Multiple Myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up - Supplementary Material

MANAGEMENT OF FRAIL ELDERLY PATIENTS

It is important to realise that one third of patients are >75 years at diagnosis and at least 30% are frail, as defined by the International Myeloma Working Group Frailty Index (IMWG-FI). The IMWG-FI, based on age, (instrumental) activities of daily living and co-morbidities, identifies intermediate and frail patients with inferior overall survival (OS) and progression-free survival (PFS) as compared with fit patients due to an increased incidence of grade III-IV non-haematological toxicity and discontinuation rate [1]. The outcome of frailty-adapted clinical trials, which would enable to direct therapy, is currently lacking. However, a recent trial in unfit patients showed an improved outcome when the dose of dexamethasone was modified following 9 induction cycles of lenalidomide and dexamethasone (Rd) [2]. Until more trials are available to guide treatment, several expert-opinion dose modification guidelines are available (see Supplementary Table S5).

NOVEL IMMUNOTHERAPIES FOR MYELOMA

At the American Society of Clinical Oncology (ASCO) and European Hematology Association (EHA) 2020 meetings, results from a phase II trial with idecabtagene vicleucel (Ide-cel; bb2121) including 128 patients infused with 150-450 × 10^6 chimeric antigen receptor-positive (CAR+) T cells (target dose range) showed 73% overall response rate (ORR) and 31% complete response (CR); ORR and CR increased to 82% and 35% with the target dose level of 450 x 10^6 CAR+ T cells (54 patients). The median PFS (mPFS) was 8.6 months and increased to 11.3 months in patients receiving 450 x 10^6 CAR+ T cells. Among patients achieving CR, median PFS was 20.2 months [3]. In addition, preliminary results of another CAR T trial (CARTITUDE-1) with 29 treated patients have been reported: 86% achieved a CR and the mPFS has not been reached with a median follow-up of 9 months [4]. Regarding 2+1 T-cell engagers, data with CC-93269, that binds bivalently to B-cell maturation antigen (BCMA) and monovalently to CD3ε, showed 43% ORR (dose 0.15-10 mg) and

89% ORR with 44% CR with the dose of 10 mg [5]. With teclistamab (a BCMA-bispecific antibody, the ORR at the highest dose was 67%, with 25% CR [6].

SUPPORTIVE CARE

Bone disease

Osteolytic bone disease is the most common complication of multiple myeloma (MM). All myeloma patients with osteolytic disease at diagnosis should be treated with antiresorptive agents, i.e. zoledronic acid [I, A] or denosumab [I, A], in addition to specific anti-myeloma therapy [7, 8]. In the largest placebo-controlled trial for myeloma patients to date, denosumab was compared with zoledronic acid. Although there was no difference regarding time to first skeletal-related event (SRE), a landmark analysis at 15 months showed a superiority of denosumab in terms of time to SREs. Furthermore, denosumab showed a better renal safety profile along with an advantage in PFS, mainly for patients who received an autologous stem cell transplantation (ASCT) [7].

Patients without bone disease, assessed by conventional radiography, should also receive bone-targeted agents, but their advantage is not clear for patients with no bone involvement on whole-body low-dose computed tomography (WBLD-CT) or positron emission tomography-computed tomography (PET-CT). In smouldering MM (SMM), bisphosphonates or denosumab are not recommended; in case of osteoporosis in monoclonal gammopathy of undetermined significance (MGUS) or SMM, antiresorptive agents have to be used according to osteoporosis guidelines [8-10].

Zoledronic acid should be given for more than two years only in patients who have not achieved a partial response (PR) after initial therapy. For patients who have achieved CR or very good partial response (VGPR), 12-24 months of therapy with zoledronic acid is adequate [8, 11]. At relapse, zoledronic acid has to be reinitiated [8, 9]. In cases of osteonecrosis of the jaw (ONJ), bisphosphonates or denosumab should be discontinued and may be re-administered if ONJ has healed (panel consensus) [9]. In patients with creatinine clearance (CrCl) <30 ml/min, bisphosphonates are not

recommended [8]. Denosumab is a reasonable approach for these patients as it is not cleared through the kidneys, although there are limited data in myeloma patients with CrCl <30 ml/min. Denosumab should be given continuously. Discontinuation of denosumab is challenging as there are no data on how to stop denosumab in myeloma patients; until these data are available, discontinuation of denosumab has to be followed by a dose of zoledronic acid, 6-9 months after the last denosumab dose for prevention of any rebound phenomenon [10]. Denosumab may be given in zoledronic acid failures but the efficacy data in this setting is very limited. For both bisphosphonates and denosumab administration, vitamin D and calcium supplementation is mandatory [8, 10].

Low-dose radiotherapy (up to 30 Gy) can be used as palliative treatment for uncontrolled pain, for impending pathological fracture or impending spinal cord compression [II, A] [8]. Balloon kyphoplasty should be considered for symptomatic vertebral compression fractures with refractory pain [II, B] [8, 12]. Surgery is recommended for long-bone fractures, bony compression of the spinal cord or vertebral column instability [8].

Anaemia and bone marrow failure

Recombinant human erythropoietin and darbepoetin alfa can be used for the treatment of myeloma-associated anaemia (haemoglobin level <10 g/dL), if other causes of anaemia have been excluded. The target is to maintain haemoglobin levels below 12 g/dL to avoid thromboembolic complications and hypertension [II, B]. Treatment with granulocyte colony-stimulating factor (G-CSF) may be required to treat chemotherapy-induced severe neutropaenia [13].

Infections

Infectious episodes require immediate therapy with broad spectrum antibiotics. Addition of prophylactic levofloxacin to active myeloma treatment during the first 12 weeks of therapy reduces febrile episodes and deaths (due to other causes, not due to infections) compared with placebo, without increasing antibiotic-resistant infections [14]. Therefore, levofloxacin prophylaxis of infection is recommended for the first 3 months of initiation of therapy, especially in patients receiving lenalidomide or pomalidomide, or in patients at high risk of infections (previous serious infections or

neutropaenia) [I, A]. *Influenza*, *Varicella zoster* and pneumococcal vaccinations are recommended (panel consensus), while acyclovir or valacyclovir for *Herpes zoster* virus prophylaxis is recommended for patients receiving proteasome inhibitor (PI)-based and daratumumab-based therapies [13]. Intravenous immunoglobulin G (IgG) prophylaxis is not routinely recommended; it can be used in patients with low IgG levels (<400-500 mg) and at least two severe infections needing hospitalisation during the last year (panel consensus]).

Renal impairment

Renal impairment (RI) is a common complication of myeloma present in up to 20% of patients at diagnosis [15]. Bortezomib-based regimens remain the cornerstone of the management of myeloma-related RI [I, B]. High-dose dexamethasone should be administered at least for the first month of therapy [II, B] [15]. In patients eligible for ASCT, bortezomib could be given in combination with thalidomide and dexamethasone [II, B] [16]. In patients who are ineligible for ASCT, bortezomib, melphalan and prednisone (VMP) can also be given [I, A] but no data exist for this regimen in dialysis patients [17]. Thalidomide is effective in myeloma patients with RI and can be given without dose modifications [II, B]. Lenalidomide is also effective and safe in patients with mild to moderate RI [II, B]. It should be administered with dose adjustments according to CrCl [18]. High-dose therapy (HDT)/ASCT is feasible in myeloma patients with RI; the dose of melphalan should be restricted to 100-140 mg/m^2 [III, C] [15]. Pomalidomide can be given at standard dose in patients with severe RI [II, B] [19]. Carfilzomib is another option for patients with relapsed/refractory MM (RRMM) and CrCl >15 ml/min [II, B] [20]. Ixazomib, lenalidomide and dexamethasone (IRd) can be safely administered in RRMM patients with CrCl ≥30 ml/min [I, A] [21]. Finally, daratumumab may be also given to patients with severe RI [III, C] [22].

All supportive care recommendations are summarised in Supplementary Table S6.

Supplementary Table S1. Diagnostic criteria for plasma cell disorders [23]

Plasma cell disorder	Definition
SMM	Both criteria must be met: • Serum monoclonal protein (IgG or IgA) ≥30g/l or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10%-60% • Absence of myeloma-defining events or amyloidosis
MM	Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma and any one or more of the following myeloma-defining events: • Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically: - Hypercalcaemia: serum calcium >0.25 mmol/l (>1 mg/dl) higher than the upper limit of normal of >2.75 mmol/L (>11 mg/dl) - Renal insufficiency: creatinine clearance <40 ml per min or serum creatinine >177 μmol/l (>2 mg/dl) - Anaemia: haemoglobin value of >20 g/l below the lower limit of normal, or a haemoglobin value <100 g/l - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT or PET-CT • Any one or more of the following biomarkers of malignancy: - ≥60% clonal bone marrow plasma cells - Involved/uninvolved serum-free light chain ratio ≥100 - ≥1 focal lesion on MRI studies (each focal lesion must be 5 mm or more in size)

CT, computed tomography; Ig, immunoglobulin; MM, multiple myeloma; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography; SMM, smouldering multiple myeloma.

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Supplementary Table S2. Myeloma staging: revised ISS [24]

Prognostic Factor	Criteria
ISS stage	
I	Serum β2m <3.5 mg/l, serum albumin ≥3.5 g/dl
II	Not ISS stage I or III
III	Serum β2m ≥5.5 mg/l
CA by iFISH	
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
A new model for risk stratification for MM	
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH

β2m, beta 2 microglobulin; CA, chromosomal abnormalities; iFISH, interphase fluorescent *in situ* hybridisation; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; R-ISS, Revised International Staging System.

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Supplementary Table S3. IMWG response criteria [25]

Response subcategory	Response criteria
IMWG MRD	
Sustained MRD-negative	MRD-negative in the BM (NGF and/or NGS) and by imaging as defined below, negativity confirmed one year apart. Subsequent evaluations can be used to further specify the duration of criteria negativity (e.g. MRD-negative at 5 years)
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF on BM aspirates using the EuroFlow standard operation procedure for MRD detection in MM (or validated equivalent method) with a minimum sensitivity of 1 in 105 nucleated cells or higher
Sequencing MRD-negative	• Absence of clonal plasma cells by NGS on BM aspirates in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of BM aspirates using the LymphosightVR platform (or validated equivalent method) with a minimum sensitivity of 1 in 105 nucleated cells or higher • MRD-negative as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET-CT or decrease to less than mediastinal blood pool SUV or decrease to less than that of surrounding normal • MRD-negative as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET-CT or

Imaging + MRD-negative	decrease to less than mediastinal blood pool SUV or decrease to less than that of surrounding normal
sCR	CR as defined below plus normal FLC ratio and absence of clonal PCs by immunohistochemistry or 2- to 4-colour flow cytometry
CR	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤5% PCs in BM
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 per 24 h
PR	• ≥ 50% reduction of serum M protein and reduction in 24h urinary M protein by ≥90% or to <200 mg per 24 h • If the serum and urine M protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M protein criteria • If serum and urine M protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in PCs is required in place of M protein, provided baseline BM PC percentage was ≥30% • In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
Progressive disease	Increase of 25% from lowest confirmed response value in one of the following criteria: • Serum M protein (absolute increase must be ≥0.5 g/dL) • Serum M protein increase ≥1 g/dl, if the lowest M component was ≥5 g/dl

	• Urine M protein (absolute increase must be ≥200 mg/24 h)
Clinical relapse	Clinical relapse requires one or more of the following criteria: • Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; • Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD of the measurable lesion; • Hypercalcaemia (>11 mg/dl); • Decrease in haemoglobin of ≥2 g/dl not related to therapy or other non-myeloma-related conditions; • Rise in serum creatinine by 2 mg/dl or more from the start of the therapy and attributable to myeloma; • Hyperviscosity related to serum paraprotein
Relapse from CR (to be used only If the endpoint is disease-free survival)	Any one or more of the following criteria: • Reappearance of serum or urine M protein by immunofixation or electrophoresis; • Development of ≥5% plasma cells in the BM; • Appearance of any other sign of progression (i. e, new plasmacytoma, lytic bone lesion or hypercalcaemia see above)

Relapse from MRD negativity (to be used only if the endpoint is disease-free survival)	Any one or more of the following criteria: • Loss of MRD-negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma); • Reappearance of serum or urine M protein by immunofixation or electrophoresis; • Development of ≥5% clonal plasma cells in the BM; • Appearance of any other sign of progression (i. e, new plasmacytoma, lytic bone lesion or hypercalcaemia)

BM, bone marrow; CR, complete response; CRAB, hypercalcaemia, renal failure, anaemia and bone disease; FLC, free-light chain; IMWG, International Myeloma Working Group; M protein, monoclonal protein; MM, multiple myeloma; MRD, minimal residual disease; NGF, next-generation flow cytometry; NGS, next-generation sequencing; PC, plasma cell; PET-CT, positron electron tomography-computed tomography; PR, partial response; sCR, stringent complete response; SPD, sum of the product of the diameters; SUV, standardised uptake value; VGPR, very good partial response.

Adapted from [25] with permission of the American Society of Hematology.

Supplementary Table S4. Risk factors associated with an increased risk of progression of smouldering myeloma to active myeloma – novel definition of high-risk smouldering MM [26]

	Proposed cut-off	Analysis	HR (95% CI) versus low risk	*P* value
Serum M protein	2 g/dl	>2 versus ≤2	1.99 (1.62-2.45)	<0.0001
Serum FLC ratio	20	>20 versus ≤20	2.04 (1.65-2.52)	<0.0001
BMPC %	20%	>20 versus ≤20	2.26 (1.83-2.79)	<0.0001

BMPC, bone marrow plasma cell; CI, confidence interval; FLC, free light chain; HR, hazard ratio; M protein, monoclonal protein; MM, multiple myeloma.

The patients in the study (n= 1151) were stratified into low-, intermediate- and high-risk groups according to the presence of risk factors (serum protein above 2g/dl, serum FLC ratio above 20, BMPC above 20%) as follows:

- low risk (none of the three risk factors; n = 143);
- intermediate risk (one of the three risk factors; n = 121);
- and high risk (≥2 of the three risk factors; n = 153).

The median time to progression for low-, intermediate- and high-risk groups were 110, 68 and 29 months, respectively ($P < 0.0001$).

Supplementary Table S5. Patient-frailty index and frailty index-defined risk factor assessment via IMWG-FI and Revised Myeloma Comorbidity Index, suggesting consideration of treatment adjustment based on patient fitness (adapted with permission from [27])

Patient risk factors				
Age >75 years				
Mild, moderately, or severely frail (patients who need help with either household tasks, personal care, or are completely dependent)				
Comorbidities (pulmonary, renal, cardiac and hepatic dysfunction) And/or Preferably with (a) IMWG-frailty index[1] and/or (b) R-MCI[2] define fit, intermediate-fit, and frail patients, in order to consider adapting antimyeloma therapy; fit level 0, intermediate fit level 1 and frail level 2.				
Frailty index risk factors				
IMWG frailty index[1]	0	1	1 + occurrence of grade 3-4 haematological AE	≥2
R-MCI[2]	1-3	4-6	7-9	
Dose level	0	1	-2	-2
Treatment doses	**Level 0**	**Level 1**	**Level 2**	
Prednisone	2 mg/kg days 1-4 of a 4-6-week cycle 60 mg/m^2 days 1-4 of a 6-week cycle	1 mg/kg days 1-4 of a 4-6-week cycle 30 mg/m^2 days 1-4 of a 6-week cycle	0.3-0.5 mg/kg days 1-4 of a 4-6-week cycle 10-15 mg/m^2 days 1-4 of a 6-week cycle	
Dexamethasone	40 mg day 1, 8, 15, 22 of a 28-day cycle	20 mg day 1, 8, 15, 22 of a 28-day cycle	10 mg day 1, 8, 15, 22 of a 28-day cycle	
Melphalan	0.25 mg/kg days 1-4 of a 4-6 week cycle 9 mg/ m^2 days 1-4 of a 6-week cycle	0.18 mg/kg days 1-4 of a 4-6 week cycle 7.5 mg/m^2 days 1-4 of a 6-week cycle	0.13 mg/kg days 1-4 of a 4-6-week cycle 5 mg/ m^2 days 1-4 of a 6-week cycle	
Thalidomide	100 (-200) mg/day	50 (-100) mg/day	50 mg qod (- 50 mg/day)	
Lenalidomide	25 mg days 1-21 of a 28-day cycle	15 mg days 1-21 of a 28-day cycle	10 mg days 1-21 of a 28-day cycle	
Pomalidomide	4 mg days 1-21 of a 28-day cycle	3 mg days 1-21 of a 28-day cycle	2 mg days 1-21 of a 28-day cycle	
Bortezomib	1.3 mg/m^2 twice weekly	1.3 mg/m^2 once weekly	1.0 mg/m^2 once weekly	

	Day 1, 4, 8, 11 every 3 weeks	Day 1, 8, 15, 22 every 5 weeks	Day 1, 8, 15, 22 every 5 weeks
Carfilzomib[a]	20 mg/m^2 day 1, 2, 8, 9, 15, 16 cycle 1, 27 mg/m^2 cycle 2 every 3 weeks	20 mg/m^2 cycle 1 → 27 mg/m^2 cycle 2, day 1, 8, 15, every 3 weeks	20 mg/m^2 day 1, 8, 15, every 4 (5) weeks
Ixazomib	4 mg day 1, 8, 15, every 4 weeks	3 mg day 1, 8, 15, every 4 weeks	2.3 mg day 1, 8, 15, every 4 weeks
Daratumumab[a]	16 mg/kg bw, cycle 1-8: weekly; cycle 9-24: day 1+15, from week 25: every 4 weeks	16 mg/kg bw, cycle 1-8: weekly; cycle 9-24: day 1þ15, from week 25: every 4 weeks	16 mg/kg bw,cycle 1-8: weekly; cycle 9-24: day 1+15, from week 25: every 4 weeks
Elotuzumab[b]	10 mg/kg bw, day 1, 8, 15, 22, cycle 1+2, from cycle 3: day 1+15	10 mg/kg bw, day 1, 8, 15, 22, cycle 1+2, from cycle 3: day 1+15	mg/kg bw, day 1, 8, 15, 22 cycle 1þ2, from cycle 3: day 1þ15
Panobinostat	20 mg day 1, 3, 5, 8, 10, 12 every 4 weeks	15 mg day 1, 3, 5, 8, 10, 12 every 4 weeks	10 mg day 1, 3, 5, 8, 10, 12 every 5 weeks

AE, adverse event; bw, body weight; cy, cycle; d, day; IMWG, International Myeloma Working Group; IMWG-FI, International Myeloma Working Group Frailty Index; qod, every 2 day; R-MCI, Revised Myeloma Comorbidity Index.

In the Endeavor study the dose of carfilzomib was 56 mg/m^2, with 17% of patients of 75 years or older. No dose modification was applied. In the Aspire study, where carfilzomib was combined with lenalidomide a lower dose of 27mg/m^2 was given, also not adapted according to age.

[1] http://www.myelomafrailtyscorecalculator.net/Geriatric.aspx.

[2] http://www.myelomacomorbidityindex.org/en_calc.html.

[a] +.

[b] No known dose adaptation in elderly and/or frail patients reported.

Supplementary Table S6. Summary of recommendations for special situations related to MM and MM complications management

Management of plasma cell leukaemia	**LoE, GoR**
Treatment should be immediate and possibly oriented toward bortezomib and/or lenalidomide-based multi-phase approaches in combination with chemotherapy agents, with short treatment-free intervals. It should ideally include induction, double ASCT, consolidation and maintenance	[II, B]
Allo-SCT should be considered in selected cases	[III, C]
Patients not eligible for transplant procedures should preferably receive continuous treatment	[III, C]
Intrathecal prophylaxis should be also considered for patients at high risk of CNS infiltration (i.e. those with a high WBC count) (panel consensus)	
In relapsed/refractory PPCL a switch to drugs not used at diagnosis should be considered, favouring combinations of lenalidomide or pomalidomide plus dexamethasone with carfilzomib or monoclonal antibodies (panel consensus)	
Management of solitary plasmacytoma	
Detection of clonal PCs using sensitive techniques in the BM is suggested [II, B], and treatment of myeloma should be started in these patients	[III, B]
Before treatment initiation, whole body MRI and PET-CT should be performed to exclude the presence of MM	[I, A]

Local RT is the preferred treatment of choice	[II, A]
Supportive care	
Bone disease	
All myeloma patients with osteolytic disease at diagnosis should be treated with antiresorptive agents, i.e. zoledronic acid or denosumab in addition to specific anti-myeloma therapy. Patients without bone disease, assessed by conventional radiography, should also receive bone-targeted agents, but their advantage is not clear for patients with no bone involvement on WBLD-CT or PET-CT	[I, A]
In SMM, bisphosphonates or denosumab are not recommended; in case of osteoporosis in MGUS or SMM, the antiresorptive agents have to be used according to osteoporosis guidelines	[III, C]
Zoledronic acid should be given for more than two years only in patients who have not achieved a PR after initial therapy. For patients who have achieved CR or VGPR, 12-24 months of therapy with zoledronic acid is adequate**.** At relapse, zoledronic acid has to be reinitiated	[I, A]
In cases of ONJ, bisphosphonates or denosumab should be discontinued and may be re-administered if ONJ has healed (panel consensus)	[II, B]
In patients with CrCl <30 mL/min, bisphosphonates are not recommended. Denosumab is a reasonable approach for these patients as it is not cleared through the kidneys, although there is limited data in myeloma patients with CrCl <30 mL/min	[II, B]

Denosumab should be given continuously. Discontinuation of denosumab is challenging as there are no data on how to stop denosumab in myeloma patients; until these data are available, discontinuation of denosumab has to be followed by a dose of zoledronic acid, 6-9 months after denosumab last dose, for preventing any rebound phenomenon	[III, B]
For both bisphosphonates and denosumab administration, vitamin D and calcium supplementation is mandatory	[I, A]
Low-dose radiation therapy (up to 30 Gy) can be used as palliative treatment for uncontrolled pain, for impending pathological fracture, or impending spinal cord compression	[II, A]
Balloon kyphoplasty should be considered for symptomatic vertebral compression fractures with refractory pain	[II, B]
Surgery is recommended for long-bone fractures, bony compression of the spinal cord, or vertebral column instability	[II, A]
Anaemia and bone marrow failure	
Recombinant human erythropoietin and darbepoetin alfa can be used for the treatment of myeloma-associated anaemia (haemoglobin level <10 g/dL), if other causes of anaemia have been excluded. The target is to maintain haemoglobin below 12 g/dL to avoid thromboembolic complications and hypertension	[II, B]
Treatment with G-CSF may be required to treat chemotherapy-induced severe neutropaenia	[II, B]
Infections Infectious episodes require immediate therapy with broad spectrum antibiotics	[I, A]

Levofloxacin prophylaxis of infection is recommended for the first 3 months of initiation of therapy, especially in patients receiving lenalidomide or pomalidomide, or in patients at high risk of infections (previous serious infections or neutropaenia)	[I, A]
*Influenza, Varicella zoste*r (inactivated vaccine) and pneumococcal vaccinations are recommended, while acyclovir or valacyclovir for *Herpes zoster* virus prophylaxis is recommended for patients receiving PI-based and daratumumab-based therapies	panel consensus
Intravenous IgG prophylaxis is not routinely recommended although highly recommended in patients receiving either TCEs or CAR-T cells; it can be used in patients with low IgG levels (<400-500 mg of IgG) and at least two severe infections requiring hospitalisation during the last year	panel consensus
Renal impairment	
Bortezomib-based regimens remain the cornerstone of the management of myeloma-related RI	[I, B]
High dose dexamethasone should be administered at least for the first month of therapy	[II, B]
In patients eligible for ASCT, VTD bortezomib could be given	[II, B]
In patients who are ineligible for ASCT, VMP can also be administered but no data exist for this regimen in dialysis patients	[I, A]
Thalidomide is effective in myeloma patients with RI and can be given without dose modifications	[II, B]

Lenalidomide is also effective and safe in patients with mild to moderate RI. It should be administered with dose adjustments according to CrCl	[II, B]
HDT/ASCT is feasible in myeloma patients with RI; the dose of melphalan should be restricted to 100-140 mg/m^2	[III, C]
Pomalidomide can be given in the dose of 4 mg/d in patients with severe RI, even on dialysis	[II, B]
Carfilzomib is another option for patients with RRMM and RI; it needs no dose modifications for patients with CrCl >15 ml/min and produces similar results in patient with and without RI	[II, B]
Ixazomib can be safely administered in combination with lenalidomide and dexamethasone in patients with RRMM and CrCl ≥30 ml/min	[I, A]
Daratumumab may be also given to patients with severe RI	[III, C]

Allo-SCT, allogeneic stem cell transplantation; ASCT, autologous stem cell transplantation; BM, bone marrow; CAR-T, chimeric antigen receptor T; CNS, central nervous system; CR, complete response; CrCl, creatinine clearance; CT, computed tomography; G-CSF, granulocyte colony-stimulating factor; GoR, grade of recommendation; HDT, high-dose therapy; IgG, immunoglobulin G; LoE, level of evidence; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; MRI, magnetic resonance imaging; ONJ, osteonecrosis of the jaw; PC, plasma cell; PET, positron emission tomography; PI, proteasome inhibitor; PPCL, primary plasma cell leukaemia; PR, partial response; RI, renal impairment; RRMM, relapsed/refractory multiple myeloma; RT, radiotherapy; SMM, smouldering multiple myeloma; TCE, T-cell engager; VGPR, very good partial response; VMP, bortezomib/ melphalan/prednisone; VTD, bortezomib/thalidomide/dexamethasone; WBC, white blood cell; WBLD-CT, whole-body low-dose CT.

Supplementary Table S7. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions

Grades of recommendation

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a] By permission of Oxford University Press on behalf of the Infectious Diseases Society of America [28].

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