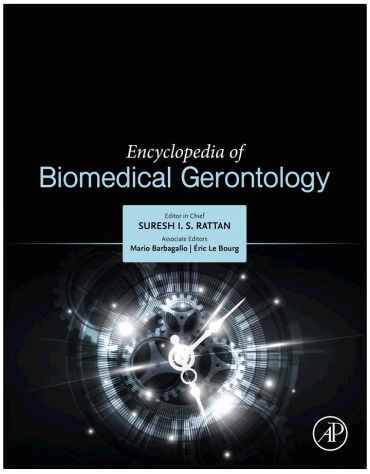

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Multiple Myeloma

Artur Jurczyszyn and Anna Suska, Department of Hematology, Jagiellonian University Medical College, Krakow, Poland

Introduction and Statistics

Multiple myeloma (MM) is a hematological malignancy characterized by clonal plasma cell proliferation accompanied by the production of monoclonal protein and signs of end-organ damage (mainly bone, blood and renal complications) (Kyle and Rajkumar, 2008). MM can be classified according to the monoclonal protein type: intact immunoglobulin MM (IIMM), light chain (kappa or lambda) MM (LCMM) and nonsecretory MM (NSMM) (**Fig. 1**).

In the United States multiple myeloma is the second most common blood malignancy after non-Hodgkin lymphoma, accounting for approximately 1.8% of all cancers and slightly more than 17% of hematologic malignancies (Noone et al., 2018). The incidence of MM increases progressively proportional to the aging of the population worldwide and increased awareness (Vélez et al., 2016). It varies from 0.4 to 5 per 100,000 individuals, with the highest rates observed in North America, Australia/New Zealand, northern Europe, and western Europe, while the lowest rate noted in Asian countries.

Multiple myeloma mainly concerns elderly patients, with slight male predominance. Typically, it is diagnosed between the ages of 65–74 years (more than 60% of all the cases), with the median age of 69 years at the time of MM diagnosis. Over 90% of MM cases refer to patients >50 years old. Only 35% of the patients are younger than 65 years at the moment of diagnosis. Individuals under 40 years of age count for up to 2% of all cases (Jurczyszyn et al., 2016). The age-adjusted incidence of multiple myeloma is 2-fold higher in African Americans than in Whites (Waxman et al., 2010). The onset of MM is earlier in Blacks. The reason for this tendency is not clear, probably genetic predisposition plays a role. Although there is an annual incidence increase at the level of 1.3% observed, the death rate decreases approximately 0.5% per year in general American population, while the mortality rate in elderly patients remains stable. The introduction of novel therapies (proteasome inhibitor- and immunomodulator-based regimens) has translated into better outcome for patients with MM, resulting in the increase of relative survival rate approximately up to 50% (**Figs. 2 and 3**).

Multiple myeloma is still a progressive and incurable disease (Rajkumar, 2016). Extending the time to progression/relapse and improvement the quality of life remain the main aims of the therapy.

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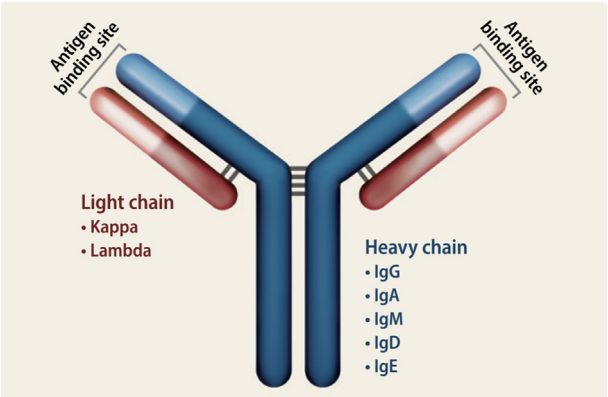


Fig. 1 Structure of a normal immunoglobulin (Ig) molecule. Each immunoglobulin molecule consists of two heavy chains and two light chains. In any Ig the two heavy chains and the two light chains are identical, creating two identical antigen-binding sites. There are five main heavy-chain types (μ, δ, γ, α, and ε) and two types of light chain (λ and κ). According to the heavy chain isotype there are five classes of Ig: IgG, IgA, IgM, IgD, IgE. In myeloma cells, mutations in the genes responsible for immunoglobulin production lead to the abnormal amino acid sequence and structure of a monoclonal protein that can be an intact immunoglobulin or its fragment. As a consequence, the normal antibody function of the immunoglobulin is lost, and the three-dimensional structure of the molecule may be abnormal. Adapted from International Myeloma Foundation: myeloma.org.

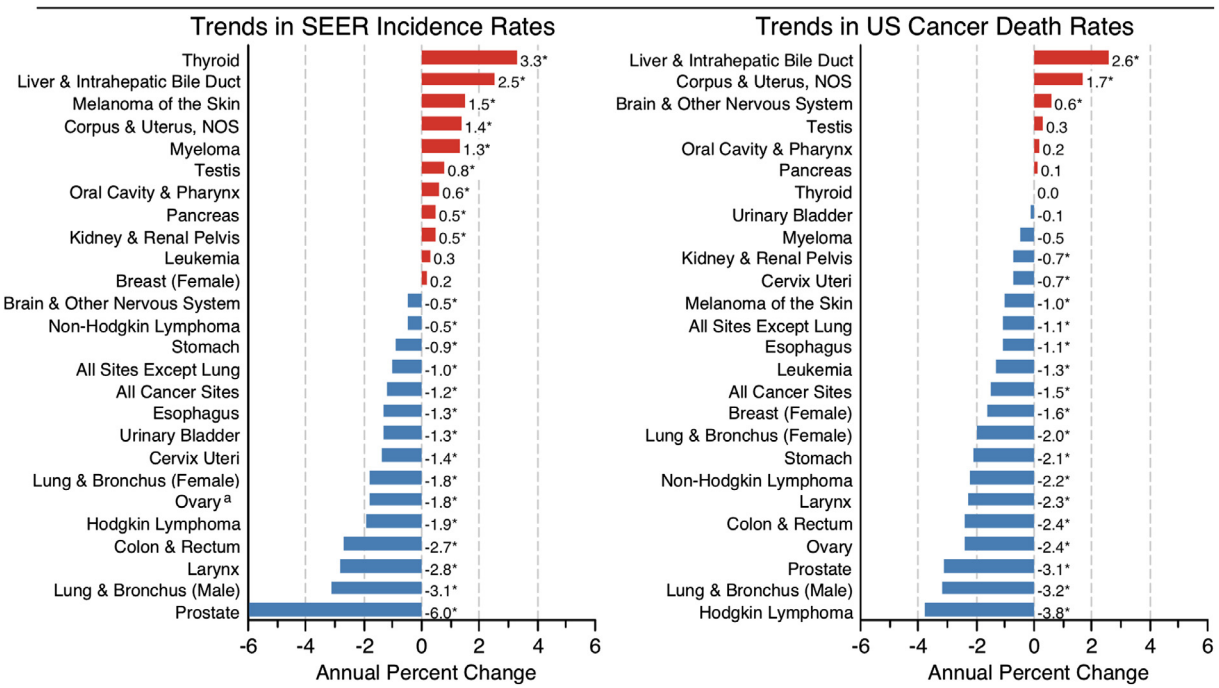


Fig. 2 Trends in incidence and death rates by primary cancer site, from 1975 to 2015. Adapted from Noone, A., Howlader, N., Krapcho, M., Miller, D., Brest, A., Yu, M., et al. (2018). *SEER Cancer Statistics Review, 1975–2015*. Bethesda, MD: National Cancer Institute. Seer [Internet]. Available from: https://seer.cancer.gov/csr/1975_2015/.

Diagnostic Criteria

According to the International Myeloma Working Group (IMWG) updated criteria (Rajkumar et al., 2014) the diagnosis of *symptomatic MM* requires the presence of clonal bone marrow plasma cells ≥10% confirmed in trephine biopsy or biopsy-proven solitary bony or extramedullary plasmacytoma and any at least one of the following myeloma defining events:

- evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically those referred as CRAB acronym:
  - C (calcium)—hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or > 2.75 mmol/L (>11 mg/dL),

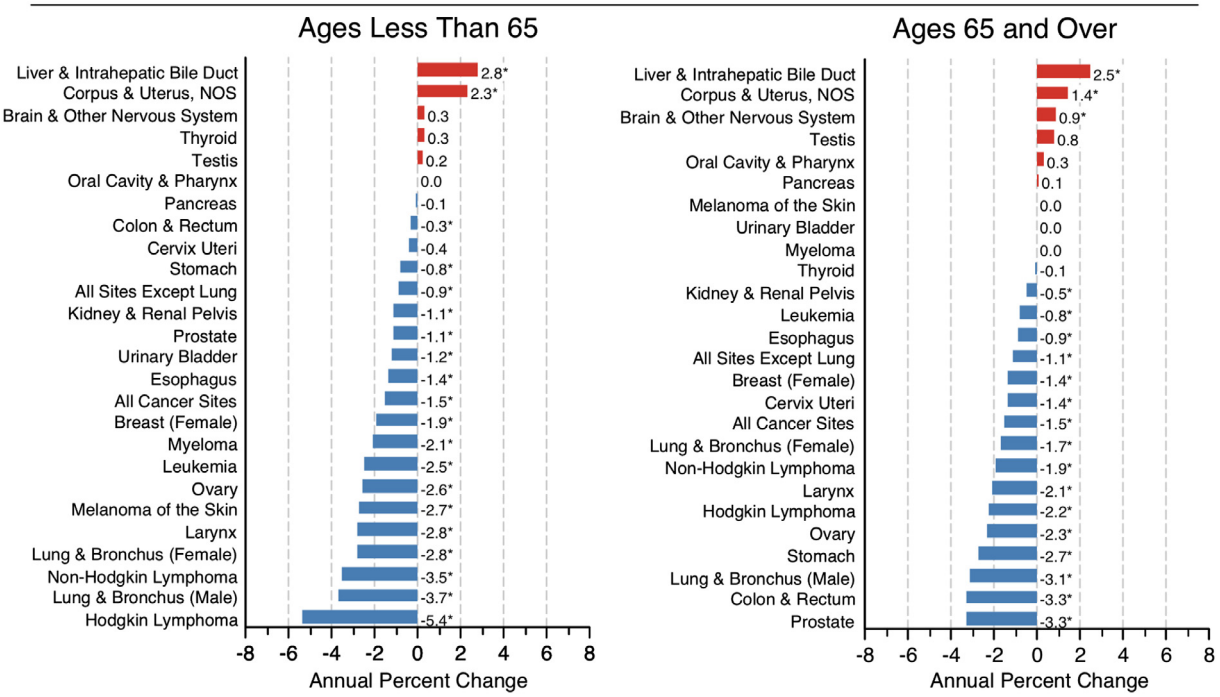


Fig. 3 Trends in death rates by age group and primary cancer site, from 1975 to 2015. Adapted from Noone, A., Howlader, N., Krapcho, M., Miller, D., Brest, A., Yu, M. et al. (2018). *SEER Cancer Statistics Review, 1975–2015*. Bethesda, MD: National Cancer Institute. Seer [Internet]. Available from: https://seer.cancer.gov/csr/1975_2015/.

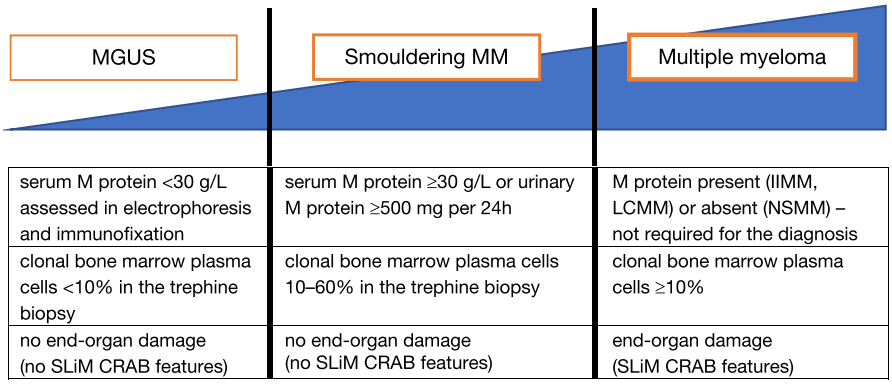
- R (renal insufficiency)—creatinine clearance <40 mL/min (measured or estimated by validated equations) or serum creatinine >177 μmol/L (>2 mg/dL),
- A (anemia)—hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L,
- B (bone lesions)—at least osteolytic lesions on skeletal radiography, computed tomography (CT), or fusion 18F-fluorodeoxyglucose positron-emission tomography—(18F-FDG PET/CT),

- any one or more of the following biomarkers of malignancy referred as SLiM acronym:
  - S (sixty)—clonal bone marrow plasma cell percentage $\geq 60\%$ with clonality established by showing kappa/lambda light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence,
  - Li (light chains)—involved to uninvolved serum free light chain ratio ≥ 100 (measured in the serum Freelite assay),
  - M (magnetic resonance)—more than one focal lesions on magnetic resonance imaging studies, each of them at least 5 mm in size.

Premalignant Stages

In most cases symptomatic multiple myeloma is preceded by premalignant stages termed *monoclonal gammopathy of undetermined significance (MGUS)* and *smouldering multiple myeloma* (SMM) (Landgren et al., 2009; Weiss et al., 2009). The diagnosis of MGUS requires the presence of monoclonal protein <30 g/L, clonal bone marrow plasma cells $<10\%$ in the trephine biopsy and the absence of hypercalcemia, renal failure, anemia, and bone lesions (all CRAB features must be absent). It accounts for over 50% of all plasma cell dyscrasia and is present in roughly 3–4% of the population over the age of 50 years (Kyle et al., 2010, 2006). The rate of progression to MM is about 0.5–1% per year (Kyle et al., 2002), with the risk influenced by some factors including the type and serum concentration of monoclonal protein and percentage of clonal bone marrow plasma cells. SMM is an intermediate clinical stage between MGUS and multiple myeloma defined as serum monoclonal protein ≥ 30 g/L or urinary monoclonal protein ≥ 500 mg per 24 h and/or clonal bone marrow plasma cells 10–60%, and as with MGUS absence of myeloma defining events mentioned above. The risk of progression to malignant disease in the first 5 years after diagnosis is much higher, at about 10% per year, with a downward trend—approximately 3% per year for the next 5 years, and 1% per year for the last 10 years (Kyle et al., 2007). The cumulative probability of progression is reported as 73% at 15 years. It is a very biologically heterogenous group, consisting of patients with a very low rate of progression comparable with MGUS, as well as patients who progress with clinical symptoms within the first 2 years of diagnosis (Landgren and Waxman, 2010) (Fig. 4).

The biologic transition from normal plasma cells to multiple myeloma precursor disease, and then to multiple myeloma consists of many overlapping oncogenic events but these events are not all present in each affected individual. The two major early events include



serum M protein <30 g/L assessed in electrophoresis and immunofixation	serum M protein ≥30 g/L or urinary M protein ≥500 mg per 24h	M protein present (IIMM, LCMM) or absent (NSMM) – not required for the diagnosis
clonal bone marrow plasma cells <10% in the trephine biopsy	clonal bone marrow plasma cells 10–60% in the trephine biopsy	clonal bone marrow plasma cells ≥10%
no end-organ damage (no SLiM CRAB features)	no end-organ damage (no SLiM CRAB features)	end-organ damage (SLiM CRAB features)

Fig. 4 Criteria for diagnosis of multiple myeloma and preceding premalignant stages. Based on Rajkumar, S.V., Dimopoulos, M.A., Palumbo, A., Blade, J., Merlini, G., Mateos, M. et al. (2014). International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncology* **15**(12), e538–e548. Elsevier Ltd; Available from: https://doi.org/10.1016/S1470-2045(14)70442-5.

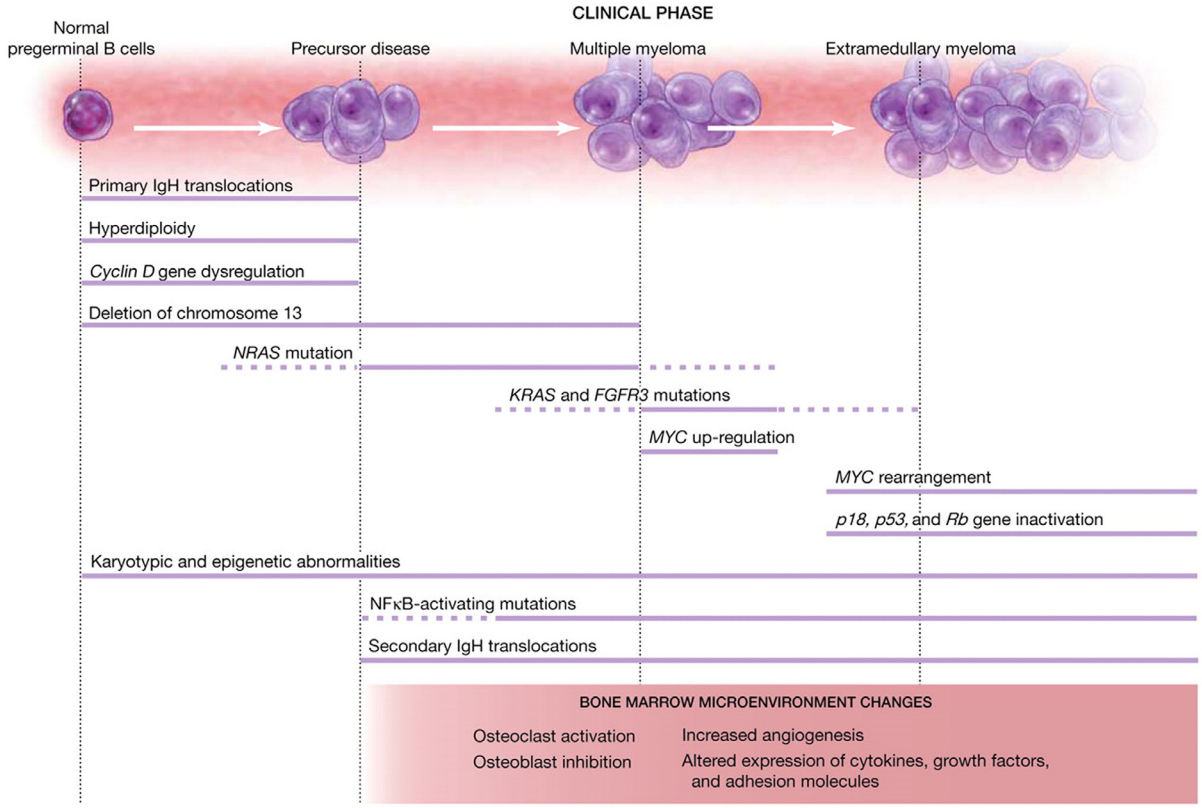


Fig. 5 Biological events related to progression to multiple myeloma. Adapted from Korde, N., Kristinsson, S.Y., Landgren, O. (2011). Monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM): Novel biological insights and development of early treatment strategies. *Blood* **117**(21), 5573–5581.

immunoglobulin heavy chain gene loci (IgH) translocations [mainly: t(4;14), t(14;16), t(6;14), t(11;14), and t(14;20)] and hyperdiploidy, although most malignant plasma cells have only one of these two genetic changes. In the subsequent stages of myelomagenesis clonal plasma cells gain further secondary translocation involving MYC, copy number variations (CNV) and somatic mutations (such as mutations in KRAS, NRAS, BRAF, P53) (Korde et al., 2011; Manier et al., 2016) that lead to disease progression (Fig. 5).

Etiopathogenesis

Etiopathogenesis of multiple myeloma is still not fully understood. MM is thought to be heterogenous multifactorial disease, encompassing a wide variety of risk factors that concern numerous life aspects (Sergentanis et al., 2017). Confirmed risk factors

include age, male sex, black race and MM among first-degree relatives. Concerning lifestyle risk factors, only obesity and overweight are associated with increased MM incidence and elevated risk for transformation of MGUS to MM, with no evidence of protective role of physical activity (Jochem et al., 2014; Wallin and Larsson, 2017). Regarding occupational exposure, there is an increased risk of MM among farmers, firefighters and hairdressers that is probably associated with the exposure to pesticides containing dichlorodiphenyltrichloroethane (DDT), phenoxyacetic acid and chlorophenols, to metal dust, aromatic hydrocarbons, aldehydes, asbestos and silica, as well as to chemicals from hair dyes, shampoos, conditioners and hair sprays (LeMasters et al., 2006; Perrotta et al., 2008; Takkouche et al., 2009). With regard to comorbidities, autoimmune diseases such as ankylosing spondylitis and pernicious anemia are associated with significantly increased MM risk (Shen et al., 2014). Interestingly, the treatment of autoimmune diseases (e.g. steroids) may also play a role in MGUS and MM pathogenesis. There is no evidence of negative impact of acute and chronic inflammatory diseases, although in these cases immune system may be deregulated (Alexander et al., 2007). Concerning medications, prior use of insulin, prednisone, and, perhaps, gout medication might promote increased occurrence of multiple myeloma. Conversely, statins, estrogen replacement therapy, and certain medical conditions might protect against multiple myeloma development (Landgren et al., 2006b). While taking into consideration family history, increased risk of MM is observed in relatives of MM patients, especially in first-degree relatives, relatives of the patient aged ≥ 65 at diagnosis, relatives of the female patient, female relatives and in African-American families (Landgren et al., 2006a; VanValkenburg et al., 2016). In summary, probably exposure to the environmental risk factors modifies the genetic predisposition to the disease development.

Staging System

The clinical outcome of antimyeloma therapy is heterogenous, with overall survival ranging from a few months up to 10 years. Therefore, IMWG created a useful tool named revised International Staging System (R-ISS) to stratify patients with newly diagnosed MM (NDMM) effectively with respect to the relative risk to their survival (Palumbo et al., 2015a). It includes the following three prognostic parameters: (1) ISS stage based on serum β2-microglobulin level (β2m) and serum albumin level, (2) chromosomal abnormalities (CA) detected by fluorescent in situ hybridization (FISH), and (3) serum lactate dehydrogenase level (LDH). Concerning CA, the presence of del(17p), translocation t(4;14), or translocation t(14;16) commonly identifies high-risk patients. The combination of ISS stage III, high-risk CA, and elevated serum LDH are associated with a significantly poorer prognosis (**Table 1**).

The R-ISS staging system has a prognostic impact when analyzed in age subgroups (patients ≤ 65 and > 65 years old) and as well as in subgroups with different treatment strategy [autologous stem-cell transplantation (ASCT) and non-ASCT]. Therefore, it is recommended to use it in clinical practice (**Table 2**).

Geriatric Assessment—Frailty Score

In newly diagnosed elderly patient geriatric assessment should be done to define the frailty profile as it predicts survival and treatment toxicities. Frailty is an increased vulnerability resulting from aging-associated loss of ability to cope with everyday or acute

Table 1 Staging system of multiple myeloma.

Prognostic factor	*Criteria*
ISS stage	
I	Serum β2-microglobulin < 3.5 mg/L, serum albumin ≥ 3.5 g/dL
II	Not ISS stage I or III
III	Serum β2-microglobulin ≥ 5.5 mg/L
CA by FISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH $<$ the upper limit of normal
High	Serum LDH $>$ the upper limit of normal
R-ISS stage—new model for risk stratification in MM	
I	ISS stage I and standard-risk CA by FISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by FISH or high LDH

Adapted from Palumbo, A., Avet-Loiseau, H., Oliva, S., Lokhorst, H.M., Goldschmidt, H., Rosinol, L. et al. (2015a). Revised international staging system for multiple myeloma: A report from international myeloma working group. *Journal of Clinical Oncology* **33**(26), 2863–2869.

Table 2 Prognostic impact of R-ISS in general population and by age groups.

	R-ISS I	*R-ISS II*	*R-ISS III*
Median progression-free survival	66 months	42 months	29 months
Median progression-free survival in patients $\leq$65 years old	70 months	47 months	34 months
Median progression-free survival in patients $>$65 years old	47 months	29 months	17 months
Median overall survival	not reached	83 months	43 months
Median overall survival in patients $\leq$65 years old	not reached	87 months	42 months
Median overall survival in patients $>$65 years old	not reached	70 months	46 months

Based on Palumbo, A., Avet-Loiseau, H., Oliva, S., Lokhorst, H.M., Goldschmidt, H., Rosinol, L. et al. (2015a). Revised international staging system for multiple myeloma: A report from international myeloma working group. *Journal of Clinical Oncology* **33**(26), 2863–2869.

stressors. However, the group of elderly MM patients is highly heterogeneous and among adults of the same age, physical and cognitive functions can be highly variable. Chronologic age, performance status, and brief physician assessment of the clinical status of the patient are not sufficient to characterize the frail population properly. Frailty score in MM proposed by IMWG is based on age, comorbidities, and cognitive and physical conditions, using in its scoring system previous three tools of geriatric assessment: the Katz Activity of Daily Living (ADL), the Lawton Instrumental Activity of Daily Living (IADL), and the Charlson Comorbidity Index (CCI). The scoring scale in each tool mentioned above is divided into subclasses with different values (0, 1 or 2). The additive total score (after summing up those values from each tool and a value of age) enables to classify the patient as fit, intermediate-fitness or frail (Palumbo et al., 2015b) (**Tables 3 and 4**).

Frail patients have increased risk of progression, non-hematologic adverse events during antimyeloma therapy, treatment discontinuation and death. Therefore, both R-ISS and frailty score should be considered in elderly patients with NDMM as a strategy of treatment outcome prediction. Although evidence-based geriatric assessment-guided treatment recommendations are still lacking, IMWG highlights that fit patients can receive full-dose, triplet therapies or even more intensive approach including auto-HSCT. Intermediate-fitness patients may benefit from doublet treatments or less intense triplets, while frail individuals should undergo a gentle, reduced-dose doublet therapy or even a palliative/supportive treatment alone.

Treatment

Primary Therapy

In most cases multiple myeloma treatment is based on systemic therapy (chemotherapy) and autologous hematopoietic stem cell transplantation (auto-HSCT). To date, the main criterion for treatment decisions is age (Cavo et al., 2011). Depending mainly on the age at the time on MM diagnosis the patient is considered as eligible or non-eligible to tolerate high-dose therapy (HDT) followed by auto-HSCT. Although there is no formal definition of young MM patient who is transplant-eligible, it is often operatively

Table 3 Geriatric assessment in multiple myeloma-scoring system.

	Age			*ADL*		*IADL*		*CCI*	
	$\leq$75	76–80	$>$80	$>$4	$\leq$4	$>$5	$\leq$5	$\leq$1	$\geq$2
Score	0	1	2	0	1	0	1	0	1

Palumbo, A., Bringhen, S., Mateos, M.V., Larocca, A., Facon, T., Kumar, S.K. et al. (2015b). Geriatric assessment predicts survival and toxicities in elderly myeloma patients: An International Myeloma Working Group report. *Blood* 125(13): 2068–2074.

Table 4 Patient status according to the additive total score.

Additive total score	*Patient status*
0	Fit
1	Intermediate-fitness
$\geq$2	Frail

Based on Palumbo, A., Bringhen, S., Mateos, M.V., Larocca, A., Facon, T., Kumar, S.K. et al. (2015b). Geriatric assessment predicts survival and toxicities in elderly myeloma patients: An International Myeloma Working Group report. *Blood* **125**(13): 2068–2074.

defined as being ≤65 years. However, IMWG highlights that age is not the only one factor taking into consideration while planning antimyeloma treatment and therefore patients who are older than 65 years may undergo auto-HSCT. Practically, in some selected individuals up to 70–75 years who are classified as fit patients, auto-HSCT still is an option and can be performed safely.

Transplant-eligible patients

When the patient is qualified as eligible for transplantation, it should be performed in the first line (up-front) treatment. Typically, prior to the transplantation procedure the patients receive a limited number of cycles of induction therapy to reduce tumor cell mass and bone marrow plasma cell infiltration before collection of peripheral blood stem cells. Nowadays, novel agents such as proteasome inhibitors (PIs) e.g. bortezomib, carfilzomib, ixazomib, and immunomodulatory derivatives (IMiDs) e.g. thalidomide, lenalidomide, pomalidomide, proven to be more effective in comparison to conventional chemotherapy used in the past, are used as in induction regimens preceding autotransplantation to enhance the depth of response before auto-HSCT and further improve outcomes after transplantation. Achievement of at least complete remission as proven to be one of the strongest predictors of long-term outcomes is the main aim of current treatment strategies. In case of failure to achieve at least very good partial response after first auto-HSCT, it is suggested to consider second ASCT (**Table 5**).

Concerning the induction regimens, it is recommended to use triplets. National Comprehensive Cancer Network (NCCN) categorized all MM treatment regimens as "*preferred*," "*other recommended*," or "*useful under certain circumstances*" (Kumar et al., 2018). In the last update to the NCCN Guidelines treatment of NDMM transplant-eligible patients, that was listed as *preferred* option include the following bortezomib-based triple-drug regimens: bortezomib/lenalidomide/ dexamethasone (VRd) and bortezomib/cyclophosphamide/dexamethasone (VCd) (**Table 6**).

In young patients with high-risk MM and poor long-term prognosis allogeneic stem cell transplantation as a frontline therapy or as a salvage treatment after the failure of the first-line chemotherapy still may be an option. However, it should be considered only when the risk of allotransplantation-related threats is lower than the risk of disease progression, even in the era of novel effective agents (Lokhorst et al., 2010).

Very fit patients aged 65–75 years may follow the same protocol like young individuals. If the patients are unsuitable for high-dose melphalan in conditioning they may undergo reduced-intensity auto-HSCT with preceding bortezomib-based induction and conditioning with melphalan in half-reduction dosage (Palumbo et al., 2014).

Table 5 IMWG uniform response criteria for multiple myeloma.

Response	*IMWG criteria*
Stringent complete remission (sCR)	CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
Complete remission (CR)	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow
Very good partial response (VGPR)	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or >90% reduction in serum M-protein plus urine M-protein level <100 mg/24 h
Partial response (PR)	>50% reduction of serum M-protein and reduction in 24 h urinary M-protein by >90% or to <200 mg/24 h; if present at baseline, a > 50% reduction in the size of soft tissue plasmacytomas is also required
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR, or progressive disease
Progressive disease (PD)	Increase of ≥25% from lowest response value in any one or more of the following: • Serum M-component and/or (the absolute increase must be ≥0.5 g/dL) • Urine M-component and/or (the absolute increase must be ≥200 mg/24 h) • Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be >10 mg/dL • Bone marrow plasma cell percentage; the absolute percentage must be ≥10% • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder
Relapse	At least one of the following is required: • Development of new soft tissue plasmacytomas or bone lesions • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion • Hypercalcemia (> 11.5 mg/dL) [2.65 mmol/L] • Decrease in hemoglobin of ≥2 g/dL [1.25 mmol/L] • Rise in serum creatinine by 2 mg/dL or more [177 mmol/L or more]

Adapted from IMWG Uniform Response Criteria for Multiple Myeloma. http://imwg.myeloma.org/international-myeloma-working-group-imwg-uniform-response-criteria-for-multiple-myeloma/.

Table 6 Primary therapy for transplant-eligible patients.

Preferred regimens
• Bortezomib/ lenalidomide/ dexamethasone
• Bortezomib/ cyclophosphamide/ dexamethasone
Other recommended regimens
• Bortezomib/ doxorubicin/ dexamethasone
• Carfilzomib/ lenalidomide/ dexamethasone
• Ixazomib/ lenalidomide/ dexamethasone
Useful in certain circumstances
• Bortezomib/ dexamethasone
• Bortezomib/ thalidomide/ dexamethasone
• Lenalidomide/ dexamethasone
• Bortezomib/ thalidomide/ dexamethasone/cisplatin/doxorubicin/cyclophosphamide/etoposide (VTD-PACE)

Adapted from Kumar, S.K., Callander, N.S., Alsina, M., Atanackovic, D., Biermann, J.S., Castillo, J. et al. (2018). Multiple Myeloma, version 3.2018: Featured updates to the NCCN guidelines. *Journal of the National Comprehensive Cancer Network* **16**(1), 11–20.

Table 7 Primary therapy for transplant-noneligible patients.

Primary therapy for transplant-non-eligible patients
Preferred regimens
• Bortezomib/lenalidomide/dexamethasone
• Lenalidomide/low-dose dexamethasone
• Bortezomib/cyclophosphamide/dexamethasone
Other recommended regimens
• Carfilzomib/lenalidomide/dexamethasone
• Carfilzomib/cyclophosphamide/dexamethasone
• Ixazomib/lenalidomide/dexamethasone
Useful in certain circumstances
• Bortezomib/dexamethasone

Adapted from Kumar, S.K., Callander, N.S., Alsina, M., Atanackovic, D., Biermann, J.S., Castillo, J., et al. (2018). Multiple Myeloma, version 3.2018: Featured updates to the NCCN guidelines. *Journal of the National Comprehensive Cancer Network* **16**(1), 11–20.

Transplant-non-eligible patients

Bortezomib/lenalidomide/low-dose dexamethasone is listed as preferred regimen for transplant-non-eligible patients, especially those who are frail or elderly with standard-risk features. For high-risk patients bortezomib/melphalan/prednisone protocol is a treatment of choice. Although triplet-drug regimens are gold standard in MM treatment, elderly or frail patients may be treated effectively with doublet regimens (e.g. lenalidomide/low-dose dexamethasone continuously until progression). Dexamethasone should be implemented in low doses as the use of high-dose dexamethasone was proven to result in higher toxicity and mortality rates, especially in patients aged ≥ 65 years (Table 7).

Maintenance Therapy

NCCN recommends lenalidomide in monotherapy as preferred maintenance regimen, stressing the need to assess the benefits of long-term use of lenalidomide in the context of potential adverse events, including severe neutropenia, risk for secondary hematological malignancies and solid tumors. Bortezomib is listed as an "other recommended" as it is well tolerated and enables to achieve higher overall response rate after auto-HSCT in transplant-eligible patients and after bortezomib-based induction in transplant-non-eligible individuals (Table 8).

Relapsed/Refractory Multiple Myeloma

The choice of treatment in the next lines, in case of refractory disease or relapse after achieving a remission, depends on the clinical context such as prior treatment and duration of response. Therapeutic options include systemic therapy with the use of traditional chemotherapeutics and novel drugs (proteasome inhibitors, immunomodulators, monoclonal antibodies),

Table 8 Maintenance therapy.

Preferred regimens
• Lenalidomide
Other recommended regimens
• Bortezomib

Kumar, S.K., Callander, N.S., Alsina, M., Atanackovic, D., Biermann, J.S., Castillo, J. et al. (2018). Multiple Myeloma, version 3.2018: Featured updates to the NCCN guidelines. *Journal of the National Comprehensive Cancer Network* 16(1), 11–20.

auto-HSCT for transplant-eligible patients who did not receive autotransplantation as part of the up-front treatment, and in patients who achieved a long remission after the first auto-HSCT, as well as experimental therapy in clinical trials. In case of late relapse (>6 months after completion of the previous therapy), patients may be retreated with the same regimen. Triplets remain gold standard, however frail elderly patients may benefit from double-regimens, with the possibility to add the third drug after the improvement of the patient's general condition. Patients with an aggressive relapse may need multidrug combinations including traditional chemotherapeutic agents as VTD-PACE (bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide).

IMWG and NCCN guidelines remain useful tools supporting therapeutic decisions, however as far as multiple myeloma is a heterogenous disease the final decision should be individually tailored to find a balance between the efficacy and toxicity of the regimens, especially in the population of elderly patients.

Difficult to Treat—Rare Conditions in the Spectrum of Multiple Myeloma

Solitary Plasmacytoma

Solitary plasmacytoma (SP) is a local mass of neoplastic monoclonal plasma cells with no or minimal (<10%) bone marrow plasmacytosis, and no sign of systemic plasma cell proliferative disorder which may present as a single bone lesion, solitary bone plasmacytoma (SBP), or as a soft tissue mass, extramedullary plasmacytoma (EMP) (Caers et al., 2018). SP is a rare condition with a cumulative incidence of 0.15/100.000, accounting for less than 5% of plasma cell malignancies. There is a twofold male predominance observed, with higher incidence in African Americans and incidence rate increasing exponentially by advancing age. Median age at the moment of SP diagnosis is 55 years (Kilciksiz et al., 2012). Diagnostic criteria of pure SP include biopsy-proven clonal plasma cell infiltration of the lesion of bone or soft tissue, no evidence of clonal plasma cells in bone marrow, normal result of skeletal survey (except for the primary solitary lesion), no additional lesions found on spine and pelvic magnetic resonance imaging (or computed tomography) and no features of end-organ damage (CRAB criteria). SBP comprises 70% of all SP cases and occurs predominantly in red marrow-containing bones (vertebrae, femurs, pelvis, ribs). EMP may develop in any tissue, but is primarily found in the head and neck region (most frequently in the sinonasal area), gastrointestinal tract and lungs. Imaging studies should include MRI to determine the extent of local disease and PET to exclude the presence of additional malignant lesions and systemic involvement. Concerning EMP, reactive processes, carcinoma and lymphoma should be considered in a differential diagnosis. Both SBP and EMP are treated locally. Fractionated radiotherapy is a cornerstone (Soutar et al., 2004). Surgery, followed by radiotherapy, should be considered in patients with pathological fractures, large, well-defined soft tissue lesions, or high risk of complications. Chemotherapy, using the same protocols as for MM, including high-dose chemotherapy followed by auto-HSCT in younger patients, is indicated in case of refractory disease and/or relapse. Patients presenting with SBP have a higher risk of developing symptomatic multiple myeloma in comparison to those diagnosed with EMP. 3-year progression rate is 10% for all SP cases, elevated in case of minimal bone marrow involvement—up to 20% in EMP and to 60% in SBP. Furthermore, it is proven that in a period of 10 years after the initial diagnosis approximately 30% of patients with EMP and 50% of patients with SBP develop MM. So far only minimal bone marrow plasmacytosis has been indicated as a prognostic factor of progression to MM. Considering the potential risk of progression to MM, local recurrence and development of new plasmacytomas, follow-ups are required (Suska et al., 2018) (**Figs. 6 and 7**).

Plasma Cell Leukemia

Plasma cell leukemia (PCL) is the most aggressive variant of the monoclonal gammopathies (Fernández De Larrea et al., 2013). It can be classified as either primary (pPCL) (accounting for 60–70% of all PCL cases) while present 'de novo' in patients with no evidence of previous MM, or secondary (sPCL) in case of leukemic transformation of relapsed/refractory multiple myeloma, with still increasing incidence observed. The diagnosis is based on the presence of more than 20% plasma cells of the total white blood cell count in peripheral blood and an absolute plasma cell count greater than 2×10^9/L (**Fig. 8**).

PCL concerns 2–4% of patients with MM. sPCL occurs in 1–2% of late-stage myeloma. As for MM, PCL is more common in African Americans than in Whites. pPCL is observed in younger patients than MM. In trephine biopsy bone marrow in extensively

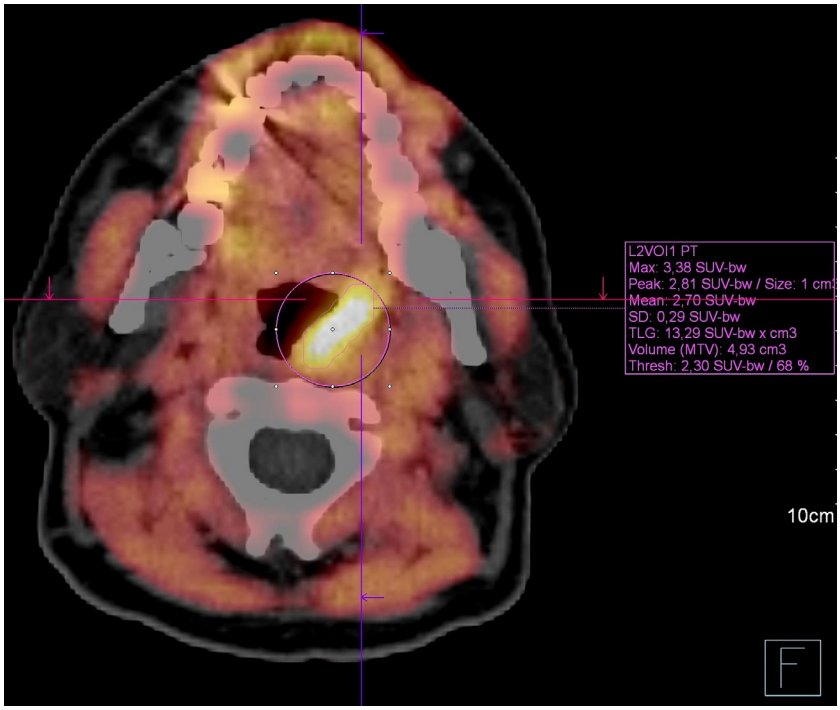


Fig. 6 18F-fluoro-ethyl-tyrosine (18F-FET) fusion positron-emission tomography (PET/CT). Solitary extramedullary plasmacytoma of palatine tonsil. Focal increase in 18F-FET uptake in the left palatine tonsil. Usually, 18F-fluorodeoxyglucose (18F-FDG) in used as a tracer in PET, however it is less specific to neoplastic cells, with highly uptake in inflammatory cells. Sinonasal region is often affected by inflammatory process, therefore in this case 18-FET was used a tracer, as it is not incorporated in inflammatory cells.

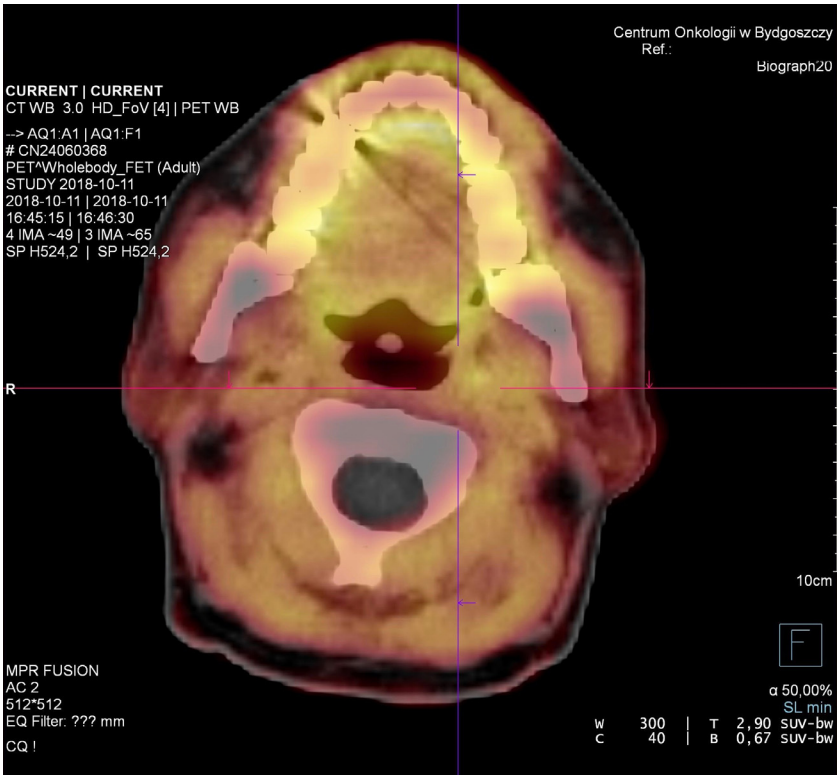


Fig. 7 18F-fluoro-ethyl-tyrosine (18F-FET) fusion positron-emission tomography (PET/CT). Posttreatment status. No focal increase in 18F-FET uptake in the left palatine tonsil.

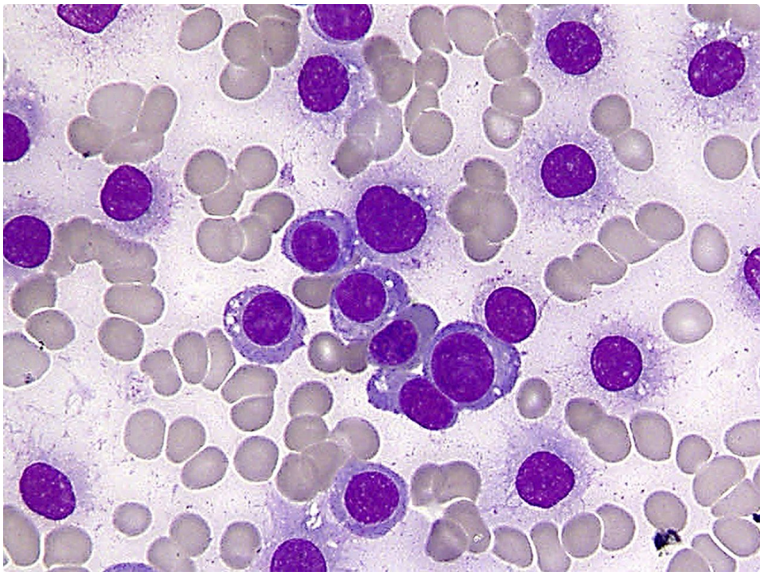


Fig. 8 Peripheral blood film: 90% plasma cells, a bluish background, rouleaux, occasional nucleated red blood, and low platelets. Adapted from Moiz, B. and Ali, S.S. (2012). Plasma cell leukemia in pregnancy. *Blood* **120**(18), 3633. Available from: http://www.bloodjournal.org/content/120/18/3633.abstract.

infiltrated by clonal plasma cells with highly pathological morphology, that results in the reduction of the space for other cell lines (red blood cells and platelets). Clinical course of PCL is very aggressive according to the high tumor burden, with profound anemia, thrombocytopenic hemorrhagic diathesis and hypercalcemia. Extramedullary involvement may present as organomegaly, predominantly hepatomegaly, splenomegaly and lymphadenopathy, and even palpable extramedullary soft-tissue plasmacytomas. Interestingly, the presence of osteolytic lesions is not so common as in MM. Age $\geq$ 60 years, platelet count $\leq 100 \times 10^9$/L and peripheral blood plasma cell count $\geq 20 \times 10^9$/L (factors of pPCL prognostic index) are independent predictors of worse survival in pPCL (Jurczyszyn et al., 2018b). Leukemic transformation of MM to sPCL is a complex, multistep process. Thus, pPCL and sPCL are two clinically and biologically different entities with the same features of high level of plasma cells circulating in the peripheral blood and poor prognosis, without significant improvement observed in MM in the past decade.

Therapy should be initiated immediately after diagnosis. The main aim of the induction is to reduce the number of neoplastic plasma cells rapidly to minimize the risks contributing to early death. Systemic therapy with chemotherapeutics and novel agents, followed by transplantation is the cornerstone. In pPCL patients $\leq$50 years old with a suitable donor, a myeloablative allogeneic transplantation can be considered. Otherwise, a tandem auto-HSCT with the following reduced-intensity conditioning allogeneic transplantation if a related or an unrelated donor is available can be considered. Transplantation should be preceded by the induction therapy with bortezomib-based regimens combined with classical chemotherapeutics including alkylating agents or anthracyclines. In transplant-non-eligible pPCL patients bortezomib-based induction regimen is the treatment of choice. Treatment of sPCL or relapsed pPCL depends on the type of and response to previous therapy. Fit patients may be qualified for intensive salvage multidrug chemotherapy and/or bortezomib-based protocols, followed by stem cell transplantation in transplant-eligible patients. In unfit patients and fit individuals but not responding to intensive chemotherapy palliative approach should be implemented. There are no specific response criteria for PCL, therefore according to the primarily leukemic nature of the disease IMWG recommends to combine in the treatment response evaluation acute leukemia and MM requirements.

sPCL is usually a terminal stage of MM with a median OS of 1–2 months (Jurczyszyn et al., 2018a). The survival of patients with pPCL is substantially better than in sPCL, with median OS of 7–12 months utilizing conventional chemotherapy. Five-year survival rate is less than 10%. Early mortality within the first months from diagnosis, reflecting the aggressiveness of the disease, is the main problem. Considering the poor outcomes observed in both groups pPCL and sPCL, novel therapy with higher efficacy is needed.

Emergencies and Supportive Care

Bone Disease

Multiple myeloma is characterized by osteolytic lesions that are detected in 70% to 80% of patients at diagnosis and increase the risk for skeletal-related events such as pathologic fractures and spinal cord compression (Terpos et al., 2013) (**Fig. 9**).

Bone disease in MM results from increased activity of osteoclasts which are responsible for bone resorption, and reduced function of osteoblasts stimulating bone formation. It is a highly disabling event that can cause pain impairing quality of life. The main

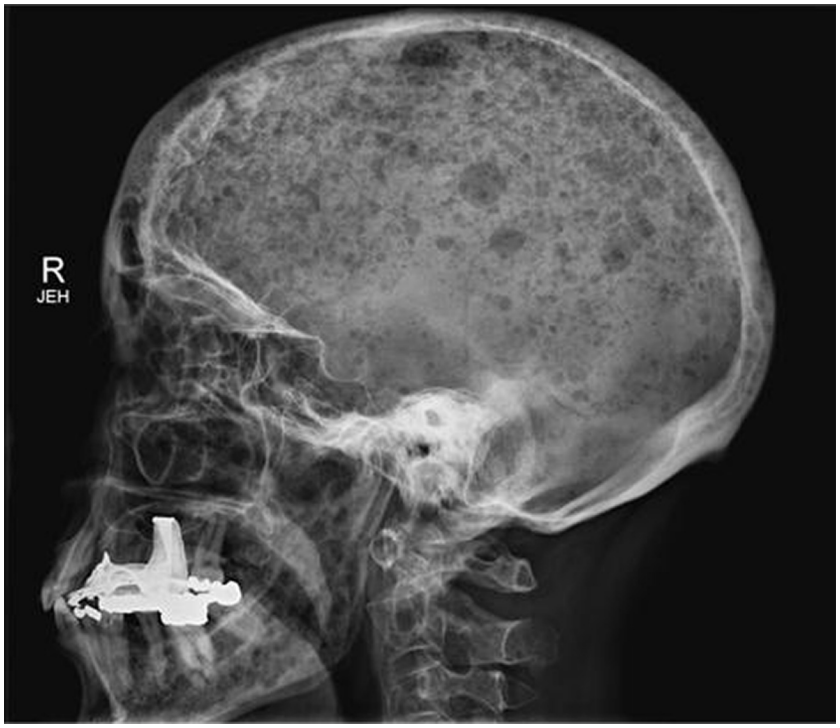


Fig. 9 Multiple small, uniform, sharply demarcated osteolytic lesions with no sclerotic margin or periosteal new bone formation involving the skull.

group of drugs used in bony disease are *bisphosphonates (BPs)* such as zoledronic acid and pamidronate, that are the inhibitors of osteoblasts-mediated bone resorption. In each patient with osteolytic bone lesions revealed on conventional skeletal survey, who is receiving antimyeloma therapy, with adequate renal function, BPs should be initiated, preferable intravenously, and at 3- to 4-week intervals. For patients with a solitary lytic lesion and no evidence of osteoporosis, BP therapy is not indicated. BPs are generally well tolerated in patients with MM. Most common adverse events associated with BP administration include: hypocalcemia and hypophosphatemia, gastrointestinal symptoms in case of oral BPs administration, and inflammatory reactions at the injection site in intravenous BPs. Renal impairment and osteonecrosis of the jaw (ONJ) are less frequent but potentially serious complications. Calcium and vitamin D3 supplementation should be used to maintain calcium homeostasis. Patients should undergo a dental check-up, accompanied by optimal everyday dental hygiene to avoid ONJ. In some cases, *orthopedic surgery* is needed. For symptomatic painful vertebral compression fractures balloon kyphoplasty is the procedure vitally improving quality of life. Radiation therapy is mainly used in solitary plasmacytoma and symptomatic spinal cord compression. As a palliative approach low-dose *radiotherapy* is indicated in uncontrolled bone pain associated with lytic lesions and as prevention from impeding pathological fractures.

Anemia

Anemia is characterized by the low hemoglobin level. It is present in approximately 75% of MM patients at the time of diagnosis. There are several factors contributing to development of anemia in MM, including bone marrow infiltration by myeloma cells with the erythropoietic line (erythrocyte precursors) displacement, deficiency of erythropoietin that normally is responsible for erythropoiesis stimulation, decreased erythrocyte precursor cells reactivity to erythropoietin, and impaired iron utilization due to increased production of hepcidin associated with chronic inflammation in the course of myeloma. It may be also a result of hematologic toxicity of the antimyeloma treatment (chemotherapy or/and radiotherapy). Anemia can be observed at any stage of MM.

Red blood cell transfusions is a standard treatment in moderate and severe symptomatic anemia, aiming to increase the hemoglobin level rapidly. The administration of erythropoiesis-stimulating agents such as erythropoietin (Epo)-α and β as well as darbepoetin, may result in the decrease in transfusion frequency and quality of life improvement. However, it can also lead to serious side-effects: thromboembolism and hypertension, therefore it has to be used with caution. Routine iron supplementation is not recommended, and administered intravenously can be effective only in absolute or functional iron deficiency.

Renal Impairment

Mild renal impairment (RI) defined as a decrease of glomerular filtration rate concerns at least 25%–50% of MM patients during the course of the disease. The pathophysiology of RI in MM is very complex (Dimopoulos et al., 2016). The main underlying

mechanism is cast nephropathy which results from the high serum concentration of immunoglobulin free light chains. Because of its excessive amount, absorption mechanisms of this kind of monoclonal protein in the proximal tubule are overwhelmed. As a consequence, FLCs can cause direct injury to proximal tubular cells through the induction of pro-inflammatory cytokine production and other pathways leading to tubular cell death. The excessive light chains reach the distal tubules, where they form tubular casts with Tamm-Horsfall protein (THP) (physiologically secreted into the urine by epithelial cells of the nephron), subsequently leading to tubular obstruction, tubular atrophy and tubular-intestinal fibrosis (Figs. 10 and 11).

In addition to this, other factors as hypercalcemia (defined as high calcium level in the blood serum), hyperuricemia (abnormally high level of uric acid in the blood), urinary tract infections, dehydration, and amyloid light chain (AL) amyloidosis (a condition characterized by the deposition in the glomeruli of fibril-forming free light chains) may also contribute to the deterioration of kidney function. Finally, therapy-driven nephrotoxicity may occur as contrast-induced nephropathy (following intravenous iodinated contrast administration in imaging techniques) or acute kidney impairment caused by the use of nephrotoxic drugs such as nonsteroidal anti-inflammatory drugs, loop diuretics and antibiotics of the aminoglycoside group.

MM patients with RI at presentation should be considered a medical emergency. Antimyeloma treatment should be initiated immediately. Bortezomib-based regimens plus high-dose dexamethasone are the first choice, as far as bortezomib is proven to be safe and effective in MM patients with RI. In case of contraindications to use bortezomib, immunomodulatory derivatives such as thalidomide and lenalidomide should be considered, with adequate dose adjustment according to renal function. It

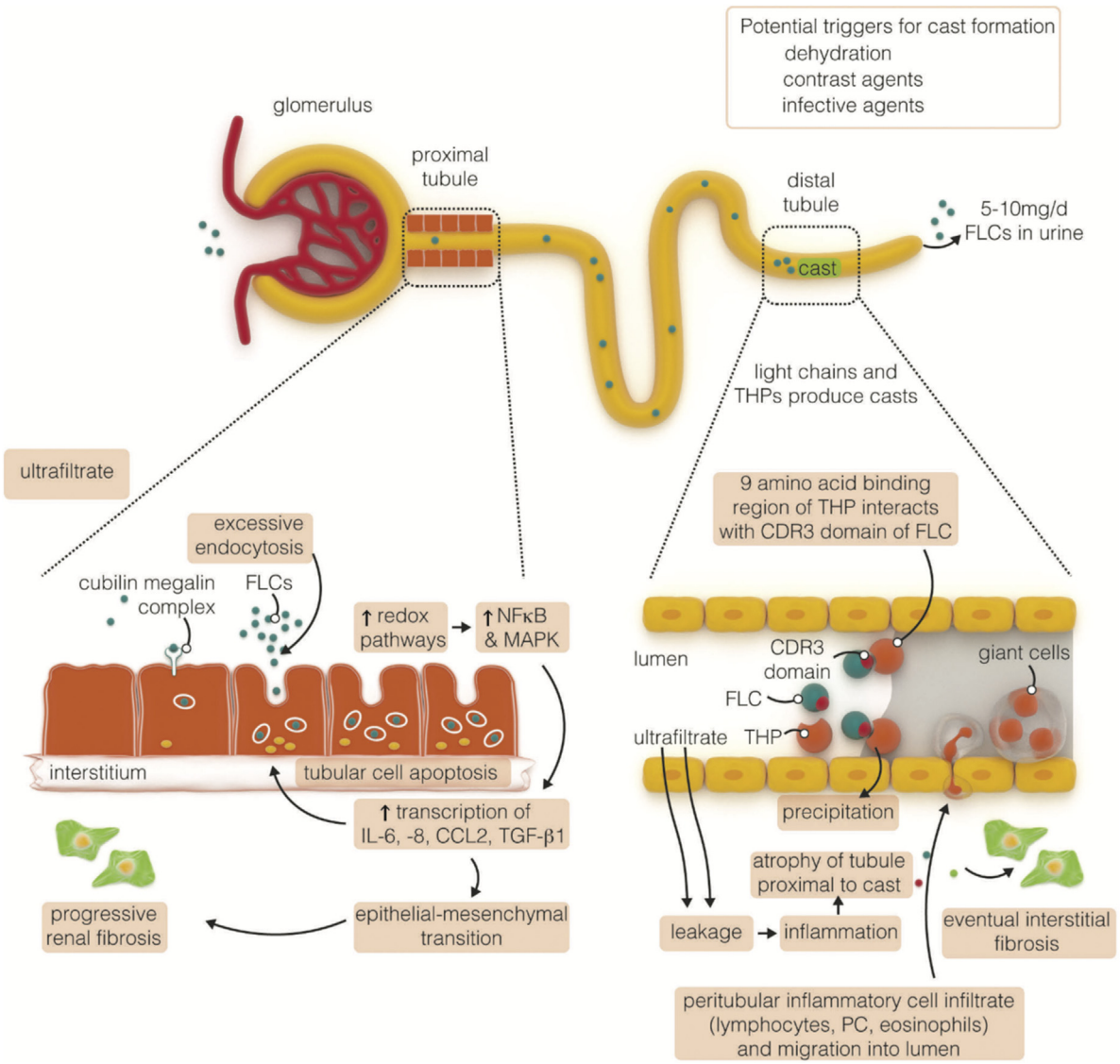


Fig. 10 Mechanisms of FLC-induced acute kidney injury. Adapted from Terpos, E., Kleber, M., Engelhardt, M., Zweegman, S., Gay, F., Kastritis, E. et al. (2015). European myeloma network guidelines for the management of multiple myeloma-related complications. *Haematologica* **100**(10), 1254–1266.

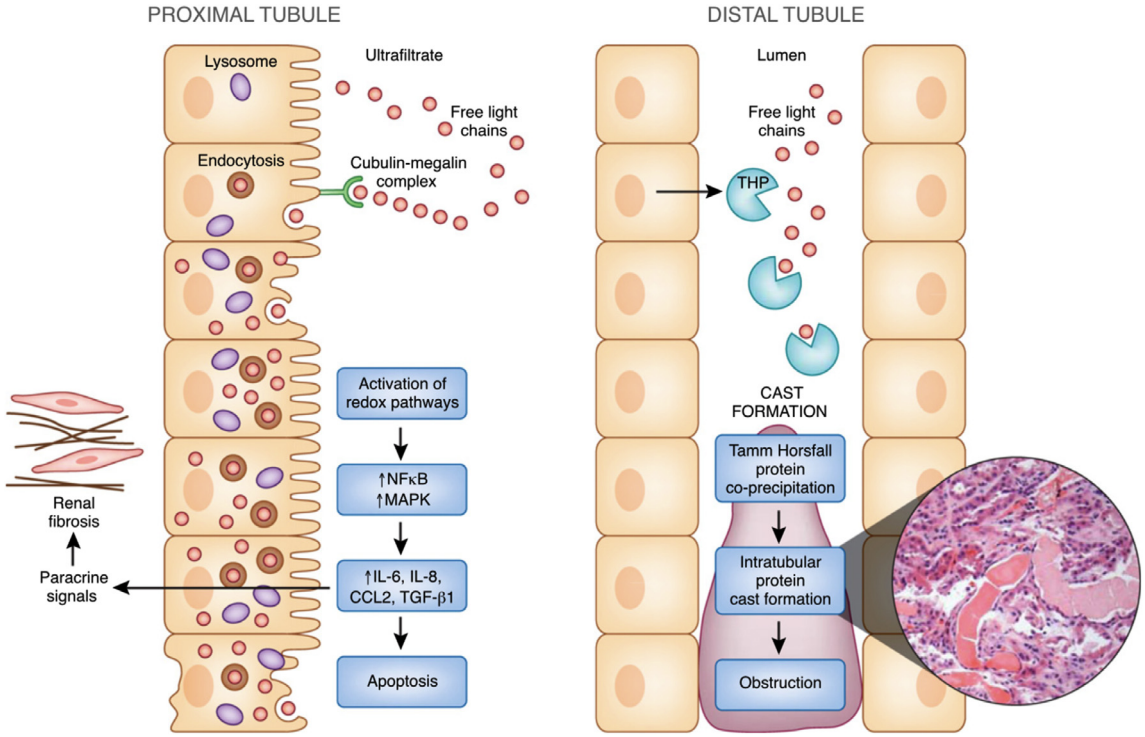


Fig. 11 Mechanism of cast nephropathy. Adapted from Lam, A.Q., Humphreys, B.D. (2012). Onco-nephrology: AKI in the cancer patient. *Clinical Journal of the American Society of Nephrology* **7**(10), 1692–1700.

must be emphasized that high-dose chemotherapy with auto-HSCT may be performed even in patients requiring dialysis (there are no contraindications), however the patient should be aware of a higher toxicity of this procedure due to the kidney failure. Additionally, supportive care is of key importance. A proper management include adequate hydration, urine alkalinization, and treatment off hypercalcemia. It is crucial to treat urinary tract infection early and effectively, and to avoid nephrotoxic agents listed previously. Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB), also known as angiotensin II receptor antagonists, used in hypertension and heart failure, should be administrated with caution as they act on the arterioles of glomeruli.

Peripheral Neuropathy

Peripheral neuropathy (PN) in multiple myeloma can be caused by the disease itself or by certain therapies, including thalidomide- and bortezomib-based regimens. It is found in up to 20% of MM patients at the time of diagnosis, and up to 75% may experience treatment-emergent neuropathy. MM-associated PN, in most cases mild intensity, is primarily sensory or both sensori-motor. It may result either from the presence of a monoclonal protein itself, or osteolytic lesions, pathological fractures, leading to the compressions of the spinal cord or spinal nerves. The main symptoms include paresthesia, numbness, burning sensation and weakness, and occur predominantly symmetric. In contrast, treatment-induced PN is usually symmetric and distal, with some differences in details depending on the treatment regimes. PN from thalidomide is dose-dependent and often permanent, and may occur even after treatment cessation. Its mechanism may be related to the inhibition of the NF-κB signaling pathway, which leads to increased programmed cell death. Bortezomib-induced PN is related to dose, schedule and mode of administration (intravenous vs subcutaneous), with symptoms progressing proximally, however, in most cases it is reversible. Probably, it results from mitochondrial dysfunction (cell energy centers) (Fig. 12).

Risk factors for the development of neuropathy include: diabetes mellitus, overweight, alcohol abuse, previous chemotherapy (such as vincristine, cisplatin), vitamin D deficiency, viral infections, as well as polymorphisms of some genes, e.g. inflammatory proteins genes or neuronal regulation genes.

In the treatment-related PN prophylaxis is of key importance. Subcutaneous (rather than intravenous) and weekly (instead of twice a week) bortezomib application significantly reduce peripheral neuropathy, without affecting the final therapy outcome. Potential treatment-emergent PN prophylaxis may also include: magnesium and vitamin supplementation, especially multi-B complex with B1, B6 and B12, folic acid and vitamin E, amino acid supplements, fish oils, omega-3 fatty acids. All MM patients with treatment protocols based on the potentially neurotoxic drugs should be routinely monitored for signs of PN with validated tools. Early reduction or temporary discontinuation of the neurotoxic drug should be adopted, as a gold standard of care.

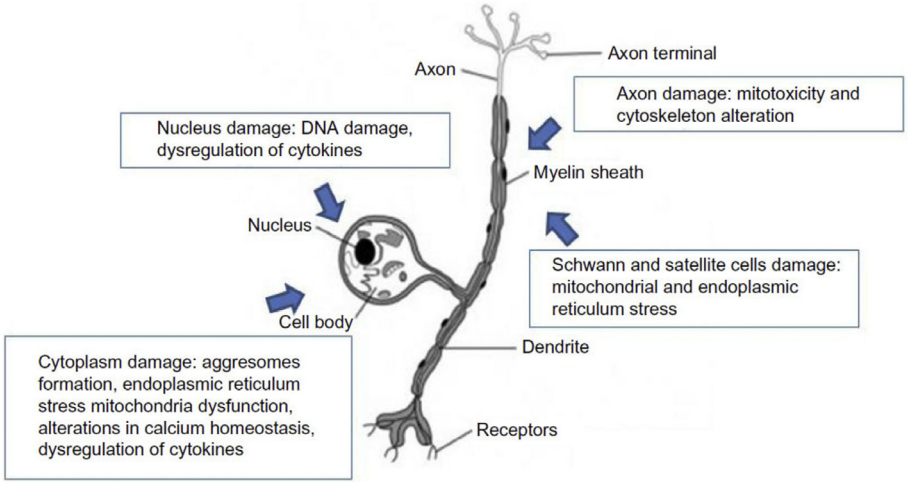


Fig. 12 Principal mechanism of neuronal damaged induced by bortezomib. Adapted from Grammatico, S., Cesini, L., Petrucci, M.T. (2016). Managing treatment-related peripheral neuropathy in patients with multiple myeloma. *Blood and Lymphatic Cancer: Targets and Therapy* **6**, 37–47.

Co-analgesics (which are not typical painkillers, but under certain conditions may present analgesic effects or enhance the effect of analgesics) including gabapentin, pregabalin, amitriptyline and duloxetine are indicated as a treatment of neuropathic pain. Additionally, neuro-rehabilitation through physical and occupational therapy might be considered (Richardson et al., 2011).

Venous Thromboembolism

There is an increase incidence of venous thromboembolism (VTE) in MM patients, approximately 8-22/1000 person years. Risk factors are related to the disease itself, patient status and implemented antimyeloma treatment.

Patient-related risk factors include:

- advanced age,
- VTE in the past medical history,
- inherited thrombophilia,
- obesity (Body Mass Index ≥ 30),
- central venous catheter in situ,
- immobility,
- paraplegia,
- dehydration,
- comorbidities (cardiac, diabetes, RI, chronic inflammatory disease, concomitant presence of myeloproliferative disorders),
- infections,
- surgery (within 6 weeks).

Myeloma-related factors include:

- hyperviscosity syndrome,
- disease burden,
- renal impairment in the course of the disease,
- hypercoagulability status induced by inflammatory cytokines.

Treatment-related factors include:

- the use of immunomodulatory derivatives: thalidomide-, lenalidomide- and pomalidomide- based regimens, particularly when combined with high-dose steroids or doxorubicin
- multiagent chemotherapy,
- concomitant use of erythropoietin.

The type of the frontline therapy matters. The incidence of VTE during upfront ranges from 1% to 2% with conventional therapies such as melphalan and prednisone, and it is doubled by the initiation of conventional chemotherapy e.g. with doxorubicin, while the use of immunomodulatory derivatives in combination with dexamethasone or chemotherapeutic agents increases the risk of up to 70% in case of no anticoagulation, and is the highest he first 4 months of therapy.

Each MM patient required thromboprophylaxis. In patients who have no or the only one risk factor for VTE listed above aspirin is considered an adequate and sufficient anticoagulation therapy. In individuals with at least two risk factors low molecular weight

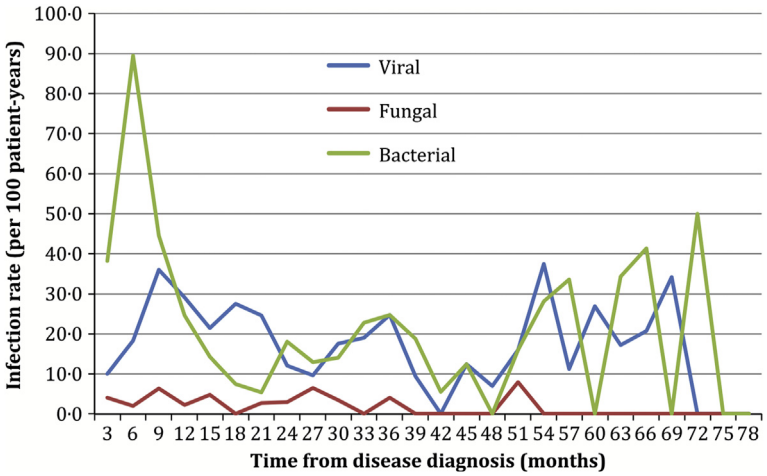


Fig. 13 Incidence rates of microbiologically defined infections in patients with multiple myeloma following disease diagnosis. Adapted from Teh, B.W., Harrison, S.J., Worth, L.J., Spelman, T., Thursky, K.A., Slavin, M.A. (2015). Risks, severity and timing of infections in patients with multiple myeloma: A longitudinal cohort study in the era of immunomodulatory drug therapy. *British Journal of Haematology* **171**(1), 100–108.

heparin (LMWH) with the prophylactic dose adjusted according to renal function, administrated subcutaneously or full-dose warfarin (vitamin K antagonist oral anticoagulant) can be used. It should be continued for at least first 4 months, until disease control is achieved or as long as the risk of thromboembolism remains high, then switch to aspirin prophylaxis is possible. In case of VTE development, antimyeloma treatment should be discontinued, and they full anticoagulation therapy should be implemented. Taking oral anticoagulants, which are vitamin K antagonists, requires systematic monitoring of INR, a normalized prothrombin time (international normalized ratio), being one of the blood coagulation parameters, to keep this value in proper ranges. Of note, INR value may vary depending on the content of foods high in vitamin K. To date, novel non-vitamin K antagonist oral anticoagulants (NOAC) such as rivaroxaban, apixaban, dabigatran, are not recommended in MM.

Infections

Infections are the main cause of death in MM patients. The risk of a bacterial infection is 7-fold higher and for viral infections 10-fold higher in MM patients compared to healthy individuals of the same sex and age. The increased risk of infection in MM results from the nature of the disease itself (dysregulation of the immune system), implemented therapy (melphalan in high dose, multidrug chemotherapy, cumulative dose of steroids), disease-related complications such as end-organ damage in active disease (especially renal failure) and age-related conditions, including frailty status as well as physical dysfunction (immobilization).

Haemophilus influenzae, *Streptococcus pneumoniae*, Gram negative *Bacilli*, influenza virus and herpes zoster virus are the most frequent pathogens. There are two main peaks of the bacterial infection incidence rate—first, the highest, at 4–6 months following disease diagnosis, and a smaller one at 70–72 months from diagnosis. Equally, the incidence rate of viral infection had a bimodal distribution with peaks at 7–9 months and 52–54 months following disease diagnosis (Fig. 13).

In terms of prophylaxis, vaccination against influenza virus is recommended for both patients and their contacts. Moreover, vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* is recommended, but with unclear efficacy due to impaired immune response observed in MM. Live vaccines are contraindicated. Antiviral prophylaxis is mandatory in patients receiving proteasome inhibitors, even at least 6 weeks after treatment discontinuation, and during transplantation procedure. Because of increased infection rate reported during lenalidomide- and pomalidomide-based protocols, it is also recommended to administer antibiotic prophylaxis at least for the first 3 months of the therapy, following local institutional guidelines. Routinely, prophylactic immunoglobulin replacement is not recommended, but it can be useful under certain circumstances in patients with severe recurrent bacterial infections and hypogammaglobulinemia (reduced gamma globulin fraction, which include antibodies responsible for the defense against pathogens).

New Developments

Investigators are now turning to immunotherapy in clinical trials for multiple myeloma. There are a lot of innovative approaches such as CAR-T cells [a type of white blood cells—T cells, with engineered chimeric antigen receptor (CAR)] and bispecific antibodies which are engineered to simultaneously target and bind to two different antigens, including Bispecific T Cell Engagers (BiTEs) designed to help engage T cells to target and destroy malignant cells. To date, encouraging results have been observed in targeting cluster of differentiation (CD)19 and B cell maturation antigen (BCMA) (Berahovich et al., 2018). Using CAR-T against a surface antigen on myeloma cells seems to mediate efficient tumor cell death even in heavily pretreated patients, however only in

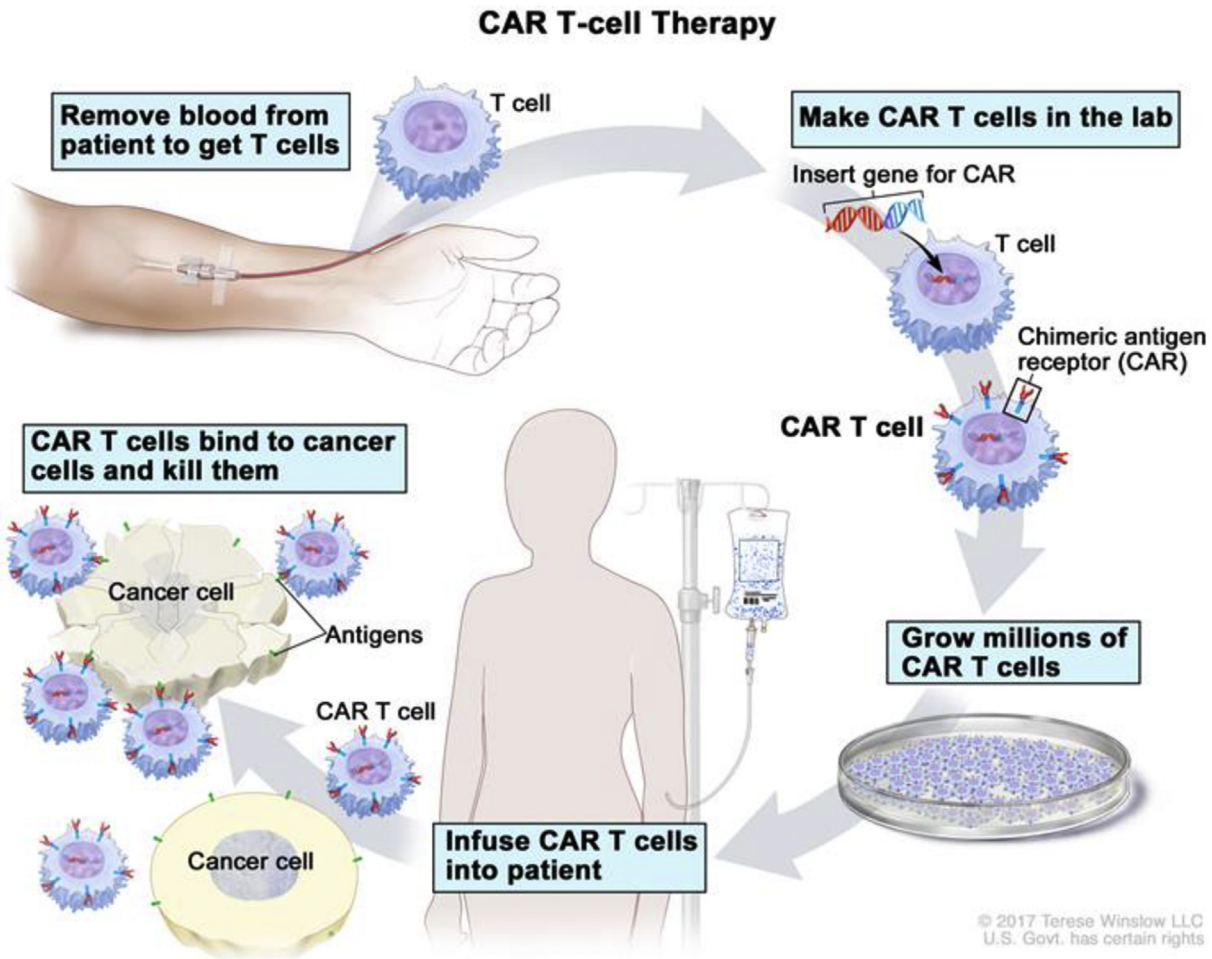


Fig. 14 The process of CAR-T cell development. Adapted from National Cancer Institute. www.cancer.gov.

a proportion of them. Moreover, the responses are short because of the lack of CAR-T cells persistence and the tumor immune escape with loss of CD19 and BCMA are observed. There are still too many question marks, therefore this interesting therapeutic modality should be used only in the context of clinical trials (Fig. 14).

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