blood

How I manage the toxicities of myeloma drugs

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The treatment of multiple myeloma is considered a continuously evolving paradigm as a result of the growing availability of new and highly effective drugs, including first- and second-generation proteasome inhibitors, immunomodulatory agents, and monoclonal antibodies. Clinical trials advocate long-term rather than short-term treatment schedules with combinations of these new anti–myeloma drug classes. Although the overall toxicity profile of the recommended regimens can be considered favorable, their increasing complexity and prolonged use warrant a heightened vigilance for early and late side effects, a priori because real-life patients can be more frail or present with 1 or more comorbidities. The treatment decision process, at diagnosis and at relapse, therefore requires myeloma physicians to carefully balance efficacy and toxicity profiles for each individual patient. Early and/or unnecessary tapering or treatment discontinuation for drug-related adverse events may not only reduce patients' quality of life, but also negatively impact their outcome. Accurate knowledge in recognizing and managing the potential side effects of present-day treatment regimens is therefore a cornerstone in myeloma care. Using 5 case vignettes, we discuss how to prevent and manage the most common nonhematological adverse events of anti–myeloma treatment regimens containing proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies. (*Blood*. 2017;129(17):2359-2367)

Introduction

With >150 000 new diagnoses per year worldwide, multiple myeloma (MM) is the second most common hematological malignancy.[1] MM is a very symptomatic cancer causing predominantly bone pain, pathological fractures, fatigue, and infections.[2] Therapeutic progress for MM has been impressive over the last years because of the introduction of several new and potent classes of anti–myeloma drugs, including proteasome inhibitors (PIs),[3-8] immunomodulatory drugs (IMiDs),[9-14] and monoclonal antibodies (MoAbs),[15-18] although corticosteroids and chemotherapy still remain key elements in the treatment algorithm. This evolution has gradually transformed MM from an acute into a chronic-type malignancy with alternating symptomatic and remission phases, allowing the majority of patients to survive for several years.[19] In the current treatment paradigm, short-term therapy has been replaced by longer-term or sometimes continuous regimens combining several highly effective anti–myeloma drugs. This increasing complexity of myeloma treatment warrants even more rigorous efforts to preserve the quality of life of patients[20] and as such requires physicians and other care providers to accurately recognize and manage the various side effects of these newer regimens. Here, we use 5 case reports to describe the most common and serious adverse events of todays frequently used non-chemotherapy-based anti–myeloma regimens as well as their recommended management.

Patient 1. A 66-year-old male MM patient with tremor, burning feet, and lightheadedness

A 66-year-old man was diagnosed with immunoglobulin G (IgG) λ MM (international staging system for myeloma/revised international staging system for myeloma: low risk). His medical history consisted of uncomplicated type 2 diabetes and well-controlled hypertension. He was considered eligible for autologous stem cell transplantation (ASCT), and induction treatment with VTD (bortezomib, thalidomide, dexamethasone) initiated the following: twice-weekly bortezomib in a 21-day cycle, thalidomide at 50 mg/d escalated to 100 mg/d thereafter, and oral dexamethasone 40 mg on the day of and the day following bortezomib. Daily thromboprophylaxis with enoxaparin 40 mg subcutaneously and herpes zoster prevention with acyclovir 2 × 400 mg/d were associated. Shortly after initiating treatment, the patient developed dexamethasone-induced hyperglycemia requiring injected insulin. During cycle 2, he complained of paresthesia in the toes and showed a grade 2 hand tremor, prompting discontinuation of thalidomide. Although both glycemia control and tremor improved, he reported progressive stabbing and burning sensations in the feet and lower legs, particularly at rest and at night, highly suggestive of bortezomib-induced peripheral neuropathy (BiPN). During cycles 3 and 4, bortezomib treatment was reduced to a once-weekly dose, and escalating-dose gabapentin resulted in a gradual alleviation of the neuropathic pain to grade 1 after several weeks. The patient had also complained of lightheadedness, associated with repetitive drops in systolic blood pressure, suggestive of bortezomib-induced autonomic neuropathy, for which the antihypertensive treatment was discontinued. Last, redness and irritation of the upper eyelids prompted repeated ophthalmologist consults. Eventually, the diagnosis of bortezomib-induced blepharitis was suggested, and systemic doxycyclin, along with topical hydrocortisone/oxytetracyclin, was prescribed resulting in symptom improvement.

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Comments about patient 1

Peripheral neuropathy

Although second-generation PIs carfilzomib[6,7] and ixazomib[8] have been introduced in the myeloma treatment algorithm, bortezomib-based regimens are still regularly used, particularly as part of induction therapy before ASCT.[21] Cyclophosphamide,[22,23] or the IMiDs thalidomide[23,24] and lenalidomide,[25] is the typical partner drug in the bortezomib-dexamethasone backbone. Switching from intravenous to subcutaneous[5] and from twice- to once-weekly administration[26] has significantly reduced the incidence and severity of BiPN compared with the pivotal studies[3,4]; still, up to one-third of patients develop clinically significant peripheral neuropathy (PN) during bortezomib treatment (Table 1).

In contrast to thalidomide-induced PN (TiPN) (Table 2), which mostly affects larger myelinated axons, BiPN preferentially targets small myelinated and unmyelinated fibers, typically causing hyperesthesia, neuropathic pain, and altered temperature sensations in the extremities.[27-29] It has been suggested that concomitant cyclophosphamide[30] or IMiD[25] treatment could reduce BiPN; however, reliable evidence is lacking. Whereas some genetic risk factors have been defined,[31,32] clinically useful predictors for BiPN and TiPN are not available, although preexisting PN does heighten the risk. Along this line, our patient may have had subclinical diabetic PN. BiPN is a dose-related condition and may occur in a subacute manner, warranting increased vigilance during the entire treatment, but particularly after the first 2 cycles.[27,33] Adequate patient education and regular screening are therefore critical, also because BiPN is more manageable in its mild forms. BiPN of grade 3 or higher results in severe disabling symptoms and is frequently associated with incomplete recovery.[33] At each hospital visit, accurate patient anamnesis, preferably using self-assessment questionnaires such as Fact-GOG NTX (functional assessment of cancer therapy/gynecologic oncology group-neurotoxicity),[34] should be accompanied by a clinical evaluation of sensation, motor strength, and reflexes whenever needed. Nerve conduction and electromyography tests have limited diagnostic value in detecting small-fiber BiPN, and their correlation with clinical symptoms can be weak.[27,29] BiPN and TiPN are preferably graded using the National Cancer Institute's Common Toxicity Criteria (CTC), version 4,[35] bearing in mind that neuropathic pain increases CTC by 1 level. Our patient's dizziness and orthostatic hypotension were suggestive of thalidomide- or bortezomib-induced autonomic PN. Such requires prompt intervention, particularly in elderly and frail patients, and those at risk for falls. If dose reduction or discontinuation of blood pressure medication is insufficient, an α-adrenergic drug such as midodrine or the mineralocorticoid fludrocortisone is recommended,[27-29] although caution is required with the latter drug in patients with preexisting heart failure.

The treatment of established TiPN or BiPN consists of dose and regimen modifications, including a switch from twice- to once-weekly bortezomib dosing.[27] Patients experience hyperesthesia, neuropathic pain, and allodynia as more disabling than hypo- or paresthesia. The recommended first-line treatment of neuropathic pain is a gradual dose escalation of gabapentin (up to 1200 mg thrice daily) or pregabalin (up to 300 mg twice daily). Potential alternatives are amitryptiline (10-100 mg daily) or serotonin norepinephrine reuptake inhibitors, such as venlafaxine (75-150 mg daily) or duloxetine (60-90 mg daily), or antiepileptics such as carbamazepine (100-600 mg twice daily).[29] Patients showing an insufficient response or a major side effect to these agents may benefit from the opioids tramadol, fentanyl, or buprenorphine and even from inhaled medical cannabis.[36] Poorly validated treatments are lidocaine patches or creams, transcutaneous electrical nerve stimulation, and acupuncture (see Table 3).[27-29] In the absence of convincing clinical evidence and with a potential risk for drug interference, we do not recommend the routine use of high-dose vitamins or other neuroprotective strategies.[27,37]

Table 1. Most common grade 3 or higher side effects of the PIs bortezomib, carfilzomib, ixazomib reported in pivotal trials

	Bortezomib		Carfilzomib		Ixazomib
Type of side effect	Vd (IV)[3]	Vd (SC)[5,7*]	Kd[7]	KRd[6]	IxaRd[8]
Hematological, %					
Anemia	10	10-12	14	18	9
Neutropenia	14	18	NR	30	23
Thrombocytopenia	29	9-13	9	17	19
Nonhematological, %					
Peripheral neuropathy	8	5	1	3	2
Diarrhea	7	2-7	3	4	6
Constipation	2	1-2	1	<1	<1
Nausea	2	0-1	1	NR	2
Vomiting	3	1-2	1	NR	1
Fatigue	5	2-7	5	8	4
Dyspnea	5	2	5	3	NR
Cardiac disease†	NR	3	6	7	3
Arterial hypertension	NR	3	9	4	3
Rash	1	NR	NR	NR	5

IxaRd, ixazomib plus lenalidomide plus dexamethasone; KRd, carfilzomib plus lenalidomide plus dexamethasone; NR, not reported; SC, subcutaneous; Vd, bortezomib plus dexamethasone.

*Twenty-one percent in Dimopoulos et al[7] received bortezomib IV.

†Cardiac failure and ischemic heart disease.

Tremor

Tremor is a well-known side effect of thalidomide,[38] although sometimes misinterpreted as related to (concomitant) dexamethasone therapy. In contrast to TiPN, which is mostly irreversible, thalidomide-induced tremor rapidly responds to dose reduction or discontinuation.

Blepharitis and other side effects

The use of bortezomib may be associated with well-known side effects other than PN, of which the most frequent ones are summarized in Table 1. Our patient suffered from bortezomib-induced blepharitis, a not uncommon but less well-known side effect that typically readily responds to topical antibiotics or systemic doxycyclin.[39]

Patient 2. A 77-year-old male MM patient with chest pain and acute dyspnea

A 77-year-old man with a 5-year history of IgG κ myeloma presented with chest pain and rising paraprotein levels. Prior treatment consisted of VMP (bortezomib-melphalan-prednisone), and lenalidomide- and pomalidomide-based regimens for subsequent relapses.

Assuming a cardiac problem, the general practitioner sought cardiological advice, but baseline electrocardiography, echocardiography, and ^{99m}Tc sestamibi were normal. Two weeks later, intractable chest pain prompted admission to the emergency department, where a distal sternal fracture was diagnosed. The patient received local radiotherapy along with a 4-day pulse course of dexamethasone and opioids. Subsequently, treatment with carfilzomib (20/56 mg/m^2) and dexamethasone (Kd) was instituted. During Kd cycle 2, the patient

Table 2. Most common grade 3 or higher side effects of the IMiDs thalidomide, lenalidomide, pomalidomide reported in pivotal trials

	Thalidomide		Lenalidomide					Pomalidomide
Type of side effect	MPT[10]	Thal-Dex[9]	RD[11-13]	Rd18[49]	Rdcont[49]	MPR[63]	MPR-R[63]	Pom-dex[14]
Hematological, %								
Anemia	14	NR	8-13	16	18	29	27	33
Neutropenia	48	9	12-41	26	28	96	100	48
Neutropenic fever	NR	NR	3	NR	NR	2	7	10
Thrombocytopenia	14	NR	6-15	8	8	50	46	22
Nonhematological, %								
Peripheral neuropathy	10	13†	2	1	<1	NR	NR	1
Diarrhea	NR	NR	3	3	4	3	1	1
Constipation	10	8	2-3	2	2	NR	NR	2
Nausea	1	4	1-3	NR	NR	NR	NR	1
Infection	13	2	10-19	21	22	10	15	30
Fatigue	8*	15	6-15	9	7	5	2	5
Dyspnea	NR	11	2-3	4	6	NR	NR	5
Cardiac disorders	2	NR	6	7	12	5	5	NR
Thrombosis or embolism	12	20	8-26	6	8	1	5	1
Rash	NR	4	1	5	6	5	5	NR

MPR, melphalan plus prednisone plus lenalidomide for 9 cycles; MPR-R, MPR followed by lenalidomide maintenance; MPT, melphalan plus prednisone plus thalidomide; NR, not reported; Pom-dex, pomalidomide plus weekly dexamethasone; RD, lenalidomide plus high-dose dexamethasone; Rd18, lenalidomide plus weekly dexamethasone for 18 cycles; Rdcont, lenalidomide plus weekly dexamethasone until progression; Thal-Dex, thalidomide plus high-dose dexamethasone.

*Listed as a combined event of somnolence/fatigue/dizziness in the original publication, but in the fatigue category in this table.

†Six percent sensory and 7% motor PN.

developed rapid weight gain along with progressive dyspnea. The diagnosis of carfilzomib-induced cardiac failure was made after having excluded other possible etiologies. Carfilzomib treatment was discontinued, and diuretics were started, following which his cardiac function recovered within 1 week.

Comments about patient 2

Cardiac failure

The second-generation PIs carfilzomib[6,7] and ixazomib[8] cause significantly less neurotoxicity than bortezomib, but share other side effects, such as mild reversible thrombocytopenia and gastrointestinal discomfort. In addition, carfilzomib may cause cardiovascular toxicity such as hypertension (in ~15%) and, rarely but more importantly, cardiac failure (see Table 1).[6,7] According to phase 2[40] and 3[6,7] studies, the incidence of severe cardiac failure in carfilzomib-treated patients (without preexisting severe cardiac comorbidity) is ~5%. The exact pathophysiology remains unknown, but endothelial effects[41] and inhibition of proteasome-dependent sarcomeric protein turnover in cardiomyocytes[42] have been discussed as contributing factors. Cardiac failure is thought to be a class effect of PIs because it has also occasionally been reported with bortezomib[43] and ixazomib.[44] Although true carfilzomib-induced cardiac failure is infrequent and usually reversible upon drug discontinuation, many myeloma patients are elderly individuals and frequently present with cardiovascular comorbidities,[45] potentially increasing their risk for drug-related cardiotoxicity. Additional risk factors are previous exposure to cardiotoxic agents or mediastinal radiotherapy, high-dose corticosteroids, cardiac amyloidosis, and concomitant doxorubicin treatment.[46] Even without measurable cardiopulmonary abnormalities, up to one-quarter of patients report mild to moderate self-limiting dyspnea after their carfilzomib infusion.[6,7] Prior to starting carfilzomib, it is recommended to screen for cardiovascular risk factors by a routine clinical examination, or, when indicated by the patient's history, a detailed cardiological assessment. Hypertension and any other cardiovascular risk factors should be adequately controlled prior to starting carfilzomib. During treatment, regular clinical surveillance with blood pressure control is recommended; serial monitoring of cardiac function by echocardiogram[47] or cardiac biomarkers such as N-terminal prohormone of brain natriuretic peptide[41] are considered of limited value in mitigating the risk for carfilzomib-induced cardiac failure. Whenever cardiac failure is suspected, carfilzomib treatment should be discontinued and a detailed cardiopulmonary evaluation performed. Once cardiac function is restored, carfilzomib treatment may be reinstalled based on an individual risk-benefit profile, however, preferably with a reduced-dose regimen.[48]

Patient 3. A 72-year-old female MM patient with weakness, night sweats, and pulmonary infiltrates

A 72-year-old woman with known IgG κ MM presented with sudden onset weakness and night sweats. First-line treatment consisted of an 18-cycle lenalidomide-dexamethasone (Rd) regimen within the FIRST trial,[49] resulting in a very good partial response. Twenty-six months later, she developed progressive disease for which a modified "Cybord" regimen was started with valaciclovir prophylaxis (500 mg/d). Upon admission, the patient had completed 2 Cybord cycles and had achieved partial remission. Physical examination revealed erythema of the uvula and soft palate, and crackles over both lower lungs. Laboratory analysis showed mild anemia, grade 3 leukopenia, and grade 2 thrombocytopenia; C-reactive protein was moderately elevated; and lactate dehydrogenase was within normal limits. Serum electrophoresis revealed increased α1- and 2-globulins, an M-spike in the γ region, and immunoparesis of polyclonal IgA and IgM. Blood gas levels were normal; blood cultures remained negative; and serum and a mouth swab were investigated for a comprehensive viral polymerase chain reaction screen and showed positivity for respiratory syncytial virus. Chest radiograph revealed ground glass opacities and irregular infiltration in the right middle/lower lobe with a small basal effusion, suggesting viral pneumonia with bacterial superinfection for which

Table 3. Prevention and management of frequent side effects of novel drugs

Type of side effect	Prevention	Management
Infections		
Herpes zoster	Antiviral prophylaxis with aciclovir or derivative	Use same drugs (aciclovir, valaciclovir, famciclovir, penciclovir) at therapeutic doses
Influenza	Vaccination	Oseltamivir, zanamivir
Bacterial infections	Vaccination against pneumococci, *H influenzae*. Antibacterial prophylaxis (quinolon or trimethoprim-sulfamethoxazole) only in patients with high risk for infections	β-Lactam antibiotics, macrolides, fluoroquinolons
Gastrointestinal disorders		
Nausea/emesis	Domperidon, alizapride, metoclopramide in case of severe nausea: 5HT3 antagonists, neurokinin-1 antagonists w/o 5HT3 antagonists	Alizapride, metoclopramide in case of severe nausea/emesis: 5HT3 antagonists (aprepitant, fosaprepitant, rolapitant), neurokinin-1 antagonists w/o 5HT3 antagonists (netupitant/palonosetron), dexamethasone
Constipation	Fiber-rich diet, adequate fluid intake, physical exercise, macrogol	Osmotic laxatives (macrogol, lactulose, sorbitol, polycarbophil), stimulant laxatives (senna, bisacodyl, sodium picosulfate); in case of opioid-induced bowel atony: naltrexone or naloxone, distigmin, pyridostigmin
Diarrhea	Normal diet	Loperamid, diphenoxylate + atropine, probiotics; in case of severe symptoms: long-acting somatostatin; in case of bile acid malabsorption, cholesevelam
Neuromusculoskeletal disorders and pain		
Peripheral neuropathy	Regular and careful monitoring of symptoms of PN	Dose reduction, regimen modification or discontinuation of neurotoxic drugs; in case of painful PN: gabapentin, pregabalin, amitriptyline, duloxetine, venlafaxine, opioids (tramadol, fentanyl, buprenorphine, others); lidocaine patches/cream, acupuncture, TENS
Orthostatic dysregulation, hypotonia	Regular and careful monitoring of symptoms, adequate fluid intake, physical exercise	Dose reduction and/or discontinuation of neurotoxic drugs or blood pressure–lowering drugs; midodrine, mineralocorticoids, physical exercise

TENS, transcutaneous electrical nerve stimulation; w/o, without.

she was treated with clarithromycin (500 mg twice daily), an antibiotic also shown to exert anti–myeloma activity in combination with IMiDs.[50] The patient reported moderate improvement within 1 day and was fully recovered within 10 days.

Comments about patient 3

Infections

A recent Swedish population-based study revealed a sevenfold higher risk for bacterial and a 10-fold higher risk for viral infections in MM patients vs controls.[51] Infection poses an important mortality risk within the first 2 to 4 months of treatment and accounts for ~20% of mortality during subsequent follow-up.[51] Reportedly, grade 3 and 4 infections occur in 29% of newly diagnosed patients receiving continuous lenalidomide and dexamethasone,[49] and in 35% receiving bortezomib-lenalidomide and dexamethasone.[52] Bacterial infections predominate during the first weeks of first-line therapy, and viral infections are more frequent during PIs and dexamethasone; in very advanced disease, the spectrum of causative microorganisms widens.[53] In 1 study, bacterial cultures revealed gram-negative in 47%, gram-positive in 39%, and multiple organisms in 14% of infections,[54] the most frequent agents being *Escherichia coli*, *Clostridium difficile*, pneumococci, *Haemophilus*, and viruses.[51,54] Viral infections are typically either reactivations of latent herpesviridae infections and, to a lesser extent, latent hepatitis, or newly acquired acute respiratory virus infections.[55]

MM predisposes to infections because of the often combined effects of immune dysfunction caused by the disease itself, the immunosuppressive effects of anti–myeloma therapy, and frequent age- and disease-related comorbidities.[54] Myeloma affects both the humoral and the cellular immune system, resulting in dysfunction of B and T cells, dendritic cells, and NK cells.[53] The majority of patients are elderly individuals, often with geriatric conditions and disabilities.[55,56] Dexamethasone has pan-immunosuppressive effects and significantly increases the risk for infections, especially when used in high doses and in elderly patients,[11] mandating dose reductions. PIs suppress T-cell function,[57] and high-dose chemotherapy is myelotoxic and, by causing mucositis, temporarily disrupts the mucosal protective barrier.

Although severe bone marrow suppression is less frequent with novel nonchemotherapy anti–myeloma regimens, hematopoiesis can be impaired. Grade 3 and 4 neutropenia are commonly seen with lenalidomide[12,13] and particularly with pomalidomide, which when combined with weekly dexamethasone resulted in an incidence of 26% and 22%, respectively, in highly refractory MM patients.[14] Infections, particularly of respiratory origin, occur predominantly during the first treatment cycles with pomalidomide. The most common grade 3 and 4 adverse events of IMiDs are summarized in Table 2.

Antibacterial prophylaxis

Whereas the majority of myeloma patients do not require antibacterial prophylaxis, it is indicated for those considered at high risk for infection. Although the local epidemiology and hospital guidelines may vary, it should be considered for elderly and frail patients, for patients with a previous history of frequent infections, for those with severe IgG immunoparesis, and for patients with severe cardiopulmonary or renal comorbidities. A *Cochrane Review* showed a significant reduction in mortality with antibiotic prophylaxis in patients with chemotherapy-associated afebrile neutropenia.[58] Although results from randomized trials in MM revealed divergent results,[59,60] antibiotic prophylaxis with either trimethoprim-sulfamethoxazole or a quinolon should be considered in patients with high risk for bacterial infections, particularly during the first few months after the start of therapy.

Intravenous immunoglobulins

Severe humoral immunodeficiency may significantly contribute to the increased risk for infections. Based on historical data,[61,62] treatment with intravenous immunoglobulins (400 mg/kg every 4 weeks) in selected patients with recurrent bacterial infections and immunoglobulin deficiency may be considered.

Prophylactic use of granulocyte colony-stimulating factor (G-CSF)

Patients with relapsed/refractory disease, patients with poor bone marrow reserve, and those receiving myelosuppressive regimens are at increased risk for neutropenia. Whereas prophylactic use of G-CSF is recommended for patients receiving regimens with a high risk for febrile neutropenia[63] and for those with additional risk factors, therapeutic use is advised for patients developing treatment-induced grade 3/4 neutropenia and/or neutropenic fever.[64] Once neutrophils have recovered to $\geq$1000/μL, no dose reductions are required; if not, treatment should be delayed until neutrophils have reached $\geq$1000/μL, with appropriate drug dose reductions thereafter. In clinical praxis, intermittent or short-term use of 30 Mio U of G-CSF is usually sufficient to restore neutropenia.

Vaccination

Reportedly, there is a consensus on the need to vaccinate MM patients and their household contacts against influenza[65,66]; however, recommendations for other vaccinations vary. Some advise to vaccinate MM patients (who do not have specific immunity) against hepatitis A and B as well as *Haemophilus influenzae* and pneumococci. The Centers for Disease Control and Prevention recommends a starting dose of PCV13 (13-valent polysaccharide conjugate) followed by a PCV23 dose (23-valent polysaccharide) at a minimum interval of 8 weeks, and any additional vaccinations using PCV23.[67] The vaccination response in patients with active MM is considered to be suboptimal at best.[68] Some studies suggest monitoring antibody levels and to revaccinate if the antibody response is insufficient.[69] Ideally, patients should be vaccinated in the premalignant phase of the disease, specifically, when presenting with monoclonal gammopathy of undetermined significance or smoldering MM. Alternatively, vaccines should be given during optimal disease control. Vaccination with live vaccines such as varicella is not recommended. Vaccination against herpes zoster is gaining interest because of the observed increase in zoster virus reactivation in patients receiving PIs, MoAbs, dexamethasone, and high-dose therapy. In that regard, results of ongoing studies with an attenuated zoster vaccine in ASCT patients[70] or with new vaccines[71] are awaited.

Antiviral prophylaxis

Prophylaxis with aciclovir or 1 of its derivatives, famciclovir, penciclovir, and valaciclovir, is recommended for all MM patients receiving treatment with PIs[72] and MoAbs.[18] The recommended dosages for prophylaxis are usually ~50% of the therapeutic doses (Table 3).

Patient 4. A 59-year-old male MM patient with a swollen lower leg, diarrhea, and rash

A 59-year-old man diagnosed with IgA κ, stage III MM with standard-risk cytogenetics, was treated with VTD induction followed by ASCT. He achieved complete remission prior to the transplant and tested negative for minimal residual disease in the bone marrow thereafter. Forty-six months after diagnosis, the patient developed a biochemical relapse. Another 6 months later, the M-spike rose to 2.6 g/dL, and low-dose whole body CT showed size increase in 2 osteolytic lesions. Although still asymptomatic, the patient was started on Rd therapy with aspirin (325 mg/d) thromboprophylaxis. Three weeks into treatment, he developed a grade III (CTC criteria) morbilliform rash on the chest and back for which Rd treatment was discontinued and oral prednisone (25 mg on alternate days) was prescribed, along with a corticosteroid ointment. The rash cleared within a week. Lenalidomide treatment was reinstituted at 10 mg/d and later, because of a favorable tolerance profile, increased to the regular 25 mg/d dose. Six weeks later, the patient experienced sudden swelling of the left lower leg. Clinical suspicion of a deep vein thrombosis was confirmed by compression sonography. Lenalidomide and aspirin were discontinued, and a therapeutic regimen of low-molecular-weight heparin (LMWH) led to substantial improvement over 2 weeks. LMWH was later reduced to a prophylactic dose, and continuous Rd was restarted. Twelve months into this regimen, the patient developed increasingly frequent episodes of imperative diarrhea, particularly after the morning medication intake. Loperamide 2 mg after each bowel movement remained without significant clinical improvement, as did specific dietary measures and probiotics. Eventually, treatment with the bile acid binder cholestagel was instituted, which led to immediate improvement of both diarrhea and tenesmus.

Comments about patient 4

Rash

Reportedly, rash is among the most common nonhematological side effects of IMiD therapy. According to a recent meta-analysis, a rash (of any grade) was noted in 27% of patients treated with lenalidomide, and a high-grade rash was noted in 3.6%.[73] Eruptions typically occur during the first month of therapy. They are described as morbilliform, dermatitis-like, acneiform, or as aspecific patchy, raised, or macular lesions, sometimes with localized urticarial appearance and associated pruritus. Reports of toxic epidermal necrolysis and Stevens-Johnson syndrome are rare.[74]

Bortezomib-induced rash is less frequent and usually of lower grade with few patients experiencing grade 3 toxicity.[3] In addition, several other drugs including antibiotics may cause rash or other skin toxicities.

Mild to moderate rashes may be treated with topical corticosteroids and/or oral antihistamines,[75] whereas for more severe rashes, it is recommended to discontinue lenalidomide and to start systemic corticosteroids. Lesions usually clear within 1 to 2 weeks, and most patients

tolerate the reinstitution of lenalidomide as well as the switch from dexamethasone to intermittent prednisone very well, without reappearance of skin symptoms.[76] Nonetheless, real-world studies indicate that a concern for rash reoccurrence prevents many clinicians from restarting lenalidomide,[75] thereby denying the patient further therapeutic benefit of IMiDs. As a special precaution for patients who are at high risk for reoccurrence of symptoms, a slow desensitization strategy may be applied.[77]

Venous thromboembolism (VTE)

VTE occurs frequently in MM patients, in particular, during initial treatment and less so during well-controlled disease or remission, or at relapse.[78] Early studies in patients on IMiDs and high-dose dexamethasone treatment reported incidence rates of up to 33%. The International Myeloma Working Group defined treatment-, patient-, and myeloma-specific risk factors and provided guidelines for prophylactic treatment (see Table 4). They recommend prophylactic dose LMWH or full-dose warfarin (target international normalized ratio 2-3) for patients who have at least 1 treatment-specific or at least 2 patient- or myeloma-specific risk factors, and acetylsalicylic acid (ASA) for patients who are at lower risk.[78] The optimal duration of prophylaxis with LMWH or warfarin for treatment-specific risk factors has not been formally studied, but individual authors recommend at least 4 to 6 months,[79] whereas ASA, because of its convenience, may be continued indefinitely. For patients on IMiD therapy, 2 additional recommendations should be considered. The risk for VTE during lenalidomide maintenance monotherapy is low,[49] obviating prophylaxis. Patients receiving IMiD-based therapy who develop a VTE despite prophylactic treatment should discontinue the IMiD and either substitute ASA with a therapeutic LMWH or warfarin regimen[80] or increase the prophylactic LMWH to a therapeutic one. When the thrombotic complication is resolved, IMiD therapy may be reinstituted at the original dose depending on a benefit-risk assessment, along with anticoagulation therapy. Data on the use of new oral anticoagulants are limited, precluding recommendations for their use for thromboprophylaxis in MM.[81]

Chronic diarrhea

Diarrhea (defined as 4 or more bowel movements of >75% water) is a frequent complication of myeloma therapy. Several factors, alone or in combination, may play a causal role. Gastrointestinal bacterial and viral infections are a frequent cause. In addition, treatment-induced mucositis, neuropathy, and pancreatic insufficiency with associated malabsorption may cause frequent and watery stools. The conventional approach consists of treating the infection, if there is one, and rehydrating the patient. Loperamide (2 mg by mouth, every 3 hours with a daily maximum of 6 doses) may reduce bowel movement frequency, and probiotics may be added in nonimmunocompromised patients. For refractory diarrhea, the somatostatin analogs depot octreotide or lanreotide may be considered.[82] Recently, bile-salt malabsorption was found to cause the diarrhea syndrome that may develop during longstanding lenalidomide treatment.[83] Typically, after a substantial uncomplicated period of lenalidomide treatment, patients develop progressively worsening diarrhea with imperative bowel movements, causing significant social inhibition. The diagnosis is confirmed using ^{75}Selenium homocholic acid taurine scanning or using a diagnostic-therapeutic approach with a gall-acid binder such as cholesevelam (Table 3). A rapid improvement of diarrhea intensity and frequency with up to 6 doses of 625 mg/d confirms the diagnosis.

Table 4. Risk factors for thrombosis and recommendations for thromboprophylaxis[78]

Risk factors		
Treatment-related	**Patient-specific**	**Myeloma-specific**
IMiDs	Age	Active uncontrolled disease
High-dose dexamethasone	Previous VTE	Hyperviscosity
Erythropoietin	Infection	
Anthracyclines	Surgical procedures	
Multiagent chemotherapy	Cardiovascular comorbidities	
	Immobilization	
	Inherited thrombophilia	
	Central venous catheter	

Recommendations for thromboprophylaxis		
Risk factor	**Number of risk factors**	**Therapy**
Treatment-specific	≥1	LMWH or warfarin
Patient-specific	1	ASA
Myeloma-specific	1	ASA
Patient- or myeloma-specific	≥2	LMWH or warfarin

Duration of lenalidomide treatment and second primary malignancies (SPM)

SPMs are slightly more frequent with long-term exposure to lenalidomide, particularly if combined with, or following exposure to, alkylating drugs like melphalan.[84] Presently, recommendations on the (dis-)continuation of lenalidomide-based therapy after diagnosis of an SPM are not available. In such rare instances, the decision is at the physician's discretion considering the type of SPM, the depth and duration of myeloma response, side effects of lenalidomide, and other available treatment options.

Patient 5. A 49-year-old female MM patient with chills and cough, and mood swings

A 49-year-old woman with a 3-year history of IgG λ MM presented with a relapse. Prior treatment consisted of VTD induction, and ASCT followed by bortezomib plus dexamethasone consolidation. At relapse, treatment was started with lenalidomide, dexamethasone, and daratumumab, as part of a clinical trial.[16] Apart from transient chills and cough during the first infusion, subsequent infusions of daratumumab were well tolerated. However, according to her partner and children, each intake of dexamethasone was complicated by insomnia and severe mood swings, negatively impacting the relationship between the patient and her family members.

Comments about patient 5

Infusion-related reaction (IRR)

Immunotherapy is changing the treatment paradigm of MM. The addition of the anti-CD38 MoAb daratumumab to bortezomib-dexamethasone,[17] and Rd[16] regimens has revealed unprecedented therapeutic efficacy for relapsed myeloma. Similar to what is seen with MoAb treatment of various other hematological and nonhematological diseases, IRRs constitute the most common adverse events of

daratumumab. Despite appropriate prevention with a steroid, antihistamine, and antipyretic drug, IRRs occur in ~45% of MM patients receiving daratumumab.[15-17] Reactions are mostly mild to moderate and usually occur with the first infusion only. The most common IRRs are nasal congestion, cough, allergic rhinitis, throat irritation, dyspnea, nausea, and chills. For the prevention of delayed IRRs, oral corticosteroids (20 mg methylprednisolone or equivalent) should be administered for 2 days after the infusion.[85] Preexisting chronic obstructive pulmonary disease constitutes a specific risk factor for bronchospasm. Accordingly, in clinical trials with daratumumab, patients known with severe asthma or a forced expiratory volume in 1 second <60% are typically excluded. Starting anti-CD38 MoAb treatment therefore requires a spirometry evaluation in all patients known or suspected to have chronic obstructive pulmonary disease. Additional pretreatment with a 10-mg dose of montelukast,[86] short- and long-term acting bronchodilators, or inhaled corticosteroids may further reduce the risk.[85] Subcutaneous administration of daratumumab might not only reduce infusion time but also IRRs.[87] Of note, the incidence of IRRs with the anti-CS1 MoAb elotuzumab, consisting mostly of pyrexia, chills, and mild hypertension, is reported to be only 10%.[18]

Psychological alterations

Optimal therapeutic benefit from the current PI-, IMiD-, and MoAb-based MM treatment regimens still requires the association with dexamethasone. Diminishing the high-dose dexamethasone regimen to a once-weekly or low-dose regimen has been shown to significantly reduce potentially life-threatening side effects without losing therapeutic efficacy.[11] However, in addition to the well-known physical side effects like diabetes, myopathy, and cataract, many patients also experience mental and psychological dexamethasone-induced side effects that are important but frequently underrecognized. Specific inquiries with the patient's partner or other family members are of value to accurately assess a potential steroid-induced psychological and/or social problem. If temporary treatment with a sedative or hypnotic does not resolve symptoms, substituting dexamethasone with prednisone may be helpful, especially in elderly and/or frail patients.[88]

Conclusions

Historically, the dose of anti–myeloma drugs and treatment duration has been largely determined by adverse events such as myelosuppression or PN. The introduction of several new potent anti–myeloma agents to the treatment algorithm, together with the traditional compounds, has allowed for various highly effective anti–myeloma regimens. However, this therapeutic diversity has brought more complexity to the treatment decision process, because different regimens perform comparably in meeting efficacy endpoints, yet may exhibit different side-effect profiles. Because the paradigm has shifted from short-term drug exposure to long-term treatment, vigilance for early and late drug toxicities has become even more important. The treatment of choice for an individual patient should therefore rely not only on disease characteristics but also on patient factors such as age, general condition, comorbidities, and side effects of prior treatment. First and foremost, a careful balance between a highly effective treatment regimen and the individual patient's tolerance profile should be considered. During treatment, a proactive approach to prevent adverse events warrants a combination of screening for risk factors, regular monitoring, and collecting patient-reported outcomes. Finally, prompt and appropriate intervention for treatment-related adverse events should be based on scientific knowledge, consensus guidelines, and clinical experience and is of paramount importance for patients with myeloma and for their families.

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