Latest advances and current challenges in the treatment of multiple myeloma

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Abstract | Effectively treating patients with multiple myeloma is challenging. The development of therapeutic regimens over the past decade that incorporate the proteasome inhibitor bortezomib and the immunomodulatory drugs thalidomide and lenalidomide has been the cornerstone of improving the outcome of patients with myeloma. Although these treatment regimens have improved patient survival, nearly all patients eventually relapse. Our improved understanding of the biology of the disease and the importance of the microenvironment has translated into ongoing work to help overcome the challenge of relapse. Several classes of agents including next-generation proteasome inhibitors, immunomodulatory agents, selective histone-deacetylase inhibitors, antibody and antitumor immunotherapy approaches are currently undergoing preclinical and clinical evaluation. This Review provides an update on the latest advances in the treatment of multiple myeloma. In particular, we focus on novel therapies including modulating protein homeostasis, kinases inhibitors, targeting accessory cells and cytokines, and immunomodulatory agents. A discussion of the challenges associated with these therapeutic approaches is also presented.

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Introduction

Multiple myeloma is a malignant monoclonal plasma cell disorder that is characterized by end-organ damage such as anemia, hypocalcemia, renal insufficiency or bone lesions.[1] Multiple myeloma accounts for 10% of all hematological malignancies and has an age-adjusted incidence of approximately four per 100,000.[2] Over the past decade exciting progress has been made in the therapeutic strategies for multiple myeloma with the development of regimens that incorporate the proteasome inhibitor bortezomib[3,4] and the immunomodulatory drugs thalidomide[5,6] and lenalidomide.[7,8] Advances in clinical practice have been predicated on a deeper understanding of the biology of the myeloma clone and its interaction with the bone-marrow microenvironment in which it resides.[9,10]

Most importantly, patients with multiple myeloma who are diagnosed today live longer, with a median survival in excess of 5 years, than those who were diagnosed before bortezomib and immunomodulatory agents were available.[11] However, despite these advances, nearly all patients relapse, as illustrated by the lack of a plateau in the survival curves from clinical trials that evaluate currently available treatment options.[12] Therefore, substantial therapeutic challenges remain. In this article, we briefly review current practice in the management of patients with multiple myeloma; outline challenges in patient care and discuss promising strategies for the development of novel therapies in the future.

Current clinical practice

Development of the current armamentarium

Recognizing the importance of the tumor microenvironment has been one of the most important advances in the field of multiple myeloma.[9,10] Adhesion of myeloma cells to accessory cells and extracellular matrix proteins in the bone-marrow milieu promotes cell growth, survival and resistance to conventional drug therapies via cell–cell interactions and the induction of cytokines.[9,10] Two findings have been the cornerstone of the improvements seen over the past decade in the treatment of patients with multiple myeloma. One was the understanding of nuclear factor (NF)-κB biology, specifically its degradation via the proteasome, and the subsequent development of the proteasome inhibitor bortezomib. The other was the use of thalidomide for the treatment of patients with multiple myeloma and the eventual development of lenalidomide and pomalidomide, which are based on the chemical backbone structure of thalidomide.

Competing interests
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Key points

- Despite recent advances, approximately all patients with multiple myeloma eventually relapse
- Recognizing the importance of the role of the tumor microenvironment has been one of the most important advances in the field
- Pomalidomide and oral proteasome inhibitors showed promising activity in preclinical studies and are now being evaluated in early clinical trials
- Antibodies, in particular elotuzumab (an anti-CS 1 antibody), are an important development; inhibitors of histone deacetylases, the phosphoinositide 3-kinase 3-kinase pathway and heat shock protein 90 are also showing promise
- Methods to augment antitumor immunotherapy of the immune system are being evaluated

Bortezomib received accelerated FDA approval in May 2003 for the treatment of patients with relapsed and refractory multiple myeloma. Subsequently, bortezomib also received full approval for the treatment of patients with relapsed multiple myeloma and as initial therapy on the basis of results from phase III trials.[13,14] The immunomodulatory drugs thalidomide, lenalidomide and pomalidomide target myeloma cells in the bone-marrow microenvironment. Specifically, these agents trigger caspase-8-mediated apoptosis, decrease binding of tumor cells to bone-marrow stromal cells, inhibit secretion of cytokines from the bone marrow (constitutive secretion as well as secretion induced by the binding of myeloma cells), inhibit angiogenesis, and stimulate immunity against myeloma cells mediated by autologous natural killer cells, T cells, or both.[7,9,10,15] Lenalidomide has both increased efficacy and a more-favorable adverse-effect profile (in particular lower rates of neuropathy and thrombosis) compared with thalidomide.[16,17] Pomalidomide has demonstrated promising activity in patients who are refractory to lenalidomide with myelosuppression as the predominant toxicity.[18–20]

Diagnostic and prognostic indicators

The international staging system for myeloma remains a highly-relevant prognostic variable in the current era.[21] Cytogenetics are important for establishing a prognosis because chromosomal abnormalities such as the del(17p) deletion and t(4;14) translocation confer high-risk disease associated with a relatively brief progression-free survival (PFS) and overall survival.[22,23] The t(14;16) translocation was linked to high-risk disease, but now data indicate that overall survival is similar in patients with or without t(14;16).[24] Other diagnostic parameters that can influence the choice of therapy are the presence of renal impairment and extensive extramedullary disease.[25–27]

Treatment of newly diagnosed disease

Regimens incorporating bortezomib, thalidomide or lenalidomide represent the standard of care and offer numerous options for treatment. The choice of therapy for patients with newly diagnosed disease is influenced by a variety of factors, including patient age, comorbidities, and eligibility for stem-cell transplantation (Figure 1). Strategies for upfront treatment of patients with multiple myeloma include two-drug regimens, such as bortezomib–dexamethasone,[28] lenalidomide–dexamethasone,[7,8] or thalidomide–dexamethasone,[29] and three-drug regimens, such as thalidomide–bortezomib–dexamethasone,[30] liposomal doxorubicin plus bortezomib–dexamethasone,[31] or lenalidomide–bortezomib–dexamethasone (RVD), with RVD showing particularly promising activity.[32] Preclinical data indicate synergistic cytotoxicity can occur from combining lenalidomide (which induces caspase-8-mediated apoptosis) with bortezomib (which induces caspase-9-mediated apoptosis) in models of myeloma.[33] RVD achieved responses in 61% of patients with relapsed, refractory multiple myeloma who were often refractory to each of the three agents alone.[34] In the setting of newly diagnosed disease, RVD produced an overall response rate of 100%, with 74% of patients achieving at least a very good partial response, and 52% of patients showing complete or near-complete responses.[32] In patients ineligible for high-dose chemotherapy, increased PFS, improved overall survival, or both, has been demonstrated when thalidomide or bortezomib were added to melphalan and prednisone (compared with melphalan–prednisone alone).[4,5]

Maintenance treatment

Unfortunately, drug resistance and relapse is seen in the majority of patients. Maintenance treatment with thalidomide prolonged PFS, but did not improve overall survival and was associated with adverse effects, even at low doses.[35,36] Indeed, 52.2% patients who were randomly assigned to thalidomide maintenance treatment discontinued therapy owing to adverse events related to treatment, including paresthesia (26.6%), drowsiness (6.8%), constipation (4.1%), eczema/rash (4.1%), hematological events (1.4%), infection (1.0%), thrombosis (1.0%), and tremor (1.0%).[36]

Results from two randomized studies published in 2010 have shown a doubling of PFS with lenalidomide maintenance therapy after autologous hematopoietic stem-cell transplantation (ASCT).[37,38] In clinical trials, second malignancies are known to be more common in patients receiving lenalidomide maintenance compared with patients receiving placebo, and factors predisposing to second malignancies are being evaluated. The role of bortezomib-based maintenance approaches, particularly in high-risk patients, is an area of ongoing investigation. At this point in time, whether all patients should receive maintenance therapy after ASCT is unclear, and the advantages and limitations of maintenance treatment must be compared with the benefits of therapy at first relapse. It is reasonable to consider maintenance for patients who do not achieve complete response or very good partial response with ASCT.[39]

Current treatment challenges

Drug resistance

The development of resistance after an initial response to treatment represents an important challenge in the treatment of patients with multiple myeloma. In addition, a subset of patients do not respond to initial treatment.[12] Clonal evolution has been studied extensively in multiple myeloma and contributes to the development

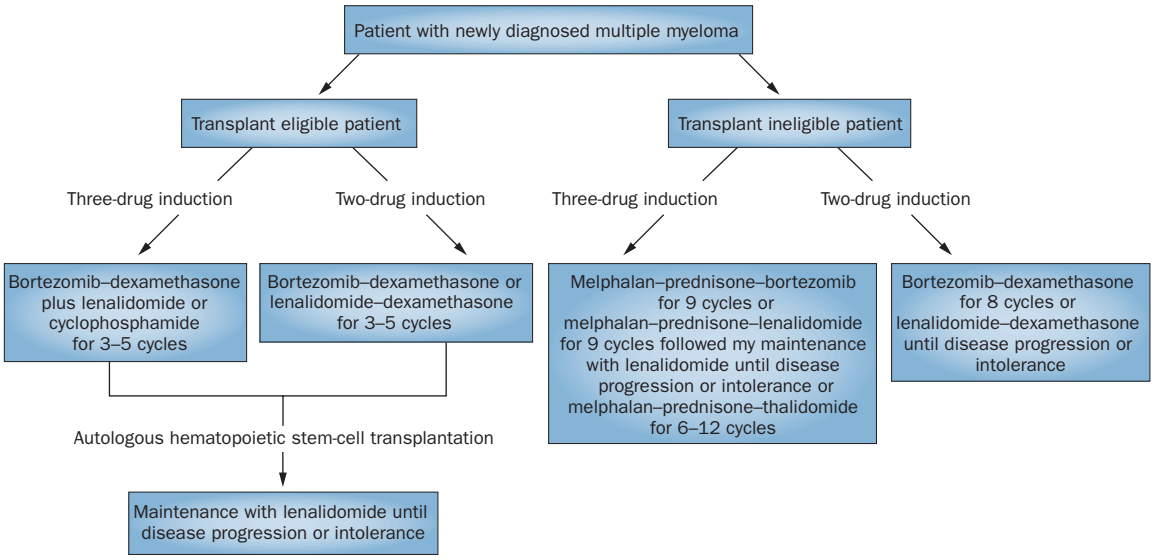

Figure 1 | Suggested approach to the treatment of patients with newly-diagnosed multiple myeloma. Several of the listed drug regimens are currently being evaluated in investigational trials. These include combination induction therapy with bortezomib and dexamethasone plus cyclophosphamide or lenalidomide, maintenance therapy with thalidomide or lenalidomide in younger patients, and melphalan–prednisone–lenalidomide followed by maintenance therapy with lenalidomide in elderly patients. If autologous hematopoietic stem-cell transplantation is delayed until the time of relapse, bortezomib-based regimens should be continued for eight cycles, whereas lenalidomide-based regimens should be continued until disease progression or the development of intolerable adverse effects. Permission obtained from Massachusetts Medical Society © Palumbo, A. & Anderson, K. Multiple myeloma. *N. Engl. J. Med.* **364**, 1046–1060 (2011).

of resistance.[40–42] Resistance mechanisms continue to be explored but are known to include hyperexpression of proteasome-related genes (for example *PSMD4*),[43] polymorphisms in the multidrug resistance-associated protein 1 and in P-glycoprotein 1,[44] and epigenetic inactivation of genes (for example, *RASD1*).[45]

Toxicity

Treatment-related toxic effects of existing agents pose another challenge. Peripheral neuropathy is observed in approximately 40% of patients who receive bortezomib (1.3 mg/m^2) twice weekly, with 14% of patients experiencing grade 3–4 neuropathy, and in approximately 25% of patients who receive the same dose once weekly, including 4% with grade 3–4 sensory neuropathy.[46] Peripheral neuropathy seems to be less frequent and less severe when bortezomib is administered subcutaneously rather than intravenously.[47] In most cases, neuropathy is reversible after discontinuation of bortezomib. Venous thromboembolism (VTE) is observed in approximately 1–5% of patients in clinical trials with single-agent thalidomide, which is similar to the background rate of such events in patients with multiple myeloma who are not treated with this agent.[48] The reported frequency of thrombotic events has been as high as 26% when thalidomide is used in combination with high-dose dexamethasone.[49] As with thalidomide, the risk of VTE among patients with multiple myeloma who take single-agent lenalidomide does not seem to be higher than that of those who do not take lenalidomide. By contrast, the use of lenalidomide in combination with high-dose glucocorticoids is associated with an at least threefold increased risk of clotting events.[17,49] Although VTE is the most-common form of thrombosis in this patient population, arterial thrombotic events have also been reported.[50] The International Myeloma Working Group panel recommends the use of aspirin in patients with one risk factor for VTE.[49] Individual risk factors for thrombosis associated with thalidomide or lenalidomide-based therapy include age, history of VTE, central venous catheter, comorbidities (infections, diabetes, cardiac disease), immobilization, surgery and inherited thrombophilia. Myeloma-related risk factors include diagnosis and hyperviscosity.[49] Low-molecular-weight heparin (equivalent to enoxaparin 40 mg per day) is recommended for patients with two or more individual or myeloma-related risk factors for VTE. Heparin is also recommended for all patients receiving thalidomide and lenalidomide in combination with high-dose dexamethasone or doxorubicin. Warfarin given to a therapeutic international normalized ratio of 2–3 is an alternative to heparin, although data in the literature about this strategy are limited.[51]

With increasing complexity of drug regimens, the question that remains to be answered is how to individualize the type and intensity of treatment. For instance, the role for ASCT as initial therapy in an era of increasingly potent targeted upfront combination therapy remains to be defined. The Intergroup Francophone du Myeloma–Dana-Farber Cancer Institute (IFM-DFCI) study of RVD with or without ASCT (NCT01208662)[52] and a trial of bortezomib–dexamethasone with or without lenalidomide (NCT00522392),[53] will help to address these questions, not only in terms of rates and depth of response,

Table 1 | Promising novel agents in clinical trials in multiple myeloma

Drug	Category	Comments
Carfilzomib MLN 9708 ONX 0912 NPI-0052	Proteasome inhibitors	Ongoing phase III trial NCT01080391[58] Oral proteasome inhibitors in phase I–II trials[62,71,72] NCT01416428[118]
Pomalidomide	Immunomodulatory drug	Ongoing phase III trial NCT01311687[119]
Perifosine	Phosphatidylinositol 3-kinase pathway inhibitor	Ongoing phase III trial NCT01002248[81]
Elotuzumab	Anti-CS-1 antibody	Ongoing phase III trials NCT01239797[120] NCT01335399[121]
ACY-1215 Panobinostat	Histone deacetylase inhibitors	Phase I NCT01323751[122] Phase III NCT01023308[123]

but also by evaluating the relative safety profile of these therapies and their effect on PFS and overall survival.

Novel therapies

Modulators of protein homeostasis

Second-generation inhibitors of the ubiquitin–proteasome cascade are now in preclinical and clinical studies. Inhibitors of de-ubiquitinating enzymes located upstream of the proteasome, such as the USP-7 inhibitor P5091, have shown activity against multiple myeloma.[54] More-potent inhibitors with chymotryptic activity (carfilzomib, ONX 0912, MLN 9708)[55,56] overcame bortezomib resistance in preclinical and early clinical trials. In phase II clinical trials, carfilzomib has achieved responses even in patients with bortezomib-refractory multiple myeloma, without causing substantial neuropathy.[57,58] Phase III clinical trials in which carfilzomib–lenalidomide–dexamethasone is compared against lenalidomide–dexamethasone in patients with relapsed multiple myeloma are ongoing (NCT01029054).[59] Both ONX 0912[55] and MLN 9708[60] are oral proteasome inhibitors that have shown promise in early phase I–II clinical trials (Table 1). A broader proteasome inhibitor, NPI-0052, targets chymotryptic, tryptic, and caspase-like activities and overcame bortezomib resistance in preclinical studies,[61] and shows early clinical promise.[62] PR-924, an inhibitor of the LMP-7 immunoproteasome subunit, also blocked growth of myeloma cells *in vitro* and *in vivo*.[63] Inhibitors of the immunoproteasome should have a favorable therapeutic index owing to the selective expression of immunoproteasome subunits in malignant, but not in normal, hematological cells.[64]

Inhibition of the proteasome upregulates aggresomal degradation of proteins, whereas blockade of aggresomal degradation with inhibitors of histone deacetylases (HDACs) induces compensatory upregulation of proteasomal activity.[65] Importantly, simultaneous inhibition of proteasomal and aggresomal protein degradation systems leads to the accumulation of polyubiquitinated proteins, followed by activation of apoptotic signaling cascades and synergistic cytotoxicity. Four classes of HDAC enzymes have been identified, and several nonspecific, pan-HDAC and class I HDAC inhibitors have been evaluated in preclinical and clinical studies. HDAC6 (a class II HDAC) has been linked to the activity of aggresomes that degrade unfolded and misfolded ubiquitinated proteins. HDAC6 inhibitors have shown promising preclinical activity.[66]

Another novel agent is MLN4924, an inhibitor of the NEDD8-activating enzyme, which targets the neddylation pathway upstream of the 20S proteasome. MLN4924, therefore, leads to molecular sequelae and has preclinical anti-myeloma activity that is distinct from that of established 20S proteasome inhibitors.[67]

Immunomodulatory agents

Pomalidomide maintains key aspects of the mechanism of action of lenalidomide, and the ability to synergize *in vitro* with proteasome inhibitors such as bortezomib.[69,70] Phase I clinical studies of pomalidomide in combination with low-dose dexamethasone showed activity in patients with multiple myeloma who were resistant to other agents, including thalidomide, lenalidomide, and bortezomib.[70] The optimal sequence of administration of next-generation proteasome inhibitors or immunomodulatory drugs is under investigation in ongoing studies (NCT01217957; NCT01415882).[71,72]

Kinase inhibitors

Abnormalities in cyclin D expression are a hallmark of myeloma cells. Consequently, inhibitors of cyclin-dependent kinases, alone or in combination with bortezomib, are now undergoing evaluation in clinical trials.[73] Inhibitors of mTOR have similarly been combined with bortezomib[74] and with lenalidomide[75] in clinical trials. In the phase I study of RAD001 with lenalidomide, stable disease or better was observed in 68% of patients (13 of 19) with grade 3–4 adverse events (≥5%) that included thrombocytopenia (11%) and neutropenia (22%).[76] In the phase II study of the temsirolimus and bortezomib combination, the proportion of patients with a partial response or better was 33% (14 of 43).[74]

Heat-shock protein 27 (HSP 27) mRNA and protein levels are increased in myeloma cells of bortezomib-refractory patients.[77] Because HSP 27 is a downstream target of p38MAPK signaling, a p38MAPK inhibitor decreased HSP 27 levels and overcame bortezomib resistance in myeloma cell-lines and cells obtained from patients with multiple myeloma.[78] Bortezomib also triggers activation of Akt, which can be blocked by the Akt inhibitor perifosine. The combination of bortezomib and perifosine overcame resistance to bortezomib in preclinical models,[79] and results of phase I–II trials with this combination therapy showed durable responses, even in the setting of bortezomib resistance. In 73 patients, this combination provided an overall response rate (ORR; defined as minimal response or better) of 41%, including an ORR of 65% in patients who relapsed following bortezomib treatment and 32% in bortezomib-refractory patients. Median PFS was 6.4 months, with a median overall survival of 25 months (22.5 months in bortezomib-refractory patients).[80]

A phase III clinical trial of bortezomib versus bortezomib with perifosine in patients with relapsed multiple myeloma is ongoing (NCT01002248).[81] Promising

data suggest that the combination of these novel agents will have a future role in the management of multiple myeloma. Other novel agents that are being translated from the bench to the bedside and tested in phase I–II clinical trials have an extended activity profile compared with currently available agents. Two examples are INK 128 and AZD 8055, which are dual inhibitors of mTORC1/2[82,83] and the composite inhibitor of mTORC1/2 and phosphoinostide 3-kinase, NVP-BEZ235.[84]

Targeting accessory cells and cytokines

Tumor-related bone disease, specifically osteolytic disease, represents a major clinical burden in many cancers, including multiple myeloma. Osteolysis is the consequence of a pathological imbalance between the activities of osteoblasts and osteoclasts in the bone-marrow niche. By targeting myeloma cells in the bone-marrow niche, bortezomib and lenalidomide also have an effect on the tumor microenvironment and stimulate formation of new bone;[85,86] while, agents targeting the multiple-myeloma bone-marrow microenvironment may also have efficacy against multiple myeloma. In the MRC Myeloma IX trial,[87] zoledronic acid was compared with clodronic acid in newly diagnosed patients with multiple myeloma who could be either suitable for ASCT or not. Zoledronic acid not only decreased the incidence of skeletal-related events, but also prolonged overall survival.[87]

Tumor necrosis factor ligand superfamily member 13B (also known as BAFF) is elevated in the bone-marrow plasma of patients with multiple myeloma and mediates osteoclastogenesis. Preclinical data showing that anti-BAFF monoclonal antibodies (mAb) can neutralize this effect and inhibit myeloma-cell growth[88] have already translated to a clinical trial, in which efficacy of these antibodies was demonstrated in relapsed patients with multiple myeloma.[89]

Myeloma cells secrete the soluble Wnt inhibitor DKK-1, which downregulates osteoblast function. In preclinical murine xenograft models of human multiple myeloma, the anti-DKK-1 mAb BHQ880 not only triggered new bone formation but also inhibited myeloma-cell growth,[90] and a clinical trial of BHQ880 is ongoing.[91]

Patients with multiple myeloma also seem to have increased levels of activin A,[92] which is involved in bone remodeling by promoting osteoclastogenesis. Myeloma-induced expression of activin A from stromal bone marrow cells downregulates gene expression of the transcription factor DLX-5 via activation of SMAD2. The physiological action of activin A can be effectively blocked by the administration of a soluble activin-A receptor. Findings from *in vivo* animal studies confirmed the anabolic effects of activin-A inhibition.[92]ACE-011 is a human fusion protein derived from the activin-receptor type IIA that binds to, and prevents signaling of, certain members of the TGF-β superfamily through the activin receptor; a clinical trial of ACE-011 in patients with multiple myeloma will begin soon.

Targeting the tyrosine protein kinase BTK has been shown to block osteoclast formation and growth, as well as myeloma-cell growth, in preclinical models,[93] and a clinical trial is planned.[94] These studies illustrate the principle that agents targeting cytokines or accessory cells in the tumor microenvironment can also impact tumor growth, further validating the utility of evaluating multiple myeloma in the context of its bone-marrow milieu.

Immune-based therapies

The emergence of therapies with mAb is a considerable advance in the field. SLAM family member 7 (also known as CS1) is a cell-surface antigen of natural killer cells that is highly and uniformly expressed at the gene and protein level in myeloma cells. Targeting this antigen with the anti-CS1 mAb elotuzumab led to the death of myeloma cells in preclinical models of multiple myeloma in the bone-marrow milieu.[95] Preliminary data indicate exciting results with the combination of elotuzumab with lenalidomide and dexamethasone.[96] Clinical trials with the mAb against CD38 antigen, which is expressed on all myeloma cells,[97] are ongoing.[98] The maytansanoid toxin that is conjugated to anti-CD138 mAbs has shown promising results *in vitro,* and xenograft models of human multiple myeloma in mice have provided the framework for a clinical trial of this immunotoxin.[99,100]

Augmenting antitumor immunotherapy of the immune system is another promising area of therapeutic development. Antibodies against killer-cell immunoglobulin-like receptors (KIRs) have been explored, with the intent of neutralizing their inhibitory effect on the function of natural killer cells and augmenting antitumor immunity.[101] Infusions of haploidentical KIR ligand-mismatched natural killer cells in the setting of ASCT,[102] dendritic-cell-based vaccines,[100] myeloma–dendritic-cell fusion vaccines, and vaccination against cancer/testis antigens expressed in myeloma cells have also been explored.[104,105]

Another promising strategy is the use of peptides for vaccination. For example, CS1, XBP-1, and CD138 are functionally important targets in myeloma cells,[106] and a clinical trial is now planned in which patients are vaccinated with pooled peptides derived from these antigens, which are predicted to be presented to the immune system and trigger immunity in patients with specific HLA types.

The existence of myeloma tumor stem cells remains controversial. Functional dependence of tumor stem-cell-like populations on signaling pathways such as the Hedgehog, Notch, and Wnt pathways has led to preclinical testing of drugs that interfere with these pathways in multiple myeloma.[107–109] Clinical activity of hedgehog inhibitors (such as GDC-0449) has been demonstrated in neoplasias (for example, basal-cell carcinoma or medulloblastoma) in which this pathway is activated by genetic mutations,[110,111] but such mutations have not yet been detected in multiple myeloma.

Role of high-throughput techniques

The use of high-throughput techniques is likely to yield further new insights into the biology of multiple myeloma. Parallel sequencing of 38 tumor genomes and comparison of these with the DNA of matched normal cells has indicated that mutations in genes involved in protein translation (seen in nearly half of the patients), histone

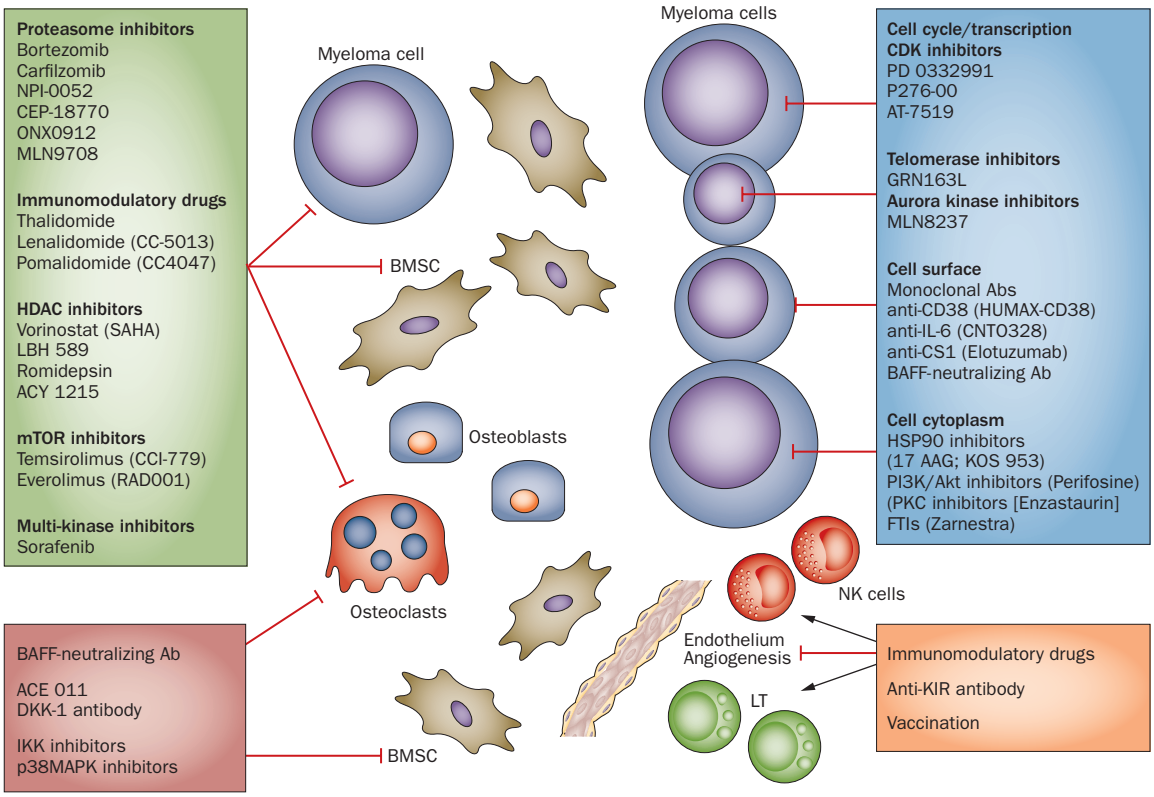

Figure 2 | Clinical trials of novel agents targeting myeloma cells and their bone-marrow microenvironment. The interaction of myeloma cells with BMSCs, as well as other components in the bone-marrow milieu (such as osteoblasts, osteoclasts, and vascular endothelial cells) is crucial for myeloma-cell pathogenesis and the development of drug resistance. Novel agents that target tumor and stromal compartments can be categorized as those that target protein dynamics (inhibitors of HSP 90 or of the ubiquitin–proteasome system), intracellular signaling kinases (inhibitors of PI3K/Akt/mTOR or MAPK pathways), the molecular machinery regulating the cell cycle (CDK inhibitors, Aurora-kinase inhibitors), membrane-bound receptors (inhibitors of CS1, CD138, among others), epigenetic modulators (inhibitors of DNA methyltransferases and HDACs), tumor vasculature and microenvironment (angiogenesis and integrin inhibitors) and agents that improve anti-MM immune responses (immunomodulatory drugs, anti-KIR antibodies, vaccination strategies). Abbreviations: BAFF, tumor necrosis factor receptor superfamily member 13C; BMSC, bone-marrow stromal cells; CDK, cyclin-dependent kinase; CS1, SLAM family member 7; DKK-1, Dickkopf-related protein 1; FTIs, farnesyl-transferase inhibitors; IKK, inhibitor of nuclear factor-κB kinase; KIR, killer immunoglobulin receptor; IL-6, interleukin 6; HDAC, histone deacetylase; HSP 90, heat-shock protein 90; LT, lymphotoxin; mTOR, mammalian target of rapamycin; NK cells, natural killer cells; PKC, protein kinase C. Adapted from *Future Oncology*, March 2010, Vol. **6**, No. 3 Pages 407–418 with permission of Future Medicine Ltd.

methylation, and blood coagulation may have relevance in multiple myeloma.[112] In addition, the important role of NF-κB signaling is evidenced by mutations in 11 proteins of the NF-κB pathway. Activating mutations of the kinase BRAF are observed in 4% of patients with multiple myeloma, suggesting the possible benefit of BRAF inhibitors in this subset of patients.[112]

Efforts are ongoing to define molecular subsets in multiple myeloma. Among the druggable targets, the t(4;14) translocation has been a particular focus. This mutation was originally associated with overexpression and additional mutations of *FGFR3*,[113,114] and mAbs against FGFR3 are now being tested in clinical trials of patients with multiple myeloma. Data also suggest a major role in the pathogenesis of the disease for the histone methyl transferase MM-SET,[115,116] which may represent a therapeutic target for patients with multiple myeloma in whom the protein is overexpressed. Functional oncogenomics that use, for example, high-throughput assays with bioluminescent tumor cells and accessory cells are now being used not only for discovery of new drug targets and validation of targeted therapies, but also to inform the design of novel, single-agent and combination therapies.[117]

Conclusions

Multiple myeloma is a heterogeneous disease without a demonstrable hallmark or fundamental aberration or lesion driving its pathogenesis. Therefore, tailoring therapies to patient subgroups or even individual patients will be necessary. Doing so successfully will require further advances in our understanding of the biology of the disease. Such advances can be achieved by the integration of a range of high-throughput techniques, including gene-expression profiling, microRNA profiling, proteomics, and DNA analyses, such as analyses of single-nucleotide polymorphisms, array comparative genomic hybridization, DNA methylation profiling, protein acetylation profiling, and whole-genome sequencing. Moreover, the molecular signature of a patient as defined

by these techniques must be obtained not only at the time of diagnosis, but also at the time of relapse in an individual patient.

Myeloma serves as a paradigm for the development of new drugs by targeting the tumor in its microenvironment, since bench-to-bedside translation of novel agents has led to multiple novel therapies and the doubling of patient survival over the past decade. Today, our goal is to provide patients with different subtypes of multiple myeloma with treatment options that will lead to improved PFS and overall survival, have favorable safety profiles and maintain quality of life, while assuring access to such therapies and containing the overall cost of care. Such progress will require innovative clinical trial designs particularly for molecularly defined patient subsets, and trials should be biomarker-driven and directed to provide proof-of-principle for a novel targeted therapeutic. Strategies for the future include the development of next-generation agents using the platform of existing agents, development of novel agents that target pathways involved in the pathogenesis of myeloma, therapies aimed at accessory cells and cytokines, and immune-based therapies (Figure 2). Targeting validated antigens in patients who are genetically defined as the ones who are most likely to respond can similarly accelerate evolution of immune-based therapies. Advances in genomics and preclinical models of multiple myeloma in its microenvironment will allow continued rapid progress towards the development of effective personalized medicine for patients with multiple myeloma.

Review criteria

A systematic literature search of the PubMed database was completed to identify all studies investigating preclinical work and clinical studies in the treatment of multiple myeloma. The following MeSH terms were used: "multiple myeloma and therapy", "multiple myeloma and antibodies", "multiple myeloma and immunotherapy", "multiple myeloma and transplantation", "multiple myeloma and treatment". Abstracts published from the annual meetings of the American Society of Hematology and ASCO in 2008, 2009, 2010 and 2011 were reviewed for the same criteria. Articles were limited to those written in English and published before 1 December 2011.

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