22.6 month median OS was 10.9 months (2.1 months - not reached). No factor was predictive of overall survival in univariate and multivariate study. Conclusions: pPCL is an aggressive neoplasm with high disease burden at presentation. Bortezomib based induction therapy followed by ASCT should be considered in all eligible patients. With current modalities survival is poor and prospective studies are required to determine treatment strategies & improve prognosis.

Keywords:
bortezomib

Plasma cell leukaemia

Tracks:
Other Plasma Cell Disorders and Amyloidosis

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Bortezomib self-injection is time-saving, cost-neutral and well received by patients with myeloma or AL amyloidosis: Results from the "SUBLIME" study

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Abstract:
Introduction: "VCD" is first-line treatment for myeloma (MM) and systemic AL amyloidosis (AL), consisting of subcutaneous bortezomib, with oral cyclophosphamide and dexamethasone. Patients can spend several hours each week travelling into hospital or waiting for Hospital in the Home (HITH) nurses for one subcutaneous injection that takes only a minute to administer. Aim: To assess the feasibility of a Self-administration of sUbcutaneous Bortezomib in muLtIple myeloma and AL-aMyloidosis at home (SUBLIME) program. We sought to determine the money, patient travel and waiting times saved, and quality of life (QOL) impact. Method: Patients undergoing VCD for MM or AL were included. Exclusion criteria included poor dexterity/vision, non-compliance or mental illness including significant anxiety. Cycle one was administered in the Day Oncology Medical Unit (DOMU), during which time, patients were taught subcutaneous administration, cytotoxic handling and disposal by the SUBLIME nurse. Once deemed safe, subsequent injections were administered by patients or carers at home. Patients were reviewed by the haematologist and SUBLIME nurse at the start of each cycle. The SUBLIME nurse telephoned patients after each self-injection. Results: 28 patients were identified from December 2018 to June 2019 inclusive. 11 patients were ineligible, 6 refused enrollment. 11 patients consented; 8 self-administered, three received injections from carers. Program feasibility was confirmed with 84 injections administered safely without adverse outcomes. 3 hours of DOMU chair time or HITH nurse travel time were saved per patient per cycle. 4 cycles of bortezomib administered in DOMU costs $2180, by HITH $2023, and by SUBLIME $1805, thus confirming SUBLIME is cost effective. Patients reported positive experiences, but formal QOL analysis will be completed at the end of the program. Conclusion: The SUBLIME bortezomib self-administration program is safe, cost-effective, reduces patient travel time, and frees up nursing time for more complex therapies. Such a program may be applicable to other subcutaneous chemotherapies, such as cytarabine.

Keywords:
amyloidosis

bortezomib

Nurse Led clinic

Tracks:
Other Plasma Cell Disorders and Amyloidosis

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CLINICAL PROFILE AND OUTCOMES OF WALDENSTRÖM'S MACROGLOBULINEMIA FROM A TERTIARY CARE CENTER IN INDIA

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Abstract:
INTRODUCTION: WHO defines Waldenström's Macroglobulinemia (WM) as a lymphoplasmacytic

lymphoma associated with an IgM monoclonal gammopathy. WM can manifest with a variety of symptoms and has an indolent course. It is important to closely monitor patients and determine the appropriate treatment indications.
METHODOLOGY: We retrospectively analyzed data from patient case records in the department of hematology over a period of 3 years from January 2016 to February 2019 at our centre. Baseline characteristics, laboratory parameters, management and outcomes were noted. RESULTS: A total of 14 patients were diagnosed with WM during the study period. Median age is 59 years (41-84 years). Nine were males and five females. Majority patients presented with anaemia (100%) followed by neurological symptoms (21%), and bleeding symptoms (7%). On examination 42% had splenomegaly, 35% had hepatomegaly, and 14 % had lymphadenopathy (14%). Two (14%) patients each had cold agglutinin disease and cryoglobulinemia at presentation. Median serum IgM level was 2.05 g/dl (range 0.5-5.2 g/dl). Ten patients (71%) had IgM kappa detected on IFE. Bone marrow findings in all patients were similar with lymphoplasmacytic infiltrates and CD138,CD20 positivity on immunohistochemistry. No cytogenetic abnormality was detected in any patient. MYD88L265P mutation testing was done in two patients and it was positive in both. Indications of treatment was anaemia in majority of patients (83%) followed by cold agglutinin disease and cryoglobulinemia. Two patients are under close follow up with no current indication for treatment. Amongst those treated six patients received BR (bendamustine rituximab), two received BDR (bortezomib dexamethasone rituximab) and two received RCVP (rituximab cyclophosphamide vincristine prednisolone). Two patients were lost to follow up before starting any treatment. Six patients had complete remission (CR) and two had partial remission (PR). All were started on rituximab maintenance. Two patients relapsed (1 post RCVP, 1 post BR) and have been started on salvage chemotherapeutic regimens. Patient relapsed post RCVP is on BR and the one relapsed post BR is on BDR. CONCLUSIONS: Median age is almost 10 years less in our study as compared to western data. The median M protein in our study was higher compared to existing literature. Patients present to us in late stages of disease when most of them have indications for treatment. It is contrary to western world where most patients are asymptomatic at presentation. Patients of WM have shown good results with combination chemotherapeutic regimens and rituximab maintenance. Similar responses have been observed in our series.

Keywords:
rituximab

Waldenström macroglobulinemia

Tracks:
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CXCR4 S338X clonality is an important determinant of ibrutinib outcomes in patients with Waldenström macroglobulinemia.

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Abstract:
Introduction: Approximately 40% of patients with Waldenström macroglobulinemia (WM) have an activating somatic mutation in CXCR4. The most common variant is CXCR4 S338X, which represents over half of CXCR4 mutations found. CXCR4 S338X mutations are primarily subclonal to mutated MYD88, but show a highly variable clonal distribution. CXCR4 mutations also confer in vitro and clinical resistance to ibrutinib, particularly nonsense variants such as CXCR4 S338X. These findings prompted us to examine the impact of CXCR4 S338X clonality on outcomes to ibrutinib in WM patients. Methods: We identified consecutive

WM patients treated at our institution between May 2012 and January 2018 who received ibrutinib. MYD88 and CXCR4 mutations were identified by AS-PCR and Sanger sequencing (Xu et al, Blood 2013; BJH 2016). Cancer cell fraction analysis was performed for patients with CXCR4 S338X mutations as before (Xu et al, BJH 2016). ROC curve analysis was used to define the optimal cutoff for CXCR4 S338X clonality. Results: A total of 147 patients with WM met inclusion criteria for this analysis. The MYD88 L265P and CXCR4 S338X mutations were identified in 147 (100%) and 37 (25%) patients, respectively. The median treatment duration on ibrutinib was 21.1 months (range 0.3-69). Patients with CXCR4 S338X had lower rates of major response (62% vs. 85%; p=0.001) and VGPR (11% vs. 35%; p=0.006) versus CXCR4 WT, and delayed attainment of both minor (1.8 vs. 1.1 months; p<0.001) and major responses (7.4 vs. 1.8 months; p<0.001). Twenty-three patients (16%) have progressed on ibrutinib. By univariate analysis, CXCR4 S338X was the only variable associated with shorter PFS (HR 5.03, 95% CI 1.91-13.2; p=0.001) with a significantly shorter median PFS compared to CXCR4 WT (44.1 months vs. NR). Among the 37 patients with CXCR4 S338X, the median clonality was 35.3% (range 0.94-86.2%). A CXCR4 S338X clonality of 25% was calculated as the optimal cutoff (sensitivity: 71%, specificity: 72%, AUC: 0.73); 23 patients (62%) had "high clonality" defined as ≥25%, while 14 (38%) had "low clonality" defined as <25%. Patients with high CXCR4 S338X clonality had lower VGPR (4%, 21%, 35%; p=0.01) and delayed major response attainment (9.7, 7.4, 1.9 months; p<0.001) versus low CXCR4 S338X clonality and CXCR4 WT, respectively. Compared to patients with CXCR4 WT, high CXCR4 S338X clonality was associated with significantly shorter PFS (HR 10.44, 95% CI 3.43-31.8; p<0.0001), whereas low CXCR4 S338X clonality did not impact PFS (HR 0.90, 95% CI 0.13-6.44; p=0.92). Patients with high CXCR4 S338X clonality also had a significantly shorter median PFS versus low CXCR4 S338X clonality and CXCR4 WT (39.9 months, NR, NR; p=0.0001). Conclusion: High CXCR4 S338X clonality is associated with delayed major responses, lower rates of VGPR, and shorter PFS to ibrutinib. Clonality assessment represents a novel biomarker for predicting outcomes on ibrutinib in WM patients carrying CXCR4 S338X.

Keywords:
CXCR4

ibrutinib

Waldenström macroglobulinemia

Tracks:
Other Plasma Cell Disorders and Amyloidosis

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MYD88 and CXCR4 Mutation Rates by Allele-Specific PCR Compared with Diagnostic Next Generation Sequencing Panels in Patients with Waldenstrom's Macroglobulinemia

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Abstract:
Background Mutations in MYD88 have been reported in over 90% Waldenstrom's Macroglobulinemia (WM) patients, nearly all of which correspond to the c.978T>C mutation resulting in an p.Leu265Pro (L265P) substitution at the protein level. CXCR4 mutations can be found up to 40% of patients with over half of them corresponding p.Ser338Ter (S338X) when translated. In this study we screened 199 patients with WM by AS-PCR for MYD88 c.978T>C and CXCR4 S338X mutations. This analysis was paired with Sanger sequencing to clarify negative results when possible. Given the increasing using of targeted next generation targeted sequencing panels in clinical diagnostics, we compared the AS-PCR

results to the Dana-Farber rapid heme panel CXCR4 and MYD88 results from the same biopsy for 150 of the samples. Methods DNA from CD19+ selected bone marrow mononuclear cells from untreated WM patients was used for the MYD88 and CXCR4 AS-PCR assays as previously described (Xu et al Blood 2013; Xu et al BJH 2016). For patients wild-type (WT) for MYD88 by AS-PCR, Sanger sequencing of the open reading frame of MYD88 was performed. DNA was also used to validate the presence of c.978T>C by Sanger when possible. The "rapid heme panel" is an Illumina MiSeq gene panel designed at the Dana-Farber/Brigham and Women's Cancer Center. Unlike the AS-PCR assays, the rapid heme panel uses unsorted marrow and relies on high coverage metrics to sequence through the normal in tumor contamination. Results Study patients presented with a median bone marrow (BM) disease involvement of 30% (range 1-95%) and a median serum IgM of 2,023 ug/dL (range 25-9,737) and an age of 65 (range 36-89) years. Of the 199 unique WM patients screened in this study, 188 (94.5%) tested positive for the c.978T>C mutation. Sanger sequencing covering the c.978T>C mutation was performed in 108/199 (54.3%) of these patients confirming the presence of the mutation in 100% of the cases. This analysis also revealed that one MYD88 WT patient had a dinucleotide substitution that resulted in L265P while another had a previously documented S243N mutation raising the MYD88 mutation rate to 190/199 (95.5%). Compared with targeted sequencing, discrepancies were observed in 61/150 (40.7%) cases where targeted the panel gave false negative results for c.978T>C but was detected by AS-PCR. CXCR4 S338X mutations were present by AS-PCR in 51/198 (25.8%) patients. Discrepancies were observed in 19/34 (55.9%) cases where the targeted panel gave false negative results for CXCR4. However, the panel was able to detect CXCR4 mutations not covered by the AS-PCR assays including an additional 16/150 (10.7%) CXCR4 nonsense mutations and 18/150 (12%) CXCR4 frameshift mutations. Conclusions MYD88 mutations are present in 95% of WM patients and was detectable by AS-PCR in all but 1% of cases. Next generation targeted sequencing panels had a much lower sensitivity likely due to hemodilution and the lack of CD19+ selection.

Keywords:
CXCR4

MYD88

Waldenström macroglobulinemia

Tracks:
Other Plasma Cell Disorders and Amyloidosis

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Feasibility of heart transplantation for patients with amyloid cardiomyopathy accompanying extracardiac organ involvement

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Abstract:
Background: Cardiac involvement is associated with poor prognosis in immunoglobulin light-chain amyloidosis (AL amyloidosis), with a median survival of 6 months without heart transplantation (HT) from the onset of symptomatic heart failure. Although HT is a promising treatment option for patients with amyloid cardiomyopathy (ACM),

consensus on its indication is not fully established because of limited experience. Method: We reviewed our prospective AL amyloidosis database to identify all patients who received HT for their ACM. Data regarding baseline characteristics, treatment and survival outcomes were obtained by reviewing the database. Result: Out of 80 patients diagnosed with ACM between Oct 2004 and Oct 2018, 11 patients who underwent HT were identified. The median age at the time of HT was 61 years (range, 43 - 75), and 54.5% (n=6) were male. According to the Revised International Staging System (R-ISS), 6 patients (54.5%) were stage II and the other 5 (45.5%) were stage I. Six patients (54.5%) had extracardiac organ involvement; colon (n=3, 27.3%) was most frequently involved, followed by stomach (n=2, 18.2%), and bone marrow (n=2, 18.2%). All patients presented with high left ventricle (LV) filling pressure measured by E/E' (median, 23; range, 15 – 44).Severe LV dysfunction (ejection fraction < 40%) was accompanied in 36% (n=4). Regarding treatment, 5 patients (45.5%) received thalidomide plus dexamethasone (TD), 3 patients bortezomib-containing therapy, and 3 patients high-dose dexamethasone. Most patients (n=9, 81.2%) underwent HT after systemic treatment [2 patients with complete response (CR), 6 with very good partial response (VGPR), and 1 with stable disease (SD)], while the other two patients proceeded with upfront HT; median time from diagnosis to transplant was 4.1 months (range, 0.6-15.3). Autologous stem cell transplant (ASCT) was performed in 4 patients (36.4%) after HT. With a median follow-up of 56.5 months, 3 patients died because of herpetic encephalopathy (13.0 months after HT, not on systemic treatment), cerebral infarction (18.3 months after HT, not on systemic treatment), and pneumonia (3.1 months after HT, not on systemic treatment); there was no death related to disease progression (1-year post-transplant survival rate, 90.9%; 2-year post-transplant survival rate 72.7%). Amyloid recurrence in the transplanted heart was not observed in any patients. All patients with extracardiac organ involvement were alive at 2 years from the HT with well-controlled amyloidosis (4 patients with CR, and 1 with VGPR), except one who had 80% clonal plasma cell on bone marrow biopsy. Meanwhile, all patients who had > 20% plasma cells in bone marrow died within 2 years. Conclusion: Our results suggests that HT might be a feasible therapeutic option even for ACM patients with extracardiac organ involvement including gastrointestinal tract involvement, as long as plasma cell count in bone marrow is less than 20%.

Keywords:
Amyloid cardiomyopathy

Extracardiac organ involvement

Heart transplantation

Tracks:
Other Plasma Cell Disorders and Amyloidosis

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Clonal Heterogeneity and Immune Tumor Microenvironment in Waldenström Macroglobulinemia

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Abstract:
Waldenström macroglobulinemia (WM) is a rare subtype of non-Hodgkin lymphoma associated with infiltration of a malignant B lymphoplasmacytic

cells in the bone marrow (BM). To better understand the WM pathogenesis, we performed high dimensional single cell analysis of WM tumor cells associated with tumor-driven immune changes in the tumor microenvironment (TME) of 66 BM samples from WM patients compared to 10 age-matched healthy donors (HD) by mass cytometry (CyTOF) technology. Our workflow has been designed based on extensive 3 CyTOF antibody panels to evaluate WM tumor within B cell lymphopoiesis concurrently with adaptive and innate immune TME in WM by state-of-art technology CyTOF. In depth analysis, we identified significant increase of 11 B subset clusters from un-switched and switched memory B cells to plasma cells that correspond to WM subclones. Moreover, decrease in frequency of B cell precursors (pro-B and pre-BI), naive B cells, and plasmablasts was observed in WM patients vs. HD. To investigate heterogeneity in signaling characteristics of WM sub-clones, highest upregulation in expression of CD184 (CXCR4) was showed in WM tumor cells of both newly diagnosed WM (NDWM) and relapsed/refractory WM groups compared to HD. In addition, unprecedented phenotypic features and molecular signature within of WM sub-clonal clusters revealed significant differences in expression of activation surface molecules (CD23, CD24, CD25, CD81, CD329, CD200, and CD319); transcriptional factors and regulators controlling B cell development (MYD88, Bcl-6, IRF-4, sXBP-1, and FGFR-3) and stemness-related markers (Oct3/4, Nanog, Sox-2, c-Myc, and Notch-1) in WM supporting the idea of sub-clonal heterogeneity insight of WM tumor. Comprehensive analysis of WM immune TME showed significant abundance in gamma/delta T cells, CD4+ and CD8+T effector cells, CD8+T effector memory cells, monocytes, and neutrophils clusters of both WM groups vs. HD. On the other hand, in WM we observed decrease of cell distribution in immature T cells, CD8+T naïve cells, plasmacytoid dendritic cells, myelo/mono progenitor clusters. Moreover, differences in expression of KIR, PD-1 and PD-L1 immune checkpoints in the TME immune clusters of WM patients were evaluated. Ibrutinib (IBRU) treatment has been effective in relapsed/refractory WM patients; therefore highest numbers of WM patients were receiving IBRU therapy in our cohort. IBRU treated WM patients had decreased frequency of naive B, CD4+T naive cells and specific clusters of un-switched and switched memory B cells. Moreover, responder vs. non-responders to IBRU therapy revealed increase of sXBP-1 and downregulation of c-Myc, Bcl-6, and FGFR-3. In sum, correspondence analysis reflecting data of each patient and immune subsets revealed stratification of WM patients with reflection on their clinical outcome, therefore providing the rational for prediction of WM patient status. This study was supported by APVV-16-0484 and VEGA 2/0076/17.

Keywords:
Heterogeneity

Immune Tumor Microenvironment

Waldenström macroglobulinemia

Tracks:
Other Plasma Cell Disorders and Amyloidosis

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Insights into the Genomic Evolution of Ibrutinib Resistant Clones in Waldenström's Macroglobulinemia

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Abstract:
Introduction Ibrutinib is a Bruton tyrosine kinase (BTK) inhibitor highly active in Waldenström Macroglobulinemia (WM) patients. Despite that, disease progression can occur due to acquired

mutations in BTK at the binding site of ibrutinib (Cys481), or in PLCG2, the protein downstream BTK (Xu, Blood 2017). However, not all resistant patients harbor these alterations. The aim of this study was to identify alternative molecular mechanisms that can drive ibrutinib resistance. Methods Five previously treated WM patients who progressed while on ibrutinib were included in the study. Tumor DNA from bone marrow CD19+ cells was collected at baseline, and at the time of progression for 3 patients. For the remaining two, only progression samples were available. Non-CD19 cells from peripheral blood were used as germline controls. Data from whole exome sequencing (WES) were analyzed following GATK Best Practice Guidelines. Small variants and indels were analyzed using Strelka and MuTect2, and copy number alterations (CNA) were called using Control-FREEC. Results CNA analysis identified del6q in all 5 patients, becoming homozygous in two of them at relapse. Another patient demonstrated a subclonal homozygous deletion at baseline that increased at the time of disease progression. We also observed del8p in 4/5 patients at ibrutinib progression with the remaining patient having a microdeletion as well. No other recurrent CNA were detected. Regarding small variants, relapse samples showed a high proportion of acquired vs. persistent mutations (median 87% vs. 13%), the former being more subclonal (MAF=8.4% vs. 13.9%). Among variants acquired at progression, BTK p.Cys481Ser was identified in 2/5 patients, who also harbored alterations in genes related to B-cell receptor signaling, such as PLCG2 p.Y495H; CD79B p.D33Y; LYN p.A2Stop and LYN p.A139T. In patients without BTK mutations, we identified several alterations that could contribute to ibrutinib resistance including ITCH p.A646S (n=2), an ubiquitin ligase whose substrates are CXCR4, LYN or SYK; RNF19B p.R30G (n=2), another ubiquitin ligase involved in STAT1-mediated transcriptional activity; FCRL3 p.E694Q (n=1), a protein that modulates the innate immune signaling in B-cells; BIRC2 p.A506E (n=1), a regulator of alternative NF-κB and MAPK signaling; and negative regulators of TLR signaling including TOLLIP p.M242R and p.R228H, and DOK2 p.Y345Stop. In one patient, a truncating SYK p.Y526Stop at baseline was not detectable at progression. Conclusion Our WES studies provide new important insights into clonal evolution associated with ibrutinib resistance in WM. Deletions on chromosomes 6q and 8p can accompany disease progression, a notable finding since these regions encompass many key regulators of BTK, MYD88/NF-κB, and apoptotic signaling. Moreover, we have also identified recurring mutations in ubiquitin ligases, innate immune signaling and TLR/MYD88 pathway regulators in ibrutinib resistant WM patients.

Keywords:
ibrutinib

Waldenström macroglobulinemia

Whole exome sequencing

Tracks:
Other Plasma Cell Disorders and Amyloidosis

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Gene expression analysis reveals vitamin D regulates genes critical to oncogenesis in MYD88 mutated B cell lymphomas.

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Abstract:
Introduction: Vitamin D insufficiency has been associated with an inferior prognosis is some types of non-Hodgkin lymphoma (Drake et al. JCO 2010). Although the underlying mechanism for this finding remains to be delineated, vitamin D is known to modulate gene expression through transcriptional regulation by the nuclear vitamin D receptor. Activating somatic mutations in MYD88 are present in 95-97% and 30% of patients with Waldenström's macroglobulinemia (WM) and diffuse large B cell lymphoma (DLBCL), respectively. Mutated MYD88 triggers Toll-like receptor (TLR) and BCR signaling through assembly of a "Myddosome" complex that

includes activated BTK, HCK, and SYK, and promotes pro-survival NF-KB. Our study may demonstrate the expression of genes critical to TLR and BCR signaling in MYD88 mutated B cell lymphomas is modulated by treatment with vitamin D3. Methods: Thirty subjects with vitamin D insufficiency (serum 25-hydroxyvitamin D [25(OH)D] < 30 ng/ml) were enrolled in a randomized, double-blinded phase I clinical trial to investigate broad gene expression changes in circulating immune cells following vitamin D3 supplementation of 600, 4,000 or 10,000 IU/d of vitamin D3 for 6 months (NCT01696409). Genetic expression analysis was performed at baseline and following the treatment period. Vitamin D responsiveness within each cohort was performed by comparing the level of genetic expression (>5%) amongst individuals with a similar rise in serum 25(OH)D. Genes with a significant fold change (>2.0-fold) were selected and reviewed for known associations to cancer pathways using DAVID Bioinformatics 6.8. Results: A dose-dependent 25(OH)D alteration in broad gene expression was observed with 162, 320, and 1289 genes up-/down-regulated for subjects in the 600, 4,000, and 10,000 IU/d dose cohorts, respectively. Genes for known cancer-related pathways were significantly regulated in the 10,000 IU/d cohort, but not in the 600 or 4,000 IU/d cohorts. In the 10,000 IU/d cohort, 104 genes (8.1%; $p<0.001$) are involved in a cancer-related pathway, of which 41 genes (39.4%; $p<0.0001$; fold change >2.0; FDR<0.01) are related to B cell lymphomas. Vitamin D3 significantly ($p<0.05$, FDR<0.01) down-regulated expression of the following genes (fold-change): MYD88 (-4.7), HCK (-4.65), SYK (-4.98), BCL2 (-3.99), IKBKB (-4.31), IL6R (-5.31), TLR4 (-5.98), NOTCH1 (-4.32), and MYC (-5.65). Vitamin D3 also significantly up-regulated expression of the following genes (fold-change): KDM6A (+4.98), NFKBIZ (+8.97), and NFKBIB (+6.31). Conclusion: Treatment with 10,000 IU/d of vitamin D3 in insufficient subjects is associated with significant down-regulation of genes critical to the growth and survival of MYD88 mutated B cell lymphomas, such as WM and DLBCL. Significant up-regulation of tumor suppressors and inhibitors of the NF-KB pathway was also observed with treatment. Future studies evaluating the cytotoxicity of vitamin D3 on MYD88 mutated tumors appears warranted.

Keywords:
MYD88

Vitamin D

Waldenström macroglobulinemia

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-200

Primary Treatment of Light Chain (AL) Amyloidosis With Bortezomib, Lenalidomide and Dexamethasone (VRD) or with Bortezomib, Cyclophosphamide and Dexamethasone (VCD/CyBorD): efficacy and toxicity

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Abstract:
Background: Limited data exist regarding efficacy and toxicity of VRD in newly diagnosed AL patients and especially compared to CyBorD which is the most commonly used regimen in this setting
Methods: we compared the outcomes of 34 consecutive patients treated with VRD to a group of patients treated with CyBorD in our department, matched for Mayo stage, NTproBNP levels and baseline dFLC levels (1:2 matching, N=68 subjects treated with CyBorD). VRD included SQ bortezomib (1.3 mg/m2 days 1, 8 & 15), lenalidomide (starting at 5 to 15 mg on days 1-21) and dexamethasone 20 mg weekly, every 28 days for 8 cycles. Lenalidomide started at 5 mg in patients with any of the following: eGFR<50 ml/min, heavy proteinuria with low serum albumin (< 2.5 gr/dl), age >75 years, Mayo stage 2 with NTproBNP>4000 pg/ml or Mayo stage 3 disease: starting dose was 5 mg in 30 (86%), 10 mg in 2 (7%) and 15 mg in 2 (7%) patients.. Results: the two groups had no significant differences in baseline characteristics except that more patients in the VRD group had eGFR <30 ml/min (23.5% vs 9%). At 1 month landmark, hematologic responses for VRD were 68% (≥VGPR:41%, PR:27%) vs 65% (≥VGPR:39%, PR:26%) for CyBorD. At 3 months, in VRD treated patients, ≥VGPR was 67% and PR was 15%, and was 45% and 31% respectively for CyBorD. In the overall ITT patient population, best response for VRD was CR:32%, VGPR: 50% and PR: 7% (>VGPR in 82%); for CyBorD was CR: 24%, VGPR: 21% (>VGPR in 45%) and PR: 25%. On ITT, cardiac and renal responses were 41% and 22% in patients treated with VRD and 38% and 31% in patients treated with CyBorD, but follow up in the VRD group is significantly shorter. Hematologic toxicity of VRD was mild but non hematologic toxicities included rash (Gr2:27%, Gr3:12%, Gr4: 3%), infections (≥Gr3:9%), constipation (≥Gr3:9%), peripheral neuropathy (Gr2: 20%), pulmonary embolism (Gr3:3%); 37.5% of patients required lenalidomide dose reduction, 9(27%) discontinued lenalidomide, 13(38%) required bortezomib dose reduction and 4 (12%) discontinued bortezomib. Hospitalization was required for 19 (56%) patients, mostly for amyloidosis related complications. In CyBorD treated patients most common toxicities included neuropathy (Gr2:15% and Gr3:3%), constipation (9%), diarrhea (9%) and infections (7%). Bortezomib dose was reduced in 42% and in 8% was discontinued due to toxicity; 51% of patients required at least one hospital admission for complications related to disease or therapy. The 3-month and 6 month mortality rate was 18% and 23% for VRD and 11% and 17% for CyborD.
Conclusion: VRD with weekly bortezomib and low dose lenalidomide is a very effective regimen, inducing deep hematologic responses in 82% of previously untreated AL patients, more rapidly than CyBorD, especially for low and intermediate risk patients, but at the expense of higher toxicity.

Keywords:
amyloidosis

bortezomib

Lenalidomide

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-201

In Cardiac AL Amyloid a Higher BMI is Associated with a Lower Rate of Cardiac Response

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Abstract:
Introduction: Light-chain amyloidosis (AL) is a clonal plasma cell disorder in which Ig light chains cause organ-specific disease due to toxic misfolded light-chain aggregates and extracellular deposition of amyloid fibrils derived from light chain proteins. Approximately half of AL amyloid patients present with cardiac involvement and survival is largely driven by the extent of heart failure. In the general

heart failure population, overweight and mild/moderate obesity is associated with lower mortality, termed the obesity survival paradox. Conversely for patients with multiple myeloma, a disease similar in pathophysiology to AL, obesity is associated with increased mortality. Hypothesis: We hypothesized that patients with cardiac amyloidosis would exhibit an obesity survival paradox and sought to determine the impact of BMI on mortality, hematological, and cardiac responses to anti-plasma cell treatment. Methods: We conducted a single tertiary center retrospective study of consecutive patients with cardiac AL amyloidosis, referred between 1/1/2009 and 09/30/2018. We collected demographics and BMI prior to treatment. We recorded the date of diagnosis and subsequent dates of hematological and/or cardiac response, mortality or end of follow-up. We constructed a Cox proportional hazards model examining the association between BMI and mortality with a restricted cubic spline function curve. Logistic regression models were constructed to examine the association between high BMI (≥ 25 kg/m2) and cardiac or hematological response. Models were adjusted for age, sex and cardiac stage at time of diagnosis. Results: Of 79 patients, 17 patients had BMI of 17-22.5, 19 a BMI of 22.6-25, 23 a BMI of 25.1-29.7, and 20 a BMI of ≥ 30 kg/m2. Crude mortality was 31/79 (39%). There was no relationship between BMI as a continuous variable and mortality (adjusted HR 0.98, 95% CI 0.91-1.06, p=0.625), although a survival paradox trend was suggested by the cubic spline curve. While there was no relationship between high BMI and hematological response (adjusted OR 1.00, 0.37-2.75, p=0.996), there was a relationship between high BMI and lower likelihood of achieving cardiac response (adjusted OR 0.23, 0.07-0.71, p=0.011). Conclusions: In this small cohort of patients with AL cardiac amyloidosis, there was no significant relationship between BMI and mortality. Hematological response was unrelated to BMI, but patients with a higher BMI were significantly less likely to achieve a cardiac response. These findings suggest that patients with higher BMI might be associated with poorer cardiac outcomes in AL amyloidosis, highlighting the importance of a multidisciplinary approach involving oncologists, cardiologists, and nutritionists in the treatment of this very complex multi-organ disease.

Keywords:
amyloidosis

body mass index

cardiac

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-202

Changes in cardiac biomarkers with daratumumab therapy in patients with light chain amyloidosis

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Abstract:
Introduction: Treatment of light chain amyloidosis (AL) is challenging – while hematologic response can be achieved, amyloid organ damage reversal can lag. Patients have high morbidity and mortality related to persistent organ dysfunction. Plasma cell-directed therapies such as immunomodulatory drugs (IMiD) and the proteasome inhibitor (PI), bortezomib, have been associated with worsening cardiac biomarkers in the early period of their use in AL, although it is unclear if this worsening is related to the drug itself, concurrent steroid (S) use, or ongoing organ damage. Daratumumab (dara) has shown remarkable hematologic response in AL. We evaluated early trends in biomarkers following use of dara. Methods: Forty-two AL patients treated

with dara, or a combination containing dara, between 4/1/2016-4/1/2019 at 2 centers were studied. Amyloidosis was staged at the time of diagnosis and prior to dara use with the 2012 revised staging system. Biomarkers, troponin T (TnT), NT pro-BNP, difference in free light chains (dFLC), and creatinine (Cr) were studied at dara start, and at 1-, 3-, and 6- months after dara. Signed Rank test was used to test differences between timepoints by stage (1/2 vs 3/4) and $p<0.05$ was considered significant. Kaplan Meier survival analysis was performed. Data cutoff was 4/1/2019. Results: The median age at diagnosis was 67 (42-91), with 61% males; 77% had cardiac involvement, 44% had renal involvement, and 47% (16) had ≥3 organs involved. At start of dara, 42% had stage 1/2 and 58% had stage 3/4. Median number of therapies prior to dara was 1 (0-7), and 42% had an autologous transplant. Median time from diagnosis to dara was 8.9 (0-108) months. Median duration of dara therapy was 6.8 (0-22) months; 19 patients remained on dara at time of data cutoff. Dara therapy included: 25, dara + S; 1, dara + alkylator (A) + S; 14, dara + PI (bortezomib/ixazomib) +/- A + S; 2, dara + IMiD (lenalidomide/pomalidomide) + S. From baseline to 1 month of treatment, the median dFLC change was -66.5 (range -909, +31) mg/L ($p <0.0001$), median NT proBNP change was +94.6 (-5,665, +11,592) pg/ml (p 0.8), median TnT 0 (-0.08, +0.13) ng/ml (p 0.5) and median Cr 0.02 (-1.85, +0.99) mg/dl (p 0.8). From baseline to 6 months, other than dFLC, no significant change was noted in NT proBNP, TnT, or Cr. When stratified by stage at treatment, no significant changes in cardiac biomarkers were noted. At a follow-up of 1 year after dara, survival was 93 (95% confidence interval 59, 99)% for stage 1/2 and 60 (34, 78)% for stage 3/4 (p 0.01). Discussion: Our results show that dara treatment rapidly lowered dFLC without worsening cardiac biomarkers in AL. The findings demonstrate that in addition to rapid dFLC reduction, dara does not impart additional AL cardiac biomarker toxicity. Thus, particularly among advanced cardiac patients, dara should be considered as an early treatment.

Keywords:
amyloidosis

cardiac

daratumumab

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-203

Mass cytometry identifies expansion of double positive and PD-1+ T cell subsets in the tumor microenvironment of patients with POEMS syndrome.

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Abstract:
POEMS syndrome is a paraneoplastic disorder characterized, among other things, by low clonal plasma cell burden, peripheral neuropathy and high VEGF levels. Plasma cell directed therapies and radiation of solitary bone lesions have been associated with long term clinical responses even in patients without a hematologic response. This suggests that current therapies might act through non-specific immunomodulation. In this study we sought to identify mechanisms of disease development by comparing the immune tumor microenvironment (iTME) of patients with POEMS syndrome to that of patients with MGUS. We included 10 patients with POEMS syndrome, 3 newly diagnosed and one relapsed who were considered together (ND/R), 3 post treatment with ixazomib, lenalidomide and dexamethasone (postIRD) and 3 at day+100 post autologous stem cell transplant (postASCT); 12 patients with MGUS were used as controls. Single-cell suspensions were obtained by thawing cryopreserved bone marrow samples. These were stained with a 33-marker mass cytometry (CyTOF) panel using standard protocols. Live CD45+ singlets were clustered with FlowSOM and visualized with viSNE in Cytobank. Given the

small sample size p values <0.05 were considered indicative of potential trends. CyTOF identified 10 CD3- subsets and 18 CD3+ subsets (T0-T17). A novel CD38/PD-1/CCR5+ CD8 T cell subset (T3) was identified along with a PD-1/CCR5+ CD4+ subset (T16). CCR5 positive T cells are implicated in tumor immunosurveillance and PD-1 expression on these cells could be a mechanism of immune escape in this scenario. Highly suppressive CD38+ Tregs were also identified. These cells increase post ASCT and can be eradicated by CD38 antibodies. The T16 population and PD-1+ T cells in general were more abundant compared to MGUS (1.5% vs 0.6%, p=0.01 and 2.5% vs 4%, p=0.04, respectively). To confirm this finding we evaluated PD-1 staining by immunohistochemistry.VEGF has been shown to promote T cell exhaustion in other settings and could be implicated in this observation. Double positive (DP) T cells with an effector memory phenotype were also expanded compared to MGUS (1% vs 2%, p=0.008). DP T cells and the T16 subset were both lower in post ASCT and post IRD patients (p=0.04). The study is limited by its small sample size. However, it is the first of its kind utilizing a multiparametric cytometry technique to dissect the iTME in this disease. Exploring the function of DP and exhausted (PD-1+) T cell subsets might provide insights in the pathogenesis of POEMS syndrome, including the potential use of checkpoint inhibitors and CD38 monoclonal antibodies for immunomodulation in this disease.

Keywords:
microenvironment

PD-1 blockade

POEMS syndrome

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-204

Incidence of Amyloidosis in the US Veterans Health Administration

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Abstract:
Background: Patients with amyloidosis have decreased survival, unless novel disease modifying therapies are introduced. Early diagnosis improves survival and identification of at-risk populations is critical to improve outcomes. The epidemiology of amyloidosis in the US Veterans Health Administration is unknown. The objective of this project is to calculate the incidence of amyloidosis in the US Veterans Health Administration. Methods: Retrospective analysis of the Department of Veterans Affairs Informatics Computing Infrastructure (VINCI) database from 2000 to 2014. Diagnosis code of amyloidosis using the International Classification of Disease-9th revision–Clinical Modification Diagnosis (ICD) code. All patients more than 18 years old registered in the Department of Veterans Affairs Informatics Computing Infrastructure (VINCI) database. Incidence 100,000 patients per year. Results: From 2000 to 2014 a total of 5,639 new patients with amyloidosis were identified, giving an incidence of 7.4 per 100,000 patients. Of them, 96% were men and 88% were older than 55 years old. The rate of incidence had increased over the years (linear trend coefficient = 1.49, p-value = 0.001) and at a faster rate over the last years (quadratic trend coefficient = 3.04, p-value < 0.001). Incidence increased predominately in patients from the Vietnam period, with a 2 fold increase from 2000 to 2014 (2.5 vs. 5.1 per 100,000 patients, respectively). Conclusions: These preliminary data suggest the incidence of amyloidosis is increasing and accelerating in the US veteran's population. Additional data on amyloidosis type and outcomes will be presented. Understanding

the epidemiological trends and at-risk populations will guide the development of tools to provide early diagnosis and appropriate access to care for patients with amyloidosis.

Keywords:
amyloidosis

EPIDEMIOLOGY

Veterans Health Administration

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-205

Clinical and prognostic impact of circulating plasma cells on peripheral blood smears in multiple myeloma at presentation and during follow-up

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Abstract:
Background: Plasma cell leukemia (PCL) is a rare variant of multiple myeloma (MM) with an aggressive clinical course and short survival. The current definition – ≥2 x 109 /L and ≥20% circulating plasma cells (CPC) on a peripheral blood smear (PBS) - may be too restrictive. We compared clinical features and outcomes of patients (pts) with MM and different % of CPC. Method: All pts with MM (or PCL) with CPC detected on PBS from 2007-2017 were identified using a single academic center electronic database. Pts were divided into primary (CPC at presentation) or secondary form (CPC in pre-existing MM) and then stratified into 3 groups based on initial % of CPC (1-4%; 5-19% and ≥ 20%) to compare clinical features and outcomes. Overall survival (OS) from first detection of CPC were estimated with Kaplan-Meier method and compared using the log rank test. Cox proportional hazards model was used for multivariate analysis. Results: Of a total of 51 pts, 21 had a primary and 30 pts had a secondary form. At presentation, 34 pts (67%) showed extramedullary disease, 33 pts (65%) had thrombocytopenia and 23 pts (45%) had evidence of tumor lysis (by the Cairo-Bishop definition) with no difference between groups of CPC. Incidence of anemia (n=45; 88%), hypercalcemia (n=23; 45%), acute renal failure (n=29; 57%) and LDH elevation (46 evaluated; n=24; 52%) were also similar between groups. Nine pts with <20% CPC initially subsequently met criteria for PCL (ie ≥ 20% CPC). For primary and secondary forms, first line treatment at CPC detection was with bortezomib-based therapy for 16/21 (76%) and 7/30 pts (23%) while 4/21 (19%) and 13/30 (43%) pts did not receive any treatment. Five pts received autologous stem cell transplant, all with a primary form and 1-4% CPC. Median OS (mOS) was of 14,6 months (mos) (95%CI: 0,0-37,0) for primary and of 2,7 mos (95% CI 0,8-4,6) for secondary forms and was not statistically different according to group of CPC (primary: 1-4% (n = 11), mOS= 18,4 mos [0,0-42,0]; 5-19% (n=7), mOS= 2,3 mos [0,5-4,2]; ≥20% (n=3), mOS = 32,0 mos [NA]; p=0,642; secondary: 1-4% (n=15), mOS = 3,1 mos [2,1-4,2]; 5-19% (n=10), mOS = 1,5 mos [0,3-2,8]; ≥20% (n=4), mOS 1,7 mos [0,0-3,4]; p=0,606). Nine pts (43%) with a primary and 15 pts (50%) with a secondary form died within 3 mos of CPC detection. On multivariate analysis, secondary forms had worse OS (RR 2,27: 95% CI 1,18-4,4), independently of % of CPC, Durie Salmon or ISS stage. Conclusion: Presence of any % of CPC on PBS in pts with MM was associated with an aggressive presentation and a poor prognosis, similar as PCL as defined by the WHO criteria. These findings are concordant with the results of previously published retrospective series and suggest that strict application of the PCL diagnostic criteria should be avoided. The importance of careful PBS examination at presentation and progression should be emphasized.

Keywords:
circulating plasma cells

Multiple myeloma

Plasma cell leukaemia

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-206

The impact on early diagnosis and survival outcome of M-protein screening-driven diagnostic approach to multiple myeloma in China: a cohort study

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Abstract:
Background: Most multiple myeloma (MM) patients in China were diagnosed only until severe complications occurred. The incidence of MM in China is 7.3 times lower than that of United States, which could have been underestimated due to high miss diagnosis and diagnostic delay rate in China. In Zhongshan Hospital, Fudan University, a large national reference center in Shanghai delivering medical service for over 3,400,000 patients annually, serum protein electrophoresis (SPEP) is routinely incorporated into liver biochemical and function tests, and therefore providing us unique opportunities to observe the prevalence of monoclonal gammopathy in a hospital population, to screen and identify patients with myeloma or other monoclonal immunoglobulins (M-protein) related disorders at earlier stage, and to evaluate the impact of M-protein screening on baseline characteristics and outcome of patients with MM. Methods: Given every patient receiving liver biochemical tests were routinely screened for M-protein by SPEP in our institute, we initiated a standardized M-protein screening procedure based on SPEP screening in hospital population. In this retrospective cohort study, we examined records of hospitalized newly diagnosed MM patients with complete data from January 2014 to December 2017. Patients were categorized by the means of detection of the disease. Patients were considered in screening-driven group if they had an incidental finding of M-protein during workup of unrelated medical conditions and had a visit with hematologist in M-protein specialized clinic or during consultation. Symptom-driven group included patients visited or were referred to hematologic department due to suspected myeloma-related end-organ damage. Baseline characteristics, treatment, overall survival (OS) and progression-free survival (PFS) were compared. Results: A total of 690,000 people was screened and 335 eligible MM patients were identified, among which 151 of them were diagnosed via screening-driven approach. Compared to symptom-driven group, patients in screening-driven group had earlier ISS stage disease (P = 0.025), lower frequency of anemia (P = .000) and bone lesion (P = .012), and lesser number of end-stage symptoms (P = 0.000). M-protein screening approach demonstrated significantly (P = 0.039, HR: 0.425) better outcome (3-yr OS, 76.9%) than those in symptom-driven subgroup (3-yr OS, 46.6%) after adjusted for age, gender, treatment, CRAB symptoms and ECOG score with a Cox proportional hazards model. Furthermore, the annual incidence of MM in Zhongshan hospital screening population is 20.82/100,000, much higher than that in whole China despite of selection bias.
Conclusion: Our data indicated that the actual MM incidence in China may have been underestimated. And we concluded that M-protein screening in hospital population by SPEP is an effective approach to improve early diagnosis rate and outcome.

Keywords:
diagnostic and prognostic

M-protein

screening

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-207

Registry of Monoclonal Gammopathies (RMG) - the monitored real-world database of the Czech Myeloma Group

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Abstract:
Introduction: Collection of „real life" clinical data in patients with hematologic malignancies becomes more and more important due to restrictions in recruitment into clinical trials. Especially low grade malignancies require long term follow-up and valid high quality data. The RMG registry was established in 2007 and has become one of the flagship projects of the Czech Myeloma Group. To date, four parts of the registry are active - module for multiple myeloma (MM), monoclonal gammopathies of undetermined significance (MGUS), AL amyloidosis (ALA) and Waldenströms macroglobulinemia (WM). Aim: We want to demonstrate current status of the RMG in terms of amount of contained data. Methods: All patients must sign a written consent before entering their data into the registry. Data concerning diagnosis, demography, treatment and survival are regularly collected and updated into the registry via online system. The data from patients with monoclonal gammo-pathies are collected predominantly prospectively. Registry is regularly monitored and data are validated by an external monitor. The database has been upgraded in the previous 2 years, the CLADE-IS system is currently in use. A new system of data visualization was introduced in 2018. Results: There are currently 23 participating centers as of May 2019 (19 from the Czech Republic and 4 from Slovakia). Data from 6665 patients with MM, 3563 with MGUS, 234 patients with WM and 38 with ALA have been collected. Together 10501 patients have been included in the registry until end of April 2019, 10000th patient was assigned to RMG on October 17th 2018. Median follow-up of MGUS patients is 5 years (0.0-35 years) and median follow-up for MM patients is 3 years (0.0-32 years). The huge amount of data allowed regular analysis and publication of treatment results of MM patients treated with novel drugs of multiple myeloma in the Czech Republic. The new prognostic models for MGUS progression and asymptomatic myeloma have been created based on registry data. Conclusion: The RMG is one of the largest MM registries with „real life" clinical data in Europe and probably worldwide. Its biggest advantage is collection of validated updated data which can be used to create rapid analyses in order to react to changing myeloma field. It helps us to create new guidelines and serves as a potent research tool. It can be also used to negotiate reimbursement process with healthcare insurance companies and government regulatory authorities for novel drugs implementation into treatment standards. Supported by project PROGRES Q40/8.

Keywords:
monoclonal gammopathies

real-world

registry

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-208

Risk of Progression Across Age and Race for Patients with Smoldering Multiple Myeloma

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Abstract:
Smoldering Multiple Myeloma (SMM) is the requisite asymptomatic phase that precedes MM. Observation until progression to MM has been the standard of care. However, the improvement in risk assessment and utility of chemoprevention strategies stemmed from large trials is beginning to shift the paradigm toward early detection of SMM by implementing screening strategies (e.g., PROMIS study). Lack of specific ICD code for SMM has been a major problem in epidemiologic studies aiming at characterizing the demographics and temporal dynamics of SMM. Here, we used the National Cancer Data Base (NCDB), which covers more than 70% of cancer pts in the USA. Data from year 2010 to 2014 was analyzed. We defined SMM as pts with ICD-O 9732 that were placed on active surveillance or did not receive any therapy in the first 3 months (m) after diagnosis (Ravindran et al. 2016). The effect of medical insurance on OS was estimated by Cox model after adjusting the effects of confounders including age, sex, race, tumor (primary vs. secondary), and Charlson score. There were 68234 patients with MM identified between the years 2010 – 2014, SMM consisted of 11643 patients of which 52 % were males. Seventy one percent of the patients were Whites and 24 % were Blacks. SMM was diagnosed 4 years earlier in Blacks at median age of 66 compared to 70 years old in Whites ($p<0.001$). The overall rate of progression was 21.2%. The time to progression to MM which was calculated as the time from diagnosis of SMM to time first therapy was same among Whites and Blacks. After controlling the effects of insurance, age and transplant, race was still not significant in predicting the time from diagnosis of SMM to first therapy ($p = 0.42$). Younger patients was more likely to get the first therapy (2.2 days per year increase of age, $p = 0.03$). The survival after starting therapy in SMM patients who progressed to MM was same for both the races, however patients with private insurance had longer OS ($p< 0.001$). Patients who were known to have SMM had better survival than patients with MM without known SMM which was statistically significant ($p<0.001$). Furthermore, this group of patient underwent less surgery after diagnosis of MM than patients without any known history of SMM (0.28% vs. 1.6%, $p<0.001$). There was no statistically significant difference between OS of SMM patients that never progressed to MM and general population adjusted for age and race. The rate of SMM progression to MM had a trend to be higher in Black than White but did not meet statistical significance (22.3% vs. 20.7%, p:0.069). There was a declining trend of progression rate by year of diagnosis ($p<0.001$). Taken together, our result shows higher rate of MM progression in younger SMM patients than old ones as well as earlier age of SMM diagnosis in Blacks. Also, this study highlights the importance of known SMM stage before MM in prolonging survival which can be indicative of benefit from screening programs.

Keywords:
Racial Disparity

screening

Smoldering Multiple Myeloma

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-209

Crystalcryoglobulinemia-induced kidney disease

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Abstract:
Background | The spectrum of kidney damage associated with monoclonal gammopathy is wide, and notably encompasses diseases secondary to the abnormal precipitation or deposition of monoclonal immunoglobulins. Crystal(cryo)globulin-induced kidney disease is a rare but dramatic complication of monoclonal gammopathy, characterized by spontaneous crystallization of monoclonal immunoglobulins in the renal and systemic vasculature. Case description | We describe the case of a 69-year-old female Caucasian patient who developed purpura, skin necrosis and rapidly progressive renal failure leading to end-stage kidney disease. Lab tests showed low serum levels of complement C3 (0.27 g/L, normal range 0.9-1.8) and C4 (0.03 g/L, normal range 0.1-0.4); a serum M-spike composed of immunoglobulin G kappa (19.9 g/L); an increased kappa to lambda free light chain ratio (5.27, normal range 0.26-1.65); and type I IgG kappa cryoglobulinemia. Urinalysis revealed microscopic hematuria and heavy proteinuria (5.35 g/day), mainly composed of albumin (95%) and of the kappa light chain. There was no hypercalcemia, anemia, nor evidence of lytic bone lesion. Complete autoimmune and viral serologic testing returned negative. Bone marrow aspiration and biopsy showed 11% monotypic κ plasma cells. On kidney biopsy, light microscopy displayed glomerular damage, with a membranoproliferative pattern of injury, and fuchsinophilic deposits on Masson's trichrome stain. Surprisingly, routine immunofluorescence staining for immunoglobulins and complement was negative, as was Congo red staining. Ultrastructural findings provided by transmission electron microscopy included crystalline material within endothelial cells and subendothelial organized microtubular deposits (thickness, 20 nm), compatible with the diagnosis of crystalcryoglobulin-induced kidney disease. Interventions and outcomes | The patient was started on hemodialysis and treated with plasma exchanges, and a regimen combining bortezomib, cyclophosphamide and dexamethasome (VCD). Skin lesions rapidly improved, but the patient remained dialysis-dependent. As no hematological response was achieved under VCD, a second line treatment with bortezomib, lenalidomide, and dexamethasone (VRD) was initiated. Conclusions | Crystal(cryo)globulinemia is a rare manifestation of multiple myeloma and results from crystallization of monoclonal immunoglobulins in the vasculature, leading to ischemia and end-organ damage. The diagnosis is challenging, as routine immunofluorescence is frequently negative (requiring pronase immunofluorescence to unmask crystallized monoclonal immunoglobulins), and relies on the identification of intravascular crystals on electron microscopy. Early intervention combining rapid removal of crystal(cryo)globulins by plasma exchanges and control of the clonal cell proliferation are warranted to reduce the burden of this rare but dramatic complication of monoclonal gammopathy.

Keywords:
monoclonal gammopathies

myeloma

Renal

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-210

Stabilization of amyloidogenic antibody light chains as a potential therapeutic strategy in AL amyloidosis

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Abstract:

Clonal plasma cells in multiple myeloma and related conditions secrete immunoglobulins, including free light chains. In systemic AL amyloidosis, these light chains (LCs) or their fragments can misfold and aggregate to form insoluble, non-native amyloid fibrils that cause organ damage and eventually death. Of the 3-4,000 Americans diagnosed each year with AL amyloidosis, 1,000 will die within a year of diagnosis, mainly due to heart failure. No drugs are approved specifically for AL amyloidosis, but off-label use of cytotoxic regimens approved for multiple myeloma can be effective. However, many patients are too sick at diagnosis to tolerate chemotherapy, especially those with significant cardiomyopathy. Treatments for frail AL amyloidosis patients are therefore urgently needed. Each patient has a unique light chain sequence. Only a minority of individuals with a plasma cell dyscrasia will develop amyloidosis. We therefore investigated the differences between AL-associated and non-AL-associated LCs. Full-length LCs from AL patients are less stable than other LCs, and full-length LCs remain soluble under conditions where their isolated variable domains readily aggregate. Disruption or proteolytic removal of the constant domain appears to be necessary to allow aggregation of LCs in vitro. The earliest studies on AL amyloid suggested that the variable domain forms the core of the fibril – these results have been confirmed recently by high-resolution structures of AL amyloid fibrils extracted from patients. These data all support the hypothesis that stabilization of antibody LCs could prevent misfolding, proteolysis and aggregation of LCs in patients, and be of benefit to patients. Stopping amyloid formation at the beginning by preventing precursor protein misfolding is a proven strategy to treat transthyretin amyloidosis. We therefore aim to develop drugs that can stabilize LCs and prevent amyloid deposition. This strategy is orthogonal and complementary to existing and emerging treatments for AL amyloidosis. We have identified small molecule stabilizers of the native dimeric structure of full-length LCs. A protease-coupled fluorescence polarization-based high-throughput screen identified small molecules that stabilize LCs against unfolding and proteolysis. Structural data demonstrate that at least one class of hits bind at the LC-LC dimerization interface within full-length light chains, utilizing variable domain residues that are highly conserved in most AL patients. The small molecule stabilizers identified bind to conserved residues at the variable domain–variable domain interface in the native dimer, stabilizing this putative non-toxic structure. We aim to develop more efficacious small molecules that could become drug candidates.

Keywords:
amyloidosis

light chain

therapy

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-211

Screening for Gaucher disease in patients with plasma cell dyscrasias

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Abstract:
Introduction Gaucher disease (GD) constitutes the most frequent lysosomal storage disease and is attributed to an inherited deficiency of

glucocerebrosidase with an autosomal recessive pattern. Although controversial, published data have demonstrated an increased incidence of monoclonal gammopathies, especially multiple myeloma (MM) in these patients. Under this prism, we decided to perform a screening test for GD in a large number of patients with plasma cell dyscrasias (PCDs). Methods We included patients with smoldering MM (sMM), multiple myeloma (MM), Waldenstrom's macroglobulinemia (WM), AL amyloidosis, light chain deposition disease (LCDD) and POEMS syndrome. All patients provided written informed consent as per Institution's policy. 2ml of peripheral blood were collected in EDTA blood collection tubes. Blood samples were then applied to the Centogene AG multiproduct DBS filter card and subsequently the card was air dried for at least 3 hours per manufacturer instructions. The samples were sent to Centogene AG central laboratories for analysis of glucocerebrosidase enzyme with liquid chromatography and mass spectrometry. In case of abnormal results, further determination of lyso-Gb1 biomarker via liquid chromatography, mass spectrometry and GBA gene mutational status via Sanger sequencing was performed. Results 285 patients with PCDs were included in the study; 243 (85.3%) were diagnosed with MM, 24 (8.4%) with sMM, 6 (2.1%) with WM, 7 (2.5%) with amyloidosis, 3 (1.1%) with LCDD and 2 (0.7%) with POEMS syndrome. Among all patients, the median glucocerebrosidase value was 8.3 μmol/L/h (standard deviation=6.8 μmol/L/h, range=3.5-97.3 μmol/L/h). 264 (92.6%) of the screened patients had normal glucocerebrosidase values, whereas 21 (7.4%) presented with abnormal measurements. Among these 21 patients, lyso-Gb1 assessment via liquid chromatography mass spectrometry was found normal in all examined specimens. Furthermore, a pathogenic mutation via Sanger sequencing was detected only in one patient (0.4%). Interestingly, two heterozygous mutations were detected in this patient; namely c.882T>G (p.His294Gln) in the exon 7 and c.1342G>C (p.Asp448His) in the exon 9. Both of them have been previously reported as disease-related pathogenic mutations. Considering the normal value of the biomarker lyso-Gb1 in this patient, it was assumed that the detected mutations were in cis, and the patient was characterized as a carrier of two disease-causing mutations in the GBA gene. Conclusion Among the 285 patients with PCDs screened, only 1 patient with MM was found carrying two heterozygous mutations for GD. Screening for GD needs to be implemented in a larger number of patients in order to assess its diagnostic value and potential benefit. Further insight into the pathogenesis of PCDs in patients with GD may provide a stronger rationale for our approach.

Keywords:
Gaucher disease

Multiple myeloma

Plasma cell disorders

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-212

Preliminary evidence of efficacy of venetoclax in relapsed and refractory AL amyloidosis.

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Abstract:
AL Amyloidosis (AL) is a plasma cell dyscrasia marked by production and deposition of toxic free light chains in organs including the heart, kidney and nervous system. While treatment regimens are generally borrowed from multiple myeloma (MM), patients typically have difficulty tolerating many of these drugs, especially the immunomodulatory drugs (IMiDs) due to high cardiac and hematologic toxicities. Recently daratumumab has been shown to be active in AL, however for patients who become refractory to daratumumab, options remain bleak and more therapies are desperately needed. Up to 60% of cases of AL harbor t(11;14) and

subsequently over-express BCL-2. As such we had begun to use venetoclax in combination with proteasome inhibitors for patients with relapsed/refractory AL. Here we report two cases of deep and durable responses to treatment with venetoclax in combination with a proteasome inhibitor. Each patient was able to obtain a complete remission (CR), one patient after two cycles and the other after just 17 days of treatment. While the treatment was overall well tolerated, one patent did develop severe hypogammaglobulinemia. Recently, however, the FDA has put a hold on studying venetoclax in MM given the results of the BELLINI trial (NCT02755597) examining the efficacy of venetoclax in MM. Preliminary results indicate an increased rate of death in the venetoclax arm when compared to placebo, largely due to infection. We hope that with proper infectious prophylaxis we can abrogate the perceived increased rate of death and the hold on venetoclax can be lifted. Given the high quality and durable responses seen in these cases we believe venetoclax warrants further study in AL and has the potential to be a major player in the fight against AL.

Keywords:
amyloidosis

BCL-2

t(11;14)

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-213

Retrospective study of AL-amyloid patients with t(11;14) treated with daratumumab

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Abstract:
Purpose: The standard of care for AL amyloidosis, in patients who are not candidates for a stem cell transplant, is based on Bortezomib-based chemotherapy. Unfortunately, patients harboring the t(11;14), who represent up to 50% of AL amyloidosis cases, have a poor response to Bortezomib. Daratumumab (Dara), a monoclonal antibody targeting CD38 approved for the treatment of patients for multiple myeloma, has been shown to be highly active in heavily pretreated patients with AL amyloidosis (Kaufman et al, Blood 2017). The activity of Dara in amyloid patients with t(11;14) is unknown. Methods: Observational, retrospective review of AL amyloidosis patients with t(11;14) treated at the Utah Amyloidosis program, who have received Daratumumab, either as a single agent or in combination. Results: 18 patients with AL amyloidosis received Dara from June 2017 through June 2019. Five (28%) had t(11;14). Patients had a median age of 62, three males and two females. There were two newly diagnosed patients enrolled in a clinical trial which combined cyclophosphamide, bortezomib, and dexamethasone (CyBorD) with Dara, while the remaining three patients had been previously exposed to CyBorD. Newly diagnosed cases on CyBorD and Dara: one achieved a complete response (CR) after two months and the other a partial response (PR) after two months. Patients previously treated with CyBorD: two were non-responders and one progressed after CR achievement. The non-responders had minimal improvement in their serum free light chains after two cycles prompting a change to Dara. One of whom received Dara, revlimid, and dexamethasone (DRd) and after two cycles showed a PR, before ultimately dying due to complications from the disease. The 2nd patient received Dara/dex and reached a CR after two cycles. The third patient received DRd and achieved a CR after two cycles. Overall, 100% patients with t(11;14) achieved a hematologic response to Dara, with 3 patients (60%) achieving a CR and 2 a PR. The median time to best response was two cycles and the responses thus far have been maintained. Dara was overall well

tolerated. Conclusions: These data suggest that Dara has activity in patients with t(11;14). A limitation of this dataset is the small number of patients included. Although Venetoclax is active in MM patients with t(11;14), it has not been tested in AL amyloidosis and the recent infectious complications observed in the Bellini trial will delay its use in MM and AL amyloidosis. Further observations are warranted to determine the value of Dara in this patient population, either in first line or at progression. In the meantime, we believe that Dara is an attractive treatment option for patients with t(11;14), either as a single agent or in combination.

Keywords:
amyloidosis

daratumumab

t(11;14)

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-214

Clinical manifestations and outcomes of primary systemic AL amyloidosis: Chiang Mai University Experience

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Abstract:
Introduction Light chain amyloidosis (AL) is characterized by the presence of monoclonal plasma cell and deposition of immunoglobulin light chain derived amyloid deposits in various organs. The outcome of patients with primary systemic AL amyloidosis is generally poor especially with organ involvement, such as cardiac and renal involvement. Treatment with chemotherapy and autologous hematopoietic stem cell transplantation (ASCT) can result in improve survival outcome in these patients. Materials and Methods This is a retrospective study. We included all patients who were diagnosed with primary systemic AL amyloidosis and treated in Chiang Mai University Hospital, Thailand within 16-year period from January 2002 to October 2018. Data obtained through the electronic database and clinical record, including demographic data, clinical presentation and laboratory characteristics, treatment and outcomes, were analyzed. Results A total of 28 patients were identified. The mean age at diagnosis was 63 years old (range 39 to 85 years old) and 71% were male (n=20).The most first clinical presentation was dyspnea on exertion (42.8%, n=12) followed by edema (35.7%, n=10). Other presentations included thickening of skin, eyelid mass, abdominal mass, lymphadenopathy, macroglossia, and numbness (1 patients each, 3.6%). The main organ involvement were cardiac (60.7%, n=17) and renal (53.6%, n=15) with 10 patients (35.7%) had both cardiac and kidney involvement. The rest of the patients had liver (10.7%), dermatologic (10.7%), and peripheral nerve involvement (3.6%). For determination of M-protein, urine Bence Jones was detected in 18 patients (64.3%), positive serum and urine protein electrophoresis were identified in 3 patients each (10.7%). Most of patients received chemotherapy (85.7%, n=24) and no one underwent ASCT. The most prescribed chemotherapy was melphalan-dexamethasone (45.8%) and melphalan-prednisolone (41.6%). Other patients received bortezomib-dexamethasone (8.3%) and bortezomib-cyclophosphamide-dexamethasone (4.1%). Among treated patients, 25% (n=6) achieved hematologic response (very good partial response 12.5% and partial response 12.5%). Kidney response was the only organ response which was occurred in 2 patients (8.3%). The mortality rate was 82.1% (n=23) with estimated 5-year overall survival of 18%. A simple Cox regression analysis identified that presence of urine Bence Jones protein is a poor prognostic factor for survival. Conclusions Primary systemic AL amyloidosis is a condition with poor prognosis. The most common organ involvement were cardiac and renal involvement. Presence of urine Bence Jones protein seems to be related to survival outcome in this study. Overall survival of

AL Amyloidosis in Chiang Mai University was poor and most of patients had poor response to treatment since the majority of patients did not novel agent-based therapy and ASCT.

Keywords:
amyloidosis

melphalan

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-215

Peripheral neuropathy and monoclonal gammopathy of undetermined significance: A population-based study including 15,351 cases and 58,619 matched controls

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Abstract:
Monoclonal gammopathy of undetermined significance (MGUS) is the precursor condition of multiple myeloma (MM) and related disorders. MGUS is relatively common and although it is often referred to as asymptomatic, individuals with MGUS have been reported to develop peripheral neuropathy (PN). However, the literature is unclear on the prevalence, implications, and even the existence of MGUS associated PN. Therefore, we were motivated to assess the prevalence and risk of PN in a large population of individuals with MGUS. We included 15,351 individuals with MGUS diagnosed 1986-2013 and enrolled from a nationwide network of hematology- and oncology centers and the Swedish patient registry. Then, 58,619 controls were matched to the cases by age, sex, and county of residence. We then cross-linked participants to data from the Swedish patient registry, cancer registry, and cause of death registry, using a national identification number. Using this data, we created a Cox model with the endpoint of PN diagnosis and censored at death, loss to follow-up, or diagnosis of MM or related disorders, additionally stratifying for diabetes mellitus (DM), a population under surveillance for PN. Participants who had PN at MGUS diagnosis were excluded from this analysis. Secondly, we evaluated the association of PN and progression of MGUS to multiple myeloma (MM) and related disorders using a multi-state model. Participants with MGUS had a higher risk of PN than matched controls (7.5% vs 3.1%; hazard ratio (HR): 2.7; 95% confidence interval (95% CI): 2.4-3.1; $p<0.001$). Participants with MGUS and DM had the highest risk of PN, twofold the risk of those with DM alone (12.4% vs 7.7%; HR: 2.1; 95% CI: 1.7-2.5; $p<0.001$). PN was associated with a reduced risk of progression to MM (HR 0.6, 95% CI: 0.4-0.8; $p<0.001$) and an increased risk of amyloidosis (HR: 2.3; 95% CI: 1.5-3.7; $p<0.001$). Our findings show that MGUS is truly associated with PN, affecting a significant proportion of individuals with MGUS. We found PN to be associated with an increased risk of AL and a reduced risk of MM. PN might increase the risk of falls, decrease quality of life, and might affect choice of therapy if MGUS progresses. These findings warrant closer monitoring of individuals with MGUS for PN.

Keywords:
MGUS

neuropathy

population-based

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-216

TREATMENT OF WALDENSTRÖM MACROGLOBULINEMIA (MW): EXPERIENCE IN REAL LIFE IN

DIFFERENT CENTERS OF THE COMMUNITY OF MADRID (SPAIN)

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Abstract:
INTRODUCTION: MW is a rare entity, with an incidence in Spain of 3.1 cases / million inhabitants / year. 25% of patients diagnosed are asymptomatic and remain untreated and controlled periodically. The remaining 75% are symptomatic patients in which we initiate the treatment. At the present time we have several treatment options. Most of these treatments do not have specific randomized prospective studies. We wanted to collect what occur in our usual clinical practice and clinical experience in different centers. PATIENTS AND METHOD: We retrospectively collected the data of the patients diagnosed with MW who had been treated in 5 centers of the Community of Madrid in the last ten years. RESULTS: A total of 28 patients had been diagnosed with MW and had been treated in the last 10 years. The average age at diagnosis was 72.3 ± 9.0 years and at the time of initiation of treatment 74.0 ± 9.1 years, which meant that the time from diagnosis to the start of treatment was dilated in terms of median 11.5 [34.75] months. 71% (n = 20) of the patients were male. 100% of the patients had an ECOG 0-1. Table 1 shows the analytical and clinical characteristics at diagnosis and at the start of treatment. From the genetic point of view MYD88 was positive in 18 patients and in 10 patients it was not performed. CXCR4 was not performed on any patient. 50% (n = 14) of patients received a 2nd line of treatment, 25% (n = 7) 3 lines of treatment and 7% (n = 2) 4 lines. The schemes administered were: Ritu-Ciclof-dexa, Ritu weekly, R-Benda, Bortezomib-Dexa-Ritu, Chlorambucil, Cyclophosphamide, R-CVP, Ritux-Dexa and Fludarabine. We did not find significant differences in the response according to the Response Criteria (6th International Workshop in MW) according to the treatment received. Only in 1 patient plasmapheresis was performed. And in none transplant. With a median follow-up of 32 [58] months, of the 22 patients who remain alive, only 4 patients have Complete Remission. Of the 6 patients who died, it was observed that 5 did so for other causes not related to the disease and only 1 patient died due to progression of the disease. Median survival was 85 months. CONCLUSIONS: The clinical and analytical characteristics of our series are similar to those described in the literature. We found a median survival of 85 months (7 years) similar to that described in other series (6-8 years). We did not find significant differences in the response according to the treatment received, probably because the treatment mainly used in 2nd line (Ibrutinib) improves the responses with prolonged treatment and we need a greater follow-up. In general, the treatments administered were heterogeneous, which helps to highlight the need for more clinical trials in this disease.

Keywords:
real-world

treatment

Waldenström macroglobulinemia

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-217

A phase 1/2 study to assess safety and dose of ixazomib in combination with cyclophosphamide and dexamethasone in newly diagnosed patients with light chain (AL) amyloidosis

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Abstract:
Introduction: AL amyloidosis is an incurable clonal plasma cell disorder characterized by tissue deposits of immunoglobulin light chain fragments leading to organ dysfunction and death. Standard treatment for newly diagnosed patients (pts) has traditionally included oral melphalan + dexamethasone as well as high-dose melphalan + ASCT. Although the combination of bortezomib, cyclophosphamide and dexamethasone (CyBorD) has activity, better tolerated treatment approaches are needed. Here we report preliminary results of a Phase 1/2, open-label, multi-institution study of ixazomib (I) in combination with cyclophosphamide (Cy) and dexamethasone (D) in newly diagnosed AL amyloidosis. Methods: Eligible pts are ≥18 years with newly diagnosed, untreated biopsy-proven AL amyloidosis according to standard criteria. A total of up to 30 pts will be enrolled, with up to 18 in the dose escalation arm (phase 1) and 12 in the maximum tolerated dose (MTD) expansion arm (phase 2) according to a classical 3+3 design. Four dose levels were evaluated in phase 1. I and Cy are given orally (PO) on days 1, 8, 15, and D 20mg PO on days 1, 8, 15, 22 of each 28-day cycle. Treatment continues for a total of 6 cycles or until disease progression, significant toxicity or withdrawal. The primary study objective in phase 1 is to establish the MTD and in phase 2 is to determine hematologic/organ response rate. Results: As of May 2019, 18 pts have been enrolled; 16 in phase 1 and 2 in phase 2. The MTD was established at dose level 3 (I 4mg and Cy 500mg). Median age is 65 years (range 46-79), 12 (67%) are male. Light chain isotype is lambda in 14 (78%). Seven pts (39%) have cardiac, 10 (56%) renal, 4 (22%) gastrointestinal, 1 (6%) hepatic, 2 (11%) soft tissue involvement, with 22% having multi-organ involvement. Four pts (22%) completed 6 cycles of therapy and 6 (33%) remain on study with a median of 3 cycles completed. Eight pts (44%) have been taken off study prior to completing 6 cycles due to no response in 5 (28%) after a median of 3.5 cycles (2-5), grade 4 hyperbilirubinemia unrelated to study drug in 1 (6%), cardiac decompensation in 1 (6%), and 1 death attributed to advanced disease. Eight of 16 pts (50%) had at least 1 drug-related adverse event (AE) (any grade), most commonly edema (19%), fatigue (19%), dizziness/lightheadedness (13%) and lymphopenia (13%). Grade 3/4 AEs were rare with grade 3 lymphopenia, anemia, and hyponatremia occurring in 13%, 6%, and 6% of pts, respectively. Of 18 evaluable pts, 7 (39%) achieved ≥VGPR with the median time to best response 2 cycles (1-5). Conclusion: The combination of ICyD for pts with newly diagnosed AL amyloidosis is safe and well tolerated. Phase 1 is completed and the recommended phase 2 dose has been established. Deep hematologic responses (≥VGPR) have occurred and time to response appears similar to standard of care induction regimens, ie CyBorD. Phase 2 response data will be updated at the meeting.

Keywords:
amyloidosis

clinical trials

ixazomib

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-218

Oncogenic activity of human MYD88L265P mutation in mature B-cells in vivo

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Abstract:
MYD88(L265P) is the most common mutation in lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM) and one of the most frequent in poor-prognosis subtypes of diffuse large B-cell lymphoma (DLBCL). Although, inhibition of MYD88(L265P) activity has been shown to be toxic to LPL/WM and DLBCL cells, providing crucial insight for potential targeted therapies, these studies were conducted in the context of pre-quiescent tumor suppressor signaling and the results bear limited information on the role of MYD88(L265P) in tumor initiation, which remains uncertain. To investigate the oncogenic potential of the somatic MYD88(L265P) mutation, we generated conditional transgenic mice overexpressing human MYD88(WT) or MYD88(L265P)-mutated proteins in antigen-experienced B-cells by using AID-Cre, since both human LPL/WM and ABC DLBCL originate from post-GC B-cells. Expression of MYD88(L265P) was lower than MYD88(WT), suggesting different maturation and/or stability of these proteins. Moreover, while MYD88(WT) was evenly distributed among the cells, MYD88(L265P) was confined to small foci within mouse GC B-cells, indicating that the L265P mutation enhances oligomerization and resembles formation of myddosome/My-T-BCR in vivo. Although, overexpression of both human MYD88(L265P) and MYD88(WT) enhanced nuclear localization of its downstream target p65 in GC B-cells, only the MYD88(L265P) cells demonstrated decreased p65(S534) phosphorylation. The decrease in S534 phosphorylation was previously shown to increase p65 stability and enhance NF-κB-dependent gene expression, suggesting different activities of mutated versus WT protein. Around 8 weeks of age, 90% of MYD88(L265P) mice, but none of the MYD88(WT) or AID-Cre control mice, developed focal granulomatous skin inflammation associated with increased serum IL-6 levels. At a median of 67 weeks, MYD88(L265P) mice developed a non-clonal, low-grade B-cell LPD with several clinicopathologic features of LPL/WM, including expansion of lymphoplasmacytoid cells, increased serum IgM concentration, rouleaux formation, increased number of mast cells in the bone marrow, and proinflammatory signaling, that progressed sporadically to clonal, high-grade DLBCL. The prominent lymphoplasmacytic infiltrate, longer latency, and BCL6 expression suggested that these neoplasms might have arisen from the LPD by acquiring cooperative genetic alterations. We therefore performed whole exome sequencing of three MYD88(L265P) DLBCLs, and detected secondary genetic lesions mirroring mutations documented in human de novo and LPL/WM-transformed DLBCL cases. These findings indicate that, while the MYD88(L265P) mutation might be indispensable for the LPL/WM phenotype, it is insufficient by itself to promote malignant transformation in B-cells and relies on other, potentially targetable, cooperating genetic evens for full lymphoma development.

Keywords:
mouse model

MYD88

Waldenström macroglobulinemia

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-219

Impact of Minimal Residual Negativity on Outcomes in Light Chain Amyloidosis

Authors:

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Abstract:
Introduction: Achievement of minimal residual disease (MRD) negativity has been associated with improved survival outcomes in multiple myeloma. Data on outcomes with MRD negativity in AL amyloidosis are limited. In this study, we evaluated outcomes in AL amyloidosis based on MRD status using next generation flow cytometry. Methods: Patients with systemic AL amyloidosis who underwent MRD assessment were included in the study. Bone marrow MRD assessment was carried out with next generation flow cytometry (sensitivity: 10 ^-5) using antibodies to CD138, CD27, CD38, CD56, CD45, CD19, CD117, CD81, kappa and lambda light chains. Results: MRD testing was available in 53 unique patients from 08/2017 to 11/2018, of which 62% (n=33) were MRD negative. Median age was 63 years and 57% (n=30) were male. Involved light chain (LC) was lambda in 72% (n=38) of patients. Median dFLC and median BMPCs at diagnosis were 15.3 mg/dL (IQR:7.2-52.9) and 9% (IQR: 4-25), respectively. Organ involvement was: kidney: 64%, heart: 53%, peripheral nervous system (NS): 15%, autonomic NS: 9%, liver: 4%. Median NTProBNP was 926 pg/mL (IQR: 163-2097). Median 24 hour urine protein was 2877 mg (IQR: 556-8475). Median lines of therapy prior to MRD evaluation was one (range 1-5); one line only: 68%;n=36). 70% (n=37) of patients received ASCT at some point in their disease course. At MRD assessment, 96% (51/ 53) patients were in VGPR (n=24) or CR (n=27). Median involved LC levels at the time of MRD assessment in MRD- vs. MRD+ patients were 1.3 vs. 1.4 mg/dL (p=0.5) There were no differences in baseline characteristics in patients who were MRD- vs. MRD+ (not shown). CR was seen in 58% MRD- vs. 40% MRD+ patients, p=0.2. MRD- rates were 76% in patients with one line of therapy and 47% in >2 prior lines, p=0.12. MRD- patients were more likely to have achieved cardiac response at the time of MRD assessment, 69% (11/16) vs. 25% (3/12), p=0.02. For renal response assessment, patients who were on dialysis prior to start of therapy were excluded. Renal response rates at MRD assessment were similar in MRD- vs. MRD+ patients, 71% (12/17) vs. 91% (10/11), p=0.2. Patients who were MRD negative continued to have renal response within one year of MRD assessment (response rates within 1 year: 82%, 14/17) Median follow-up after MRD testing was 14 months. PFS (both organ and hematologic), from the time of MRD assessment was significantly better in MRD- vs. MRD+ patients. Median PFS was not reached in either group, but the estimated 1 year PFS was 100% (33 patients, 0 events) vs. 71% (20 patients, 5 events), p=0.006, respectively. Conclusion: Patients with AL amyloidosis who achieve MRD negativity by flow cytometry (10^-5) have significantly better cardiac response rates and longer PFS from the time MRD assessment than those who have residual plasma cells. Future studies which evaluate MRD at more uniform time points and in a homogenous cohort are needed to validate these results.

Keywords:
amyloidosis

Minimal residual disease

Tracks:
Other Plasma Cell Disorders and Amyloidosis

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Venetoclax For The Treatment of Translocation AL Amyloidosis

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Abstract:
Background Venetoclax is a B cell lymphoma 2 (BCL-2) inhibitor active in multiple myeloma, particularly those harboring t(11;14) associated with high BCL-2 expression. Approximately 50% of patients with immunoglobulin light chain (AL) amyloidosis have t (11;14), making venetoclax a suitable agent to consider in this rare disease. We aimed to identify the safety and efficacy of venetoclax in patients with AL amyloidosis. Methods We conducted a retrospective review of all patients with AL amyloidosis treated with venetoclax between February of 2017 and May of 2019 at the Mayo Clinic. Results 12 patients treated with venetoclax for relapsed AL amyloidosis were identified. Median age was 64 years (range 52-76) and 75% (n=9) were male. Median number of prior lines of therapy was 2 (range 1-4). Previous therapy exposures included proteasome inhibitors, oral alkylators, immunomodulatory drugs, daratumumab and stem cell transplant in 100%, 92%, 25%, 33% and 25% respectively. Most common organs involved were renal (75%) followed by heart (50%), neurological (25%) and gastrointestinal (17%). The t (11;14) was detected on fluorescence in situ hybridization (FISH) studies of the bone marrow in 11 out of 12 patients. Venetoclax was used as a single agent or doublet in combination with dexamethasone in 7 (58%) patients. The dose used was 800mg in 7 (58%) and 400mg in 5(42%) patients and dose titration was utilized in 8 (67%) patients. Median duration of therapy was 5 months (range 1-27 months) and at last follow-up 7 (58%) patients remain on venetoclax. Of 8 evaluable patients for hematologic response, 3 achieved CR and 4 achieved a VGPR and one patient did not respond to therapy (overall response rate 87%). BCL2 expression by immunohistochemistry was assessed in 5 patients all of whom had strong expression [all had (t11;14)]. Of these, 3 were evaluable for hematologic response (CR n=2, VGPR n=1). Median time to best hematologic response was 3.4 months (range 1.6-8.4 months). At last follow up, 1/4 patients with cardiac involvement achieved a cardiac response 3 months after initiation of venetoclax . 2/6 evaluable patients with renal involvement achieved a renal response at 10 and 16 months post initiation of venetoclax respectively. After a median follow-up of 11.5 months, two patients have progressed at 4 and 5 months post initiation of venetoclax therapy respectively and none have died. No patient experienced tumor lysis syndrome and gastrointestinal side effects were reported in 6 patients (mild-predominantly loose stools). Reasons for discontinuation of therapy included, dose limiting cytopenias (n=1), dyspnea (n=1), failure to respond (n=1) and attainment of desired response (n=2). Conclusion Venetoclax is a safe and efficacious agent in patients with AL amyloidosis and has the ability to induce both hematologic and organ responses. Prospective trials are needed to further elucidate the role of this agent in patients with AL amyloidosis.

Keywords:
amyloidosis

BCL-2

Venetoclax

Tracks:
Other Plasma Cell Disorders and Amyloidosis

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The role of bone marrow biopsy in patients with plasma cell disorders; should all patients with a monoclonal protein be biopsied?

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Abstract:
Background The prevalence of monoclonal gammopathy of undetermined significance (MGUS) increases with age, however many patients remain asymptomatic lifelong. Patients require thorough clinical and laboratory assessment and some may require invasive investigations such as bone marrow aspirate and biopsy (BMB) to identify symptomatic disease requiring therapy. Methods We conducted a retrospective review of all patients diagnosed with MM, SMM and MGUS at the Mayo Clinic Rochester between 1st January 2000 and 31st December 2016. Patients diagnosed with SMM, MM or MGUS between 1st January 2000 and 31st December 2016, seen at the Mayo Clinic within 90 days of diagnosis and with available data to assess whether any of the following CRAB features (hypercalcemia, renal dysfunction, anemia and bone lesions) were present at diagnosis. The MM patients were categorized as "without CRAB/FLC" (laboratory values within reference range for calcium, creatinine, hemoglobin and absence of lytic lesions assessed by conventional skeletal survey and an FLCr<100) or "with CRAB/FLC" (an abnormality detected in at least one of these variables). Patients with SMM were categorized as "myeloma-like" (serum M-protein of ≥3g/dL or urinary M-protein ≥ 500 mg per 24 hours) or "MGUS-like" (remaining patients). The primary outcome of the study was to identify the proportion of patients with SMM and MM in whom the BMB was the sole factor in establishing the diagnosis and who would have been classified as low risk MGUS without a BMB. Results: 2254 MM, 397 SMM and 5836 MGUS patients met study eligibility criteria and were included in further analysis. 29 (1.3%) MM patients "without CRAB/FLC" were identified where BMB or advanced imaging was critical for diagnosis, 8 (0.3% of MM cohort) of whom were diagnosed with MM solely based on BMB findings (plasma cells >60%). Without BMB or advanced imaging these patients would have been classified as: low-risk MGUS (n=0); low-intermediate-risk MGUS (n=11); intermediate-risk (n=12); high-risk MGUS (n=1); and unclassifiable due to missing FLC values (n=5). 314 (79%) MGUS-like SMM patients were identified in whom the classification of SMM was based on BMB findings. Without BMB 97 would be classified as low- or low-Intermediate-risk MGUS and 151 Intermediate- or high-risk MGUS; 66 had missing information precluding classification. Of these patients only 3 (<1% of whole SMM cohort) were low risk MGUS without laboratory abnormalities in hemoglobin, calcium and renal function. Conclusions and Relevance In patients presenting with low risk MGUS and normal hemoglobin, calcium and renal function the risk of missing a diagnosis of SMM and MM by omitting bone marrow aspirate and biopsy is less than 1%. Bone marrow biopsy should be deferred in these patients in preference to clinical and laboratory monitoring.

Keywords:
bone marrow biopsy

diagnosis MM and SMM

MGUS

Tracks:
Other Plasma Cell Disorders and Amyloidosis

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Outcome of first-line therapy in patients with systemic light-chain amyloidosis: A multicentre analysis

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Abstract:
Introduction: The most prevalent type of amyloidosis and at the same time has the worst prognosis is the AL amyloidosis or light chain amyloidosis. It has been estimated an incidence of 0.9 cases per 100,000h per year. It is very important to define strategies to help us optimize the diagnostic process in order to reduce the frequent premature death in these patients, generally linked to delays in diagnosis. Materials / Methods Retrospective study of the total patients diagnosed with AL amyloidosis in several centers, from March 2012 to March 2018. Data regarding demography, diagnosis, treatment and follow-up was extracted from the clinical records, and the different hematological and organ responses was evaluated. Survival curves were constructed according to the Kaplan-Meier method. Results We analyzed 44 patients with newly diagnosed AL amyloidosis. Median age was 65 years (range 40-90), and 10 pts were considered ASCT candidates. Involvement of kidney, heart, peripheral nerve , liver and other organs (digestive, bone marrow) were found in 28 (35%), 14 (17.5 %), 26 (32.5%), 4 (5%) and 8 (10%) cases, respectively. The stage of the disease was rated according to Mayo Stage 2012 obtaining the following results: stage I: 25%, stage II: 25 % Stage III : 17.5% and stage IV: 42.5% The hematological responses (HR) were: CR 22.72%, VGPR 29.54%, PR 13.63%, SD 20.45%, NR (not evaluable) 13.63% The organ response was 50% (n = 22). The OS was 35 months (95% CI 4.2-65.7). The patients were classified according to first line treatments based on bortezomib: A) CyBordex (cyclophosphamide, bortezomib and dexamethasone, n = 23, B) VTD (bortezomib, thalidomide and dexamethasone) n = 2, C) VMP (bortezomib, melphalan and prednisone) n = 2, D) BD (bortezomib and dexamethasone) n = 12, and other regimens A) MP (melphalan and prednisone) n = 4 and B) CP (cyclophosphamide and prednisone) n = 1. Hematological responses (at least VGPR) of CyBordex, VTD, VMP, BD were of: 60.89%, 100%, 100% and 41.66% respectively; and organ response was : 47.82%, 100%, 25% and 41.66% respectively. The rate of premature death within the first six months was 22.72%. Conclusions: A retrospective study in which the majority of AL patients have an average age of 65 years, who are diagnosed in advanced stages and with a small number of cases that are HSCT candidates. It should be noted that almost the same number of responses were achieved from the organ response as well as from the HR (including CR + VGPR): 50%. Regimens based on bortezomib in newly diagnosed AL amyloidosis show results that seem comparable to those previously published in the literature. To improve these outcomes it is necessary to define the role of proteasome inhibitors the role of new therapies. It's still yet to define the role of proteasome inhibitors in the first line in combination with new molecules in order to improve responses. Educational interventions are important.

Keywords:
amyloidosis

Analysis

First- line

Tracks:
Other Plasma Cell Disorders and Amyloidosis

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MGCS : an IgG-lambda monoclonal gammopathy associated with renal failure, lung disease and cutis laxa

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Abstract:
Renal diseases are frequently associated with monoclonal gammopathies. Heavy chain deposition disease (HCDD) is an extremely rare condition, one of the 3 entities of monoclonal immunoglobulin deposition disease (MIDD). It is characterized by the presence of nodular glomerulosclerosis and glomerular and tubular deposition of monoclonal HC without associated light chains (LC). Here, we reported a case of HCDD associated with other manifestations, e.a. pulmonary fibrosis and cutis laxa. A 38-year-old Polish woman was referred to the emergency room for a 2-month history of fatigue, 10 kg weight gain and NYHA II dyspnea. She has been treated in 2014 by corticosteroids for a nephrotic syndrome responsible to acute renal failure, attributed to a minimal change glomerulonephritis, evolving with time to a progressive decrease of her renal function. In addition, she presented a 3-year history of skin changing appearance with premature ageing of the face, neck, chest, arms and feet. On physical examination, she looked much older than her age, with a sagging of the skin and a lack of elasticity that predominates in the neck, axillary regions, back and abdomen. She had peripheral edema and a blood pressure at 160/90 mmHg. Initial lab tests revealed a terminal stage chronic renal failure (creatinine, 10.24 mg/dL) with microcytic anemia (hemoglobin, 7.2 g/dL), hypogammaglobulinemia (IgG, 5 g/L) with a discreet IgG Lambda M-protein and low C3 levels. Both kappa and lambda light chains were elevated with a normal kappa/lambda ratio, and associated to a significant proteinuria (4.78 g/L) with excess lambda LC and micro-hematuria. Kidney biopsy confirmed the presence of nodular glomerulosclerosis with peritubular anti-IgG staining and 'powdery punctate' deposits along the inner aspect of the tubular basement membranes, confirming the diagnosis of HCDD. IgG and C3 deposits were also reported on skin biopsies, in addition to elastic fibers degenerative changes responsible for cutis laxa. Functional pulmonary evaluation revealed a marked restrictive syndrome with a decreased diffusion capacity suggesting an interstitial lung disease, probably related to the elastolysis seen in cutis laxa. Bortezomib-based chemotherapy was started, with the prospect to collect stem cells later on, and in case of complete hematological response, proceed to kidney transplantation. Monoclonal gammapathies are rarely found in patients under the age of 40, and can be associated with numerous clinical manifestations such as MGRS. HCDD is an extremely rare condition, in which patients presented with nephrotic syndrome, hematuria and hypertension, develop progressive renal failure, but can be successfully treated with chemotherapy.

Keywords:
cutis laxa

heavy chain deposition disease

MGRS

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-224

Dysregulation of the B-Cell Receptor Pathway Through Alternative Splicing in Waldenstrom's Macroglobulinemia

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Abstract:
Background: B-cell receptor (BCR) and toll-like receptor (TLR) pathway activation are key drivers of pro-survival signaling in many B-cell and plasma cell malignancies. Both pathways are notable for their activation of common cascades that include BTK, PI3K/AKT, MAPK1 and MAPK3 (ERK1 and ERK2 at the protein level) signaling, as well as the activation and nuclear translocation of nuclear factor kappa-B (NFkB). In Waldenstrom's Macroglobulinemia (WM), the TLR pathway is driven by activating mutations in MYD88 that are found in 95-97% of patients. Activated BCR signaling in WM has also been observed (Argyropoulos et al, Leukemia 2016), but the contributions of BCR signaling to WM pathophysiology remain to be clarified. Methods: RNA isolated from CD19+ bone marrow mononuclear cells of WM patients, as well as CD19+CD27+ selected memory B-cells (MB) and CD19+CD27- B-cells (PB) derived from the peripheral blood of 9 healthy donors was prepared for 50 base pair paired-end next generation sequencing. RNA sequencing data was evaluated for alternative splicing and intron retention using Salmon, RSEM, MISO and quantification of intronic read coverage with the rsubread Bioconductor package in R. Results: LYN was among the top alternatively spliced genes in the MISO analysis and was validated by PCR. An alternative 5-prime splicing site was preferentially used in MYD88 mutated WM but not in MB, PB, PC or MYD88 wild-type samples. Notably this was not detected in the Salmon or RSEM isoform analysis despite being an isoform determining event. Stimulation of healthy donor CD19+ cells with lipopolysaccharide demonstrated no change in LYN splicing, while transcription of IL6, a downstream target of LPS induced TLR signaling, was significantly induced. These findings suggest that normal TLR signaling was not responsible for isoform changes observed in LYN, and are indicative of an oncogenic phenotype. Moreover, a LYN p.Ise297Asn mutation was identified by us in a WM patient harboring a MYD88 p.Ser243Asn mutation and recurrent heterozygous copy number losses in LYN have been previously documented by us (Hunter et al, Blood 2013) suggesting recurrent somatic dysregulation of this BCR pathway gene. CD79B is a critical component of the BCR pathway and CD79B coding mutations have been observed in 7-15% of WM patients (Hunter et al, Blood 2013; Poulain et al, AJH 2013). In our analysis, we identified mutationally driven intron retentions in CD79B in 3 WM patients. This is particularly notable as these CD79B retentions described here have been successfully cloned and were found to impact the ITAM domain of the protein that is essential for intra-cellular signaling. Conclusion: The findings from this study identify transcriptional aberrations in LYN and CD79B, both important components of the BCR pathway in patients with WM. Functional characterization of BCR signaling associated with aberrant WM-related CD79B and LYN transcripts is underway.

Keywords:
BCR

splicing

Waldenström macroglobulinemia

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-225

Histologic and Molecular Correlates in Patients with AL Amyloidosis in Remission But With Persistent Renal Disease

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Abstract:
Background: Seventy percent of patients with light chain (AL) amyloidosis present with renal

involvement. The phases of the disease include asymptomatic seeding, increasing proteinuria, and progression to end stage renal disease. In an attempt to identify genes relevant to renal reprogramming due to persistent disease, renal biopsies from treated AL patients were obtained for systematic histologic evaluation and transcriptional profiling. Correlates were sought between these two approaches. Methods: Renal biopsies from 10 patients with persistent proteinuria (>500mg/day) following hematologic responses to anti-plasma cell therapy were scored independently by 2 expert renal pathologists employing a novel histologic tool that assessed scarring, fibrosis and the distribution of amyloid, and were successfully evaluated by transcriptional profiling in the Michigan Kidney Translational Medicine Core lab. Clinical data and histologic scores (CSIC = composite scarring injury score, AS = amyloid score) were correlated to the expression profiles of tubular and glomerular gene sets. Results: Baseline characteristics are in Table 1. Using a false discovery rate corrected P-value of < 0.10, numerous genes of interest were identified (Table 2). Transcriptional profiling revealed 2 distinct patient clusters (G1 and G2) within the tubular and glomerular gene expression sets. The histopathologic features were different between G1 and G2; the amyloid score was significantly higher in G2 in both the tubular (7.0 vs. 4.25; p=0.03) and the glomerular (6.92 vs. 4.38; p= 0.04) compartments. The differential expression for the genes of interest between G1 and G2 were also determined (Table 2). Conclusion: This effort has generated multiple genes of interest. ICQD and PODXL, in particular, correlated with the distribution of amyloid in the capillaries and mesangium. We are currently comparing these expression profiles to those of other nephropathies to identify genes whose expression levels may be specific to AL nephropathy, hopefully leading to further novel histologic and protein-based investigations. Table 1. ID Status Creatinine eGFR 24h urinary protein (mg) 1 VGPR 0.90 101 3645 2 VGPR 1.90 42 3249 3 CR 1.80 43 6121 4 VGPR 1.12 76 17032 5 VGPR 1.28 68 5810 6 VGPR 0.88 71 1610 7 VGPR 0.80 82 4023 8 PR 1.14 62 3367 9 VGPR 1.23 64 9339 10 VGPR 1.00 72 6338 Table 2. Genes G1 G2 Function IQCD + - Unknown SF3A2 + - Splicing factor ASPHD1 + - Peptidyl-amino acid modification NSFLC1 - + Establishment of mitotic spindles, regrowth of Golgi, transport vesicle ZSCAN30- + DNA-binding transcription VSIG8 - + RNA binding JRK - + DNA binding, mRNA binding PODXL - + Cell adhesion

Keywords:
amyloidosis

proteinuria

Transcriptional profiling

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-226

Monoclonal Gammopathies and their Significance: A Retrospective Analysis of Monoclonal Gammopathy and Renal Disease

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Abstract:
Background: Monoclonal gammopathy of renal significance (MGRS) describes a subtype of patients with monoclonal gammopathy of unknown significance (MGUS) who have kidney disease due to immunoglobulin deposition. Early identification of MGRS and treatment with chemotherapy can prevent progression to kidney failure. There is limited data on the characteristics of populations with concomitant MGUS and chronic kidney disease (CKD), and on the prevalence of diagnosed MGRS in this population in the real world. Methods: Through retrospective chart review, we identified 246 patients with ICD-9 or -10 codes denoting both MGUS and chronic kidney disease (CKD) between the years of 2000 and 2017. Patients with related overt malignancies such as multiple myeloma, Waldenstrom's macroglobulinemia, and amyloidosis

at onset were excluded, leaving 144 evaluable patients. Results: The median age was 78, and females made up 41.0% of the population. At time of MGUS diagnosis, the median eGFR was 48 mL/min/1.73 m2, and in patients with a quantifiable gammopathy, the median M-protein was 0.54 g/dL. A total of 53/144 (36.8%) patients had a bone marrow biopsy and 19/144 (13.2%) underwent kidney biopsy. MGRS was considered as a cause of kidney dysfunction in 20/144 patients (13.9%), but only 6 were further worked up by kidney biopsy. In 3/144 (2.1%) patients, MGRS was confirmed by kidney biopsy. Ten of (6.9%) the total population and 1 (5%) of the patients with suspected or confirmed MGRS (n=20) developed malignant transformation. Conclusion: MGRS should be considered in the differential diagnosis of patients with MGUS and co-existing chronic kidney disease. Based on our findings, renal biopsy is underutilized in the work up of this treatable disease. We propose a simple algorithm for workup of suspected MGRS (see Figure 1).

Keywords:
CKD

MGRS

MGUS

Tracks:
Other Plasma Cell Disorders and Amyloidosis

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Monoclonal gammopathy of clinical significance : about a case of nodular pulmonary amyloidosis.

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Abstract:

Amyloid proteins can infiltrate virtually all organs. Diagnosis is usually difficult owing to its diverse clinical presentation. Involvement of the lung is relatively common, but rarely symptomatic, and most commonly observed in localized (primary) forms of amyloidosis. We report here a case of nodular pulmonary amyloidosis that evolved over a 10-year period. A 61 year-old woman was referred for a suspicion of pulmonary amyloidosis. She has been diagnosed at the age of 30 with rheumatoid arthritis (RA) that required for years, hydroxychloroquine. In 2008, a chest x-ray described lung and pleural calcifications that were attributed to RA. A small IgG lambda monoclonal component was noted in 2013. The patient remained substantially asymptomatic until December 2014, when she developed tachycardia with paroxystic atrial fibrillation. Echocardiography was normal. The association of cardiopulmonary symptoms along with a clinical history of autoimmune disease and the presence of a monoclonal gammopathy raised the suspicion of amyloidosis. Progressively, she presented a worsening of dyspnea (NYHA grade 2). The cardiac work-up failed to identify any abnormality pointing out cardiac amyloidosis with cardiac biomarkers remaining in the normal range. Respiratory function test highlighted a mixed defect along with signs of impaired CO diffusion. The light chain lambda M-component was measured at 40.8 mg/l (N <26.3 mg/l), with a normal kappa/lambda ratio. Multiple myeloma was ruled out. FDG-18 pet-scan confirmed the presence of multiple sub-pleural and parenchymatous hypermetabolic nodules. Biopsies of a sub-pleural nodule and peri-umbilical fat aspiration were not contributive. Transthoracic CT-guided biopsy identified foci of amorphous eosinophilic material, positive for TTF1 and cytokeratine-7 by immunostaining, consistent with the diagnosis of pulmonary nodular amyloidosis, AL lambda subtype. So far, the patient did not receive any specific treatment, as suggested in the literature, and her medical condition remains stable. Standard bortezomib-based chemotherapy will be proposed in case of worsening of her respiratory situation. Nodular pulmonary amyloidosis is an extremely rare condition that can be asymptomatic and misdiagnosed for years. It is usually diagnosed

incidentally on chest x-rays. In most cases, it is localized, and association to systemic amyloidosis is uncommon. Differential diagnosis includes primary or metastatic neoplasms and granulomatous diseases. Management depends on the severity of symptoms. Treatment is usually not required.

Keywords:
amyloidosis

MGUS

Tracks:
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SP-228

Distribution of circulating tumor cells in Waldenström's Macroglobulinemia

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Abstract:
Waldenström's Macroglobulinemia (WM) is a B-cell malignancy characterized as bone marrow infiltration with lymphoplasmacytic cells and IgM secreting. Presence of circulating tumor cells in WM was reported in previous studies by flow cytometry, clonotypic IgM V/D/J rearrangement, or activating MYD88 mutation analysis. To better understand the distribution of circulating tumor cells between bone marrow and peripheral blood during the course of WM and pharmacological intervention, we performed an analysis for a large cohort of WM patients using MYD88 L265P mutation as a biomarker to quantitate tumor cells. Paired samples of bone marrow (BM) and peripheral blood (PB) were collected from 199 untreated, 155 non-ibrutinib treated, and 52 ibrutinib treated WM patients. DNA was extracted from CD19-selected cells. MYD88, CXCR4, and BTK genotypes were determined by AS-PCR and Sanger sequencing. As expected, most patients had higher tumor cell fraction in BM than PB. Interestingly, some patients showed similar amount of tumor cell fraction between the two compartments or even higher tumor cell fraction in PB than BM. To compare the distribution of circulating tumor cell between treated vs untreated patients, those with significant amount of circulating tumor cells were assigned as "high circulating tumor cells" group (PB dCT / BM dCT $\leq$ 1), whereas those with less circulating tumor cells were assigned as "low circulating tumor cells" group (PB dCT / BM dCT > 1). The frequency of patients with "high circulating tumor cells" was similar between untreated and non-ibrutinib treated patients (13.6% vs 17.4%, p=0.3718). In contrast, the difference between untreated and ibrutinib treated patients was significant (13.6% vs 30.8%, p=0.0017). The results suggest that presence of large amount of circulating tumor cells in WM is not uncommon and ibrutinib therapy for previously heavily treated patients may cause redistribution of tumor cells between the compartments. Of the patients treated with ibrutinib, 15 were progressors on ibrutinib. Importantly, 14/15 (93.3%) of the progressors had significant amount of circulating WM at baseline or during ibrutinib treatment. 10/15 (66.7%) of the progressors were positive for CXCR4WHIM mutations. Most of the CXCR4WHIM mutations were CXCR4S338X (90.9%). Of the 15 progressors, 11 had DNA collection at or near the time-point of progression. 5/11 (45.5%) were positive for the BTK C481S mutations. The overall results suggest that presence of significant amount of circulating WM cells is associated with ibrutinib resistance and circulating WM cells may be used as biomarker to improve the strategy of ibrutinib treatment.

Keywords:
Circulating Tumor Cells

Waldenström macroglobulinemia

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-229

MGUS predicts worse prognosis in patients with coronary artery disease

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Abstract:
Background: Monoclonal gammopathy of undetermined significance (MGUS) is the premalignancy of many hematological malignancies including multiple myeloma. Methods: We performed a prospective, randomized cohort to analyze all 87 coronary artery disease (CAD) patients with MGUS and random 178 CAD patients without MGUS admitted in our hospital from January 1, 2015 to December 31, 2017. Patients were followed up via regular patient visits and telephone, and the median follow-up period was 2.9 years. The end point of follow-up was considered to be the occurrence of major adverse cardiac events (MACE). Results: We compared the biochemical and clinical data of CAD patients with and without MGUS, including age, gender, diagnosis, smoking status, history of CAD, stent numbers, the type and concentration of monoclonal protein; values of serum glucose, Hb1Ac, estimated glomerular filtration rate (eGFR), cardiac troponin T (cTNT), low density lipoprotein (LDL), C-reactive protein (CRP), N-terminal pro-brain natriuretic peptide (NT-proBNP) and coagulation function which contained activated partial thromboplastin time (APTT), prothrombin time (PT) and fibrinogen. Only age (P = 0.003) and gender (P = 0.032) were regarded as statistical significance. CAD patients with MGUS had a higher risk of MACE than those without MGUS (log-rank P = 0.0015) and in the linear regression models of NT-proBNP and cTNT, which were certified to be the most famed risk factors of CAD patients, MGUS was statistically significant correlated with NT-proBNP ($\beta = 0.152$, P = 0.022). After adjustment for other markers in the stepwise multivariate Cox regression model, MGUS was still related to the increasing risk of MACE incident (P = 0.002, HR = 2.308). To quantify the effects of the risk factors on the incidence of MACE, we constructed the nomogram based on the Cox regression model. The concordance index (C-index) was 0.667 and the calibration curve showed that it was more accurate to predict non-MACE probability of 1-year than that of 2- and 3-year. Conclusions: MGUS might be added into the risk model of CAD and it is valuable and necessary to screen MGUS in CAD patients.

Keywords:
coronary artery disease

MGUS

prognostic impact

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-230

The BCR component SYK is activated by mutated MYD88 and the combined inhibition of SYK and BTK produces synthetic lethality in MYD88 driven B-cell lymphomas.

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Institutions:
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Abstract:
Background: Activating MYD88 mutations promote Toll-like receptor (TLR) signaling through assembly

of a "Myddosome" complex that includes activated BTK and promotes NF-κB and MAPK/ERK1/2 pro-survival signaling. Mutated MYD88 also upregulates and transactivates HCK that activates BTK, AKT and ERK1/2. Both BTK and HCK are targets of ibrutinib that is active in MYD88 mutated B-cell malignancies. Despite high response rates, complete responses to ibrutinib are lacking, and other MYD88 triggered pro-survival pathways may contribute to primary drug resistance. B-cell receptor (BCR) signaling has been observed in MYD88 mutated B-cell lymphomas, even without activating BCR pathway mutations.[Argyropoulos et al, Leukemia 2016] We therefore explored cross-talk between TLR and BCR pathways in MYD88 mutated B-cell malignancies. Methods and Results: PhosFlow and western blot analysis on MYD88 and BCR signaling components showed high levels of SYK phosphorylation (p-SYK) in MYD88 mutated Waldenstrom's Macroglobulinemia (WM) cell lines (BCWM.1, MWCL-1) and ABC subtype diffuse large B-cell lymphoma (DLBCL) cell lines(TMD-8, HBL-1, OCI-Ly3) versus MYD88 wild-type cell lines (OCI-Ly7, OCI-Ly19, Ramos, RPMI-8226) as well as high levels of p-SYK in primary MYD88 mutated WM patient bone marrow lymphoplasmacytic cells (LPCs) compared to healthy donor peripheral blood B-cells. While, knockdown of MYD88 or use of a MYD88 signaling inhibitor abrogated SYK activation in both MYD88 mutated cell lines and primary WM patient LPCs. The overexpression of mutated but not wild-type MYD88 amplified p-SYK in MYD88 mutated and wild-type B-cell lymphoma cells. Co-immunoprecipitation (Co-IP) experiments identified activated SYK (p-SYK) in complex with MYD88 in MYD88 mutated WM and ABC DLBCL lymphoma cells. Confocal microscopy study confirmed co-localization of MYD88 with SYK. Knockdown of SYK or use of inhibitors targeting SYK (tamatinib or entospletinib) blocked downstream p-STAT3 and p-AKT signaling and potently reduced cell growth and survival in MYD88 mutated WM and ABC DLBCL cells. CellTiter-Glo® cell viability analysis showed that combining ibrutinib and SYK inhibitors (tamatinib or entospletinib) produced synthetic killing of MYD88 mutated lymphoma cells. Conclusion: Our findings extend the spectrum of mutated MYD88 pro-survival signaling to include SYK directed BCR cross-talk in MYD88 mutated lymphomas. Targeting SYK in combination with ibrutinib produces synthetic lethality, providing a framework for the clinical investigation of ibrutinib with SYK inhibitors in MYD88 mutated lymphomas.

Keywords:
B-cell lymphoma

MYD88

SYK

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-231

Mutated MYD88 regulates transcription of the pro-survival kinase HCK in MYD88 driven B-cell lymphomas.

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Abstract:
Background: Activating mutations that lead to constitutive growth and survival signals are one of the major drivers for the development of cancer. By whole genome sequencing, we discovered the highly recurring MYD88 L265P (MYD88L265P) mutation in >90% of WM patients.[Treon et al, N Engl J Med., 2012] Hematopoietic cell kinase (HCK) is a member of the SRC family tyrosine kinases (SFKs), and is normally expressed in cells of myeloid and B-

lymphocyte lineages. In B-lymphocyte lineages, HCK is commonly expressed in earlier B-cell progenitors and is downregulated in mature B-cells. In contrast, HCK is aberrantly overexpressed and hyperactivated by mutated MYD88 and activates BTK, AKT, and ERK1/2 to support B-cell lymphoma cell growth and survival. Ibrutinib, a pleiotropic inhibitor that is active in MYD88 mutated B-cell lymphomas, also targets HCK.[Yang et al, Blood, 2016] To continue, we thought to clarify the regulatory mechanism for the aberrant expression of HCK in MYD88 mutated B-cell lymphomas. Methods and Results: To clarify the signaling cascades responsible for aberrant HCK expression in MYD88 mutated B-cell lymphomas, we performed promoter binding transcription factor (TF) profiling, PROMO weighted TF consensus binding analysis, and chromatin immuno-precipitation (ChIP) studies. We identified PAX5 and mutated MYD88 downstream signaling mediators, STAT3, AP-1, and NF-kB, as important drivers of HCK transcription. Knockdown of PAX5, a crucial regulatory factor required for B-cell commitment and identity, abrogated HCK transcription in MYD88 mutated lymphoma cells. ChIP studies showed that the transcription factors NF-kB-p65 (NF-kB complex component), STAT3 and JunB (AP-1 complex component) exhibit robust direct binding to the HCK promoter of MYD88 mutated cells in comparison to MYD88 wild-type cells. In addition to transcription factors NF-kB-p65 and STAT3,[Ngo et al, Nature, 2011; Treon et al, N Engl J Med., 2012] JunB showed great relevance to mutated MYD88 signaling with increased phosphorylation by the overexpression of MYD88 L265P compared to wild type MYD88. JunB knockdown reduced HCK expression on western blot analysis in WM cells, demonstrating that JunB is important for HCK transcription regulation. Deletion of STAT3, AP-1 or NF-kB binding sites on HCK promoter greatly reduced corresponding TFs binding and HCK promoter activity. Moreover, inhibitors to STAT3, AP-1 and NF-kB reduced HCK mRNA levels in MYD88 mutated cells, particularly in combination. Conclusion: The findings provide new insights into the transcriptional regulation of HCK by MYD88 driven transcription factors, and opportunities for further advancing targeted therapeutics in MYD88 driven B-cell malignancies.

Keywords:
B-cell lymphoma

HCK

MYD88

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-232

ESTIMATING THE GLOBAL EPIDEMIOLOGY OF AMYLOID LIGHT-CHAIN AMYLOIDOSIS WITH AN INCIDENCE-TO-PREVALENCE MODEL

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Abstract:
BACKGROUND Amyloid light-chain (AL) amyloidosis or primary systemic amyloidosis is characterized by clonal plasma cell proliferation and dyscrasia, leading to multi-organ dysfunction. Given the lack of global epidemiology data for this condition, we estimated the diagnosed incidence and 20-year prevalence of AL-amyloidosis in 2018 in 28 European Medicines Agency (EMA) member states, United States, Canada, Brazil, Japan, South Korea, Taiwan, and Russia. METHODS Reliable country-specific registries for AL amyloidosis are limited, thus a systematic literature review (SLR) was conducted (from 2005 and onwards in PubMed) to identify country-specific and age- and gender-specific diagnosed incidence rates and survival data-point inputs for our incidence-to-prevalence model. Four population-based studies (identified in the SLR) and the United Nations' country- and age-

specific population estimates from 1999 to 2018 were used in the model. When country-specific incidence rates or survival data were not available, extrapolations based on data from other countries were made. Resultant region and country-specific incidence and 20-year prevalence estimates in 2018 (i.e., persons diagnosed within the past 20 years and still alive in 2018) were reported per million population (PMP). RESULTS In 2018, there were 29,777 diagnosed 20-year prevalent cases of AL-amyloidosis across the 28 EMA member states, based on which the 20-year diagnosed prevalence in Europe was 58.09 PMP, ranging from 42.99 PMP for Cyprus to 65.38 PMP for Italy. Overall incidence was 11.74 PMP, ranging from 8.94 PMP for Cyprus to 13.29 PMP for Italy. Outside of Europe in 2018, there were 43,790 people diagnosed with AL amyloidosis in the past 20 years across the United States, Canada, Brazil, Japan, South Korea, Taiwan, and Russia, with an overall 20-year prevalence of 47.49 PMP, ranging from 32.22 PMP for Brazil to 71.08 PMP for Japan. Incidence for these countries ranged from 6.72 PMP for Brazil to 14.30 PMP for Japan. CONCLUSIONS AL amyloidosis is an ultra-rare condition worldwide with an estimated 20-year prevalence that is well below the prevalence criteria of EMA's orphan medicinal product designation of less than or equal to 500 PMP. Overall, there were only 51.27 PMP AL amyloidosis cases globally diagnosed in the past 20 years in 2018, although prevalence may be slightly higher in certain regions and countries. Given limited registry and published data on this condition, extrapolations had to be made for certain countries, highlighting the need for increased awareness and research in this rare but highly lethal disease.

Keywords:
amyloidosis

EPIDEMIOLOGY

Rare

Tracks:
Other Plasma Cell Disorders and Amyloidosis

NURSE SYMPOSIUM ORAL ABSTRACT PRESENTATIONS

NS-088

Understanding the financial impact of cancer: Examining the 'COST' Measure in the Australian context.

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Abstract:
Introduction: Universal access to free medical care is pivotal to the Australian health care system. Despite this, some patients with cancer and their families experience substantial costs when accessing care. The resulting financial distress can impact on treatment-related decision making. It is therefore important for health professionals to assess patients' financial distress and financial coping strategies. The 'COST' instrument is a patient-reported outcome measure (PROM) developed in the USA that may be appropriate for use in Australia. Aims: 1) To develop a deeper understanding of cancer patients' experiences of the financial impact of cancer, how it influences treatment decision making and the strategies individuals use to meet costs. 2) To examine the appropriateness of the COST instrument in the Australian context. Methods: This is a qualitative study using in-depth interviews to explore the financial experience of cancer patients. Participants also completed the COST instrument and provided feedback on the completeness of the questionnaire in terms of their experience. A revised questionnaire was formulated for further testing. Ten additional patients provided feedback on the clarity and relevance of additional items. Results: Twenty-four cancer patients or family members were interviewed. Of these 10 patients had multiple

myeloma. Four themes were identified from the data: 1) a ripple effect on many aspects of daily life, extending to family income, work, and social life; 2) influences on decision making regarding cancer treatment, finances and family; 3) shifting financial capability as treatment periods extended and resources were depleted, often made worse by the challenges of negotiating income support through agencies not geared towards the long-term treatment effects of cancer; and, 4) attitudes and expectation where discussion of financial impacts was difficult for some, and none of the participants expected to be fully supported for all costs. The majority of participants found the COST instrument easy to complete and relevant to their experience. Based on feedback, four items were added to the questionnaire: 1) I worry about my family's financial stability; 2) I am worried about the financial impact of my cancer and cancer treatment on my family's lifestyle; 3) I am aware of the financial assistance services available for people receiving cancer treatment; 4) I know how to access income support (e.g. income insurance, government benefits) if I need it. Conclusion: Many aspects of the lives of patients and families were affected as a consequence of the financial impacts of cancer and cancer treatment. The COST instrument, with the addition of 4 items, is potentially appropriate for use in the Australian context. Phase 2 of this project will involve validating the extended instrument for use in Australia.

Keywords:
Financial toxicity

Tracks:
4th Nursing Symposium

NS-089

Patient Reported Outcome Measures in multiple myeloma: real-time rePorTing to improve care (My-PROMPT) - a pilot randomised controlled trial

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Abstract:
Background: Multiple myeloma (MM) is associated with high burden of disease, compromising patients' health-related quality of life (HRQOL). Whether incorporating patient reported outcome (PRO) measures into routine care improves MM outcomes has not been studied. In order to design a clinical trial to evaluate impact of real-time PRO reporting on outcomes, feasibility and acceptability to clinicians and patients of delivering such an intervention needs to be evaluated. Methods: We performed a pilot, randomised controlled trial to assess feasibility of real-time reporting of PRO in newly diagnosed MM to treating clinicians. The intervention arm completed a disease-specific PRO measure (MyPOS) before 4 clinic visits (T1-4): baseline, 1, 6 and 10 months. Treating clinicians were given a summary of MyPOS results before visits. The control arm completed MyPOS at T1 and 4. Evaluations of the intervention were completed by patients at T3 and clinicians after T1, 2 and 3. Follow-up interviews were also conducted. Primary feasibility outcomes were patient and clinician satisfaction scores for MyPOS use. Secondary outcomes included change in MyPOS from T1 to 4 between groups. Analysis of covariance was used to assess difference in change in MyPOS. Results: Thirty-two patients were enrolled, 16 randomised to each arm. Baseline characteristics were well matched other than more males in the control arm (81 v 25%, $p<0.001$). Patients' median satisfaction

score for MyPOS use was 5 (1=Not at all satisfied, 5=Very satisfied, n=13), and median satisfaction score for 15 clinicians over T1 to T3 visits (n=39) was 85 (1=Not at all satisfied, 100=Very satisfied). In patient evaluations, 92% felt completing MyPOS helped communicate concerns to doctors, 75% indicated their doctor had discussed MyPOS responses in the consultation, 100% thought time to complete MyPOS was 'about right', and 92% felt comfortable answering the questions. All clinicians thought the MyPOS summary was available in a timely manner, 80% used survey results to discuss patient concerns, and 83% thought the intervention either reduced, or had minimal or no impact on duration of consultation. Median total MyPOS score was 18 (IQR 14-35) in intervention and 25 (IQR 20.5-29.5) in control group at T1 (higher=worse). There was no significant difference in change in total MyPOS score (median [IQR] change -4 [-1, -10] vs -9.5 [+2.5, -14], p=0.18) or Symptoms and function subscale score (-0.5 [+3, -1] vs 0 [+3.5, -5], p=0.62) from T1 to 4 between intervention and control groups, respectively. However, the study was not powered to detect differences in MyPOS. Males had greater reduction in MyPOS score compared with females (p=0.015). Conclusion: Findings support feasibility and acceptability of real-time reporting of a PRO measure to clinicians before patient visits and will inform design of a larger, randomised controlled trial to assess health benefits of the intervention, including impact on HRQOL.

Keywords:
Patient Reported Measures

Quality of Life

Trial

Tracks:
4th Nursing Symposium

NS-090

The Steroid Symptom Questionnaire Multiple Myeloma (SSQ-MM): Feasibility, acceptability, reliability and internal consistency.

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Abstract:
Background: Corticosteroids remain the backbone of treatment for myeloma, recognised to cause a wide range of side effects. To date, as no instrument exists, the frequency and severity of these side effects are not reported as part of the routine care. The Dexamethasone Symptom Questionnaire Chronic (DSQ-Chronic) was designed to report side effects associated to dexamethasone given as an anti-emetic in cancer patients. We adapted the DSQ-C to reflect the higher doses and duration of treatment in a Multiple Myeloma (MM) population. The Steroid Symptom Questionnaire Myeloma (SSQ-MM) is an 18-item 4 point Likert-scaled patient-report measure (PRM), where 1 = Not at all and 4 = very much, designed to describe the incidence and severity of steroid related side effects experienced in the past 7 days. Higher mean SSQ-MM scores equate to higher overall symptom burden. Aims: Testing of the psychometric properties of the Steroid Symptom Questionnaire Myeloma (SSQ-MM) in a multi-centre cross sectional study. Methods: Patients with a diagnosis of active MM and currently taking steroids as part of their MM treatment were recruited from 3 Australian hospitals. Patient demographic data were captured via self-report. Clinical data were captured from medical records. All participants completed the SSQ-MM at 2 time points, 1 week apart followed by a brief evaluation of the instrument. Analysis included descriptive statistics; feasibility and acceptability assessed by rates of and time to complete and findings from the evaluation. Internal consistency reliability was assessed using Cronbachs alpha, test-retest was assessed using intraclass

correlation coefficient (ICC) and paired t-test was used to assess repeatability. Results: Seventy patients participated in the study of which 62 are currently available for analysis. Participants had a mean (SD) age of 66.8 (12) years; 4.6 (3.2) years since diagnosis; males 36 (58.1) and females 26 (41.9) and median (min-max) 2 (0-8) prior lines of therapy. At time of study dexamethasone mean (SD) dose per week was 24.0 (13.7) milligrams. Completion rates at T1 & T2 (%) were 100% with mean (SD) time to complete at T1 9.8 (6.2) and T2 8.9 (6.6) minutes. Cronbachs alpha was acceptable: 0.76 (T1) and 0.81 (T2) and the ICC was 0.91 indicating excellent consistency between the two administrations. The tool was repeatable. Mean scores at T1 were 1.92 (SD 0.35) and at T2 1.87 (SD 0.40), p = 0.10. The most frequently reported symptoms n (%) were loss of energy/fatigue 58 (93.5); disturbed sleep 58 (93.5) and agitation/nervous 48 (77.4). The most bothersome symptom was disturbed sleep 27 (43.5). All patients reported they found the SSQ-MM was an accurate and comprehensive description of the side effects relating to steroids. Conclusions: The SSQ-MM demonstrates high levels of feasibility, acceptability, repeatability and internal consistency. A larger study to further test validity and associations with HRQoL is und

Keywords:
Patient Reported Measures

Steroids

symptom burden

Tracks:
4th Nursing Symposium

NS-091

Lenalidomide-Related Diarrhea Correlates with Disease Control in Newly-Diagnosed Patients with Multiple Myeloma

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Abstract:
Background: Lenalidomide-related diarrhea (LRD) is a common and important symptom with negative physiologic and psychological consequences. In our center, histopathologic findings of inflammation with lymphocytic infiltrate were observed in 4 patients with LRD, suggesting a possible immunologic cause. Therefore, we hypothesized that LRD may be a sign of effective immune stimulation that could correlate with improved myeloma control. Patients and Methods: The charts of 602 patients who were treated with lenalidomide for multiple myeloma at the Cleveland Clinic from 1/2005-12/2013 were reviewed. Patients were excluded if they received concurrent chemotherapy, underwent hematopoietic cell transplantation, or had a pre-existing diarrhea condition among other reasons (Table 1). Patients were categorized as having LRD if the patient complained of diarrhea requiring intervention on at least two separate visits. Since IgA is secreted into the bowel lumen and therefore responsible for antibody – based immune protection in the GI tract, IgA MM patients were specifically evaluated. Results: 62 patients with newly-diagnosed myeloma were analyzed. The median onset of diarrhea was 19 months. To test the hypothesis of LRD on duration of response (DOR), 44 of the 62 patients who were in remission at least 19 months were analyzed. 24 of these 44 patients had LRD and 20 did not. Patients with LRD had a longer DOR than patients without LRD (62.6 vs. 43.4 months ($t = -2.058$, $df = 42$, $p = .046$). In 27 patients with non-IgA MM, serum IgA levels did not correlate with diarrhea. Conclusion: This study suggests LRD correlates with improved disease control. Prospective and larger studies correlating gut biopsies to outcomes are needed to confirm our observations and determine which immunologic effectors are most important.

Keywords:
Lenalidomide

response to therapeutic

symptom burden

Tracks:
4th Nursing Symposium

NS-092

Examining the Association between Insurance Status as an Access to Care Proxy and 5-year Multiple Myeloma-Specific Survival in US Adults

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Abstract:
Background: Advances in multiple myeloma (MM) treatment, including novel agents and autologous stem cell transplant, have led to improved outcomes in survival. However, these treatment regimens are time intensive, complex and length of treatment is indefinite. Supportive care for complications including bone disease, hypercalcemia and anemia is frequently needed. Given this treatment burden, access to care may be influential in survival. Methods: This is a retrospective analysis to assess the association between health insurance status, as an access to care proxy, and 5-year MM-specific survival using Surveillance, Epidemiology, and End Results (SEER) data. Participants in this analysis were 15 years and older, diagnosed with MM during 2007-2011. The covariates investigated were age, sex, race/ethnicity, marital status and median household income (MHI). SAS® was used to perform a descriptive analysis including odds ratios (OR), 95% confidence intervals (CI) and Chi-square testing. Stratum-specific data at each level of the covariates was analyzed for interactions. Logistic regression was performed to inform the best model for measuring the association. Results: Among participants (n=20,599), 79% had private insurance or Medicare (insured), 11% had Medicaid, 3% were uninsured and 7% had unknown insurance status. Additionally, 60% were 65 years of age or older, 54% were male, 62% were Non-Hispanic White and 55% were married. Participants were distributed into quintiles based on MHI of county of residence. Within the sample, 58% achieved 5-year MM-specific survival. Controlling for age, race/ethnicity, marital status and MHI, the odds of 5-year MM-specific survival for Medicaid, uninsured, and unknown insurance were all significantly less than insured. Compared to insured, the OR of achieving 5-year MM-specific survival for Medicaid was 0.76 (CI: 0.69, 0.87), uninsured was 0.82 (CI: 0.69, 0.98) and unknown was 0.68 (CI: 0.61, 0.77). This means participants with Medicaid were 0.76 times as likely to achieve 5-year MM-specific survival compared to insured participants. Conclusion: Within this sample, a significant relationship between insurance status and 5-year MM-specific survival exists when controlling for covariates. Ability to access care, influenced by insurance status, impacts prompt diagnosis, time to treatment, completing recommended treatment and access to supportive care which all effect survival outcomes. Limitations of this analysis, study design and representativeness of the sample, prohibit generalizability or causation but findings are supported by Chamoun et al. (2019) who concluded that insurance plays an important role in survival. Additionally, Adamson et al. (2019) indicated that intervention can successfully address some of these issues such as access to care and time to treatment. Further investigation of nursing led interventions to improve access, such as patient navigation, should be evaluated.

Keywords:
health insurance status

multiple myeloma-specific survival

Tracks:
4th Nursing Symposium

NS-093

An Advanced Practice Provider-led, Outpatient Consult Clinic for Patients with Monoclonal Gammopathy of Undetermined Significance (MGUS) and Plasma Cell

Disorders (PCDs): The Cleveland Clinic Experience

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Abstract:
Background: The vital role which advanced practice providers (APPs) fulfill within outpatient clinics in the United States continues to expand. Rapid access to specialized healthcare is critical to patients diagnosed with monoclonal gammopathy of undetermined significance (MGUS) to differentiate MGUS from other more serious plasma cell disorders (PCDs). Physicians have historically been the key consultant providers tasked with correctly diagnosing PCDs. Yet, prompt specialty evaluation can be limited by factors such as physician access and patient availability. Key indicators of health care quality measured within hospital systems include: (1) the time from request of specialty consultation to when the patient is seen, and (2) whether an accurate diagnosis has been made. It is our opinion that experienced and well-trained specialty APPs are well-suited to fill the access gaps in healthcare by providing patients with more flexible appointment options and a prompt and accurate diagnosis. There are no known reports of existing APP-led outpatient PCD clinics. Thus, here we report the Cleveland Clinic experience. Purpose: To report the Cleveland Clinic, APP-led consult experience and its' overarching goals to improve patient access to a specialty evaluation of MGUS, prompt diagnosis, and treatment when necessary. Methods: Prior to seeing outpatient consults independently, two outpatient APPs (Faiman and Hamilton) within the PCD clinic were approved by the Taussig Cancer Institute administrators and granted the special privilege to see all patients referred for MGUS independently. As of 2014, each had 12 and 5 years of APP experience. A standard procedure and decision-making algorithms were created with input from physicians, nurses and nurse practitioners based on International guidelines for the initial workup of patients with PCDs. Consultations were requested through a central scheduling call center, or by direct communication with a consulting provider. Results: From 1/2014-2/2019, 354 patients were identified via a secure electronic data base based on the documented ICD-10 diagnosis code and cross-referenced by the APPs computerized clinic schedule. 58/354 patients (16%) patients who were seen traveled from outside of Ohio. Age ranged from 22-89 years. All patients were referred to the clinic with a diagnosis of MGUS or a related PCD. The average length of time from the appointment request to the originally scheduled appointment was 9.6 days. All patients were provided with a scheduled follow up visit at the time of the initial consult, or informed of the need for follow up and disease monitoring was discussed and documented in the medical chart. Conclusion: An APP led, PCD consult service is feasible and can improve access to specialty health care. We plan to report additional quality metrics and outcomes at the meeting.

Keywords:
amyloidosis

MGRS

MGUS

Tracks:
4th Nursing Symposium

NS-094

'Developing a support and information group for Myeloma patients and their carers in a private healthcare setting'

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Abstract:
Background: With the progression of myeloma drug therapy over recent years there has become a clear differential in treatment options between NHS and private patients. Due to access to new therapies not funded by the NHS, it has been identified that private myeloma patients and their carers have a unique set of needs that can be addressed through information, advice, and supportive care. Through consultation with Myeloma UK it was identified that Private patients do not engage with support and information groups usually attended by and currently available to NHS patients. Patients have reported that they felt separated due to the different treatment options and general isolation over opportunities for peer to peer support given the nature of private healthcare facilities. Aim: To scope and pilot a support and information group for myeloma patients and their carers being actively treated or under surveillance at HCA Healthcare UK @ UCH and The LOC. Method: A focus group was held at the beginning of the trial period where needs were identified through facilitated conversations and post discussion questionnaires. 77% of the focus group attendees preferred a combination of support, education and information as a group format. It was decided that each meeting would have a guest speaker or education session followed by discussion and networking to encourage peer to peer support. Three groups were run a 6 month trial period. Meetings were facilitated by Clinical Nurse Specialists and a Psychologist to highlight and action any patient/carer needs. Meetings were run every 6-8 weeks with continuous evaluation to help modify content/format for future meetings. Results: Patients/Carers were 'very interested' in research/clinical trials, treatment discussions, side effect management, stem cell transplants and family/relationship issues. Qualitatively attendees enjoyed "open discussion", "meeting other patients and carers", and that they had a "route to more support and information". From the evaluations there were high rates of satisfaction across all three meetings, with 100% of attendees indicating that the group was beneficial and relevant to their needs. 94% agreed or strongly agreed that they felt better supported from attending the group and 89% of patients and carers agreed or strongly agreed that they benefited from meeting others living with myeloma. Importantly there were zero responses that indicated dissatisfaction. Conclusion: The success of this group has been based around the clear differential in care, treatment and support in this patient group vs that of their NHS peers. By continuing to provide focussed education and offering opportunities for peer to peer support, we will improve the experience of patients and carers accessing myeloma treatment within the private sector.

Keywords:
carer

Information

Peer to Peer Support

Tracks:
4th Nursing Symposium

NS-095

Red Flag Symptoms of AL Amyloidosis in Patients with Myeloma

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Abstract:
Background AL amyloidosis, like myeloma, is a plasma cell dyscrasia, caused by deposition of amyloid fibrils derived from immunoglobulin light chains in vital organs. Overt organ dysfunction from AL amyloidosis occurs in approximately 10% of patients with myeloma, subclinical AL amyloidosis may occur in up to 30% of patients. Patients with AL amyloidosis can have multiple organ systems involved. We aim to increase awareness of

symptoms associated with AL amyloidosis to represent a path to earlier diagnosis. Methods We performed a retrospective review of 79 patients seen at our center from 2009 to 2018 with evidence of myeloma based on the IMWG criteria and biopsy proven AL amyloidosis by Congo red staining. We examined organ involvement, patient symptoms, median time between symptom onset and diagnosis, median time between diagnosis of myeloma and AL amyloidosis. Abdominal fat aspirate results were tallied. Results A total of 992 patients with AL amyloidosis were seen from 2009 to 2018, of these 79 were classified as myeloma associated AL amyloidosis representing 8% of total AL cases at this center. Of the 79 patients 55% (n=44) had cardiac involvement, 44% (n=35) renal involvement, 43% (n=34) soft tissue involvement, 26% (n= 21) gastrointestinal involvement, 16% (n=13) autonomic and peripheral nervous system involvement and 3.7% (n=3) hepatic involvement. Those patients with two or more organ systems involved were 57% (n=46). Of these 79 patients, 33% (n=26) presented with complaints related to soft tissue involvement; the most common being joint pain due to arthropathy (n=13) followed by soft tissue masses (n=8) and macroglossia (n=5), 25% (n=20) presented with cardiac symptoms of dyspnea (n=10), chest pain (n=4), edema (n=2), and syncope (n=2); 8% presented with fatigue, 7% with gastrointestinal complaints, 5% with periorbital ecchymosis. The median time between symptom onset and diagnosis of amyloidosis was 7 months (range 1-118). The median time between the diagnosis of myeloma and amyloidosis was 1 month (range 1-187). Those patients with a Congo red positive fat aspirate for amyloidosis equaled 78% (n=62). Conclusions In summary, 8% of AL amyloidosis patients at our center have co-occurring myeloma. The most common organ involvement was cardiac followed by renal. The most common presenting symptoms were related to soft tissue involvement. The delay from symptom onset to diagnosis highlights the need for increased awareness and supports screening of high risk patients, including those with MGUS or myeloma, for AL amyloidosis using measures of end organ function. Abdominal fat aspiration is a fast, minimally invasive procedure to aid in the diagnosis of AL amyloidosis. The majority of patients had 2 or more organ systems involved demonstrating a need for a multidisciplinary approach to accurately identify organ involvement and to provide supportive care during plasma cell directed therapy while awaiting organ response

Keywords:
amyloidosis

multidisciplinary

Plasma cell disorders

Tracks:
4th Nursing Symposium

NS-096

Information needs of myeloma patients along the illness trajectory

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Abstract:
Background: The life expectancy of myeloma patients has increased significantly since the year 2000. Today myeloma is a chronic disease that occurs in many stable and non-stable phases. The primary interest of chronically ill people is not the disease itself, but their efforts to cope with the irritations caused by disease and therapy. Coaching and guidance of patients can positively influence their adherence to therapy and leads to a better quality of life and overall survival. To achieve this, an assessment of information needs of myeloma patients along their illness trajectory is required. Aim: Assessment of information needs of myeloma patients along the illness trajectory. Methods: In this prospective descriptive cross-sectional study at a large university hospital in Germany, first, the satisfaction of myeloma patients with the routinely applied counseling was assessed with the EORTC QLQ Info-25 module, and second, information needs

were explored by a self-administered questionnaire derived from the literature. Each result was assigned to its current phase in the illness trajectory. Results: In sum, 73 myeloma patients could be included in the survey who answered one of the two questionnaires. These could be assigned to four different phases: first-line therapy (P1), maintenance therapy (P2), second-line therapy (P3), and second-line maintenance therapy (P4). Of these patients, 36 answered the EORTC QLQ Info-25 questionnaire, 14 patients in P1, 16 in P2, and 6 in P3. With increasing disease duration, the patients felt better informed. There was still a need for advice in P3 with regard to information about the treatment and information of other services with a mean value of 60%. Another 38 patients answered the self-administered questionnaire about information needs of myeloma patients, 6 patients of P1, 19 of P2, 6 of P3, and 7 of P4. Digestion, fatigue and pain were the most common information needs across all phases. In P1, influence on lifestyle and family/social environment, and information on therapy and medication were the most common information needs, while in P2 these were replaced by physical symptoms such as fatigue, leucopenia, digestion, and pain. In P3, breathing and skin/mucosa were additional information needs, in P4 also sensory neuropathy. Conclusion: To our knowledge, this is the first study that assessed information needs of myeloma patients along their illness trajectory and the various stages of the disease. Although the satisfaction with the received information has increased in the course of the disease, the later phases still have information needs. While at time of diagnosis the influence of myeloma on the own life-style and the social environment are a large topic, during the illness trajectory physical issues come to the foreground. Nursing counseling should primarily address pain, digestion, fatigue and neuropathy.

Keywords:
chronic disease

illness trajectory

Information

Tracks:
4th Nursing Symposium

NURSE SYMPOSIUM POSTER ABSTRACTS

NS-300

Relationship between exercise, fatigue levels and patient attitudes to exercise: The multiple myeloma patient. An integrative review.

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Abstract:
INTRODUCTION: Fatigue is experienced by most multiple myeloma (MM) patient, significantly impacting quality of life. Whilst exercise is recognised as minimising fatigue in general cancer populations, exercise presents specific challenges for MM patients due to disease and treatment related symptoms. The objective of this review was to explore existing research (i) relating to MM patient beliefs, perceptions and preferences towards exercise/physical activity and to determine how effectively these findings are being integrated into exercise research designs, and, (ii) determine the effect of exercise interventions on fatigue levels experienced by MM patients. METHOD: An integrative review was undertaken as this process allows for inclusion of both qualitative and quantitative primary research thereby providing increased depth and breadth of the topic. English language papers were identified that described MM patient attitudes relating to exercise/physical activity and/or fatigue level outcomes from interventional and retrospective studies. RESULTS: Low levels of exercise uptake were reported compared to other cancer groups. Belief systems, ownership of self-care and social support were identified as exercise facilitators. Barriers included disease and treatment related symptoms and low personal motivation. In determining the impact of exercise on fatigue levels,

there is heavy reliance on pilot, feasibility and retrospective studies. Whilst there is emerging evidence of exercise benefit on fatigue levels, the outcomes for this specific patient cohort are still largely undetermined. CONCLUSIONS: Further robust research is required to better understand the relationship between exercise and fatigue management in MM patients. IMPLICATIONS FOR PRACTICE: Structured fatigue assessment should be undertaken at diagnosis and critical disease time points. Access to exercise clinicians is important for patients in order to minimise injury and promote confidence in physical activity engagement. Exercise program design requires flexibility to meet patient reported preferences; behavioural approaches should be incorporated to increase uptake.

Keywords:
exercise

myeloma

patient beliefs

Tracks:
4th Nursing Symposium

NS-301

Strengthening the myeloma nursing network in Australia and New Zealand (ANZ): Leading best supportive care

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Abstract:

Background: Patients with multiple myeloma (MM) are living longer with a chronic and complex cancer that adversely impacts health related quality of life (HRQoL). Modern health care approaches include provision of patient-centred care from a multidisciplinary team (MDT) with expertise and experience in MM. As part of the MDT, specialist nurse roles incorporate ongoing patient education; delivering complex therapies; assessing, monitoring and managing disease and treatment adverse effects; provision of patient support, coordination and navigation within complex health environments, whilst remaining up-to-date. The Haematology Society of Australia and New Zealand (HSANZ) Nurses Group formed a Myeloma Special Practice Network (M-SPN) with a primary objective to improve nursing care quality and outcomes for individuals with MM. Aim: We describe projects undertaken by the M-SPN that promote best practice in MM treatment administration; support formation of specialist MM nursing roles; optimises patient education and provides ready access to MM clinical resources. Method: A mapping exercise was undertaken to identify existing MM clinical and patient resources. Gaps were identified, and new content prioritised for development by group consensus. Lead authors were assigned to projects and working groups established. A successful grant application supported medical writing/formatting input. Physician colleagues and patients reviewed content and members provided feedback on all resources before final proof. Results: The e-platform myINTERACT was identified to host existing and future MM resources, and the resultant myeNURSE app enables members to access content at point of care on hand held devices or desktop. Three nurse guidelines were written: 1. Bortezomib and 2. Daratumumab providing consensus on administration and patient management. Daratumumab guideline is published in peer review journal and included in the bibliography for Daratumumab national treatment protocol. 3. The 'Myeloma Information Pathway' helps clinicians identify information needs of MM patients/carers in a timely manner linking to reliable up-to-date resources. A guide to write and implement a business case for Specialist Myeloma Nurse Roles

was adapted with permission, from the existing Myeloma UK Nurse Business Case document. A patient resource 'Understanding Tests and Investigations for MM' was also developed. All are accessible via HSANZ website as tools to support MM care. Conclusion: The M-SPN successfully identified and developed MM specific consensus and information resources to support nurses working in the MM space. The myeNURSE app provides members with ready access at the point of care to a wide range of MM clinical and information resources that support nurses to remain up to date in complex and changing practice environment. Future work includes an online patient treatment scheduler within the myeNURSE app as a tool for education and aid medication adherence

Keywords:
Nursing Consensus Guideline

nursing considerations

Patient education

Tracks:
4th Nursing Symposium

NS-302

Bortezomib Induced Peripheral Neuropathy: A Systematic Review of Phase III Trials

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Abstract:
Background: Bortezomib is a proteasome inhibitor commonly used for the treatment of multiple myeloma (MM). Its proven efficacy has resulted in increased survival rates in both the newly diagnosed and relapsed/refractory cohorts. Bortezomib-induced peripheral neuropathy (BIPN) is a disabling and common toxicity associated with this treatment, typically requiring dose reduction, delay or cessation of treatment protocol. It typically presents as numbness, tingling and paraesthesia manifesting in the peripheral domain in a glove and stocking distribution. Aims: This review aimed to investigate the incidence, risk factors, trends and variability associated with the development of BIPN. Methods: A systematic review using Medline, PubMed, Cochrane Central Register of Controlled Trials, Embase, Scopus and Web of Science was undertaken, with additional studies identified by investigating authors' bibliographic references cited by original and review articles. Articles that reported on neuropathy in phase III randomised control trials involving bortezomib in any treatment arm for the treatment of MM were included in this review. Independent extraction of articles were completed by 2 authors using predefined data fields. Results: A total of 43 full text articles met criteria, which examined 23 phase III trials (N=8,218). Overall incidence of neuropathy ranged from 8.4%-80.5% (median=37.8%) and severe neuropathy (grade 3-4) ranged from 1%-33.2% (median=8%). Similar reports of neuropathy of any grade and severe neuropathy were observed between the newly diagnosed and relapsed cohort. Bortezomib regimens with reduced dose intensity were associated with reduced neuropathy incidence. Increased cumulative dosing levels, intravenous compared to subcutaneous administration and combination therapy with thalidomide were associated with higher rates of BIPN. BIPN is largely reversible with 64%-79% reporting improvement in 2-4 months, and 60%-68% experiencing complete resolution in 4-6 months. Complete resolution was more likely in patients who had dose reductions according to protocol. Conclusions: This analysis systematically investigated BIPN in phase III trials and reinforced BIPN as a significant toxicity. The wide range of incidence between trials highlight the need for more valid and sensitive measures to accurately capture the incidence and severity of BIPN. With MM survival rates increasing since the introduction of bortezomib, a better understanding of risk factors and reversibility profiles is necessary to minimise

the number of cancer survivors living with residual treatment side effects.

Keywords:
Adverse effects

bortezomib

peripheral neuropathy

Tracks:
4th Nursing Symposium

NS-303

The Princess Margaret Cancer Centre Experience: Transitioning to GCSF Alone for Stem Cell Mobilization in Myeloma Patients

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Abstract:
Background: Historically at Princess Margaret Cancer Centre, cyclophosphamide and GCSF was the standard stem cell mobilization regimen used for transplant eligible multiple myeloma patients. Limitations to this regimen included chemotherapy associated toxicity such as febrile neutropenia, and unpredictability regarding the ideal planned apheresis start date. With the recent validation of open-vial sterility of plerixafor allowing for broader access at our centre (Seki et al. Can J Hosp Pharm 2017;70:270), an opportunity was identified to transition to a less toxic GCSF alone mobilization regimen. Objectives: To determine the mobilization success of GCSF alone in comparison to cyclophosphamide and GCSF based on: the ability to collect on the planned start date of apheresis, the number of days required on the apheresis machine to reach target CD34 numbers, the percentage of patients requiring salvage plerixafor, and success rates of meeting target CD34 counts. Methods: A retrospective audit of 74 consecutive multiple myeloma patients undergoing stem cell mobilization with either cyclophosphamide and GCSF (Group 1, n=46) or GCSF alone (Group 2, n=28) over a 4 month period was performed. After adoption of our GCSF alone mobilization regimen, an additional 63 patients were reviewed to validate results of the change. Results: Within Group 1, 29/46 (63%) of patients were ready to collect on the first planned date of apheresis versus 26/28 (93%) of Group 2 patients mobilized with GCSF alone (p=0.004). The average number of days spent on the apheresis machine (1.3 versus 1.6 days), the proportion of patients requiring plerixafor (15 vs 18%; p=0.57), and the proportion of patients successfully meeting target (98 vs 96%) appeared similar between Group 1 and 2. These findings were validated with the audit after adoption of GCSF alone mobilization, identifying that 56/63 (89%) of patients were ready to collect on the first planned date of apheresis, spent an average of 1.5 days on the apheresis machine, and 22% required salvage plerixafor. 60/63 (95 %) of patients in the validation group met target for collection. Conclusion: At our institution, the transition to GCSF alone as stem cell mobilization for myeloma patients has allowed for more accurate prediction of readiness to start apheresis, thus allowing for optimal resource utilization within this large volume transplant program. While GCSF alone may appear less efficient than cyclophosphamide and GCSF with a trend toward longer time on apheresis and higher use of plerixafor, this did not ultimately affect the mobilization success of meeting target CD34 numbers sufficient to proceed to transplant. Additionally, shortening a 9 day mobilization regimen to a less toxic 4 day regimen may be less burdensome for both the patient and family during this time period.

Keywords:
Multiple myeloma

Stem Cell Mobilization

Tracks:
4th Nursing Symposium

NS-304

Optimizing Patient Care Through the Use of Clinical Pathways and Standard Operating Procedures When Treating Patients with Systemic AL Amyloidosis

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Abstract:
Beginning with a comprehensive, multidisciplinary evaluation leading to treatment of patients with high dose melphalan (HDM) and autologous stem cell transplantation (SCT) requires excellent coordination of care, clear communication and collaboration within the team. The use of clinical pathways (CPs) provide direction in delivering precise and intentional care for a specific patient population. CPs were first used in a hospital setting in the 1980's in response to changes in healthcare, shifting the focus from volume to quality. Standard operational procedures (SOPs) describes activities necessary to meet regulatory guidelines. Our comprehensive evaluation assesses organ involvement, performance status, patient support systems and patient's physical and emotional ability to adhere to an outpatient treatment program, follow-up care and participate in clinical research protocols. Weekly meetings are held to discuss evaluation results, determine eligibility and identify concerning issues before a patient is scheduled. Once treatment begins the hematologist provides the majority of care with the multidisciplinary team on hand for consults. Patients are seen in the clinic daily, staying the better portion of the day, synonymous to that of a day hospital. Patient rounds include toxicity evaluations, physical exams, medication review and reinforcement of the treatment plan. Necessary interventions may occur at that time in addition to scheduled care per CP. Instructions are provided describing expected toxicities, symptom management, medications and emergency instructions. Prophylactic antiemetics, antimicrobials and growth factors are used as part of supportive care. A detailed medication chart with education is provided. The most common reason for hospitalization is febrile neutropenia, severe GI side effects and volume depletion. CPs and SOPs were developed in effort to direct coordinated, quality of care. Both are reviewed annually for revisions based on current evidence and program experience with a mechanism to document any deviations. Educational courses are held regularly for staff to ensure adherence to CPs and SOPs when caring for patients with AL amyloidosis (AL). AL is a plasma cell dyscrasia in which light chains misfold, form fibrils and deposit in vital organs causing organ dysfunction. HDM/SCT can produce hematologic remission organ response, and prolong survival. HDM/SCT was developed for the treatment of AL amyloidosis at Boston University Medical Center in 1994. The program has been FACT accredited since 2000 and has participated in data submission to CIBMTR since 2014. In summary, CPs and SOPs are necessary tools to use when treating patients with AL in the out-patient setting. CPs provide a well-orchestrated sequence of interventions offering a predictable course in patient care while SOPs provide safety, efficiency, quality of care and uniformity, reducing miscommunication and failure to comply with industry regulations.

Keywords:
amyloidosis

multidisciplinary

Stem Cell Transplant

Tracks:
4th Nursing Symposium

NS-305

Adaption of the Dexamethasone Symptom Questionnaire in a Multiple Myeloma Population: Item generation, content and face validity of the 'Steroid Symptom Questionnaire – Multiple Myeloma' (SSQ-MM)

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Abstract:
Background: Corticosteroids (steroids) play a central role in the treatment of MM and are widely recognised to cause a wide range of side effects that adversely impact health related quality of life (HRQoL). Patient reported outcome measures (PROMs) are tools that enable patients to report their health status and the presence and severity of symptoms. A range of PROMs are available to assess symptoms in MM but no such tool exists to measure the impact of steroids in this population. The Dexamethasone Symptom Questionnaire Chronic (DSQ-C) is an 18-item measure, initially developed to determine the incidence and severity of symptoms experienced by cancer patients given dexamethasone prophylaxis for moderately emetic chemotherapy. Aim: Adaption of the DSQ-C in a multiple myeloma population (DSQ-MM). Establish consensus, test content and face validity. Methods: A three phase study, with phase 1 and 2 completed: Phase I: Understand what is known about the impact of steroids associated with therapy for MM. Phase II: Adaption of the Dexamethasone Symptom Questionnaire (DSQ), for a MM population: Phase III Preliminary validation of the tool in a multi-centre cross sectional study. This abstract presents findings from Phase II. Phase II: The European Organisation for Research and Treatment in Cancer (EORTC) Guidelines for Developing Questionnaire Modules guided the research. Findings from phase I informed preliminary item generation/omission from original DSQ. Expert groups were utilised to work toward consensus and test content and face validity of the adapted DSQ-MM. Purposeful sampling was used to form representative groups. Patient/carer group completed the draft tool then attended a focus group interview where each item was further discussed to gain consensus. Clinicians participated in an online survey of the tool scoring each item for relevance followed by a group tele-conference where consensus on content was obtained. Items within the DSQ-MM were added, reworded or removed in accordance with findings. Results: Clinician expert group (n=10) included nurse specialists (Australia & USA), psychologist, pharmacists, haematologists and a nurse academic. The consumer expert group (n=8) included 5 patients and 3 of their spouses. There was a high level of agreement from both groups as to content of DSQ-MM. Qualitative responses lead to further refinement including the renaming of the tool to 'Steroid Symptom Questionnaire Multiple Myeloma' (SSQ-MM). All members of the expert groups were in agreement on the final content of SSQ-MM. The final content will be presented at this presentation. Conclusions: The development of a psychometrically sound SSQ-MM has the potential for improving steroid toxicity management and to improve treatment outcomes for this patient group. Properties of feasibility, acceptability and validity are being tested in a larger multi-centre cross sectional study.

Keywords:
corticosteroids

Quality of Life

Supportive Care

Tracks:
4th Nursing Symposium

NS-306

Development of a Participatory Patient Decision Aid for Patients with Multiple Myeloma

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Abstract:
Background: Shared- Decision Making (SDM) is an important aspect of patient engagement in which the healthcare provider invites the patient and caregiver to collaborate on healthcare decisions. Patient decision aids (PDAs) following criteria set forth by the International Patient Decision Aid Standards (IPDAS) Collaboration have been shown to improve the quality of care delivered and health outcomes (1,2) and foster SDM by preparing patients to understand their condition, clarify values, and discuss priorities with their healthcare provider. No PDAs for patients with multiple myeloma (MM) exist. Thus, the International Myeloma Foundation Nurse Leadership board (NLB) seeks to develop a participatory PDA for patients with MM. Methods: In September 2018, the NLB met with the objective to develop an instrument to aid MM patients and caregivers in deciding preferences in treatment following the IPDAS checklist. The board discussed best practices in the diagnosis and management of MM, reviewed existing PDAs and personal experiences in assisting patients in the decision-making process. A review of the literature (ROL) was conducted by searching PUBMED, CINAHL and Google Scholar to identify the most comprehensive and easy to use PDAs in cancer treatment. A series of questions were constructed based on the ROL, existing cancer-related PDA models and expert nurse and patient opinion. Using a 2-stage, evidenced informed Delphi consensus model, NLB members and select patients provided input on content for the MM-specific PDA until all of the PDA questions were agreed upon. Results: One study highlighted the importance of an interactive PDA tool for patients with MM (4). A second discrete choice study evaluated patient preferences (3), and 3 others evaluated patient preferences and value mapping (5-7). While treatment preferences have been investigated, no PDAs in MM were identified. Recurring themes among value mapping research and existing cancer-related PDAs underscored the important balance between quality and quantity of life, and willingness to accept hematologic side effects rather than symptoms. Based on NLB member input and data from previous studies, a first-phase, 12 question PDA was developed and included a basic disease overview and a series of questions. Conclusion: Nurse Experts plan to develop the first ever, participatory PDA for patients with MM to prepare patients for treatment discussions, and to prioritize what treatment is best for them. Next steps will be to study the PDA in a prospective clinical trial to assess the acceptability, reliability and validity of the PDA.

Keywords:
Decision aid

Multiple myeloma

patient centered communication

Tracks:
4th Nursing Symposium

NS-307

Quality of life assessment in multiple myeloma patient and their caregivers.

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Abstract:
Project Summary: Quality of life (QOL) is the general well-being of individuals and societies, outlining negative and positive features of life. It observes life satisfaction, including everything from physical health, family, education, employment, wealth, religious beliefs, finance and the environment. Multiple myeloma treatments are on the cutting edge. Quality of life screening is not done, or the measurement necessary for eligibility to enroll on a clinical trial or to start a new conventional therapy This was a pilot project of

screening patients and their caregivers for quality of life. The goal was to identify areas that oncology clinicians could better assist and care for multiple myeloma patients and their caregivers. Background: Multiple myeloma has had many drug advances over the past decade. Many quality of life studies have been done in oncology, but none in multiple myeloma specifically, involving both patient and their caregiver. Advances in research and treatment for multiple myeloma are extending patients' lives. Many patients are living with significant side effects and disabilities requiring assistance from caregivers and equipment. Process: The purpose of the pilot was described to patients and their caregivers both verbally and with a written letter attached to each survey. Questionnaires were on paper, they were provided a clipboard, pencil and an envelope to seal the questionnaire when it was completed. The FACT-MM screening tool was utilized for patients. FACT-MM was developed with the aim to create a disease-specific, patient-reported outcomes (PRO) measure as part of the FACT measurement system to assess multiple myeloma (MM)-related symptoms. FACT-MM is 42 compilations of questions divided into 5 QOL domains: physical well-being, social/family well-being, emotional well-being, functional well-being, and additional concerns. The Caregiver quality of life index –cancer, was the questionnaire utilized for caregivers. The Caregiver Quality of Life Index- Cancer (CQOLC) scale is a 35-item cancer-specific instrument that assesses the caregiver of a cancer patient's quality of life, including: physical, social, emotional, and financial aspects of well-being, and functioning. Findings: There was a direct correlation between patient and their caregiver's quality of life in very specific areas. It was noted that approximately 40-66% of patients complained of: lack of energy, easily fatigued, trouble walking because of pain and emotional ups and downs. The contrast to this is that caregivers complained 60-83% of increased level of stress, fear that their loved one will die and feeling upset to see their loved on deteriorate. This pilot project opened communication with patients, their caregivers and healthcare providers. Subjects completed their surveys independently but then were able to talk about it and other related topics that prior to this might have been uncomfortable.

Keywords:
end of life

functional well-being

Quality of Life

Tracks:
4th Nursing Symposium

NS-308

Introducing Self Administration of Bortezomib (Velcade) to Myeloma Patients

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Abstract:
Background: Multiple Myeloma (MM) is the second most common haematological cancer, with around 5,540 new cases diagnosed in the UK each year. Of these, 33% of patients who are diagnosed are living more than 10 years with a further 47% surviving 5 years or more (1). MM remains a treatable but incurable disease. Gold standard treatment as approved by for induction or first relapse therapy is a bortezomib based regime. This can mean weekly or twice-weekly trips to the local hospital to receive their treatment (2). The Myeloma team of the University Hospital of Wales aimed to introduce self-administration of bortezomib to give patients more control of their treatment. As MM is recognised as a chronic disease rather than a disease of palliation, it is important to ensure strategies to improve patients' health related quality of life. Being able to offer fewer visits to the hospital and encouraging a patient to take control of their treatment is a step forward for the team in Cardiff. The team in Cardiff carried out evaluation of bortezomib practice. Our review showed patients spent around 2 hours at the hospital for bortezomib treatment. Patients voiced their concerns their visit

taking so long for a short procedure. Methods: Patients were included in this study who met inclusion criteria and were allowed to receive bortezomib. The team decided to have the following in place before proceeding with education of bortezomib self-administration. Key areas of concern included: ➢ Stability of drug - agreed with pharmacy 7 days. ➢ Information needs - Written step by step guides for patients ➢ Training - empower staff to teach and educate patients on administration ➢ Safety in the home- safe handling and disposal ➢ Remote monitoring - Nurse assessment, 24 hours telephone access ➢ Patient group- Consultant and CNS have overall decision who will be offered self-administration Results: All patients who received first dose of bortezomib in the hospital setting where they were taught the procedure. Subsequent cycles were given the comfort of their home. Patient feedback has been outstanding. There has been no missed doses or drug wasted. All patients that have self-administered have voiced this was the preferred way and felt comfortable self-administering bortezomib. Conclusion: Self-administration of bortezomib with patient education is feasible. In the future, we would like to explore a longer stability date and reassess the patient inclusion criteria to include more patients. 1. Cancer Research UK (2013) Myeloma Statistics.cancerresearch.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma 2. NICE.2007.Bortezomib monotherapy for relapsed multiple myeloma (online) NICE .Available at: http//www.nice.org.uk 3. Moreau, P.et.al.2011.Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: A randomised, phase 3, non-inferiority study. The Lancet Oncology12(5),pp.431-440

Keywords:
bortezomib

Quality of Life

treatment

Tracks:
4th Nursing Symposium

NS-309

Nursing implications for multiple myeloma patients undergoing chimeric antigen receptor (CAR) T-cell therapy.

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Abstract:
Purpose: Discuss considerations for CAR-T therapy, including establishing protocols for cytokine release syndrome (CRS) management, multidisciplinary measures, prophylactic therapy, CAR-T administration, acute/long-term toxicity management, and patient education. Interventions: Prior to initiation: Establish protocols for CRS management including in-servicing departments, identifying communication strategies, assembling "CRS attending" schedule. Social work assessment is imperative to assist with logistics necessary for frequent visits to CAR-T institution. Identifying a reliable caregiver and setting expectations are important for safe outcomes. Discussion of cost implication and financial clearance is essential. Leukapheresis: Nurses perform apheresis assessment, including venous access and infectious disease screening. It is an outpatient procedure that may last up to 6 hours. Common side effects include hypocalcemia, cytopenia, syncope, and citrate toxicity. The expected time of manufacturing can take up to 6 weeks. Bridging chemotherapy: Patients may need therapy to control disease and maintain performance status while awaiting CAR-T manufacturing. It starts after leukapheresis as T-cell quality is not affected. Close coordination between manufacturer and treating provider is essential to determine timing of therapy. Lymphodepletion: T-cell lymphodepleting chemotherapy given prior to CAR-T improves clinical outcomes by decreasing T-cell rejection. Pneumocystis pneumonia/shingles prophylaxis and intravenous immunoglobulin should be started. Administration: CAR-T can be given

inpatient or outpatient. Pre-medication with diphenhydramine and acetaminophen is given 1 hour prior. It is a single IV infusion, due to acuity of treatment, recommended to have 1:1 nurse to patient ratio. Require hospitalization for 2 weeks and must stay nearby for up to 14 days post discharge for intensive monitoring and supportive care. Monitoring: Vigilant monitoring is required for CRS/neurological toxicity, especially in first 30 days. CRS is interleukin-6 driven and can be treated with tociluzimab, anakinra or corticosteroids. Rapid recognition of CRS symptoms critical to ensure best outcomes. Patients are in medical oncology unit, but may require transfer to intensive care unit for severe symptoms. Patients who develop CRS post discharge will require re-admission for management. Supportive care: Prolonged pancytopenia requiring growth factors/transfusions post CAR-T therapy is common. Opportunistic infections from chronic immunodeficiency related to B-cell aplasia is expected and requires interventions. There are no established guidelines for post CAR-T vaccination or standard antimicrobial prophylaxis. Education: Patient education must include a caregiver and multidisciplinary approach. Nurses must instruct patients to report fevers, tachycardia, headache, confusion. The caregiver is pivotal in supporting the patient during the entire CAR-T journey. Discussion:

Keywords:
CAR T cells

nursing considerations

Tracks:
4th Nursing Symposium

LATE BREAKING ORAL ABSTRACT PRESENTATIONS

OAB-84: Circulating Tumor Cells (CTCs) for Comprehensive and Multiregional Non-Invasive Genetic Characterization of Multiple Myeloma (MM)

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Abstract:
Background: Patients (pts) undergo multiple bone marrow (BM) aspirates for genetic screening that beyond painful, may not be fully representative due to patchy BM involvement, spatial genomic heterogeneity, or extramedullary (EM) disease. Cell-free DNA shows high concordance with BM plasma cells (PCs), but are restricted to a few recurrent mutations since comprehensive genetic characterization (eg. whole-exome sequencing, WES) is applicable to <25% of samples. By contrast, CTCs are detectable in virtually all pts and are prognostic, but their applicability for non-invasive genetic characterization of MM has been poorly investigated. Aim: Compare the genetic landscape of CTCs vs matched BM clonal PCs and EM plasmacytomas, and validate standardized assays for CTCs' detection, isolation and genetic characterization. Methods: We used EuroFlow next-generation flow (NGF) to detect and isolate

peripheral blood (PB) CTCs and matched BM clonal PCs from 38 MM pts. In 8 cases, clonal PCs from EM plasmacytomas were also FACSorted. PB T cells were used as germline control. In the training set, we performed custom WES in matched CTCs, BM and EM clonal PCs from the 8 pts with all three spatially distributed clones. For validation, we compared mutations, copy number alterations (CNA) and translocations present in CTCs and BM clonal PCs using the Chromium Exome Solution (n=8), and solely CNA using the Affymetrix CytoScan platform (n=22). Results: In the training set, 193/226 (85%) and 231/269 (86%) mutations present in BM and EM clonal PCs, respectively, were detectable on CTCs. All MM recurrent mutations found in BM or EM clonal PCs were present in CTCs. Of note, there were 39 mutations in EM plasmacytomas that were present in CTCs but absent in BM clonal PCs, and up to 50 mutations were uniquely detected in CTCs. After showing that CTCs harbor most BM and EM mutations and unveil variants undetectable in single BM aspirates, we evaluated the performance of standardized assays to screen mutations and/or CNA in low cell numbers (ie. CTCs). Using 10XGenomics, 250/266 (94%) of total mutations and all MM recurrent mutations present in BM clonal PCs were detectable on CTCs (eg. KRAS, BRAF, TP53 or FAM46C). 101/119 (85%) CNA and 2/2 (100%) IgH Tx present in BM clonal PCs were detectable in CTCs. Using the Cytoscan, there was 100% concordance between CNA in CTCs and BM clonal PCs, both at the chromosomal arm and interstitial levels. All mutations in TP53 were detectable in CTCs. Furthermore, +1q, del1p, del17p or t(4;14) were always detected in CTCs whenever present in BM clonal PCs, and confirmed by FISH. Conclusions: We showed in the largest series in which CTCs were genetically characterized, that these are a reliable surrogate of MM pts' genetic landscape inside and outside the BM. Because NGF is broadly used, quantification, isolation and genetic characterization of CTCs may emerge as an optimal and standardized approach for non-invasive risk-stratification of MM patients.

Track:
Multiple Myeloma Genomics

OAB-85: Single-Cell Characterization of Multiple Myeloma (MM) Immune Microenvironment Identifies CD27-negative T cells as Potential Tumor-Reactive Lymphocytes

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Abstract:

The increasing use of immunotherapies urge the optimization of immune monitoring to help tailoring treatment based on better prediction of patients' response according to their immune status. Thus, we characterized the MM immune microenvironment at the single-cell level to identify clinically relevant subsets for effective immune monitoring. We used a semi-automated pipeline to unveil full cellular diversity based on unbiased clustering, in a next-generation flow (NGF) cytometry immune monitoring dataset developed from diagnosis to VRD induction, autologous transplant and VRD consolidation (n=231 MM patients enrolled in the GEM2012MENOS65 trial). Deep characterization of T cells was performed using 17-color flow and combined single-cell (sc) RNA/TCR sequencing. Simultaneous analysis of the entire dataset unbiasedly identified 25 cell clusters (including 9 myeloid and 13 lymphocytes subsets) in the MM immune microenvironment. Up to 120 immune parameters derived from the cellular abundance of each cluster and different cell ratios were determined at all time points. Overall, we observed that a prognostic score including the CD27-/CD27+ T cell ratio (HR:0.21, p=0.013) and ISS (HR:1.41, p=0.015) outperformed each parameter alone (HR:0.06, p=0.007). To gain further insight into the biological significance of the CD27-/CD27+ T cell ratio, we performed scRNA/TCRseq in 44,969 lymphocytes from 9 MM patients. Downstream analysis unveiled that CD27- T cells were mostly CD8 and included senescent, effector and exhausted clusters. By contrast, CD27+ T cells were mainly CD4 and the remaining CD8 T cells had a predominant immune suppressive phenotype. Such T cell clustering was validated by 17-color flow that confirmed the cellular distribution identified by scRNAseq, as well as higher reactivity for PD1, TIGIT, BTLA and TIM3 in CD27+ vs CD27- T cells. Simultaneous scTCRseq revealed a median of 12 clonotypes per patient. Interestingly, most clonotypes where found in CD27- (74/90) as opposed to CD27+ T cells and, using the VDJB database, the CDR3 sequences of clonotypic effector/exhausted CD27- T cells were predicted to recognize known MM-related epitopes such as MLANA, HM1.24 (CD319), or IMP2. In selected patients, we performed exome- and RNA-sequencing of tumor cells and analyzed their HLA profile. Using the T Cell Epitopes – MHC Binding Prediction tool from the IEDB Analysis Resource, we found expression of mutated genes (e.g. UBXN1, UPF2, GNB1L) predicted to bind MHC class I molecules on tumor cells and potentially recognized by autologous clonotypic CD27- T cells. In conclusion, we show for the first time that potential MM-reactive T cells are CD27-negative and that their abundance in the immune-microenvironment of newly-diagnosed MM patients is prognostic, possibly due to their reactivation after treatment with IMiDs and autologous transplant. Because NGF is broadly used, these results are readily applicable for effective T cell immune monitoring.

Track:
Multiple Myeloma Microenvironment

OAB-86: Activity of Melflufen in RR MM Patients with Extramedullary Disease in the Phase 2 HORIZON Study (OP-106): Promising Results in a High-Risk Population

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Abstract:
Introduction: Outcomes for RRMM patients (pts) with extramedullary disease (EMD) remain very poor despite recent advances in therapy. Historically, EMD occurring at relapse has been reported in up to 24% of pts (Haematologica. 2014) but more recent data suggests the incidence is rising with rates up to 40% reported (Blood. 2012). Data describing outcomes for RRMM pts with EMD are limited and recent reports have failed to demonstrate substantial responses to currently available treatment (Am J Hematol Oncol. 2017; Blood. 2016 Abs.5709; Eur J Haematol. 2019; Blood. 2016; Exp Hematol Oncol. 2016). Only daratumumab (dara) has significant single-agent activity with an overall response rate (ORR) of 17% (3 of 18) reported in dara-naïve pts. The phase 2 HORIZON study is investigating melflufen, a novel aminopeptidase-activated conjugated alkylator, plus dexamethasone (dex) in pts with RRMM refractory to available therapies (NCT02963493). Our report describes outcomes in RRMM pts with EMD in HORIZON and is the largest prospective clinical trial cohort of such pts with EMD described to date. Methods: Pts must have received ≥2 prior lines, been exposed to an IMiD- and proteasome inhibitor (PI)-based therapy, be refractory to pomalidomide and/or dara. Pts received melflufen 40 mg IV on day 1 of each 28-day cycle and dex 40 mg weekly (20 mg for pts aged ≥75 years) until progressive disease or unacceptable toxicity. The primary endpoint is ORR (≥ partial response per IMWG criteria). EMD assessment at screening was required for pts with known or suspected soft tissue and/or bone-related extramedullary plasmacytomas. Results: At data cutoff (06 May 2019; median follow-up 10.8 months) 121 pts have been treated: 96 of 121 pts were anti-CD38 refractory and of these 88% were at least penta-class refractory (resistant to 2 IMiDs, 2 PIs, and anti-CD38 therapy). Of the remaining 25 pts, 92% were at least quad-class refractory (i.e. 2 IMiDs and 2 PIs). Updated interim data (30 Jul 2019) demonstrated that 45 pts had EMD at screening, 57 pts had no known EMD, and 19 pts have data pending, with an EMD incidence of 44% (i.e. 45/102 patients with available EMD data). Importantly, the incidence of EMD was associated with prior anti-CD38 therapy (p=0.0016), with 43 of 45 EMD pts reported in the anti-CD38 exposed group. The ORR for pts with EMD (n=45) was 24% compared with an ORR of 30% in pts without EMD (n=57). Median duration of response (DOR) was 3.1 months for pts with EMD, compared with a median DOR of 7.5 months in pts without EMD. Further data, including baseline pt characteristics, safety and additional analysis, will be presented at the meeting. Conclusion: Melflufen/dex demonstrates encouraging activity in advanced RRMM pts with EMD. Response rates appear higher than observed in prior studies. These results support continued investigation in ongoing and future clinical trials of melflufen-based combination therapy for this population of exquisite unmet medical need.

Track:
Treatment of Previously Treated Myeloma

OAB-87: Daratumumab + Lenalidomide, Bortezomib & Dexamethasone Improves Depth of Response in Transplant-eligible Newly Diagnosed Multiple Myeloma: GRIFFIN

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Abstract:
Introduction: Daratumumab (DARA), a human CD38 mAb, is approved as monotherapy and in combination with standard-of-care (SoC) regimens for MM. In phase 3 studies, DARA-based regimens improved response rates, depth of response including stringent complete response (sCR) and minimal residual disease (MRD) negativity, and progression-free survival (PFS). In autologous stem cell transplant (ASCT)-eligible NDMM pts, RVd followed by high-dose therapy (HDT), ASCT, and consolidation is SoC in the US. GRIFFIN is a phase 2, randomized, active-controlled, US study of DARA plus RVd (D-RVd) in ASCT-eligible NDMM pts. A safety run-in showed no safety concerns. Here we present the primary analysis of the randomized portion of the study. Methods: Pts were randomized 1:1 to RVd ± DARA, stratified by ISS stage and creatinine clearance. Pts received 4 induction cycles, stem cell mobilization, HDT, ASCT, 2 consolidation cycles, and maintenance with R ± DARA for 24 months. During induction/consolidation (Cycles [C] 1-6), pts received V 1.3 mg/m^2 SC on Days (D) 1, 4, 8, and 11; R 25 mg PO on D1-14; and d 40 mg QW every 21 D. DARA 16 mg/kg IV was administered on D1, 8, and 15 of C1-4 and on D1 of C5-6. During maintenance (C7-32), pts received R 10 mg (15 mg in C10+ if tolerated) on D1-21 every 28 D ± DARA 16 mg/kg IV Q8W (or Q4W per pt decision after Amendment 2). The primary endpoint was the sCR rate by the end of consolidation per IMWG computer algorithm. The study had 80% power to detect a 15% improvement with a 1-sided alpha of 0.1 (equivalent to 2-sided alpha of 0.2). Results: A total of 207 pts were randomized. Baseline characteristics were well balanced between arms. Median (range) age was 60 (29-70) yrs, and 48%, 37%, and 14% of pts were ISS stage I, II, and III, respectively. The study met its primary endpoint; D-RVd improved the sCR rate by end of consolidation (42.4% vs 32.0%; odds ratio 1.57; 95% CI, 0.87-2.82; P=0.1359) at the pre-set 2-sided alpha of 0.2. D-RVd achieved higher overall response (99% vs 92%), ≥VGPR (91% vs 73%), and ≥CR (52% vs 42%) rates vs RVd. The rate of MRD negativity (10^–5 NGS) among pts achieving ≥CR was higher with D-RVd (59% vs 24%). At median follow-up of 13.5 months, duration of response, PFS, and OS data are immature. Median stem cell yield was 8.1 vs 9.4 × 10^6 cells/kg for D-RVd vs RVd. Grade 3/4 TEAEs (≥10%) included neutropenia, lymphopenia, thrombocytopenia, and leukopenia. There was no difference in the rate of grade 3/4 infections between arms. Infusion reactions occurred in 41% of DARA-treated pts (mainly grade 1-2 and with the first infusion). Conclusions: D-RVd induces higher response rates and greater depth of response, including sCR and MRD negativity, than RVd. The overall safety profile of D-RVd is consistent with previous reports of DARA and RVd, and stem cell mobilization and ASCT are feasible with D-RVd. Assessment of the effect of DARA maintenance on sCR improvement and MRD rates is ongoing.

Track:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

LATE BREAKING POSTER ABSTRACTS

SP-300
A rare case of Plasmablastic type of Multiple Myeloma in a middle-aged African American male

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Abstract:
Introduction Multiple Myeloma (MM) is a disease of the aging and the median age of diagnosis is 65 years. As per the SEER registry analysis report, its highest incidence is noted in African American(AA) males. Plasmablastic MM (PBMM), a rare variant of MM, is associated with faster progression and higher incidence of rapidly progressive renal failure. We describe a case of Stage 3 PBMM diagnosed in a 53-year-old AA male diagnosed during evaluation of chest pain. In addition, multiple rare and distinguishing high-risk cytogenetic features were noted on FISH analysis. Case Presentation A 53-year-old African American male presented with acute chest pain. On admission, he was noted to have hypercalcemia, anemia, and acute kidney injury (AKI) with a creatinine of 2.9 mg/dL (baseline creatinine 0.8 mg/dL). Computed tomography of the Chest showed diffuse lytic lesions in ribs, spine, and iliac crests along with a posterior mediastinal mass. On further evaluation, Serum protein electrophoresis showed an M protein (IgG Kappa) of 7.04 g/dL, Kappa/Lambda Free light chain ratio >200. Beta 2 microglobulin was 7.27 mcg/mL. Given the severity of AKI, chemotherapy was promptly initiated to a good response. Later, bone marrow biopsy revealed 95% plasma cells with 5% plasmacytoid blasts. Fluorescence in situ hybridization (FISH) analysis showed concurrent loss of RB1 and P53, atypical IgH gene rearrangement, and positive copies of CKS1B and FGF3. Based on the above features, MM staging assessed to be stage 3 as per the Revised International Staging System (R-ISS) with multiple other high-risk cytogenetic features as noted above. The patient underwent autologous bone marrow transplant 6 months later. Discussion Multiple Myeloma in young patients has a milder course of progression with a good survival outcome. PBMM, a rare morphological subtype of MM, is associated with a higher incidence of rapidly progressive renal failure, a shorter overall and disease free survival. In the multicenter studies by Greipp et al, PBMM was associated with median overall survival of 1.9 years as compared to 3.7 years of median survival time seen in non-PB cases. High-risk cytogenetic including P53 deletion, del 17(p) and RB1 loss are associated with poor prognosis. CKS1B amplification was associated with bone marrow plasmacytosis. Patients with CKS1B amplification had a significantly shorter progression-free survival than those without such amplification. IgH gene rearrangements have been well studied for their role in ontogeny of MM. PBMM, irrespective of the cytogenetic type, is categorized as high-risk and is associated with a worse prognosis.

Keywords:
cytogenetics

Plasmablastic

Plasmacytoid Dendritic Cells

Tracks:
Multiple Myeloma Genomics

SP-301

Role of lncRNAs as prognostic factor and potential therapeutic target in Multiple Myeloma

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Abstract:
Deregulation of long non-coding RNAs (lncRNAs) is emerging as a common feature of human tumors, suggesting that their investigation may uncover novel oncogenic mechanisms. Previous studies suggested that the alteration of some lncRNAs might play an important role in multiple myeloma (MM); however, the complete expression landscape of lncRNAs has not been elucidated. In the present work we characterized the lncRNAs transcriptome of MM determining their potential involvement in this disease. Firstly, we performed paired-end strand-specific RNA-seq (ssRNA-seq) in 38 purified plasma cell (PC) samples from MM patients, 3 bone marrow PCs (BMPCs) of healthy donors, and in distinct normal B-cell populations (Naïve, Centroblasts, Centrocytes, Memory and Tonsilar PCs). We identified 40,511 novel lncRNAs, representing more than half of MM transcriptome (56%) and which, together with the previously annotated lncRNAs, comprised most of the MM transcriptome (82%). We studied the transcriptional heterogeneity in MM, observing that lncRNAs showed a more heterogeneous expression than coding genes, suggesting that these elements could contribute to the heterogeneity of MM. To determine differentially expressed genes, each MM patient was compared to normal BMPCs, detecting 10,351 lncRNAs overexpressed and 9,535 downregulated in more than 50% of patients, focusing on a group of 989 lncRNAs specifically upregulated in MM (MM-specific lncRNAs), considering the B-cell populations. Next, we aimed to determine whether upregulation of those lncRNAs was under epigenetic control, analyzing the distribution of six histone marks (H3K4me3, H3K4me1, H3K27ac, H3K36me3, H3K27me3, and H3K9me3) by ChIP-seq. We compared MM cases to normal B-cell subtypes and detected 89 lncRNAs with de novo epigenomic activation and expression in MM, suggesting an epigenetic rewiring in MM. We focused on LINC-SMILO, de novo epigenetically active and expressed lncRNA in MM. Knockdown of LINC-SMILO in 3 different MM cell lines (MM.1S, MM.1R and KMS-11) by 2 different shRNAs resulted in reduced proliferation and induction of apoptosis, associated with activation of ERVs (Endogenous retroviruses) and increase in interferon induced genes (measured by MARS-seq), which results in the activation of Interferon pathways, essential for MM cells survival. Finally, we aimed to determine whether lncRNAs could improve the current prognostic of MM patients. Using the IA11 release of CoMMpass data, we analyzed lncRNAs by COX regression and Backward elimination of Stepwise regression analysis, obtaining that the overexpression of the lncRNA PDLIM1P4 together with 1q amplification and 17p deletion stratified MM patients in three different risk groups. In summary, our study shows the complexity of lncRNA transcriptome in MM, and suggests that some of these lncRNAs have prognostic influence or can be used as potential therapeutic targets for MM.

Keywords:
epigenetic

LncRNA

Transcriptomic Analysis

Tracks:
Multiple Myeloma Genomics

SP-302

CAR-directed cytotoxicity of NK cells: an alternative tool to treat and to study multiple myeloma and NK biology

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Abstract:
Treatment options for multiple myeloma (MM) include targeted inhibitors, antibodies, and immunomodulatory drugs (IMiDs). However, eradicating the disease remains a major clinical challenge and new therapeutic strategies are needed. Recently, chimeric antigen receptor (CAR) T-cell therapy has shown striking activity and high rates of complete responses (CR) in other lymphoid malignancies. We speculate that targeted natural killer (NK) cells represent an alternative, powerful therapeutic strategy. While we expect that CAR T cells may be more active on a cell-by-cell basis, the CAR NK cells are off-the-shelf reagents with

capacity for in vitro expansion and unprecedented versatility, potentially enabling repeated treatments and justifying their use. We created and assessed the in vitro cytotoxicity of B-cell maturation antigen (BCMA) CAR-expressing NK cells using the NK92 cell line. Then, we utilized the CRISPR/Cas9 screen to understand how MM cells can potentially escape the cytotoxicity of CAR NK92 cells and therefore, the mechanisms of NK-killing. The co-culture of CAR NK92 and a MM cell line, OPM2 triggers activation, release of INFγ, and cytotoxicity of NK92. The specificity of CAR-binding is validated via the knockout of BCMA on OPM2. Subsequently, a genome-wide CRISPR-Cas9 screen on OPM2 reveals additional mechanisms required for CAR NK92 cytotoxicity, such as heparan sulfate, etc. Our results indicate that CAR NK cells represent an attractive, alternative cell-based immunotherapy option for MM. Furthermore, our genetic screen hinted on additional regulators for the cytotoxicity of NK cells.

Keywords:
immunotherapy

nk car

signaling

Tracks:
Multiple Myeloma Signaling

SP-303

The disease journey for patients with multiple myeloma treated with novel agents: a retrospective cohort study in Taiwan

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Abstract:
Objectives: Novel agents have been available for first-line treatment of multiple myeloma (MM) in Taiwan since 2009. At present, little is known about the disease journey of patients treated with novel agents in Taiwan. We constructed a disease-progression model to describe the disease journey in patients aged ≥18 years with newly diagnosed MM in Taiwan who received first-line treatment with novel agents (thalidomide or bortezomib). Methods: This retrospective cohort study utilized the Taiwan National Healthcare Insurance Research database, a population-based claims database covering the entire population of Taiwan. All newly diagnosed MM patients (ICD-9 codes 203.0X or 203.0 or 203) from 2007-2015 were enrolled. Patients with any pre-existing primary cancer other than MM were excluded. Eligible patients who had received treatment for their MM were followed up until death or end of the observation period (December 31, 2017), whichever occurred first. Results: A total of 1534 patients received first-line treatment with novel agents alone during the study period. The mean age of patients was 65.5 years (SD ±12.1) and 53.8% were male. The mean/median interval between diagnosis and treatment onset was 1.5/0.7 months and the mean/median duration of first-line treatment with thalidomide or bortezomib was 12.7/6.3 months. 26.1% of patients died during first-line treatment and 10.0% of patients remained on first-line treatment until study end. 64.0% (981/1534) of patients received second-line treatment. The mean/median duration of second-line treatment was 19.5/12.0 months. 26.3 % of patients died during second-line treatment and 24.7% remained on second-line treatment until study end. There were 481 patients (49.0% of 981 who received second-line treatment) who received third-line treatment. The mean/median duration of third-line therapy was 17.5/10.3 months. 26.8% patients died during third-line treatment and 35.3% of patients remained on third-line treatment until study end. Conclusion: MM continues to have high mortality despite the availability of novel agents. Comparison of these results with disease progression models for other drugs can inform treatment options and related outcomes to promote optimal management of patients.

Keywords:
bortezomib

Mortality

Multiple myeloma

Tracks:
Multiple Myeloma Novel Agents

SP-304

Artificial Intelligence to Assist Better Myeloma Care, is It the Time?

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Abstract:
Myeloma treatment made an enormous progress during the last decade. Armamentarium is grossly enlarging each year in the field of treatment. Parallel to the progress achieved to provide better care for myeloma patients, machine learning processes via artificial intelligence (AI) algorithms and big data analysis gained a remarkable progress. AI has rapidly diffused into various health sciences and cancer care also. Despite the advent of many efficacious treatment approaches and drugs, still we are not able to cure myeloma. Among the main limitations and barriers to cure, heterogeneity of phase 3 trials and lack of well organized and updated real life data are the ones that has to be addressed properly. Very recent and prestigous guidelines to provide evidence to a better myeloma care takes phase 3 randomized trials into account both in frontline and relapsed setting. Saying that frontline therapy is somehow standardized, relapsed setting is poorly organized among standardized recommendations for an individual myeloma patient. Regarding the heterogeneity of phase 3 trials and even published real life data, machine learning can possess an integrative approach to input individual patient data from datasets of randomized trials and well-established patient registries and to assist providing the best approach for an individual myeloma patient as an output via AI. We are now initializing our own nation-wide patient registry (Turkish Myeloma Patient Registry) system integrating machine learning process and planning to obtain assistance via training AI with patient specific demographic and disease related factors and efficacy and safety data of different treatment approaches as input variables and survival outcomes and patient reported outcomes as output variables, in a near future. We are also eager to co-operate with other national, multi-national databases and also the data providers of phase 3 randomized trials in the field to better optimize the artificial intelligence as an assistance tool in clinical decision making.

Keywords:
artificial intelligence

Multiple myeloma

Real-World Data

Tracks:
Multiple Myeloma Novel Agents

SP-305

CLR 131 Demonstrates High Rate of Activity in a Phase 1, Dose Escalation Study in Patients with Relapsed or Refractory Multiple Myeloma (RRMM)

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Abstract:
Background: CLR 131 is a novel targeted radiotherapeutic that exploits the selective uptake and retention of phospholipid ethers by tumor cells. Based on preclinical and clinical experience and the radiosensitivity of MM, CLR 131 is being examined in a RRMM Phase 1 open-label, dose escalation trial (NCT02278315). Escalating single doses of CLR 131 from 12.5-31.25 mC/m2 were evaluated, along with fractionated doses 31.25-40 mCi/m2. Methods:

The primary objective is to determine safety and tolerability of CLR 131 as a single or fractionated dose. Secondary objectives are to determine the recommended Phase 2 dose, schedule, and therapeutic activity in RRMM. Eligibility includes progressive disease, permitting patients with relapsed or refractory disease to at least 1 PI and 1 IMiD, and prior ASCT. In the cohort presented, CLR 131 is administered as a 37.5 mCi/m2 dose fractionated as 2, 30 minute intravenous infusions (18.75 mCi/m2 on day 1 and day 7) with 40 mg dex orally qw for 12 weeks. Adverse events (AEs) are graded by NCI-CTCAE v4.03. Results: Data on 4 subjects enrolled to cohort 6 (37.5 mCi/m2 fractionated CLR 131) is presented here. Median age for cohort 6 was 66 years (range 59-83) and included 2 males and 2 females. The majority of subjects (3/4) were high risk by cytogenetics, median bone marrow plasma cell involvement was 25% (range 10-60%). Number of prior therapies averaged 4 (range 3-6). 50% of subjects had prior ASCT and none had prior radiation therapy. One subject was dual class refractory, 1 was quad-refractory and 2 were penta-refractory, including being refractory to daratumumab. The overall response rate for cohort 6 was 50% - 2 subjects achieved a partial response (PR); the other 2 subjects achieved a minimal response (MR). One subject with a PR experienced a 61% reduction in κ FLC and the other a 68% reduction in λ FLC; 1 subject with an MR had a 39.1% reduction and the other a 48% reduction in m-protein. Both subjects with a PR and 1 subject with an MR were high risk by cytogenetics. CLR 131 has been well tolerated. There have been no reported deep vein thrombosis, pulmonary embolisms and no treatment emergent deaths. Grade 3-4 treatment emergent AEs occurring in over 25% of subjects have been neutropenia (50%), anaemia (75%) and thrombocytopenia (100%); with an average 2 weeks to recovery from nadir. Fatigue (grade 1-2) and ECG changes (grade 1) have also been noted. Three subjects entered with anemia and 1 also had leukopenia. As no DLTs were seen, dose escalation continues. Conclusions: CLR 131 represents a first in class targeted radiotherapeutic for RRMM. These data suggest that RRMM including high-risk patients can experience meaningful clinical benefit from treatment with CLR 131 with an acceptable and expected safety profile in the fractionated dose cohorts. Based upon this encouraging activity in late line RRMM patients, this dose of CLR 131 is being further evaluated in a larger population in a Phase 2 trial.

Keywords:
CLR 131

Phospholipid ether

Radiotherapeutic

Tracks:
Multiple Myeloma Novel Agents

SP-306

STANDARDIZATION OF HIGH SENSITIVITY MINIMAL RESIDUAL DISEASE MONITORING IN MULTIPLE MYELOMA: AN EXPERIENCE IN TERTIARY CANCER CENTRE

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Abstract:
Introduction: Minimal residual disease (MRD) status is the most relevant prognostic marker in multiple myeloma (MM). Recently, IMWG has incorporated MRD-negative status as a criterion to define stringent clinical response (sCR) using next-generation flow cytometry (NGF) i.e. high-sensitivity flow cytometry (HSFC). Herein, we present our experience in the standardization of HSFC and MRD monitoring in MM. Methods: We

standardized HSFC MRD-assay in MM using Euroflow bulk-lysis and stain method. A ten-color two-tube antibody panel was used which included antibodies against CD19, CD20, CD27, CD28, CD38, CD45, CD56, CD81, CD117, CD138, CD229, CD319 and Cytoplasmic-kappa and lambda. Sample were acquired using Navios flow-cytometer and data was analyzed using Kaluza-software. Limit of detection (LOD) and lower limit of quantitation (LLOQ) were determined using spiking and dilution experiments. Results: LOD and LLOQ of the HSFC-MRD was found to be 10 events (sensitivity of 0.0003%) and 25 events (sensitivity of 0.0008% with CV of 23.8%). We studied HSFC-MRD in 128 bone marrow samples from 99 MM patients (age-median-54 years, range-29 to 74 years and M:F ratio-4.2). Number of cells studied for MRD ranged from 700,000-9,900,000 with median of 3,400,000. MRD was detectable in 62.7% (79/128) samples and MRD levels ranged from 0.0002% to 23.4% with median 0.2%. Correlation with serum M protein showed a correlation coefficient of 0.59 with 12% cases showing MRD positivity without detectable M protein. CD19, CD45, CD27, and CD56 demonstrated highest frequency of abnormal expression in MRD detection (i.e. 100.0%, 90.9%, 87.0%, and 87.0%), followed by CD117, CD200, CD81, CD28, CD38, and CD20 in decreasing order (i.e. 62.3%, 54.5%, 50.6%, 35.1%, 16.9% and 10.4%). Median (range) of LAIP detected in MRD was 6 (2-8) using these markers. We were also able to develop infinicyt-based database using clonal and normal plasma cells in which would allow us automated objective identification of clonal plasma cells.

Keywords:
Flow Cytometry

Minimal residual disease

Multiple myeloma

Tracks:
Myeloma Response Assessment including MRD

SP-307

PEGFILGRASTIM VERSUS FILGRASTIM IN THE SUPPORTIVE CARE OF HEAVILY PRETREATED MULTIPLE MYELOMA IN TREATMENT WITH POMALIDOMIDE-DEXAMETHASONE

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Abstract:
Pegfilgrastim is a pegylated long-acting recombinant form of G-CSF that extends the half-life and allows for once-per-cycle dosing, requiring less frequent dosing than nonpegylated G-CSF. The objective of this study was to compare the efficacy and safety of pegfilgrastim in patients affected by heavily pretreated MM, treated with pomalidomide-dexamethasone, in order to determine whether a single subcutaneous injection of pegfilgrastim is as effective as daily injections of standard filgrastim, in terms of haematological toxicity, febrile neutropenic episodes, antibiotic usage and hospedalization duration. We enrolled 33 patients (19 M and 14 F) median age at diagnosis 69 years (r. 52-84), and median age at start of treatment 76 years (r.56-90) treated with several lines of treatments (median 7, r. 2-11), every refractory to all the drugs previously received, received Pomalidomide-Dexamethasone (P 4 mg for 21 days, D 40 mg days 1,8,15,22, pegfilgrastim day +8) every 28 days, until progression. Since first course, received in domestic setting, with a very good compliance, patients performed blood counts once weekly and received, from day +8 to day +19, prophylactic oral chinolonic antibiotics and anti-fungal drugs. During neutropenia after first cycle, Filgrastim (5 μgr/kg/day for 3 days) was given if neutrophils count was <1500 x 10^9 cells/L. Median number of filgrastim administrations was 4.8 (r. 3-6); nadir neutropenia was registered after a median of 10.7 days (r. 7-14); median of

nadir neutrophil count was 1.17 x 10^9 cells/L (r.0.3 – 1.5), with maximum duration of 14 days. From the second course, all patients switched to prophylaxis with pegfilgrastim (6 mg), injected subcutaneously with a single administration on day +3 independently from the neutrophil count at that time. During pegfilgrastim, neutropenia was never longer than 8 days, with a consequent reduction of neutropenia-related infections. Median nadir neutrophil count, evaluated for every patients for at least three courses of therapy (r. 3-6) registered at day +11, was 1.39 (r.0.9-2.2). Only 4 patients needed a supplement of 3 administrations of filgrastim. Pegfilgrastim was well tolerated in all patients: main side effects in our patients were mild fever and bone pain (21.2%). In conclusions, in patients affected by heavily pretreated MM treated with pomalidomide-dexamethasone, pegfilgrastim seems to reduce the incidence of severe neutropenia and infections and may increase the possibility to maintain the scheduled time of treatment.

Keywords:
Pegfilgrastim

Pomalidomide

Supportive Care

Tracks:
Multiple Myeloma Bone Disease

SP-308

CARFILZOMIB-LENALIDOMIDE-DEXAMETHASONE IN THE MANAGEMENT OF LENALIDOMIDE-REFRACTORY MULTIPLE MYELOMA

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Abstract:
Carfilzomib is an epoxyketone proteasome inhibitor of second generation, proved to be effective and safe in relapsed and refractory Multiple Myeloma (rrMM), in combination with dexamethasone or lenalidomide and dexamethasone. In this retrospective observational trial, it has been evaluated efficacy and safety of carfilzomib, in combination with lenalidomide-dexamethasone (KRD) as salvage regimen in patients with rrMM, refractory to lenalidomide, whose prognosis is particularly severe. 41 patients (23 M/18 F), with rrMM, median age at diagnosis 63.7 years (r. 43-82), median age at start of treatment 67 years (r. 48-84) previously treated with several lines of treatments (median 3, r. 2-11), underwent to KRD regimen (ASPIRE trial schedule) for a median treatment cycles of 8 (r 2-18). ISS was equally distributed, and all patients had previously been treated with bortezomib and IMIDs, and were refractory to this agents. 61% (19/31) of them had undergone at least to a single ASCT. According to IMWG criteria, after a median follow-up of 9 months (r. 2-18), ORR was 68,2% (28/41: 9 CR, 12 VGPR, 7 PR) with 5 progressive diseases (PD) and 8 patients in stable disease (SD): this can be considered as an impressive result in this subset of rrMM patients, refractory to lenalidomide. In particular, for 11 patients, KRD was, after having achieved at least a PR, a bridge to second/third autologous SCT. Median time to response was 1.3 months (r.1-4), median OS from diagnosis was 62 months (r. 9-170), median OS from start of Carfilzomib was 11 months (r. 2-18). Carfilzomib was well tolerated, with grade 2 anemia in 39%(16/41) of patients, successfully managed by ESAs, without necessity of blood transfusions; 29% (12/41) grade 3-4 neutropenia (pegfilgrastim in primary prophylaxis was given, no ospedalization was required, no septic shocks were observed); 34% (14/41) grade 2, 21% (9/41) grade 3 and 12% (5/41) grade 4 thrombocytopenia, without hemorrhagic events and transfusion-dependency. Moreover, it was observed pneumonia in 39% (16/41) of patients, treated by common antibiotic drugs and always solved. A cardiac monitoring was performed for all patients: hypertension (grade 2-3) in 34% (14/41) of patients; fatigue in 39% (16/31) of patients. Carfilzomib-

Lenalidomide-Dexamethasone has shown significant efficacy in a particularly severe setting of patients, relapsed and refractory to all available therapeutic resources, also lenalidomide, and it could be considered as a bridge to a second autologous or allogenic SCT.

Keywords:
carfilzomib

carfilzomib-lenalidomide-dexamethasone

refractory

Tracks:
Treatment of Previously Treated Myeloma

SP-309

POMALIDOMIDE-DEXAMETHASONE IN THE MANAGEMENT OF HEAVILY PRETREATED MULTIPLE MYELOMA

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Abstract:
Pomalidomide is a new generation IMID, with a very good compliance, thanks to oral administration, which can be used also in heavily pretreated patients, in a domestic setting. In this retrospective observational trial, It has been evaluated efficacy and tolerance of pomalidomide plus dexamethasone (PD) as salvage regimen in heavily pretreated patients with relapsed and refractory MM (rrMM), whose prognosis is particularly severe. 33 patients (19 M/14 F), with rrMM, median age at diagnosis 69 years (r. 52-84), and median age at start of treatment 76 years (r.56-89) treated with several lines of treatments (median 7, r. 2-11), every refractory to all the drugs previously received (also Bortezomib, Thalidomide and Lenalidomide), received Pomalidomide-Dexamethasone (Pomalidomide 4 mg for 21 days, Dexamethasone 40 mg days 1,8,15,22, pegfilgrastim day +8) every 28 days, until progression. ISS was equally distributed, and cytogenetic at relapse was evaluable in 14 patients. All the patients had previously been treated with schedule containing bortezomib and IMIDs. 60% (20/33) of them had undergone at least to a single ASCT. All patients were relapsed and refractory to last therapies received before PD. Pomalidomide was well tolerated, with grade 3 anemia in 51% (17/33) of patients, 36.3% (12/33) grade 3 neutropenia (pegfilgrastim in primary prophylaxis was given, no hospitalization was required, no septic shocks were observed), 30.3% (10/33) grade 3-4 thrombocytopenia without hemorrhagic events and transfusion-dependence. No severe extra-hematologic toxicity was observed. According to IMWG, ORR1 (≥PR) was 45.4% (15/33: 4 CR, 5 VGPR, 6 PR), but, considering that we are evaluating a cohort of heavily pretreated patients, with poor prognosis, another parameter should be considered, ORR2 (≥SD), considering stable disease as a successful result in progressive MM. ORR2 was 78.7% (26/33: 4 CR, 5 VGPR, 6 PR, 11 SD). These can be considered as impressive result in this subset of patients. Oral treatment gives a really good compliance, in frail and unfit patients, and response, when present, is always really fast (median time to response: 2 months (r.1-6)), median OS from diagnosis was 92 months (range 21-234), median OS from start of pomalidomide was 9 months (range 1-25). Pomalidomide-dexamethasone has shown significant efficacy and a very good compliance, thanks to oral administration, in a particularly severe setting of heavily pretreated patients, relapsed and refractory to all available therapeutic resources.

Keywords:
Heavily pretreated

Pomalidomide

Real-World Data

Tracks:
Treatment of Previously Treated Myeloma

SP-310

BENDAMUSTINE-BORTEZOMIB-DEXAMETHASONE (BVD) IN HEAVILY PRETREATED MULTIPLE MYELOMA: OLD/NEW IN NOVEL AGENTS' ERA

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Abstract:
Bendamustine is a bifunctional alkylating agent, with low toxicity, proved to be effective in relapsed, refractory and in new diagnosed Multiple Myeloma (MM). In this retrospective study, It has been evaluated efficacy and tolerance of Bendamustine, in combination with bortezomib-dexamethasone (BVD) in patients with relapsed and refractory MM (rrMM), whose prognosis is particularly severe. A retrospective real-life analysis of patients with rrMM who had been treated with BVD as salvage therapy has been performed. 56 patients (31 M/25 F), with rrMM, median age at diagnosis 57.3 years (r. 36-82), median age at start of treatment 61.8 years (r.37-83) treated with several lines of treatments (median 6, r. 2-11), every refractory to all the drugs previously received (also Bortezomib), received BVD (B 90 mg/sqm days 1,2; V 1.3 mg/sqm days 1,4,8,11, D 20 mg days 1,2,4,5,8,9,11,12, Pegfilgrastim day +4) every 28 days, until progression. All patients had previously been treated with schedule containing bortezomib and IMIDs, and 30% had also received radiotherapy. 67%of them had undergone at least to a single auSCT. All patients were relapsed and refractory to last therapies received before BVD. Bendamustine was well tolerated, with grade 3 transfusion-dependent anemia in 41% of patients, and 37% grade 3 neutropenia (no ospedalization was required, no septic shocks were observed). No severe extrahematologic toxicity was observed, only grade 1 gastrointestinal side effect (nausea), treated by common antiemetic drugs. According to IMWG, after a median follow-up of 14 months (r.2-36), ORR was 64% (36/56: 4 CR, 7 VGPR, 16 PR, 9 MR) with 8 PD and 12 patients in SD, which can be considered as an impressive result in this subset of rrMM patients. In particular, for 11 patients, BVD was, after having achieved at least a PR, a bridge to second auSCT, and for two patients a bridge to alloSCT. Three patients have shown a notable PR after failure of novel agents (i.e. Carfilzomib and Pomalidomide). Median time to response was 1.2 months (r.1-3), median OS from diagnosis was 62.7 months (r.6-151), median OS from start of Bendamustine was 9.8 months (r.2-36). The triplet Bendamustine-Bortezomib-Dexamethasone has shown significant efficacy in a particularly severe setting of patients, relapsed and refractory to all available therapeutic resources, and, in particular cases, it could be considered as a bridge to a second autologous or allogenic SCT.

Keywords:
Bendamustine

BVD

Salvage treatment

Tracks:
Treatment of Previously Treated Myeloma

SP-311

Phase II study of the combination of daratumumab, ixazomib, pomalidomide, and dexamethasone as salvage therapy in relapsed/refractory multiple myeloma

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Abstract:
The combination of daratumumab, pomalidomide and dexamethasone (DPd) has previously demonstrated deep and durable responses, including high rates of MRD negativity, in a heavily pretreated

patient population. Quadruplet regimens offer an opportunity to further improve upon these results. We report preliminary findings from an ongoing phase 2 multicenter trial of the addition of ixazomib to the combination of DPd in patients with relapsed/refractory multiple myeloma. The primary objective is to determine overall response rate and the safety and tolerability of this novel regimen. Key secondary endpoints include PFS, OS and MRD negativity rates. Eligible patients may have received >/=1 and grade 2 occurred with daratumumab administration. No DLTs occurred in the first six patients in the safety run-in. The overall response rate of the cohort is 100% with 3 patients achieving a stringent complete response (CR), and 3 patients achieving a very good partial response (VGPR) after a median of 7 cycles of treatment. One patient discontinued therapy due to influenza A, the other five remain on therapy. Minimal residual disease assessments are being performed by EuroFlow for patients in VGPR or better due to concern for daratumumab interference. The quadruplet regimen DIPd in patients with relapsed/refractory myeloma is well-tolerated and has shown early safety in an initial safety run-in analysis. Enrollment continues in an expansion cohort to assess efficacy.

Keywords:
Combination therapy

myeloma

relapsed/refractory multiple myeloma

Tracks:
Treatment of Previously Treated Myeloma

SP-312

Relapse of Multiple Myeloma after Autologous Stem Cell Transplant Presenting with CNS Involvement without Evidence of Bone Marrow Involvement

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Abstract:
In October 2015, a 58-year-old male was presented to Hematology, Oncology and Stem Cell Transplantation Research Center; Tehran University of Medical Sciences, Tehran, Iran, with complaints of bone pain and decreased urine volume about 2 months prior to admission. Initial laboratory findings demonstrated a normocytic, normochromic anemia with a hemoglobin of 8.2 g/dL, a white blood cell count (WBC) of 6,500 cell/mm3, and a platelets count of 245,000/mm. He had a creatinine of 4.2 mg/dL, calcium of 12.5 mg/dL, albumin of 3.7 g/dL, total protein of 11.7 g/dL, Beta-2 microglobulin of 13.8mg/L, and an erythrocyte sedimentation rate (ESR) of 135 mm/hr. Serum protein electrophoresis (SPEP) and immunofixation electrophoresis (IFE) were performed that demonstrated immunoglobulin G kappa monoclonal gammopathy. A bone marrow biopsy showed more than 80 percent involvement by abnormal appearing plasma cells, confirmed by CD138+ immunohistochemical stain. In addition, a thorough cytogenetic evaluation revealed the deletion of 1q21 and t(4;14). A skeletal survey showed multiple well-defined lytic lesions (punched-out lesions) in the skull. Based on the Revised International Staging System (R-ISS), the diagnosis of stage III multiple myeloma was established. The patient completed induction therapy with bortezomib-cyclophosphamide-dexamethasone (VCD) regimen and achieved a complete response after 4 courses of treatment. After the treatment period, the renal function was completely improved and all laboratory parameters were within the normal range. A repeat bone marrow biopsy following treatment did not show any evidence of multiple myeloma. In August 2016, the patient was scheduled for autologous bone marrow transplantation. Single-agent high-dose Melphalan at the dosage of 200 mg/m2 was used as a conditioning regimen prior to an autologous stem cell transplant. Bone marrow transplantation was performed successfully without any complication. Subsequently, the patient was placed on Lenalidomide maintenance one month after the autologous bone marrow transplantation. After 5 months of transplantation, the patient suffered from severe headache and pelvic pain. In fundoscopic examinations, bilateral pupil edema was detected. A lumbar puncture was performed and CSF smear revealed the presence of numerous plasma cells suggestive of CNS involvement, which

indicated a relapse of the MM. Interestingly, results of other diagnostic tests such as serum and urine protein electrophoresis with immunofixation, serum free light chains, and bone marrow aspiration and biopsy were all unremarkable. The patient was consulted with Dr. James R. Berenson, who is the Founder of the Institute for Myeloma and Bone Cancer Research (IMBCR). Dr. Berenson suggested the DKBP-BD treatment regimen to be the best option. The DKBP-BD regimen consisted of a 28-day cycle of Dexamethasone, Carfilzomib, Bendamustine, Pomalidomide, Clarithromycin, and Daratumumab.

Keywords:
bone marrow transplantation

CNS involvement

Multiple myeloma

Tracks:
Myeloma Transplant and Maintenance Strategies

SP-313

VRd versus VCd as induction therapy for newly diagnosed multiple myeloma: A Phase III, randomized study

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Abstract:
Three-drug based induction regimens are a current standard of care for autologous stem-cell transplantation (ASCT)-eligible, newly diagnosed, multiple myeloma (MM) patients (pts). Bortezomib, lenalidomide and dexamethsone (VRd), bortezomib, cyclophosphamide and dexamethasone (VCd) and bortezomib, thalidomide and dexamethasone (VTd) are commonly used triplets. We conducted a randomized trial to compare VRd versus VCd for induction in patients with newly diagnosed multiple myeloma. Overall 125 patients (median age years (range, to) were randomly assigned to receive receive 4 cycles of VRd (n=65) or VCd (n=60). Patients received Inj Bortezomib 1.3 mg/m2 subcutaneously weekly x 16 weeks, Tab dexamethsone 40 mg per week, and cap lenalidomide 15 mg daily day 1-15 every 28 days OR cyclophosphamide 300 mg/m2 day1,8 and 15, (total dose was calculated and given orally over 22 days every 28 days. All patients received acyclovir and septran prophylaxis. Patients were monitored on monthly basis for toxicity and response was evaluated at the end of 4 cycles as per IMWG criteria. Patients median age was 58 years (range, 31 to 70), 73(58.4%) were males. Patients characteristics were similar in both groups as regards to ISS stage (ISS III –VRd : 43.1%,VCd : 38%), high risk cytogenetics (VRd -12.1% vs VCd-11.1%), BM plasma cells %, and extramedullary disease. On intention to treat analysis – after 4 cycles – 61.5% of patients in VRd arm achieved ≥VGPR compared to 48.3% in VCd arm, p 0.09 (primary end point). CR rates were superior in the VRD arm; 35.4 % (sCR-9.2%) vs 18.3% (sCR-5%), p< 0.02. Hematologic toxicity and peripheral neuropathy was not significantly different in 2 arms. This study is registered with clinical trials registry (REF/2016/08/012008). Triplet induction therapy VRd was superior as regards to response rates for the VRd arm.

Keywords:
induction

Trial

triplet therapy

Tracks:
Treatment of Newly Diagnosed Myeloma Transplant Eligible

-B-

-H-

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-U-

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-W-

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