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MULTIPLE MYELOMA (P KAPOOR, SECTION EDITOR)

Common Adverse Effects of Novel Therapies for Multiple Myeloma (MM) and Their Management Strategies

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Abstract

Purpose of Review The purpose of this review was to evaluate management strategies for common adverse effects of novel therapies in multiple myeloma (MM), including immunomodulatory drugs, proteasome inhibitors, monoclonal antibodies, and a histone deacetylase inhibitor.

Recent Findings There are several adverse effects that occur across multiple classes of antimyeloma drugs, including rash, peripheral neuropathy, infusion reactions, and cardiotoxicity, but most can be managed without complete discontinuation of the agent or abandonment of the class. Additionally, several agents have critically important drug-drug interactions or dose-modification implications in hepatic or renal insufficiency that can be easily overlooked, and exacerbate adverse effects.

Summary As treatment of MM moves from fixed-duration traditional chemotherapy to novel agent-based regimens, commonly administered continuously until disease progression or intolerable toxicities, providers must adopt their management strategies for both acute and long-term adverse effects. Early and frequent monitoring for therapy-related complications, dose adjustments when needed, and timely treatment for toxicities are all important steps toward ensuring longevity of treatment from a limited array of therapeutic options that currently exist for a disease with a relapsing and remitting course.

Keywords Toxicities · Immunomodulatory drugs · Proteasome inhibitors · Daratumumab · Elotuzumab · Panobinostat

Introduction

Multiple myeloma (MM) is expected to account for approximately 1.8% of new malignancies and 10% of all hematologic malignancies diagnosed in 2018 [1]. Although it remains incurable, the past two decades have brought substantial advancements in the treatment of newly diagnosed and relapsed refractory disease. While traditional cytotoxic chemotherapy and corticosteroids still play a pivotal role, novel therapies, including monoclonal antibodies, have been instrumental in transforming multiple myeloma into a more chronic condition, necessitating continuous long-term therapy [2••, 3•]. As overall survival improves, management of therapy-related complications is paramount to preserving the quality of life and therapeutic options. In this article, we aim to describe the presentation and management of common adverse effects with novel agents for the treatment of MM, including proteasome inhibitors, immunomodulatory agents, monoclonal antibodies, and histone deacetylase inhibitors.

This article is part of the Topical Collection on *Multiple Myeloma*

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Hematologic Toxicity

Thrombocytopenia and neutropenia remain the most significant contributors to regimen toxicity despite the advent of novel and targeted agents. When multiple agents are integrated into a regimen, the likelihood of hematologic toxicity increases. For example, the addition of daratumumab to lenalidomide and dexamethasone increased the frequency of grade 3 and 4 neutropenia from 37 to 52%, while the addition of ixazomib increased the frequency of grade 3 and 4 thrombocytopenia from 9 to 19% [3•, 4]. Table 1 outlines monitoring parameters with newer agents and dose adjustment recommendations in the setting of neutropenia and

Table 1 Hematologic toxicity monitoring and dose adjustments for novel agents in multiple myeloma

Therapy	Hematologic toxicity monitoring	Dose adjustment for thrombocytopenia	Dose adjustment for neutropenia
Immunomodulatory drugs			
Lenalidomide [5] Available: 2.5-, 5-, 10-,15-, 20-, and 25-mg capsules	CBC weekly for 2 cycles, then every other week for 1 cycle, then every 4 weeks thereafter.	Platelets < 30,000/mm^3: interrupt therapy, follow CBC weekly Platelets return to ≥ 30,000/ mm^3: resume at next lower dose level. Do not dose below 2.5 mg daily. Repeat for each subsequent platelet drop below 30,000/mm^3	ANC < 1000/mm^3: interrupt therapy, follow CBC weekly ANC returns to ≥ 1000/mm^{3}and no other toxicity: resume at full dose. If other toxicities, resume at next lower dose level. Repeat for subsequent ANC drop below 1000/mm^3.
Pomalidomide [6] Available: 1-, 2-, 3-, 4-mg capsules	Monitor complete blood counts weekly for the first 8 weeks and monthly thereafter.	Platelets < 25,000/mm^3: interrupt therapy, follow CBC weekly Platelets return to ≥ 50,000/mm^3: resume at 1 mg less. Repeat for each subsequent platelet drop below 25,000/mm^3	ANC < 500/mm^{3}or febrile neutropenia: interrupt therapy, follow CBC weekly ANC returns to ≥ 500/mm^3: resume at 3 mg. Repeat for subsequent ANC drop below 500/mm^3.
Thalidomide [7] Available: 50-, 100-, 150-, 200-mg capsules	No monitoring specified in package insert as rate of hematologic toxicity much lower. Consider weekly CBC for at least the first cycle and monthly thereafter.	Monitor for signs and symptoms of bleeding including petechiae, epistaxis, and gastrointestinal bleeding, especially if concomitant medication may increase the risk of bleeding. Dose reductions, delays, or discontinuation may be required.	If ANC decreases to below 750/mm^3 while on treatment, the patient's medication regimen should be re-evaluated and, if the neutropenia persists, consideration should be given to withholding thalidomide if clinically appropriate.
Proteasome inhibitors			
Bortezomib [8]	CBC prior to each dose of bortezomib. Mean platelet count nadir is 40% of baseline. No evidence of cumulative thrombocytopenia or neutropenia.	Platelets < 30,000/mm^3 (other than day 1): interrupt therapy, follow CBC weekly If several doses in consecutive cycles are withheld due to toxicity: reduce dose by 1 dose level (from 1.3 to 1 mg/m^2, or from 1 to 0.7 mg/m^2)	Consider dose modification of accompanying agents.
Carfilzomib [9]	CBC frequently throughout therapy noting myelosuppression nadirs between days 8 and 15 of each 28-day cycle	Platelets < 10,000/mm^{3}or evidence of bleeding with thrombocytopenia: withhold dose; if recovery to > 10,000/mm^{3}or bleeding controlled, continue at same dose level For subsequent drops < 10,000/mm^3, repeat and consider 1 dose level reduction when resuming	ANC < 500/mm^{3}with or without febrile neutropenia: withhold dose; if ANC recovers to ≥ 500/mm^{3}and fever resolves, resume same dose. For subsequent drops < 500/mm^3, repeat and consider 1 dose level reduction when resuming
Ixazomib [10] Available: 2.3-, 3-, and 4-mg capsules	Platelet counts at least monthly during treatment, consider more frequently during the first 3 cycles; CBC as clinically necessary	Platelets < 30,000/mm^3: withhold lenalidomide and ixazomib. For the first occurrence, dose reduce lenalidomide first. For subsequent occurrence, repeat holding both agents and alternate dose adjustment between ixazomib and lenalidomide.	ANC < 500/mm^3: withhold lenalidomide and ixazomib. Consider adding G-CSF support. For the first occurrence, dose reduce lenalidomide first. For subsequent occurrence, repeat holding both agents and alternate dose adjustment between ixazomib and lenalidomide.
Histone deacetylase inhibitor			
Panobinostat [11] Available: 10-, 15-, 20-mg capsules	Platelets should be 100,000/mm^{3}and ANC 1500/mm^{3}prior to therapy initiation. Monitor the CBC weekly (or more often as clinically indicated) during treatment.	Platelets < 50,000/mm^3: interrupt therapy, monitor CBC weekly until platelets ≥ 50,000/mm^3, then restart at the next lowest dose level	ANC < 750/mm^3 (with or without febrile neutropenia): interrupt therapy, resume at next lowest dose level when ANC > 1000/mm^{3}and febrile neutropenia, if present, resolves.
Monoclonal antibodies			
Daratumumab [12]	Monitor CBC periodically throughout treatment according to the manufacturer's prescribing information for background therapies.	Dose delay may be required to allow recovery of platelets. No dose reduction is recommended. Consider supportive care with transfusions.	Dose delay may be required to allow recovery of neutrophils. No dose reduction is recommended. Consider supportive care with growth factors.
Elotuzumab [13]	Monitor CBC periodically throughout treatment according to the manufacturer's prescribing information for background therapies.	No dose adjustments required for thrombocytopenia	No dose adjustments required for neutropenia

CBC complete blood count, *ANC* absolute neutrophil count, *G-CSF* granulocyte colony-stimulating factor

thrombocytopenia. Particular attention is warranted when agents are used in new combinations or those not approved by the Food and Drug Administration (FDA). In those instances, adjustments utilized in the original report(s) may be useful. While dose adjustments are a reasonable starting point, a wider scope of associated concerns may also need to be addressed, including management of concomitant therapeutic anticoagulation or venous thrombosis prophylaxis, institution of growth factor, or use of prophylactic antibiotics. An extensive discussion of these topics is outside the scope of this article, but in general if platelets are below 50,000/mm^3, consider holding full-dose anticoagulant or antiplatelet therapy that is administered concurrently with immunomodulatory drugs (IMiD) for venous thromboembolism prophylaxis, and switching to a prophylactic dose of low molecular weight heparin provided that thrombocytopenia is not severe (< 30,000/mm^3).

Rash

Although a variety of classes can cause cutaneous toxicities, IMiDs, particularly lenalidomide, are notorious in this regard.

Immunomodulatory Drugs (Lenalidomide, Thalidomide, and Pomalidomide)

Antimyeloma therapy-related rash is primarily attributable to IMiD therapy, with a recent meta-analysis in all cancers showing a 27% incidence of all-grade rash with lenalidomide, although the incidence in MM may be as high as 43% [14, 15]. The mechanism behind IMiD-associated rash is poorly understood, although broadly has it been attributed to either a hypersensitivity reaction or directly related to the mechanism of the drug [16, 17]. Grade 3 or higher rash is relatively uncommon at 3.6%, and the incidence or severity of rash is not dependent on the dose of lenalidomide or whether it is combined with dexamethasone. Prior IMiD exposure and proven tolerance to a different IMiD does not reduce the likelihood of rash occurrence [16]. IMiD-related rash generally presents in the first month of therapy as morbilliform, dermatitis, or acneiform with localized urticarial appearance and associated pruritis [16, 17]. However, delayed-onset rashes have been reported [15]. Evidence for IMiD class cross-reactivity for cutaneous toxicities is scant, and most of the patients subsequently exposed to another IMiD can tolerate it without experiencing similar cutaneous toxicity [16].

Ixazomib

Ixazomib is approved as combination therapy with lenalidomide and dexamethasone (IRd), complicating interpretation of any associated rash. The incidence of rash with IRd was 36 versus 23% with placebo-Rd [3•]. The presentation of rash was similar to that associated with lenalidomide, occurring most often in the first 3 months of treatment, and was generally self-limiting.

Management of Rash

Patients should be evaluated for concomitant medications known to cause rash, such as antibiotics and allopurinol. Lenalidomide can be continued for grade 1 rash (< 10% of body surface area). Interruption of therapy is required for the management of grade 2 or 3 (10–30% of Body Surface Area BSA or > 30% BSA, respectively), and permanent discontinuation is recommended for grade 4 (life-threatening) cutaneous toxicity. Recently, a more pro-active management strategy has been suggested, including the use of low-potency topical corticosteroids and oral antihistamines (cetirizine or diphenhydramine) until resolution of grade 1 rash; dose interruption with the aforementioned therapeutic intervention for grade 2, with resumption of therapy when rash improves to grade 1; and oral corticosteroids instead of topical steroids for grade 3 rash [17]. A therapy hold and subsequent dose reduction of the IMiD is recommended for a grade 2 or 3 rash in current clinical trials. Lastly, changing weekly dexamethasone to thrice weekly prednisone 30–60 mg orally on alternating days may give more consistent corticosteroid exposure [16]. In a retrospective case series of 52 patients with IMiD rash, 93% were able to tolerate continued therapy with the same IMiD, utilizing dose adjustment, corticosteroid modulation, and supportive care. In rare cases of persistent rash or angioedema, desensitization may be considered [18, 19].

When interruption is considered for the management of rash with IRd regimen, lenalidomide should be withheld first until the rash recovers to grade 1.

An improvement or resolution of rash with this approach would be suggestive of lenalidomide—which has a much shorter half-life than ixazomib—as the culprit. Following recovery, lenalidomide should be resumed at the next lower dose. If rash persists despite this intervention, or recurs, ixazomib should be withheld as well until recovery to grade 1 or lower.

Peripheral Neuropathy

Bortezomib

The risk of developing bortezomib-induced peripheral neuropathy (PN) is up to 80% [20, 21]. The presentation is predominately sensory, and can manifest as hyperesthesia, hypoesthesia, paresthesia, neuropathic pain, and/or weakness which may start distally and progress proximally. Neuropathy

may also be autonomic in nature due to damage in small nerve fibers and manifest as orthostatic hypotension [22]. The incidence increases with pre-existing PN and cumulative dose, but tends to plateau with the standard twice weekly intravenous regimen between 42 and 45 mg/m^2 of exposure [23, 24]. Additionally, there is evidence to support that both disease (MM) and host-related genetic factors may increase the risk of peripheral neuropathy [25]. Several reports have documented a reduced risk of PN with subcutaneous versus intravenous route of administration and weekly versus twice weekly of bortezomib, without compromising its efficacy; and this route and frequency of administration is now preferred [26–28]. Bortezomib-induced PN is thought to be somewhat reversible, with 64% of patients with grade 2 or greater events experiencing improvement or resolution in a median of 3.6 months with dose modification or drug discontinuation [29]. Concomitant use of strong CYP3A4 inhibitors may increase the rate of PN although definitive evidence is lacking [30].

The first-line management of bortezomib-induced PN is dose modification [29], if patients develop grade 1 PN with pain (asymptomatic loss of deep tendon reflexes or paresthesias) or grade 2 PN (moderately symptomatic limiting instrumental activities of daily living) per National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI CTCAE). However, consideration should be given to pre-emptive adjustment (e.g., reduce dose by one level or switch twice-weekly to once-weekly) for patients with grade 1 paresthesia, weakness, and/or loss of reflexes without pain or change in function [23]. Early bortezomib dose adjustments have demonstrated a reduction in neurotoxicity with similar cumulative dose and efficacy [31].

Carfilzomib

In single-agent trials with carfilzomib, 72% of patients had active grade 1 or 2 PN at baseline; however, a majority (87.3%) did not report a change in their PN-related symptoms during treatment. Grade 3 PN was reported in 1.3% of patients suggesting that the risk of PN with carfilzomib alone is low, likely due to limited off-target activity [32]. When carfilzomib is used in combination with other agents, including IMiDs, agents more likely to cause PN should be dose reduced first. While there are no specific recommendations for dose modification with carfilzomib in the setting of PN, if concomitant agents have been adjusted, dose reduction of carfilzomib can be considered [9].

Ixazomib

Greater than one quarter of patients in the ixazomib trial for relapsed/refractory MM have a medical history of PN at study entry, and greater than 50% reported tingling in their hands or feet at baseline.

The incidence appeared to be slightly greater in the ixazomib group versus the placebo group (27 versus 22%), mainly sensory, grade 1 or 2, and 2% reporting grade 3. Only 14% in the ixazomib group reported worsening of existing neuropathy, versus 17% with placebo [3•]. For grade 1 PN with pain or grade 2 without pain, ixazomib should be withheld until recovery to grade 1 or lower without pain or return to patient's baseline and resumed at the same dose level. For grade 2 PN with pain or grade 3 PN, ixazomib should be withheld until recovery to grade 1 or lower, without pain, or return to patient's baseline, and then resumed at one dose level lower [10].

Thalidomide

The incidence of thalidomide-induced PN is up to 75% in patients who receive over 12 months of therapy, and the presentation is predominantly sensory/sensorimotor neuropathy, typically with tingling or painful distal paresthesias affecting the hands and feet probably also including tremor [23]. The incidence is cumulative and dose-dependent and may occur even after therapy has been discontinued, but generally presents over the course of several months [33]. There is inconclusive evidence for the reversibility of thalidomide-induced PN, and permanent nerve damage is possible. Tremor is often rapidly reversible and often responds to a dose reduction or discontinuation of therapy [34•].

The first-line management of thalidomide-induced PN is dose modification; however, validated tools for dose modification are lacking. A majority of current clinical trials and expert consensus recommend limiting doses to < 200 mg/day to minimize PN, discontinuing once grade 2 PN occurs and restarting with a 50% dose reduction when PN returns to grade 1 or less. Additionally, reduction of the dose of thalidomide when targeted responses have been achieved would help minimize this toxicity [23].

Pomalidomide and Lenalidomide

The incidence of peripheral neuropathy in pomalidomide plus dexamethasone trials is reported at approximately 11 to 15% with grade 3 or 4 less than 1% [35, 36]. Long-term follow-up data from a lenalidomide and dexamethasone trial suggest a low incidence of lenalidomide-induced PN at 2.8%, with no grade 4 events [37]. There are no specific recommendations for dose modifications of lenalidomide or pomalidomide in the setting of PN though any incidence of grade 3 or 4 toxicity should result in holding of therapy until symptoms resolve to grade 2 or less and the dose should be reduced by one level. Other agents known to cause PN should be dose reduced first with treatment emergent neuropathy when given concurrently [5, 6].

Treatment of Peripheral Neuropathy

Treatment of PN in MM remains poorly investigated. Neuroprotective interventions remain investigational and are currently not recommended outside of clinical trials [38]. A majority of evidence in chemotherapy-induced PN management derives from data related to treatment with vinca alkaloids, taxanes, and platinum compounds in solid tumors with minimal data in hematologic malignancies [39]. Based on existing evidence, preliminary treatment strategies generally include gabapentinoids (gabapentin or pregabalin), tricyclic antidepressants (amitriptyline, nortriptyline, and imipramine), serotonin and norepinephrine reuptake inhibitors (duloxetine, venlafaxine), and antiepileptics (carbamazepine and oxcarbazepine) [40]. Due to potential side effects and drug-drug interactions, these agents should be initiated, titrated, and managed by a prescriber familiar with their use. Opioid analgesics have been used successfully in refractory PN [41]. Topical therapies including baclofen, amitriptyline, and ketamine have also shown promise [42]. Alternative, non-pharmacologic therapies including acupuncture, biofeedback, or meditation have also been used, with varying success [43, 44].

Venous Thromboembolism

Lenalidomide, Thalidomide, and Pomalidomide

In MM, the incidence of venous thromboembolism (VTE) is 5 to 10%, but can be as high as 30%, and patients are at a particularly increased risk during the early phases of treatment [34•, 45]. The International Myeloma Working Group (IMWG) has defined patient-, disease-, and treatment-specific risk factors to consider when selecting anticoagulation therapy in MM patients [46]. Individual risk factors include obesity (body mass index ≥ 30 kg/m^2), history of VTE, central line, pacemaker, associated disease (cardiac, chronic renal, diabetes, acute infection, immobility), surgery, use of erythropoietin, or blood clotting disorders. Disease risk factors are the diagnosis of myeloma itself and the presence of hyperviscosity. Therapy-related risk factors include the use of IMiD in combination with high-dose dexamethasone ($\geq$ 480 mg/month), doxorubicin, or multi-agent chemotherapy regimens such as bortezomib, thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide (VDT-PACE).

Prevention of VTE

When selecting an agent for thromboprophylaxis, patients with more than one treatment-related risk factor or a combination of two or more individual and myeloma risk factors should receive prophylactic low-molecular weight heparin (LMWH), such as enoxaparin 40 mg subcutaneously once daily or full-dose warfarin targeting an INR of 2 to 3. We now have evidence suggesting that direct-acting oral anticoagulants (DOAC) such as rivaroxaban or apixaban may be utilized as a more convenient substitute for warfarin or enoxaparin [47, 48]. All other patients, including those with no risk factors outside of their diagnosis and only one individual risk factor, can receive aspirin 81 to 325 mg once daily [46]. The optimal duration of prophylaxis with LMWH, warfarin, or DOAC is ill-defined [49]. Aspirin can be continued for as long as patients are on IMiDs; not infrequently, patients have more than one supporting indication for the use of aspirin, including diabetes mellitus or cardiovascular disease. Development of VTE while on prophylactic anticoagulation necessitates discontinuation of the offending IMiD and initiation of full-dose anticoagulation. IMiDs are resumed after therapeutic anticoagulation is achieved and maintained provided the benefits of reinitiating therapy outweigh risks.

Gastrointestinal Adverse Events

Nausea and Vomiting

A majority of agents utilized to treat MM, outside of traditional chemotherapies for hematopoietic stem cell transplant and salvage treatment, do not have high emetogenic potential, and combination with corticosteroids offers both treatment and antiemetic benefits. In the recently updated American Society of Clinical Oncology (ASCO) guidelines, agents such as daratumumab and pomalidomide are categorized as minimal risk (< 10%) and do not require antiemetics as premedication routinely while all other agents are categorized as low-risk [50]. A majority of antimyeloma agents will be prescribed in combination regimens where concurrent weekly dexamethasone can serve as the antiemetic agent. In the case of ixazomib, which requires administration on an empty stomach and has demonstrated up to 22% incidence of vomiting, patients may take dexamethasone with the first meal of the day, wait approximately 2 h, then take their oral ixazomib with or without oral pre-treatment with a serotonin receptor antagonist [10]. These guidelines represent a more aggressive treatment strategy, versus the current National Comprehensive Cancer Network recommendations which continue to categorize all oral multiple myeloma medications as minimal to low-risk, with the exception of panobinostat, and do not recommend any pre-medication [51]. Panobinostat has demonstrated a 36% incidence of nausea and 36% incidence of vomiting [52•]. In our routine practice, outside of the use of alkylating agents, ixazomib and panobinostat, we have not observed nausea or vomiting to be a major issue requiring antiemetics.

Diarrhea

While attributable to a multitude of agents, diarrhea, defined as four or more bowel movements of more than 75% water, is most commonly associated with panobinostat (68%, grade 3/4 25%), lenalidomide (41%), pomalidomide (35%), and ixazomib (34%). Infectious causes (bacteria or viral) should be ruled out if patients have had recent hospitalization, infectious contacts, or antibiotics. Patients should be encouraged to maintain hydration, eat smaller portions, and limit caffeine, alcohol, and dairy. If infectious causes are ruled out or unlikely, treatment with loperamide can be considered. The exception is panobinostat treatment. Patients should initiate loperamide at the first sign of abdominal cramping, loose stools, or the onset of diarrhea. Panobinostat therapy should be interrupted if the patient is having four to six stools per day and both interrupted and dose decreased for seven or more stools per day [11]. Lenalidomide-associated diarrhea has been linked to bile acid malabsorption. Treatments with a reduced dietary fat intake to less than 20% of total calories and colesevelam 625 mg × 6 capsules/day have been successful in reducing stool frequency and improving stool consistency [53, 54].

Cardiac Adverse Events

Proteasome Inhibitors

Multiple myeloma patients have up to a 66% incidence of cardiovascular disease at baseline [55]. Assessment of any cardiac events in MM must consider this baseline risk as well as the cardiotoxicity associated with traditional chemotherapy including alkylating agents, anthracyclines, and stem cell transplants [56, 57]. Proteasome-mediated cardiotoxicity is thought to be related to accumulating intracellular proteins in cardiomyocytes normally cleared via the proteasome pathway [58]. Overall, the risk of bortezomib cardiotoxicity appears to be low [59]. In contrast, carfilzomib cardiotoxicity includes hypertension, arrhythmia, heart failure, ischemic heart disease, and cardiomyopathy [60]. Cardiotoxicity does not appear to be correlated to cumulative exposure although some reports suggest that peak drug levels, duration of exposure, and variability in volume of distribution may be contributors [61]. However, evidence is conflicting on whether high doses of carfilzomib (greater than or equal to 45 mg/m^2) have a higher incidence of cardiovascular toxicity, suggesting that caution should be used if once-weekly regimens are routinely applied in practice [61, 62]. The ENDEAVOR trial which compared carfilzomib and bortezomib head to head noted hypertension in 15 versus 3%, severe dyspnea in 16.3 versus 5.4%, serious heart failure in 2.2 versus 0.6%, and deep vein thromboses and pulmonary embolisms in 10.2 versus 6.2%. [63] While the heart failure appears to be somewhat reversible, serial echocardiograms appear to be of no practical use in predicting such events [61, 64]. Expert opinion suggests that the presence of cardiovascular disease alone does not prohibit the use of carfilzomib therapy; however, patients must be closely observed. If heart failure is noted, there is observational evidence to suggest that a rechallenge after optimizing management of the cardiac condition may be an option [61].

Panobinostat

Panobinostat carries a boxed warning for severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes [11]. The incidence of death associated with panobinostat was higher (8%) than placebo (5%) owing to a higher incidence of myocardial infarction, cerebrovascular accident, and cardiac arrest [52•]. An ECG should be performed prior to therapy initiation and periodically throughout treatment to verify a QTc less than 450 ms. During clinical trials, ECGs were performed prior to each cycle [52•]. If during treatment the QTc is greater than or equal to 480 ms, panobinostat should be interrupted. Potassium, calcium, and magnesium should be corrected, and additional medications should be evaluated for the potential for contribution to QTc prolongation [11]. Because of panobinostat's propensity to cause diarrhea, electrolyte repletion is paramount of therapy success.

Infusion Reactions

Daratumumab and Elotuzumab

Immunotherapy with the CD38-directed fully human monoclonal antibody daratumumab is drastically changing multiple myeloma outcomes [2••]. Infusion reactions occur in approximately 50% of patients, with greater than 92% or more of reactions occurring with the first dose of therapy [12]. A majority of reactions are grade 1 or 2 with approximately 5–10% grade 3. The most commonly reported symptoms include dyspnea, bronchospasms, cough, nasal congestion, throat irritation, and nausea [4, 65, 66]. Pre-medication is required with an antipyretic, antihistamine, and corticosteroid a minimum of 1 h and maximum of 3 h prior to initiation of daratumumab, which may allow patients to administer oral pre-medications at home to save infusion chair time [12]. Some evidence suggests the addition of montelukast prior to the first dose of daratumumab can reduce the rate of infusion reaction by up to 15% [67]. Post-infusion corticosteroids should be given for prevention of delayed infusion reactions unless alternative steroids are indicated by the combination regimen. Pre-existing pulmonary obstructive disease is a known risk factor for hypersensitivity reaction, and patients with an FEV lower than 60% were excluded from clinical trials. In routine

Table 2 Drug interactions and dose modifications in hepatic and renal insufficiency for novel agents in multiple myeloma

Therapy	Drug interactions	Dose modifications in hepatic insufficiency	Dose modifications in renal insufficiency
Immunomodulatory drugs			
Lenalidomide [5] 25 mg orally once daily with or without food on days 1–21, 28-day cycle	- Monitor digoxin plasma levels due to increased Cmax and AUC - Concomitant erythropoietin-stimulating agents or estrogen-containing therapies may have an increased risk of thrombosis	Safe in mild hepatic impairment, minimal data in moderate to severe hepatic impairment. Toxicity may be worse in concomitant renal impairment.	CrCl 30–60 mL/min: 10 mg/day CrCl < 30 mL/min (no dialysis): 15 mg every other day CrCl < 30 mL/min (dialysis): 5 mg daily. On dialysis days, administer the dose following dialysis.
Pomalidomide [6] 4 mg orally once daily without food (2 h before or 2 h after a meal) on days 1 through 21, 28-day cycle	Avoid concomitant use of strong CYP1A2 inhibitors. If a strong CYP1A2 inhibitor must be used, reduce pomalidomide dose by 50%.	Reduce dose by 25% in patients with mild-to-moderate hepatic impairment (Child-Pugh A or B) Reduce dose by 50% in patients with severe hepatic impairment (Child-Pugh C)	Reduce dose by at least 25% in patients with severe renal impairment requiring dialysis. On dialysis days, administer the dose following dialysis.
Thalidomide [7] 200 mg orally once daily preferably at bedtime at least 1 h after the evening meal, ongoing	- Use caution in combination with sedatives and hypnotic agents, which slow cardiac conduction; properties may be additive - It is not known whether concomitant use of hormonal contraceptives further increases the risk of thromboembolism. - Concomitant erythropoietin-stimulating agents or estrogen-containing therapies may have an increased risk of thrombosis	No dose adjustment information available.	No dosage adjustment is needed for patients with renal impairment or patients on dialysis.
Proteasome inhibitors			
Bortezomib [8] Variable schedules	- Closely monitor patients receiving bortezomib in combination with strong CYP3A4 inhibitors. - Avoid concomitant use of strong CYP3A4 inducers	Reduce dose in moderate or severe hepatic to 0.7 mg/m^2. A subsequent dose escalation to 1.0 mg/m^2 or dose reduction to 0.5 mg/m^2 may be considered based on patient tolerance.	No dosage adjustment is needed for patients with renal impairment or patients on dialysis. Dialysis may reduce bortezomib concentrations. Bortezomib should be administered after dialysis.
Carfilzomib [9] Variable schedules	No known major drug interactions	Reduce dose by 25% in patients with mild or moderate hepatic impairment.	No dose adjustment is required in patients with baseline mild, moderate, or severe renal impairment or patients on chronic hemodialysis.
Ixazomib [10] 4 mg orally on an empty stomach, once on days 1, 8, and 15, 28-day cycle	Avoid concomitant use of strong CYP3A inducers [73]	Reduce the dose of ixazomib to 3 mg in moderate (total bilirubin greater than 1.5–3 x ULN) or severe (total bilirubin greater than 3 x ULN) hepatic impairment.	Reduce the starting dose of ixazomib to 3 mg in patients with CrCl < 30 mL/min or ESRD requiring hemodialysis.
Histone deacetylase inhibitor			
Panobinostat [11] 20 mg orally with or without food once every other day for 3 doses per week, weeks 1 and 2, 21-day cycle	- Reduce dose to 10 mg when coadministered with strong CYP3A inhibitors. Instruct patient to avoid star fruit, pomegranate or pomegranate juice, and grapefruit or grapefruit juice - Avoid coadministration with strong CYP3A4 inducers - Avoid coadministration with sensitive CYP2D6 substrates or CYP2D6 substrates that have a narrow therapeutic index - Concomitant use of antiarrhythmic medicines and other drugs that are known to prolong the QT interval is not recommended	Reduce the starting dose to 15 mg in patients with mild hepatic impairment and 10 mg in patients with moderate hepatic impairment. Avoid use in patients with severe hepatic impairment.	CrCl ≥ 30 mL/min: no dose adjustment CrCl < 30 mL/min or ESRD: no dosage adjustment information available.

Table 2 (continued)

Therapy	Drug interactions	Dose modifications in hepatic insufficiency	Dose modifications in renal insufficiency
Monoclonal antibodies			
Daratumumab [12] 16 mg/kg IV Weeks 1–8: weekly Weeks 9–24: every other week Weeks 25+: every 4 weeks	- Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. - Daratumumab may be detected on serum protein electrophoresis and immunofixation assays used for monitoring disease.	Mild or moderate hepatic impairment has no clinically meaningful impact on daratumumab pharmacokinetics.	CrCl > 15 mL/min: no dose adjustment necessary. Has not been evaluated in ESRD on hemodialysis
Elotuzumab [13] 10 mg/kg IV Weeks 1–8: weekly Weeks 9+: every other week	Elotuzumab may be detected on serum protein electrophoresis and immunofixation assays used for monitoring disease.	Mild or moderate hepatic impairment has no clinically meaningful impact on elotuzumab pharmacokinetics.	No dose adjustment is required in patients with baseline mild, moderate, or severe renal impairment or patients on chronic hemodialysis.

AUC area under the curve, *CrCl* creatinine clearance, *CYP* cytochrome P450 enzyme, *IV* intravenous, *SQ* subcutaneous, *ESRD* end-stage renal disease

practice, patients with obstructive airway disease require post-infusion maximization of inhaled long- and short-acting bronchodilators and inhaled corticosteroids [12]. A newer formulation, in combination with hyaluronidase, may allow subcutaneous daratumumab administration and a reduced infusion reaction rate [68].

Elotuzumab, a humanized monoclonal antibody that targets SLAM7, has substantially less infusion reaction potential with a reported incidence of 10%. Infusion reactions typically manifest as fever, chills, and hypertension. All reactions are reportedly grade 3 or less in general, with only 1% of reactions being grade 3 [13]. Despite an improved tolerability profile and recent report of improvement in overall survival with elotuzumab plus lenalidomide/dexamethasone versus lenalidomide/dexamethasone alone, the lack of single agent activity of elotuzumab is a major limitation [69, 70•].

Carfilzomib

Infusion reactions with carfilzomib can occur up to 24 h after treatment and include a variety of flu-like symptoms including fevers, chills, rigors, flushing, vomiting, weakness, dyspnea, hypotension, chest tightness, arthralgias, myalgias, and angina [71]. In early studies, these symptoms occurred concurrently with electrolyte abnormalities and were originally proposed as a tumor lysis syndrome-like reaction [72]. The incidence rates are generally less than 5% and mitigated by (1) pre-hydration with 250 to 500 mL of intravenous fluids prior to each dose in cycle 1 and post dose as needed; and (2) pre-treatment with low-dose dexamethasone 4 mg orally or intravenously, or as specified by the combination regimen. If carfilzomib is being given as a monotherapy regimen, dexamethasone can be discontinued after the first cycle and reinstituted if symptoms recur [9]. Patients can also take dexamethasone at home, up to 4 h prior to carfilzomib to reduce infusion wait time. Caution should be utilized in patients with existing volume overload as pre- and post-hydration can increase the risk for heart failure. Hydration should be tailored to meet the individual patient needs.

Drug Interactions and Dose Modifications

Several, often-overlooked, concerns of targeted newer agents include drug-drug interactions, dosing in organ dysfunction, and food or laboratory effects. Table 2 outlines major drug interactions, administration recommendations, and available information for dosing in the setting of organ dysfunction. Pharmacogenomics data is gaining mainstream accessibility, and abnormalities in CYP3A4, CYP2D6, or CYP1A2 may be particularly helpful in predicting toxicity. Consultation with a pharmacist is recommended [73].

Conclusion

The wide range of novel agents available for the management of multiple myeloma presents both the opportunity for continuous therapy to the patient, but can create a significant burden for care providers attempting to manage overlapping toxicities that may persist long after therapy has been discontinued. With our improved understanding of the field, the focus must begin to shift from selecting a regimen not only for its efficacy data, but also for its tolerability and patient satisfaction. Long-term treatment requires active reporting of adverse effects by the patients and routine vigilant monitoring by the clinicians to ensure prompt and appropriate intervention for the mitigation of both acute and chronic complications.

Compliance with Ethical Standards

Conflict of Interest Kristen B. McCullough, Miriam A. Hobbs, and Jithma P. Abeykoon each declare no potential conflicts of interest.

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- • Of importance
- •• Of major importance

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