New Agents in the Treatment of Multiple Myeloma

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Authors' disclosures of potential conflicts of interest are found at the end of this article

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Treatment options for patients with newly diagnosed and relapsed multiple myeloma (MM) have been rapidly evolving. Several new agents have been approved by the US Food and Drug Administration (FDA) in the past year, three of which introduced new mechanisms of action. The first-in-class histone deacetylase inhibitor panobinostat (Farydak) was approved in February 2015, under FDA Breakthrough Designation status. More recently, three new drugs have been approved for the treatment of MM. Daratumumab (Darzalex), the first monoclonal antibody indicated for the treatment of MM, was approved on November 1; ixazomib (Ninlaro), the first oral proteasome inhibitor, was approved on November 20, 2015; and elotuzumab (Empliciti), the first-in-class immunostimulatory agent, was approved on December 1, 2015. There are several other promising compounds currently in clinical trials. Familiarity with the mechanisms of action, pharmacokinetics, dosing, common and serious adverse events, and strategies for clinical management is essential for safe and effective integration of these agents in risk-adapted treatment of patients with MM.

PANOBINOSTAT

Indication

Panobinostat was approved by the FDA on February 23, 2015, to be used in combination with bortezomib and dexamethasone for the treatment of MM in patients who have received at least two prior chemotherapy regimens (Novartis Pharmaceuticals, 2015).

Formulation

20-mg capsules.

Pharmacology/Mechanism of Action

Gene expression and cell signaling are highly coordinated processes, involving numerous epigenetic mechanisms. These can include modifications of DNA and chromatin structure, including methylation, phosphorylation and ubiquitination (Quina et al., 2006). The regulators of this process consist of histone acetyltransferase and histone deacetylases (HDAC). Together, these participate

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in regulation of gene expression, cell signaling, cell growth, and survival (Narlikar et al., 2002). Human cancers have been shown to have uncontrolled or aberrant HDAC signaling in a variety of diseases, and many therapies have been aimed at inhibiting this pathway. HDAC inhibitors (HDACi) work by inhibiting histone acetylases in the chromosomes, thus repressing the effect of the cell signaling to promote homeostasis. HDACi function by inhibiting specific pathways that regulate chromatin structure, relaxing the chromatin and allowing specific genes to turn on their homeostatic signaling pathways. These consist of either class I-based specific inhibition or nonselective inhibitors that inhibit multiple classes.

Panobinostat is a nonselective histone deacetylase inhibitor (pan-HDACi) that shows activity against all class I, II, and IV HDACs (Prince et al., 2009). It has also been demonstrated to target other non-histone proteins such as p53, HSP90, and HIF1-α that regulate oncogenic signaling pathways (Hideshima et al., 2011). The combination of panobinostat and bortezomib has been shown to have a synergistic effect in preclinical models of MM through inhibition of the proteasome and signaling pathways (Catley et al., 2006; Ocio et al., 2010). See Figure 1 for an illustration of panobinostat's mechanism of action.

Dosing and Administration

Panobinostat capsules are administered orally at 20 mg once every other day for 3 doses per week (days 1, 3, 5, 8, 10, and 12) of weeks 1 and 2 over a 21-day cycle, for 8 cycles. Bortezomib is given in conjunction with panobinostat and dexamethasone on days 1, 4, 8, and 11, with dexamethasone being given on days 1 and 2, 4 and 5, 8 and 9, and 11 and 12, corresponding to the day of and day after bortezomib administration (Table 1). After 8 cycles, panobinostat is administered orally at 20 mg once every other day for 3 doses per week (days 1, 3, 5, 8, 10, and 12) of weeks 1 and 2 of a 21-day cycle for cycles 9 to 16; bortezomib is administered on days 1 and 8 at 1.3 mg/m^2, with dexamethasone 20 mg recommended to be administered on the day of and day after bortezomib administration prior to treatment (Table 1). Prior to the start of chemotherapy, a CBC count, serum electrolyte panel, and electrocardiogram (ECG) should be performed.

Panobinostat should not be given to pregnant or lactating women. In addition, panobinostat has not been studied in patients with renal failure or in pediatric populations. It is recommended to reduce the starting dose of panobinostat in patients with mild or moderate hepatic impairment (Novartis Pharmaceuticals, 2015). Additional guidelines for dose modification are included in Table 2.

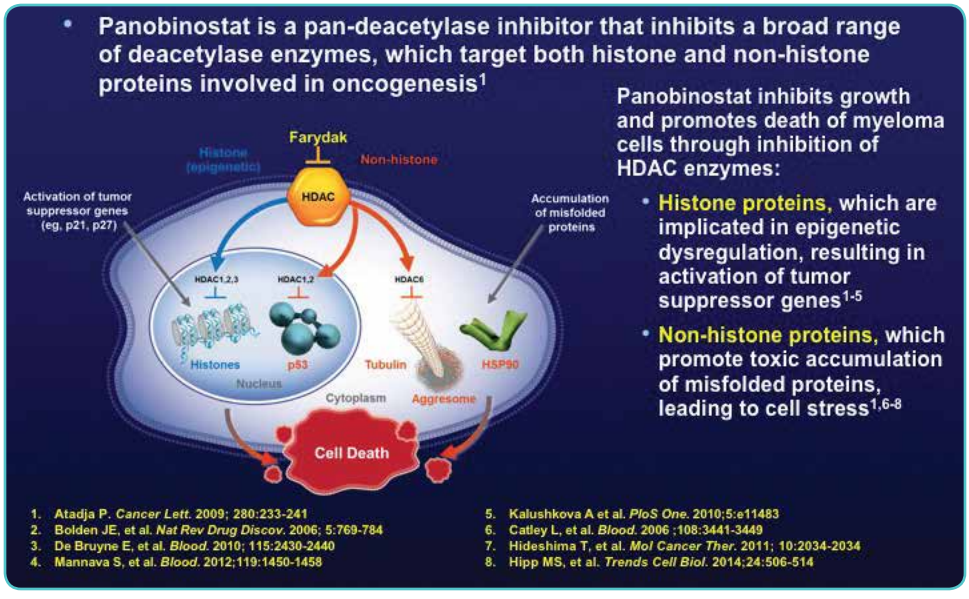

Figure 1. Panobinostat mechanism of action.

Table 1. Panobinostat Recommended Schedule (21-day cycle)

Cycles 1 to 8	Week 1 Days					Week 2 Days					Week 3
Panobinostat	1		3		5	8		10		12	Rest period
Bortezomib	1			4		8			11		Rest period
Dexamethasone	1	2		4	5	8	9		11	12	Rest period

Note. Recommended dosing schedule for panobinostat in combination with bortezomib and dexamethasone during cycles 1 to 8. Panobinostat is dosed orally at 20 mg, bortezomib is dosed at 1.3 mg/m^2, and dexamethasone is recommended at a dose of 20 mg. Information from Novartis Pharmaceuticals (2015).

Clinical Trials: Efficacy and Safety

Panobinostat was originally studied as a single agent in relapsed/refractory MM patients in a phase II study (Wolf et al., 2013). Of the 38 patients treated with panobinostat 20 mg 3 times a week as monotherapy, 1 patient had a partial response (PR) and 1 patient had stable disease (SD). Preclinical studies showed positive results when evaluating the combination of bortezomib and panobinostat (Ocio et al., 2010). Based on these preclinical and clinical studies, the combination regimen of these two agents was further evaluated in MM.

In the phase Ib dose-finding study of panobinostat and bortezomib, panobinostat was dose escalated with bortezomib in four different cohorts on a 21-day cycle (San-Miguel et al., 2013). The maximum tolerated dose established in the study was oral panobinostat 20 mg and bortezomib 1.3 mg/m^2. Overall response rate (ORR) in the expansion phase was 73.3%, with 52.9% in the escalation phase. In patients who were bortezomib-refractory, the ORR was 26.3%. Grade 3/4 adverse events included thrombocytopenia (85.1%), neutropenia (63.8%), and asthenia (29.8%). Five patients (33.3%) discontinued therapy as a result of adverse events.

Based on these findings, a phase II, two-stage, single-arm, open-label study of panobinostat, bortezomib, and dexamethasone was conducted to evaluate ORR in MM. Secondary endpoints included evaluation of minimal response, time to response, duration of response, progression-free survival (PFS), overall survival (OS), and safety and tolerability (Richardson et al., 2013). Fifty-five patients were enrolled on the study, with a median of four prior regimens. The overall response rate was 34.5%, with one near-complete response (nCR) and 18 PR. Median exposure and progression-free duration (PFD) were 4.6 and 5.4 months, respectively. The median duration of response was 6 months. Grade 3/4 adverse events included thrombocytopenia (63.6%), fatigue (25%), and diarrhea (20%). A single patient experienced grade 3 peripheral neuropathy during the study.

A recent multicenter, double-blind, phase III study (Panorama 1) compared panobinostat, bortezomib, and dexamethasone to placebo, bortezomib, and dexamethasone in patients with relapsed or relapsed and refractory MM. Patients received either panobinostat 20 mg or placebo on a 21-day schedule. A total of 768 patients were enrolled in the study, with a median follow-up of 6.47 months in the panobinostat arm and 5.59 months in the placebo group (San Miguel et al., 2014). Median PFS was significantly longer in the panobinostat arm (11.99 months) compared with placebo (8.08 months; $p < .0001$). Overall survival endpoints had not been reached at the time of publication, but a reported median overall survival of 33.64 months for the panobinostat group and 30.39 months for the placebo group had yielded no statistical significance ($p = .26$).

Serious adverse events (SAEs) occurred in 60% of patients who received bortezomib, panobinostat, and dexamethasone compared with 42% of patients in the control arm (San Miguel et al., 2014). The most frequent (≥ 5%) treatment-emergent SAEs reported for patients treated with panobinostat were pneumonia (18%), diarrhea, (11%), thrombocytopenia (7%), fatigue (6%), and sepsis (6%). Cardiac arrhythmias occurred in 12% of patients in the panobinostat arm versus 5% in the control arm. Panobinostat may prolong cardiac ventricular repolarization

Table 2. Panobinostat Dose Modifications for the Most Common Drug-Related Toxicities

Hematologic toxicities

Thrombocytopenia	**Platelets < 50 × 10^9/L CTCAE grade 3**		**Platelets < 50 × 10^9/L with bleeding CTCAE grade 3**	**Platelets < 25 × 10^9/L CTCAE grade 4**
	Maintain panobinostat dose. Monitor platelet counts at least weekly		Interrupt panobinostat. Monitor platelet counts at least weekly until ≥ 50 × 10^9/L, then restart at reduced dose	Interrupt panobinostat. Monitor platelet counts at least weekly until ≥ 50 × 10^9/L, then restart at reduced dose
	Maintain BTZ dose		Interrupt BTZ until thrombocytopenia resolves to ≥ 75 × 10^9/L - If only 1 dose was omitted prior to correction to these levels, restart BTZ at same dose - If ≥ 2 doses were omitted consecutively, or within the same cycle, BTZ should be restarted at a reduced dose	
Neutropenia	**ANC 0.75–1.0 × 10^9/L CTCAE grade 3**	**ANC 0.5–0.75 × 10^9/L CTCAE grade 3 (≥ 2 occurrences)**	**ANC < 1.0 × 10^9/L (CTCAE grade 3) with febrile neutropenia (any grade)**	**ANC < 0.5 × 10^9/L CTCAE grade 4**
	Maintain panobinostat dose	Interrupt panobinostat until ANC ≥ 1.0 × 10^9/L, then restart at same dose	Interrupt panobinostat until febrile neutropenia resolves and ANC ≥ 1.0 × 10^9/L, then restart at reduced dose	Interrupt panobinostat until ANC ≥ 1.0 × 10^9/L, then restart at reduced dose
	Maintain BTZ dose	Maintain BTZ dose	Interrupt BTZ until febrile neutropenia resolves and ANC ≥ 1.0 × 10^9/L - If only 1 dose was omitted prior to correction to these levels, restart BTZ at same dose - If ≥ 2 doses were omitted consecutively, or within the same cycle, BTZ should be restarted at a reduced dose	
Anemia[a]	Interrupt panobinostat until Hb ≥ 10 g/dL; restart at reduced dose			

Nonhematologic Toxicities

Diarrhea	**Moderate diarrhea (4–6 stools/day) CTCAE grade 2**		**Severe diarrhea (≥ 7 stools/day) IV fluids or hospitalization required CTCAE grade 3**	**Life-threatening diarrhea CTCAE grade 4**
	Interrupt panobinostat until resolved. Restart at same dose		Interrupt panobinostat until resolved. Restart at reduced dose	Permanently discontinue panobinostat
	Consider interruption of BTZ until resolved. Restart at same dose		Interrupt BTZ until resolved. Restart at reduced dose	Permanently discontinue BTZ
Nausea or vomiting	**Severe nausea CTCAE grade 3/4**		**Severe/life-threatening vomiting CTCAE grade 3/4**	
	Interrupt panobinostat until resolved, then restart at reduced dose		Interrupt panobinostat until resolved, then restart at reduced dose	

Drug-drug interactions

- Strong CYP3A4 inhibitors: Reduce panobinostat dose
- Strong CYP3A4 inducers: Avoid concomitant use with panobinostat
- Sensitive CYP2D6 substrates: Avoid concomitant use with panobinostat
- Anti-arrhythmic drugs/QT-prolonging drugs: Avoid concomitant use

Note. CTCAE = Common Terminology Criteria for Adverse Events; BTZ = bortezomib; ANC = absolute neutrophil count; Hb = hemoglobin. Information from Novartis Pharmaceuticals (2015).
[a]Defined as Hb < 8 g/dL CTCAE grade 3.

(QT interval). Therefore, panobinostat should be given with caution in patients with cardiac dysfunction. Adverse reactions that led to discontinuation of panobinostat occurred in 36% of patients and included diarrhea, fatigue, and pneumonia. Deaths occurred in 8% of patients in the panobinostat arm versus 5% on the control arm; the most common causes of death were infection and hemorrhage. Hepatic dysfunction (elevated levels of aminotransferases and total bilirubin) occurred in patients treated with panobinostat. Therefore, liver function should be monitored prior to treatment and regularly during therapy.

Implications for the Advanced Practitioner and Recommended Supportive Care

Important safety considerations for use of panobinostat include management of diarrhea (25% severe), correction of blood electrolyte abnormalities, and assessment of cardiac abnormalities with ECG. Baseline and ongoing monitoring should be employed on at least a monthly basis, with CBC and chemistry panel (including potassium and magnesium). ECG monitoring should be performed at baseline, with periodic monitoring in all patients. In addition, patients who receive bortezomib are at risk to develop peripheral neuropathy (PN). To reduce this risk, bortezomib should be given subcutaneously. All patients should be monitored closely for the onset of PN (Moreau et al., 2012).

Corticosteroids such as dexamethasone can lead to numerous side effects such as hyperglycemia, mood swings, insomnia, and proximal muscle weakness. Prior to starting a corticosteroid-containing regimen, patients should be screened for a history of diabetes, mood disorders, and psychiatric illnesses. Periodic monitoring of blood glucose levels, mood disturbances, and irregular sleep patterns is recommended (Faiman et al., 2008).

Gastrointestinal side effects also can occur, particularly diarrhea. Dietary considerations and strategies to minimize nausea and gastrointestinal upset (e.g., avoidance of greasy, fried, heavy meals, use of prophylactic antiemetic agents) should be discussed (Smith et al., 2008). Antidiarrheal agents should be used as indicated. Panobinostat is metabolized through the CYP3A pathway, so dose modifications may be necessary or alternative medication used while the patient is on panobinostat.

IXAZOMIB

Indication

Ixazomib is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least 1 prior therapy.

Formulation

Capsules: 4 mg, 3 mg, and 2.3 mg.

Pharmacology/Mechanism of Action

In the presence of excess immunoglobulin excreted by MM cells, misfolded proteins accumulate in the endoplasmic reticulum (ER). These proteins are degraded by the proteasome in a process termed ER-associated degradation (ERAD; Vembar & Brodsky, 2008). The ubiquitin-proteasome system (UPS) regulates cellular protein homeostasis and is responsible for targeted protein degradation, including misfolded proteins from the ER (Mitsiades, 2015). Proteasome inhibition prevents degradation of misfolded proteins, leading to ERAD impairment and cell death (Hertz, 2012). Multiple myeloma cells are particularly susceptible to proteasome inhibition due to their highly proliferative nature, overproduction of defective proteins that are then degraded by the UPS, and upregulation of specific intracellular signaling pathways dependent on 26S proteasome protein substrates (McBride & Ryan, 2013; see Figure 2).

Ixazomib is a second-generation boronate proteasome inhibitor that inhibits the proteolytic chymotrypsin-like β5 subunit of the 20S proteasome (Kupperman et al., 2010). Ixazomib has shown improvement in both pharmacokinetic and pharmacodynamic parameters compared with bortezomib, with similar efficacy in the control of myeloma growth and prevention of bone loss (Gentile et al., 2015; Richardson et al., 2015). In *in vitro* studies, ixazomib demonstrated a sixfold faster dissociation half-life than bortezomib (18 vs. 110 min), with similar median lethal doses. In preclinical studies, ixazomib was shown to enhance osteoblast formation and to inhibit osteoclast activity and RANKL-induced NF-κB activation in human preosteoclasts, reducing MM-induced

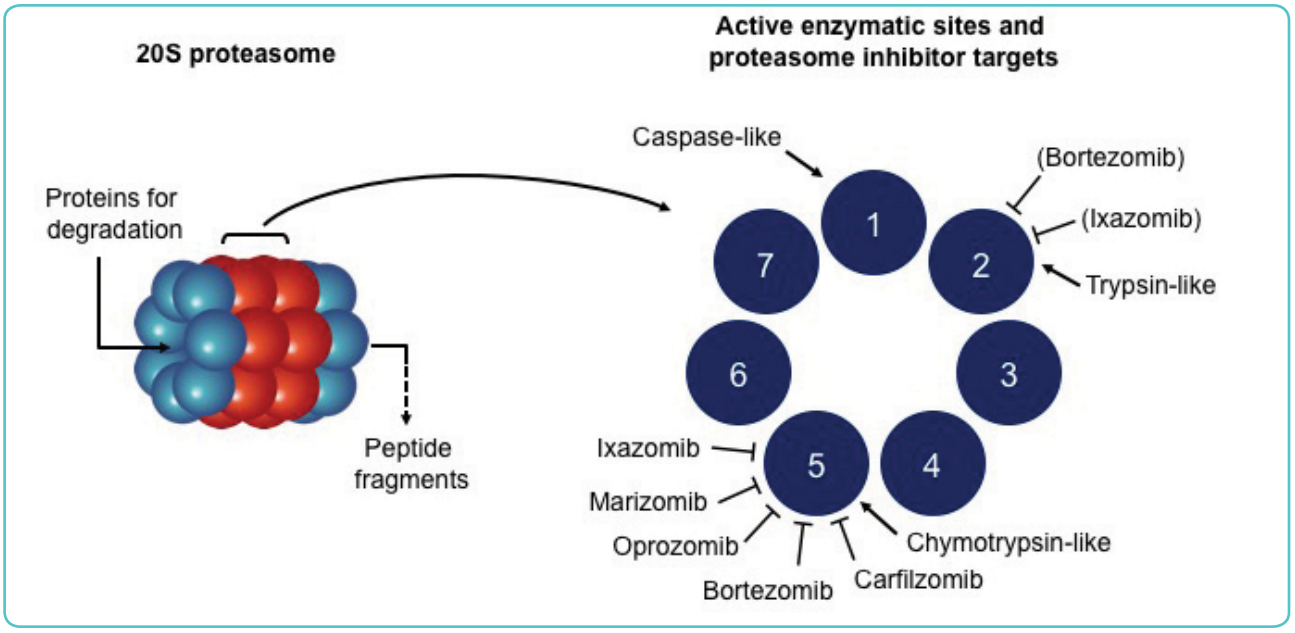

Figure 2. Molecular targets of proteasome inhibitors. Adapted from McBride & Ryan (2013).

bone loss (Garcia-Gomez et al., 2014; Kupperman et al., 2010). In clinical studies, oral ixazomib was rapidly absorbed, with a median time to maximum plasma concentration of 1 hour and a terminal half-life of 3 to 11 days. Body size had no impact on pharmacokinetics, thus enabling a fixed dose (4 mg) of ixazomib in ongoing phase III studies. Ixazomib has not required dose modification for mild or moderate renal impairment in clinical trials data reported to date.

Dosing and Administration

Ixazomib 4 mg is administered on days 1, 8, and 15 every 28 days in combination with lenalidomide 25 mg on days 1 to 21 every 28 days; dexamethasone 40 mg is given on days 1, 8, 15, and 22, for up to 12 induction cycles. This is followed by maintenance ixazomib monotherapy on days 1, 8, and 15 every 28 days until progression (Kumar et al., 2014; Takeda, 2015).

Clinical Trials: Efficacy and Safety

Ixazomib has been investigated in numerous clinical trials as a single agent or in combination with approved agents for the treatment of newly diagnosed MM (NDMM), RRMM, and as maintenance therapy following autologous hematopoietic stem cell transplantation (AHSCT; Gentile et al., 2015; Richardson et al., 2015). Fifty patients with previously untreated multiple myeloma were enrolled in a recent phase 2 study of ixazomib (Kumar et al., 2014). The overall best confirmed/unconfirmed responses in the 21 patients included: CR or better in 11 (52%), near-CR or better in 13 (62%), and VGPR or better in 15 (71%), plus 6 (29%) PR. The median time to first response (PR or better) was 0.99 months (range, 0.92–5.78), and time to best response was 7.46 months (range, 1.02–24.74).

Three ongoing, international phase III studies are investigating ixazomib in combination with lenalidomide-dexamethasone in patients with RRMM (TOURMALINE-MM1–C16010), in NDMM patients not eligible for AHSCT (TOURMALINE-MM2–C16014), and as maintenance therapy compared to placebo following AHSCT (TOURMALINE-MM3–C16019). Additional trials are evaluating ixazomib in combination with dexamethasone or pomalidomide, dexamethasone and panobinostat for RRMM, and combinations of ixazomib, cyclophosphamide, and dexamethasone or ixazomib, melphalan, and prednisone in the frontline setting (Gentile et al., 2015). The dosing of ixazomib in these trials varies in frequency (weekly or twice weekly) and in strength;

however, a fixed 4-mg weekly dosing based on phase I/II pharmacokinetic data is being used in ongoing phase III trials (Richardson et al., 2015). In addition, continuous dosing (until disease progression or unacceptable toxicity) is the current standard approach for treatment in these trials.

The TOURMALINE-MM1 study enrolled patients with a diagnosis of MM who had received 1 to 3 prior therapies (Kumar et al., 2014). Patients who were refractory to lenalidomide or proteasome inhibitor-based therapy (bortezomib or carfilzomib) were excluded. Patients were randomly assigned to receive ixazomib 4 mg on days 1, 8, and 15 or placebo with lenalidomide 25 mg on days 1 through 21, with dexamethasone 40 mg on days 1, 8, 15, and 22. Treatment was given every 28 days until disease progression or unacceptable toxicity. Evaluation was based on the International Myeloma Working Group (IMWG) Uniform Response Criteria. At interim analysis, among the 722 patients randomized to the ixazomib/lenalidomide/dexamethasone arm, a significantly longer PFS was demonstrated compared to the placebo/lenalidomide/dexamethasone arm. Based on these preliminary data, a NDA application for ixazomib was submitted to the FDA on July 14, 2015, and was approved by the FDA on November 20, 2015.

In the phase II study conducted by Kumar et al. (2014), 55 patients were treated with weekly ixazomib (4 mg) in combination with lenalidomide (25 mg on days 1–21, every 28 days) and weekly dexamethasone (40 mg). Twenty-nine patients discontinued the study to proceed to transplant, 15 (71%) patients had drug-related AEs, and only 2 (10%) patients had grade 3 drug-related AEs (hypokalemia, thrombocytopenia). No grade 4 AEs were observed. The most common grade 1/2 drug-related AEs were diarrhea (n = 8, 38%), nausea and pain in extremity (each n = 3, 14%), and anemia and headache (each n = 2, 10%). No PN was reported. Only 1 patient required an ixazomib dose reduction due to an AE (neuralgia).

Similar safety data have been reported in other phase I/II trials, with manageable AEs (Gentile et al., 2015; Richardson et al., 2015). The most common AEs reported across trials included skin rashes, gastrointestinal AEs (nausea, vomiting, diarrhea), thrombocytopenia, and fatigue. Importantly, grade ≥ 3 peripheral neuropathy is rare, and no significant cardiac toxicity has been noted to date (Richardson et al., 2014).

Implications for the Advanced Practitioner and Recommended Supportive Care

All patients should be premedicated with 5-HT_3 antiemetic drugs prior to each dose of ixazomib to prevent nausea and vomiting. Antidiarrheal agents (e.g., loperamide) are recommended to mitigate diarrhea (Smith et al., 2008). Electrolyte monitoring (e.g., potassium) to identify and correct electrolyte abnormalities should be performed. A CBC with differential should be obtained to monitor neutropenia and thrombocytopenia, with intervention (dose reduction or discontinuation of the causative agent) if necessary. If patients receive lenalidomide with ixazomib, standard aspirin or low-molecular-weight heparin prophylaxis with regular physical activity is recommended (Palumbo et al., 2014). Patients should be educated regarding additional side effects of medications and urged to report side effects to the treatment team. As an all-oral regimen, the combination of ixazomib, lenalidomide, and dexamethasone provides a convenient, safe, and effective treatment regimen for patients with MM. Integration of strategies to improve adherence and persistence to the treatment plan are critical to optimize outcomes (Kurtin et al., 2015b).

Corticosteroids are the backbone of antimyeloma therapy. Drugs such as dexamethasone are given in combination with all of the above medications but can lead to many side effects such as hyperglycemia, mood swings, insomnia, and proximal muscle weakness. Prior to starting a corticosteroid-containing regimen, patients should be screened for a history of diabetes, mood disorders, and psychiatric illnesses. Periodic monitoring of blood glucose levels (to assess for hyperglycemia), and of mood disturbance and sleep patterns related to corticosteroids is recommended (Faiman et al., 2008). Objective monitoring of responses to the regimen with routine MM labs (Kurtin et al., 2015) should be documented on a monthly basis.

Disclosure

Dr. Beth Faiman has acted as a consultant, a lecturer, and served on speakers bureaus for Celgene Corporation, Takeda Oncology, and Amgen. Dr. Ali

McBride has acted as a lecturer and served on speakers bureaus for Takeda Oncology. Ms. Hollie Devine has no potential conflicts of interest to disclose. Ms. Charise Gleason has acted as a consultant for Celgene Corporation and Takeda Oncology. Ms. Sandra Kurtin has received honoraria from and acted as a consultant for Celgene Corporation, Takeda Oncology, Amgen, Bristol-Myers Squibb Company, and Novartis International AG. Members of the International Myeloma Foundation Nurse Leadership Board served as reviewers for this work. The authors are solely responsible for the content.

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