Med Oncol (2010) 27:S43–S52
DOI 10.1007/s12032-010-9542-z

ORIGINAL PAPER

Management of disease- and treatment-related complications in patients with multiple myeloma

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Published online: 14 May 2010

Abstract Treatment of myeloma has dramatically changed after introduction of novel agents, such as thalidomide, lenalidomide and bortezomib, with a significant improvement in response rate and survival of patients with myeloma. For newly diagnosed patients not eligible for transplant, the standards of care are now considered melphalan and prednisone (MP) plus thalidomide and MP plus bortezomib. Ongoing randomized trials are evaluating lenalidomide plus MP and lenalidomide plus dexamethasone. For newly diagnosed patients eligible for transplant, new induction regimens included the combination of high-dose dexamethasone plus thalidomide, high-dose dexamethasone plus lenalidomide (RD) and high-dose dexamethasone plus bortezomib (VD). The combinations RD, VD and bortezomib plus pegylated-liposomal-doxorubicin have received the US Food and Drug Administration approval for the treatment of relapsed myeloma. Different efficacious regimens are therefore now available for patients with myeloma. Disease control leads to improvement of all myeloma-related complications (anemia, bone disease, immune dysfunction and renal impairment), but physicians should take into account the choice of the therapeutic strategy, the expected toxicity profile of each of these regimens, together with the patient's biologic age and comorbidities. Supportive care is an essential part of myeloma therapy, both for the treatment of myeloma-related complications, together with anti-myeloma treatment, and for the management of treatment-emergent adverse events. This chapter will provide an overview of frequency and management of main complications related to the disease itself and to the use of new drugs in newly diagnosed and relapsed patients with myeloma.

Keywords Myeloma · Adverse events · Therapy · New drugs

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Introduction

Multiple myeloma (MM) is an incurable malignancy characterized by anemia, bone disease, renal impairment and immune dysfunction. Anemia with fatigue is the most frequent feature at presentation, as well as bone pain secondary to bone disease. Hypercalcemia, related to bone disease and renal failure may require urgent treatment. Immune dysfunction results in a higher risk of infections. All these symptoms commonly improve with disease response to therapy.

Treatment of MM has dramatically changed in the last decade, with a significant improvement in response rate and survival. For years, standard treatment for patients with MM not eligible for autologous stem cell transplant (ASCT) has been the combination of melphalan and prednisone (MP). For over 10 years, the vincristine–doxorubicine–dexamethasone (VAD) combination has been used as pre-transplant induction regimen [1–3]. In young patients (defined as patients younger than 65 years), randomized trials demonstrated superior response rate and survival with high-dose therapy compared to conventional chemotherapy [4]. However, none of these trials compared treatment regimens including novel agents.

Recently, novel agents have been introduced, in combination with conventional chemotherapy and steroids, for the treatment of MM. For newly diagnosed patients not eligible

for ASCT, the standards of care are now considered melphalan and prednisone plus thalidomide (MPT) [5–7] and melphalan and prednisone plus bortezomib (MPV) [8]. Ongoing randomized trials are evaluating lenalidomide plus MP (MPR), lenalidomide plus high-dose dexamethasone (RD) and lenalidomide plus low-dose dexamethasone (Rd) [9, 10]. For newly diagnosed patients eligible for ASCT, new induction regimens include the combination of high-dose dexamethasone plus thalidomide (TD) [11–13], high-dose dexamethasone plus lenalidomide (RD) [9, 10] and high-dose dexamethasone plus bortezomib (VD) [14]. Thalidomide has been used as post-transplant maintenance, but treatment has been correlated to a high rate of discontinuation, mainly related to peripheral neuropathy [15, 16]. Lenalidomide, more efficacious than the parent drug in preclinical assays, is now under clinical evaluation as post-transplant consolidation and maintenance. In relapsed patients, randomized trials demonstrated the efficacy and safety of RD, VD and bortezomib plus pegylated-liposomal-doxorubicin [17–20]. These combinations have consequently received the US Food and Drug Administration (FDA) approval for the treatment of relapsed MM.

Treatment choice should be based on scientific evidence (improved progression-free survival [PFS]), provided by a randomized trial. Different efficacious regimens are now available for both newly diagnosed and relapsed patients. Disease control leads to control and improvement of all myeloma-related complications, but in the choice of the therapeutic strategy, physicians should take into account the expected toxicity profile (treatment-emergent adverse events [AEs]) of each of these regimens, as well as patient's biologic age and comorbidities. Supportive care is an essential part of myeloma therapy, both for the treatment of myeloma-related AEs, together with anti-myeloma treatment, and for the management of treatment-related complications. Adverse events should be graded according to the National Cancer Institute-Common Terminology Criteria (version 3.0) [21]. Prompt dose reduction in case of treatment-related AEs can significantly reduce early discontinuation rate and consequently improve treatment efficacy. This chapter will focus on frequency and management of main complications related to the disease itself (Fig. 1) and to the use of novel agents (Table 1) in the treatment of newly diagnosed and relapsed patients with MM. Data on frequency of treatment-related toxicities refer to randomized trials only.

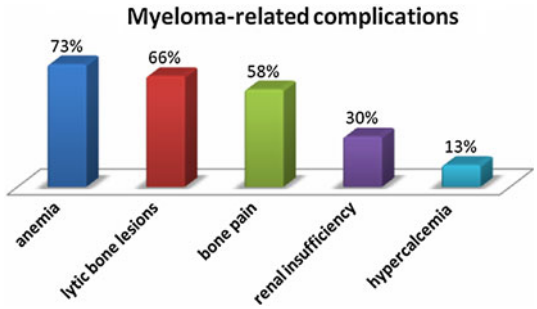

Fig. 1 Most frequent myeloma-related complications

Hematologic adverse events

Anemia

Anemia, typically normochromic and normocytic, is frequent at myeloma presentation (73% of cases). It becomes even more common in patients with recurrent or refractory disease. It is generally related to myeloma itself and commonly improves with disease response to therapy.

In different combination regimens, including novel agents plus dexamethasone or plus MP, grades 3–4 anemia has been reported in 3 to 19% of cases [5, 6, 8, 13, 17–20, 22].

Since myeloma-related anemia commonly improves with disease response to therapy, erythropoiesis-stimulating agents (ESAs) should be considered when, despite response to chemotherapy, there has not been an increase in hemoglobin concentration.

Erythropoiesis-stimulating agents can be prescribed to treat chemotherapy-associated anemia. Iron status should be monitored during treatment to prevent functional iron deficiency and support increased erythropoiesis. Transferrin saturation should be at least 20% and ferritin should be at least 100 ng/mL. Adequate iron supplementation should be administered whenever necessary to ensure erythropoiesis support and avoid depletion of iron stores. In patients with asymptomatic anemia, ESAs are recommended when the hemoglobin concentration is <9 g/dL; for patients with heart disease or those with symptomatic anemia, treatment can begin for hemoglobin concentration between 10 and 12 g/dL. If hemoglobin has not risen from 1–2 g/dl after 1–2 months of treatment, the probability of response is low and treatment should be stopped. The ESA dose should be adjusted, in responding patients, to maintain a hemoglobin concentration of 11–12 g/dL, in order to avoid anemia-related symptoms. The benefit of these drugs should be carefully evaluated in patients with hemoglobin concentration >12 g/dL, since in patients with cancer they can create serious health problems. It has been reported in particular an increased risk of thrombosis, in patients at high-risk for developing clots [23].

Thrombocytopenia

Thrombocytopenia is generally not related to the disease itself, except in case of very aggressive disease. It is a quite common side effect in patients treated with bortezomib, lenalidomide and alkylating agents, while it is rare in

Table 1 Common, occasional and rare adverse events related to the use of new drugs in patients with myeloma

Drug	Common adverse events (incidence >15%)	Occasional adverse events (incidence 5–14%)	Rare adverse events (incidence <5%)
Thalidomide alone or plus steroids	Venous thromboembolism	Neutropenia	Cutaneous rash
		Thrombocytopenia	Cardiac events
		Infections	Seizure (rare)
		Peripheral Neuropathy	
		Fatigue	
Thalidomide in combination with chemotherapy	Neutropenia	Thrombocytopenia	Cutaneous rash
		Infections	Stevens–Johnson syndrome/toxic epidermal necrolisis
		Peripheral Neuropathy	
		Venous thromboembolism	
		Gastrointestinal events	
		Cardiac events	
Lenalidomide alone or plus steroids	Neutropenia	Thrombocytopenia	Peripheral neuropathy
	Infections	Gastrointestinal events	Cutaneous rash
	Venous thromboembolism	Fatigue	Stevens–Johnson syndrome/toxic epidermal necrolisis
			Cardiac events
Lenalidomide in combinations with chemotherapy	Neutropenia	Infections	Gastrointestinal events
			Stevens–Johnson syndrome/toxic epidermal necrolisis
	Thrombocytopenia	Venous thromboembolism	
		Cutaneous rash	
Bortezomib alone or plus steroids	Neutropenia	Peripheral Neuropathy	Venous thromboembolism
	Thrombocytopenia	Gastrointestinal events	Fatigue
			Rash
			Toxic epidermal necrolisis
			Acute hepatic failure
			Acute respiratory
			Distress syndrome
			Interstitial pneumonia and acute pneumonia
			Cardiac events
Bortezomib in combinations with chemotherapy	Neutropenia	Infections	Venous thromboembolism
	Thrombocytopenia	Peripheral neuropathy	Toxic epidermal necrolisis
	Gastrointestinal events	Fatigue	Cutaneous rash
			Cardiac events

patients treated with thalidomide alone or plus steroids. In the newly diagnosed setting, grades 3–4 thrombocytopenia has been reported in 23% of patients treated with MPR [22] and in 21 to 38% of patients receiving VMP [8, 24, 25]. In relapsed patients treated with the RD regimen, incidence of grades 3–4 thrombocytopenia was 10–12% [19, 20]: incidence was higher in patients with impaired renal function [26]. In relapsed patients treated with bortezomib, grades 3–4 thrombocytopenia was reported in 15 to 30% with bortezomib alone [17, 18] and 22% with bortezomib plus pegylated-liposomal-doxorubicin [18]. Thrombocytopenia, in patients treated with thalidomide-based regimens, has been reported mainly when thalidomide has been combined with myelotoxic agents, such as melphalan (incidence of grades 3–4 thrombocytopenia varies from 3 to 14% in newly diagnosed patients treated with MPT) [5, 6, 27].

When grade 4 thrombocytopenia (platelet count $<25{,}000/mm^3$) occurs, treatment should be interrupted and then restarted when the thrombocytopenia resolves to at least grade 2 (platelet count $\geq 50{,}000/mm^3$). Dose reduction of the myelotoxic drugs should be considered if repeated grade 4 thrombocytopenia occurs.

Neutropenia

Neutropenia is not likely to be related to myeloma. It is a common AE of both lenalidomide and alkylating agents, less frequent with bortezomib. In newly diagnosed patients treated with RD, grades 3–4 neutropenia has been reported in 21% of cases [28]. Incidence increased to 52% in patients treated with MPR, due to the myelotoxic effect of melphalan [22]. With the VMP combination, grades 3–4 neutropenia is reported in about 40% of patients [8, 24, 25]. Mild neutropenia has been reported in 3–15% of patients receiving thalidomide [27] but, as expected, the incidence increases in combination including myelotoxic chemotherapy: 16–48% of newly diagnosed patients treated with MPT experienced grades 3–4 neutropenia [5–7]. In relapsed patients treated with RD, although the incidence of grades 3–4 neutropenia ranged from 30 to 46% [19, 20, 26], the incidence of febrile neutropenia occurred in less than 4% of patients [19, 20]. The incidence of neutropenia was slightly higher in patients who had received prior ASCT [29]. Neutropenia is less frequent in relapsed patients treated with bortezomib alone, but again increases when myelotoxic chemotherapy is added to bortezomib (from 15% with bortezomib alone [17, 18] to 30% with the addition of pegylated-liposomal doxorubicin to bortezomib) [18].

In patients considered at high risk of neutropenia on the basis of age, medical history, disease characteristics and the expected myelotoxicity of the treatment regimen, prophylaxis with granulocyte-colony-stimulating factor (G-CSF) is recommended. If the expected rate of neutropenia is high, as in case of multi-agent chemotherapy regimens, the use of pegylated G-CSF should be considered.

If a patient experiences grade 4 neutropenia (neutrophil count $<500/mm^3$) during treatment cycles, treatment should be interrupted and G-CSF should be administered until the toxicity resolves to at least grade 2 (neutrophil count $\geq 1{,}000/mm^3$); in addition, in case of repeated grade 4 neutropenia despite G-CSF administration, appropriate dose reduction of the myelotoxic drug is recommended. If the neutrophil count is $<1{,}500/mm^3$ on the first day of a new cycle, treatment should be delayed and restarted at a lower dose when at least grade 1 toxicity (neutrophil count $>1{,}500/mm^3$) is reached.

Non-hematologic adverse events

Bone disease

Bone disease associated with myeloma is an important cause of morbidity and mortality. Almost 70% of newly diagnosed patients present with osteolytic lesions on skeletal survey.

Pathological fractures can occur on long bones, as well as on vertebral bodies. Fractures of long bones generally involve the upper arm or the femur, and they usually require stabilization by surgical fixation and osteosynthesis. Vertebroplasty can be an option in patients with vertebral collapse but does not restore vertebral height [30].

Hypercalcemia is a frequent metabolic complication of MM, sometimes aggravated by decreased renal calcium excretion in patients with concomitant renal failure. Symptomatic hypercalcemia requires immediate treatment. Appropriate treatment should start with intravenous saline, with forced saline diuresis whenever necessary, and monitoring of central venous pressure and serum electrolytes. Steroids, that are usually included in MM upfront treatment, have not only an anti-myeloma effect, but affect also intestinal calcium absorption and bone turnover. Bisphosphonates play an essential role in the standard treatment for MM hypercalcemia.

Bone pain is frequently the predominant symptom of active disease, at diagnosis or at relapse. It generally improves with chemotherapy and disease control, but specific treatment is required in most of the patients. It is important to try to quantify the intensity of pain by pain scale, to allow appropriate monitoring of treatment efficacy. The use of analgesics should be based on established principles of the World Health Organization (WHO) Guidelines on Cancer Pain Relief [31], but the support of expertise from in-hospital pain clinics could be necessary. Treatment should start with simple non-opioid analgesic (like paracetamol), efficacious especially for low to moderate pain, administered orally. Non-steroidal anti-inflammatory drugs should be avoided due to the potential risk of gastric irritation and side effects on renal function. When simple non-opioid analgesics are not efficacious in controlling pain, an opioid should be administered, starting with a weak opioid, such as codeine, that generally provides efficacious control of moderate pain, with or without a non-opioid analgesic, to a strong natural opioid such as morphine or a synthetic opioid such as oxycodone that can control moderate to intense pain. Treatment can start with oral administration but may sometimes require intravenous administration. Fentanyl given as slow release transdermal patches may be a valuable alternative to slow release morphine for moderate to severe chronic pain. Common side effects of opioids include the following: constipation, usually manageable with simple laxatives, drowsiness and sedation, typically associated with initial treatment. Another measure for bone pain control is local radiotherapy (the recommended dose for pain control is 8 Gγ single fraction) [32]. The use of radiotherapy, however, should be limited as the long-term use of radiation can affect hematopoietic reserve and bone healing.

Bisphosphonates are recommended in patients with MM suffering from lytic bone disease or osteoporosis. Bisphosphonate treatment prevents, reduces and delays MM-related skeletal events and is part of the treatment of hypercalcemia and pain control. Treatment with bisphosphonates is recommended for all MM patients with lytic bone disease or severe osteoporosis. Intravenous administration (pamidronate or zoledronic acid) should be preferred, but oral administration (clodronate) can be an option for patients not able to attend hospital visits. In patients with renal impairment, creatinine clearance (CLcr), electrolytes and albuminuria should be monitored. Dose adjustment of bisphosphonates is recommended in patients with renal impairment according to CLcr [33]. Treatment should be given for 2 years, but it can be extended in case of persistent active disease and can be resumed in case of recurrence of bone disease at relapse. Bisphosphonate treatment-related complications include the following: gastrointestinal events related to oral administration, inflammatory reaction on injection site, acute systemic reaction, hypocalcemia and hypophosphatemia, acute and chronic renal failure and avascular osteonecrosis of the jaw. Gastrointestinal complications are usually minor and include diarrhea, nausea and abdominal pain. In rare cases, patients may present esophagitis and ulceration. Local inflammatory reactions include swelling and phlebitis. Acute systemic reaction are mainly represented by influenza-like symptoms, that generally resolve on their own in about 2 or 3 days and are easily manageable with analgesics like paracetamol. Hypocalcemia is usually mild and can be prevented with calcium and vitamin D3 supplement. Acute renal failure may be clinically reversible, while permanent kidney damage due to tubular necrosis can lead to chronic renal failure [33]. Osteonecrosis of the jaw is uncommon, but potentially serious. It is a condition characterized by necrotic-exposed bone in the maxillo-facial region [34]. The cause is uncertain and likely multifactorial. The risk increases with prolonged duration of treatment with bisphosphonates and dental procedures or trauma. The incidence seems higher with zoledronic acid treatment and lower with pamidronate, uncommon with clodronate. All patients should receive a complete dental examination before treatment. Existing or high-risk dental conditions such infections must be treated before bisphosphonate therapy. Patients should be educated regarding optimal dental hygiene. During bisphosphonate treatment, unnecessary dental procedures should be avoided; if they are necessary, temporary bisphosphonates interruption is recommended [33]. The first treatment of osteonecrosis of the jaw is discontinuation of bisphosphonates. Management should be by a qualified dental specialist [34].

Renal failure

Renal impairment is reported in 20 to 40% of newly diagnosed patients with MM [35]. The pathogenesis is multifactorial. One of the main causes is the capacity of the light-chain component of the immunoglobulin to provoke proximal tubular damage (cast nephropathy). Other causes include other MM-related complications, such as hypercalcemia, hyperuricemia and infections, as well as dehydration and therapy-related complications, such as use of nephrotoxic drugs, including aminoglycosides and non-steroidal anti-inflammatory agents [NSAIDs] [23]. The prognosis of patients with renal failure is strongly linked to the reversibility of renal impairment. The median survival of patients with reversible renal failure is similar to that of patients with normal renal function, while patients with irreversible renal impairment have a median survival of less than 6 months [36].

The choice of the appropriate treatment regimen is critical in MM patients with impaired renal function. Administration of thalidomide and bortezomib can be initiated without dose reductions. With bortezomib, rapid decrease in light chains may be observed, preventing further deterioration of renal function. It has been hypothesized that bortezomib may accelerate the kidney response not only by rapidly decreasing the monoclonal concentration, but also by reducing the inflammation in the kidney, inhibiting the nuclear factor-kappa-B (NFKB) [37]. Based on a pharmacokinetic study in patients with renal impairment due to non-malignant conditions, adjustment for the starting dose of lenalidomide in MM patients with renal impairment to maintain appropriate exposure are recommended. The adjustments are as follows: in patients with moderate renal impairment (CLcr $\geq$30, <60 mL/min), lenalidomide should be started at 10 mg once every 24 h; in patients with severe renal impairment (CLcr <30 mL/min not requiring dialysis), the starting dose should be 15 mg once every 48 h; and in patients with an end stage renal failure (CLcr <30 mL/min requiring dialysis), lenalidomide dose should be started at 5 mg once daily on dialysis days, the dose should be administered following dialysis. It is important to convert serum creatinine to CLcr and use CLcr for dosage adjustments in patients with renal impairment [38].

Infections

Both the disease and its treatment increase risk of infections in patients with MM. The risk is higher in case of active disease but decreases with response to therapy. The major cause of infections in MM is the impairment in immune function. Neutropenia, related to use of myelotoxic drugs,

can contribute to an increased risk of infection. Prolonged use of high-dose steroids compromises defenses against fungal and viral infections. A recent phase III study that compared the Rd combination vs. RD reported a significantly higher incidence of grades 3–4 infections in the high-dose dexamethasone group (16 vs. 9%, $P = 0.04$) [10]. Incidence of grades 3–4 infections in relapsed patients treated with RD varies from 10 to 22% [19, 20]. Despite the concomitant use of chemotherapy and the higher rate of neutropenia, in newly diagnosed patients treated with MPR, severe infections were reported in about 10% of cases. Ciprofloxacin was administered, in this trial, as antibiotic prophylaxis [22]. Grades 3–4 infections, in patients receiving bortezomib-based regimens, regardless of the concomitant use of steroids or chemotherapy, are similar in the newly diagnosed and relapsed setting (2 to 13%) [8, 17, 18, 24, 25]. Herpes zoster infections have been reported as a possible AE associated with bortezomib, since NFKB, a major target of bortezomib, is known to be involved with T-cell immunity. In the VMP vs. MP trial, patients treated with VMP had a higher incidence of herpes zoster than patients treated with MP alone (14 vs. 4%), with acyclovir prophylaxis incidence decreased to 3% [8]. In addition, a retrospective analysis of the incidence of herpes zoster among 282 patients treated with a bortezomib-containing regimen shows that bortezomib can increase the incidence of herpes zoster regardless of disease duration, previous treatments and concomitantly administered drugs [39]. In thalidomide-based regimens, grades 3–4 infections have been reported in 7% of patients receiving TD [13] and in 10–14% of patients treated with MPT [5, 6].

Prophylactic trimethoprim-sulphamethoxazole is indicated at least during the first 2–3 months of chemotherapy or during steroid administration. Acyclovir prophylaxis is recommended for all patients receiving bortezomib-based therapy. Routine antibiotic prophylaxis could be considered for the first 3 months of therapy, where the risk of infection is higher; it is recommended particularly in patients receiving high-dose dexamethasone, in elderly patients, in patients with comorbidities that increase the risk of infections (i.e. chronic obstructive pulmonary disease, diabetes, renal function impairment) and in patients with an increased infection rate. Prophylactic administration of intravenous immunoglobulin cannot be recommended routinely for patients with hypogammaglobulinemia and MM and/or recurrent infections on the basis of current evidences, but should be considered only an individual basis [40].

Fever in patients with myeloma should not be underestimated, in particular in case of concomitant neutropenia. Treatment should start promptly with broad-spectrum antibiotics, active against the most common pathogens: most frequent causes of infections in newly diagnosed patients with MM are E. Coli, S. Pneumonia and H. Influenzae; in patients with renal insufficiency and in relapsed/refractory patients, more than 90% of infections are caused by Gram-negative bacilli or S. Aureus [41]. Treatment can start with oral antibiotics, but intravenous antibiotics are indicated in case of severe systemic infection. In myeloma patients with compromised renal function, the benefits related to the use of nephrotoxic antibiotics (such as aminoglycosides) must be carefully evaluated before administration, and they should be avoided, whenever possible.

Peripheral neuropathy

Peripheral neuropathy is rarely a complication of myeloma; if present, it is more commonly related to amyloidosis or osteosclerotic myeloma. There is also a known relationship between gammopathy (60% of cases are IgM gammopathy) and neuropathy. However, in patients with myeloma, neuropathy is more likely to be related to bortezomib and thalidomide therapy. Thalidomide causes mainly sensory neuropathy, while with bortezomib, both sensory and painful neuropathy are reported. Incidence of grades 3–4 neuropathy is similar in thalidomide or bortezomib-based regimen, in both relapsed and newly diagnosed settings, and varies from 2 to 13% [5–8, 13, 17, 18, 24, 25]. Both thalidomide- and bortezomib-related neuropathies are cumulative and dose-dependent [27, 42], but the evidence of clinical improvement of bortezomib-induced neuropathy after discontinuation is considerable, in contrast to thalidomide-related neuropathy [43].

There are currently no effective medications able to relieve neuropathic symptoms. Therefore, patients with recognized symptoms of neuropathy should be referred promptly for medical care, since prompt dose reduction and discontinuation are the mainstays for the management of peripheral neuropathy. The following dose reductions are recommended according to the grade of neuropathy and the neurotoxic agent:

- Thalidomide-related neuropathy: no dose adjustment is required for grade 1 neuropathy. In case of grade 2 neuropathy, it is recommended to decrease the dose by 50%; treatment should be interrupted for grade 3 neuropathy and restarted after a 50% dose reduction when neuropathy resolves to at least grade 1 [27].
- Bortezomib-related neuropathy: for grade 1 peripheral neuropathy with pain and for grade 2 sensory peripheral neuropathy, a dose reduction to 1.0 mg/m^2 is recommended; for grade 2 painful neuropathy or grade 3 peripheral neuropathy, treatment should be withheld until peripheral neuropathy resolves to at least grade 1 and then re-started at 0.7 mg/m^2; in the case of grade 4 peripheral neuropathy, treatment should be

discontinued [42]. Results of the VMP vs. VMPT study suggest that an alternative can be to reduce the twice weekly infusion (starting dose 1.3 mg/m^2 twice a week for a total of 4 doses every treatment cycle) to a weekly infusion (same dose 1.3 mg/m^2 once weekly for a total of 4 doses every treatment cycle) in case of grade 1 painful neuropathy or grade 2 sensory peripheral neuropathy and to stop treatment if grade 2 painful neuropathy or grade 3 neuropathy occurs, then restart on a weekly basis (1.0 mg/m^2 once weekly for a total of 4 doses every treatment cycle) when at least grade 1 is reached. If further dose reductions are needed, 0.7 mg/m^2/week can be considered; in case of grade 4 peripheral neuropathy patients should stop treatment.

– In contrast, grades 3–4 peripheral neuropathy is very rare in patients treated with lenalidomide and lenalidomide has been administered to patients who have received prior thalidomide treatment without further deterioration of preexisting thalidomide-related neuropathy [19, 20].

Venous thromboembolism

Risk of venous thromboembolism (VTE) increases in patients with cancer, and patients with hematological neoplasia have the highest risk of thrombosis. In patients with MM, incidence of VTE varies from 3 to 10%. The type of drug used to treat the disease is an important factor determining the risk of VTE. No increased risk of VTE is related to bortezomib therapy. Thalidomide and lenalidomide alone do not increase the incidence of VTE, but it substantially increases when dexamethasone or chemotherapy are added, in particular in newly diagnosed patients, since the risk of VTE at relapse is lower [44]. In a randomize trial comparing TD vs. high-dose dexamethasone alone, where no specific thromboprophylaxis was mandated, in newly diagnosed patients, the incidence of thrombotic events was 18 vs. 3%, respectively, in the two groups [13]. With the MPT combination, VTEs were reported from 3 to 12% of patients in different studies [5–7, 45]. It should be noticed that in the Italian study, VTE incidence significantly decreased (from 20 to 3%) after the introduction of prophylactic enoxaparin [5]. In newly diagnosed patients treated with RD, VTE has been reported in 26% of patients; incidence was significantly lower with the use of low-dose dexamethasone (12% with the Rd combination) [10]; in patients treated with MPR, VTEs are reported in about 10% of cases [22]. In both studies, aspirin was recommended as anti-thrombotic prophylaxis.

At present, there are no data on what is the best thromboprophylaxis to use in patients with MM treated with immunomodulatory agents. To address this issue, the Italian Myeloma Network GIMEMA designed a phase III study to compare the efficacy and safety of low-molecular weight heparin (LMWH), low-fixed-dose warfarin (1.25 mg/day) or low-dose aspirin as VTE prophylaxis in newly diagnosed patients, who received primary induction with thalidomide-based regimens: preliminary results did not show any significant relation between VTE risk and patient age, induction regimens or thromboprophylaxis [46].

In asymptomatic patients, baseline coagulation tests and screening for VTE are not recommended. Presence of risk factors for thrombosis in patients with MM treated with immunomodulatory agents should be evaluated, since in these patients the choice of thromboprophylaxis should be tailored according to the presence of risk factors that may increase the risk of VTE. Risk factors can be classified into individual risk factors (history of VTE, inherited thrombophilia age, obesity, comorbidities such as cardiac disease, chronic renal disease, diabetes, infections, immobilization, presence of central venous catheter and surgical procedures), myeloma-related risk factors (diagnosis and hyperviscosity) and therapy-related risk factors (high-dose dexamethasone, doxorubicin, or multiagent chemotherapies, immunomodulatory compounds). Therapy-related risk factors should be considered per se as high-risk risk factors. If none or one individual or MM-related risk factor is present, aspirin (81–325 mg/day) is indicated. If two or more individual or myeloma-related risk factors are present, LMWH (equivalent of enoxaparin 40 mg/day) or full-dose warfarin (international normalized ratio [INR] targets 2–3) are preferred. LMWH or full-dose warfarin is recommended for patients with therapy-related risk factor. Prophylaxis is generally recommended for at least the first 4–6 months. Patients who experienced VTE during treatment can continue on treatment or can be retreated after stabilization. Patients who experienced VTE while on aspirin should have received LMWH; patients treated with prophylactic LMWH should be switched to therapeutic doses. After 6 months of therapeutic anti-coagulation, prophylaxis can be restarted [44].

Gastrointestinal adverse events

Gastrointestinal (GI) events are common side effects of myeloma therapy. Rarely are they related to myeloma, the only exception is constipation related to severe hypercalcemia in case of uncontrolled disease. Constipation is the most common gastrointestinal AE related to thalidomide treatment. In newly diagnosed patients treated with MPT, incidence of grades 3–4 GI toxicities (essentially constipation) varies from 4 to 11% in different studies [5, 6, 45]. The main frequent gastrointestinal event in lenalidomide-treated patients is diarrhea. However, grades 3–4 GI events were reported in only 2% of newly diagnosed patients

treated with MPR [22]. Higher rates were reported in relapsed patients receiving RD (7–10% grades 3–4 GI AEs, with similar low percentages of diarrhea, nausea and constipation) [19, 20]. Both constipation and diarrhea have been reported with bortezomib-based regimens. In patients treated with VMP, severe GI toxicities vary from 5 to 17%, with the higher rate reported in the VMP vs. MP trial, where the main toxicity was diarrhea [8, 24, 25]. In relapsed patients treated with bortezomib, the main frequent AE reported was again diarrhea (rate of grades 3–4 GI toxicities: 6 to 14%) [17, 18]. In case of constipation, patients should maintain a high fluid intake and a high fiber diet if medically appropriate. If necessary, stool softeners and osmotic laxatives can be administered. Patients suffering from diarrhea should maintain a high fluid intake; anti-diarrheal drugs can be used in case of diarrhea, after exclusion of active infections. In case of severe (grades 3–4) toxicity, a 50% dose reduction of the drug is recommended.

Dermatologic adverse events

Both thalidomide and lenalidomide can cause dermatologic toxicity, most frequently rash, dry skin and mouth and atrophic lesions. These events are generally mild to moderate and easy to manage. Rare but serious AEs are toxic epidermic necrolysis (TEN) and Stevens–Johnson syndrome (SJS) [27]. In patients treated with thalidomide-based regimens, grades 3–4 dermatological toxicity AEs varies from 1 to 8% [5, 6, 45]; similar rates are reported with lenalidomide-based regimen [19, 20, 22]. Stevens–Johnson syndrome and toxic epidermal necrolysis are rapidly progressive conditions characterized by epidermal detachment and mucosal involvement. The appearance of a maculopapular rash that covers the entire body is a possible early sign. In Stevens–Johnson syndrome, up to 10% of the body surface area is affected, while toxic epidermal necrolysis is defined as involvement of more than 30%. Stevens–Johnson syndrome is a life-threatening condition that occurs in less than 1% of thalidomide-treated patients. Toxic epidermic necrolysis is associated with mortality rates greater than 30% [27].

Dermatological toxicity is rare with bortezomib-based regimens (incidence varies from 1 to 5%, with the higher rate reported with the association of bortezomib and pegylated-liposomal doxorubicin in relapsed patients, where the main AE was hand–foot syndrome related to pegylated-liposomal doxorubicin) [17, 18].

Coadministration of thalidomide or lenalidomide and agents with known dermatologic toxicity (e.g., sulfonamides, allopurinol, cotrimoxazole) should be monitored closely. In case of mild toxicity, temporary discontinuation generally leads to resolution of the rash. If necessary, treatment should begin with anti-histamines; if rash persists, low-dose prednisone (10–20 mg/day for up to 14 days) should be added. In case of grades 3–4, AEs treatment can be resumed, after complete resolution, with 50% dose reductions. After toxic epidemic necrolysis or the Stevens–Johnson syndrome, re-administration of the responsible drug is contraindicated.

Management of patients with significant co-morbidities

It is recommended that patients with significant co-morbidities, such as diabetes, renal failure and cardiopulmonary disease, receive a baseline evaluation by a specialist (respectively, a diabetologist, nephrologist, cardiologist and pneumologist) before starting treatment, in particular if they present with severe disease. It is generally recommended also a proper follow-up to evaluate if treatment, especially during the first months, causes an impairment of renal or cardiopulmonary functions or lack of appropriate glycemic control. As explained earlier, all patients with significant comorbidities have a higher risk of infections and should therefore receive anti-biotic prophylaxis at least during the first months of therapy (see Sect. "Infections"). Many comorbidities (like diabetes, cardiac disease and others) can increase risk of thrombosis: appropriate anti-thrombotic prophylaxis should therefore be adopted (see Sect "Venous thromboembolism"). Different drugs, with a different toxicity profile, should be avoided or given with specific cautions in patients with comorbidities:

- Diabetes: steroids are part of almost all treatment schemas for patients with myeloma. Diabetic patients are at high risk of hyperglycemia, also severe, when they start a new treatment regimen containing steroids. Glycemic levels should be therefore carefully monitored and hypoglycemic treatment adapted to the new therapy. Use of high-dose steroids should be avoided whenever possible. In patients presenting with diabetic neuropathy, the benefit of treatment with neuropathic agents should be carefully evaluated.
- Renal impairment: hydro-electrolytic and acid–base balance should be carefully monitored, in particular in case of active disease (both at diagnosis and at relapse) when the risk of tumor lysis syndrome is higher. Treatment with nephrotoxic drugs should be avoided whenever possible, and dose reductions according to renal function are mandatory in case of drugs excreted by the kidney (see Sect. "Renal failure" for details).
- Cardiac disease: in patients with congestive heart disease or rhythm disturbances, hydro-electrolytic balance should be carefully monitored, in particular if

patients have concomitant renal failure. In case of decrease ejection fraction, treatment with anthracyclines should be avoided if possible or appropriate dose reduction should be adopted. In case of bradicardia, treatment with thalidomide is not recommended. Rare but serious AEs reported during bortezomib administration are hypotension throughout therapy, acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction (including reports in patients with no risk factors for decreased left ventricular ejection fraction): benefits and risks of bortezomib treatment in patients with pre-existing cardiopathy should be therefore carefully evaluated.

– Pulmonary disease: since there have been reports of acute diffuse infiltrative pulmonary disease of unknown etiology such as pneumonitis, interstitial pneumonia, lung infiltration and acute respiratory distress syndrome in patients receiving bortezomib, benefits and risks of bortezomib in patients with pre-existing pneumopathy should be carefully evaluated.

Conclusions

At present, different efficacious therapeutic options are available for patients with myeloma. Physicians can choose the best treatment regimen for each patient balancing efficacy and toxicity, taking into account patient characteristics (age and comorbidities). Patients with renal impairment can be treated with both thalidomide and bortezomib base-regimens, without any dose modification, while lenalidomide can be used after appropriate dose reduction. Lenalidomide-based regimens should be preferred for patients with pre-existing neuropathy. Patients with risk factors for VTE can be safely treated with bortezomib-based regimens, without increasing their risk of thrombosis; immunomodulatory compounds can be administered with appropriate anti-thrombotic prophylaxis. Prompt management of treatment-related complications and dose reduction in case of AEs can further improve treatment efficacy by reducing discontinuation rate. Supportive treatment remains, however, an essential part of the therapeutic management of myeloma, both for treatment of myeloma-related complications (anemia, bone disease, renal failure and infections) and for therapy-related adverse events.

Conflict of interest statement Francesca Gay declares no conflict of interest (other than the honorario reported below). Antonio Palumbo received honoraria from Celgene, Pharmion and Jansen-Cilag. The authors received an honorarium for their participation in this supplement.

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