LETTER TO OUR READERS

Dear Colleague:

It is my distinct pleasure to offer this newsletter entitled “Considerations in Multiple Myeloma: Side Effect Management,” the fifth issue in a series of newsletters featuring topics relevant to your multidisciplinary team approach to caring for patients with multiple myeloma (MM).

Together with a faculty of hematologists/oncologists, oncology nurses, and oncology pharmacists, we focus our discussion on one topic for each newsletter. Previous issues focused on patients with renal dysfunction, treatment-naive patients, difficult-to-treat populations of MM patients, and health economics. This issue will focus on the side effects associated with various agents and treatment regimens used to treat MM.

It is our sincere hope that the information presented here is of value to you in your care of patients with MM.

Sincerely,

Sagar Lonial, MD
Associate Professor of Hematology and Oncology
Emory University

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Target Audience
This educational publication is designed for physicians, nurses, and pharmacists who wish to enhance their knowledge concerning the management of side effects associated with multiple myeloma therapy.

Learning Objectives
At the completion of this educational activity, participants should be able to
- Summarize the most common side effects associated with novel agents used in the treatment of multiple myeloma (MM)
- Identify the side effects associated with these agents in various combination regimens
- Discuss appropriate management strategies for MM patients experiencing treatment-related side effects and disease-related complications

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LETTER TO OUR READERS
Sagar Lonial, MD

CME INFORMATION

MANAGEMENT OF MULTIPLE MYELOMA: FOCUS ON TREATMENT-RELATED SIDE EFFECTS

MANAGING THE TOXICITIES OF MULTIPLE MYELOMA THERAPIES
Lillian Chou, PharmD; Cindy Ippoliti, PharmD

Mission Statement
Multidisciplinary Cancer Care newsletters provide a forum for sharing expert interdisciplinary treatment perspectives on patient care with the ultimate goal of promoting ongoing professional education to physicians, nurses, and pharmacists in the hematology/oncology community.

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Overview

The American Cancer Society estimates that approximately 19,920 new cases of multiple myeloma (MM) will be diagnosed in the United States in 2008 and more than 10,000 individuals will die of the disease.1 The 5-year relative survival rate for MM is around 34%. This rate is based on patients diagnosed and initially treated more than 5 years ago. Advances in treatment may result in better outcomes for patients diagnosed more recently.2

The approach to the treatment of MM has undergone a radical transformation over the past decade. The emergence of novel biologic therapies, including the immunomodulatory drugs thalidomide and lenalidomide and the proteasome inhibitor bortezomib, are changing the therapeutic paradigm for patients of all ages.1 However, these novel therapies are not without toxicities which may interfere with adherence to therapy, affect quality of life, and in some instances, be life-threatening.3 In order to achieve optimal outcomes from treatment and maintain quality of life, it is imperative that these side effects are appropriately managed.

The most common side effects associated with thalidomide are constipation, fatigue, somnolence, rash, and peripheral neuropathy (PN).3,6 Key grade ≥3 toxicities observed with thalidomide plus dexamethasone combination therapy include deep vein thrombosis (DVT), PN, and weakness.7,8

Lenalidomide, an analogue of thalidomide, was developed with the aim of improving clinical efficacy while offering a better safety profile. Data suggest that lenalidomide is better tolerated than thalidomide in several aspects. For instance, lenalidomide usually does not cause clinically significant somnolence, constipation, or neuropathy. However, this agent is associated with more myelosuppression than thalidomide.9,10

The most common grade ≥3 toxicities associated with lenalidomide are myelosuppressive disorders, mainly neutropenia and thrombocytopenia, which are manageable with dose reductions and growth factor support.10,11 The safety profile of combination therapy with lenalidomide plus dexamethasone is predictable, with neutropenia, thrombocytopenia, anemia, and PN reported. The risk for thromboembolic events is elevated in patients treated with lenalidomide plus dexamethasone in both the frontline12 and relapsed settings.13-16

Peripheral neuropathy has emerged as an important side effect of multiple myeloma therapy.

Peripheral Neuropathy

PN has emerged as an important side effect of MM therapy. This toxicity can have an adverse effect on quality of life and may interfere with optimal treatment.19 PN is commonly associated with the agents bortezomib and thalidomide. In some cases, patients with MM may have neuropathy prior to the initiation of treatment. However, experience from clinical trials in the relapsed setting indicates that the presence of baseline neuropathy does not affect the overall incidence of PN during bortezomib treatment.19

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Based on findings from the phase 2 SUMMIT (Study of Uncontrolled Multiple Myeloma Managed with Proteasome Inhibition Therapy) and CREST (Clinical Response and Efficacy Study of Bortezomib in the Treatment of Relapsing Multiple Myeloma) studies, management guidelines that were developed for bortezomib-induced PN advocate a stepwise strategy for dose reduction, dose interruption, and, if necessary, treatment cessation, enabling a greater number of patients to continue on bortezomib therapy.19,20 These guidelines were subsequently tested in the phase 3 APEX (Assessment of Proteasome Inhibition for Extending Remissions) trial, in which bortezomib-related PN was shown to be reversible in the majority of patients.21 Similarly, in the SUMMIT and CREST trials, PN was shown to resolve or improve in 71% of patients with grade ≥3 PN and/or PN requiring discontinuation.20 Comparable results have been observed in the frontline setting.22,23

In a retrospective analysis of a phase 2 trial of thalidomide in MM, 56% of patients developed symptoms of PN; these symptoms improved in 27% of patients with or without dose reduction or after discontinuing treatment, remained stable in 52%, and worsened in 15%.24 In another study of thalidomide, the incidence of PN increased from 38% at 6 months to 73% at 12 months, with...
81% of responding patients developing this toxicity. To minimize the risk of neuropathy, the researchers suggested that treatment with thalidomide be limited to 6 months or less. Specific management strategies for PN are based on the grade of severity and the associated signs and symptoms, and may include dose and schedule modifications, pharmacologic interventions, nonpharmacologic approaches, and patient education.

At the 2007 American Society of Hematology (ASH) annual meeting in Atlanta, Georgia, Bibas and colleagues presented the results of a study of maintenance treatment with low-dose thalidomide to minimize PN in 54 patients with advanced/relapsed MM. Patients received thalidomide 100 mg/day; if well tolerated, the dose could be increased to a maximum of 400 mg/day. Of 52 evaluable patients, 11 (20%) progressed and 5 (9%) achieved stable disease. Twenty-seven patients (50%) responded to treatment, with 22 and 5 achieving partial response (PR) and complete response (CR), respectively. Seventeen patients experienced symptomatic neuropathy, and their thalidomide dosage was reduced to 100 mg/day for 10 days/month. In 2 of the 17 patients, a mild distal sensory-motor neuropathy had been observed before thalidomide treatment, and after 6 months of therapy, these 2 patients showed a mild clinical and electrophysiological progression of the disease.

During the subsequent 58-month follow-up evaluation, none of the 17 patients who had dose reductions showed progression of clinical and electrophysiological findings; 2 patients, however, had to discontinue therapy due to severe painful paresthesias. After a median of 8 months' follow-up, 10 patients were alive and in remission (2 CR and 8 PR) and 5 showed disease progression. Two of the 8 patients who had achieved a PR discontinued therapy because of severe neurotoxicity. The authors concluded that the incidence of thalidomide-induced neuropathy can be reduced by using lower doses of thalidomide to maintain a high rate of response with less toxicity.

At ASH 2007, Caravita and colleagues reported results of a study evaluating the incidence and severity of PN in 179 MM patients (median age, 66.7 years) who received bortezomib as a single agent or in combination with either dexamethasone, chemotherapy, or thalidomide. The overall response rate (≥PR) was 86%. PN of grade ≥2 was seen in 73 patients (41%) and grade 3/4 in 32 (18%). Responses were independent of the occurrence of PN. Onset of bortezomib-related PN occurred at a median of 84 days (range, 10–449) after initiation of therapy, leading to discontinuation of therapy in 31 patients (17%); resolution or improvement of PN occurred in 16 (51.6%) of the 31 patients at a median of 140 days (range, 27–346) after bortezomib discontinuation.

Preliminary results of 2 phase 1 dose-escalation trials of carfilzomib (PR-171), an investigational tetra peptide proteasome inhibitor, in 54 subjects with various hematologic malignancies, including MM, showed no incidence of painful PN in either study.

Thromboembolic Events

Due to increased baseline hypercoagulability, patients with multiple myeloma are at increased risk of developing venous thromboembolism compared with the general population.

Due to increased baseline hypercoagulability, patients with multiple myeloma are at increased risk of developing venous thromboembolism compared with the general population. Thromboembolic events can affect physiologic functions such as breathing, cognition, and overall function, and should be considered medical emergencies. Impairment resulting from these events can interfere with therapy, treatment options, and patient adherence. Patient education, focused nursing assessment, and proactive prophylaxis against thromboembolic events may increase positive patient outcomes.

Thromboembolic events are a particular risk factor for MM patients treated with lenalidomide or thalidomide, especially in combination with higher dosages of steroids or chemotherapy. Rajkumar and colleagues reported the results of a study involving 207 patients with newly diagnosed MM randomized to receive thalidomide plus dexamethasone or dexamethasone alone. The response rate in patients receiving combination therapy was significantly higher than that achieved with dexamethasone alone (63% vs 41%, respectively); however, increased DVT was associated with thalidomide, such that the authors recommended prophylactic anticoagulation if thalidomide plus dexamethasone is given.

The National Comprehensive Cancer Network Clinical Practice Guidelines for multiple myeloma recommend that the benefit of adding thalidomide to dexamethasone be weighed against the increased risk of side effects. They also suggest that dexamethasone be given alone in patients with a low tumor load, adding thalidomide to the regimen only if no response is seen after 1 to 2 months of therapy.

Data from a randomized phase 3 study of lenalidomide plus high- or low-dose dexamethasone in newly diagnosed MM patients suggest that rates of toxicities were higher in patients receiving the high-dose dexamethasone combination, notably, grade ≥3 thromboembolic events (18% vs 5%). In addition, studies have shown a greater risk of DVT in patients with prior thalidomide exposure.
Safety data from studies using bortezomib in combination with thalidomide or lenalidomide do not indicate an elevated thromboembolic risk with these combinations. Zangari and colleagues reported a low incidence of DVT during the induction phase of their study of bortezomib, thalidomide, and dexamethasone. Palumbo and colleagues reported that no thromboembolic events were observed in a group of 30 patients with relapsed MM who were treated with bortezomib plus melphalan, prednisone, and thalidomide (MPT), despite the absence of any anticoagulant prophylaxis. The incidence of VTE reported by Palumbo and colleagues in 2006 was significantly higher when MPT was given without bortezomib.

Management of DVT involves prophylaxis with therapeutic doses of warfarin (WAR) or low-molecular-weight heparin (LMWH). Aspirin (ASA) may also reduce the risk of thromboembolic events, but it has been suggested that ASA prophylaxis should be reserved for patients unable or unwilling to take WAR or LMWH.

At ASH 2007, Palumbo and colleagues presented interim results from a prospective, multicenter phase 3 trial by the Italian Multiple Myeloma Network. This study evaluated the safety and efficacy of LMWH, low-dose ASA, or low-dose WAR as anticoagulant prophylaxis in 200 newly diagnosed MM patients (median age, 58 years) receiving novel thalidomide-containing regimens (thalidomide-dexamethasone, thalidomide-dexamethasone-bortezomib, or thalidomide-bortezomib-melphalan-prednisone). Patients receiving bortezomib-melphalan-prednisone were used as controls. The incidence of VTE was 3% (2/65) in the LMWH group, 9% (6/66) in the ASA group, 3% (2/69) in the WAR group, and 6% (2/35) in the control group; the differences were not statistically significant. The incidence of bleeding was 0% (0/65) with LMWH, 3% (2/66) with ASA, and 3% (2/69) with WAR.

Zamagni and colleagues reported results of a study investigating the relationship between thrombophilic alterations and VTE risk in 266 MM patients who received 4 months of therapy with thalidomide plus pulsed high-dose dexamethasone in preparation for double autologous stem cell transplantation (ASCT). The risk of VTE was higher among the first 19 patients who did not receive any thromboprophylaxis and lower among the remaining 247 patients who did receive thromboprophylaxis with fixed low-dose WAR (P = .04) (Figure 1). After VTE occurred, most patients continued with thalidomide plus dexamethasone therapy and full thromboprophylaxis, without evidence of progression of thrombosis. The study authors concluded that thromboprophylaxis with fixed low-dose WAR apparently decreased the rate of VTE.

Zangari and colleagues reported results from a study of 69 bortezomib-naive patients with relapsed MM who had normal baseline prothrombin time (PT), partial thromboplastin time (PTT), and platelet counts >100 x 10^9/L. Patients were treated with bortezomib, dexamethasone, thalidomide, cisplatin, and doxorubicin along with prophylactic anticoagulation therapy. Coagulation factors were assessed at baseline and within 1 hour of the first dose of bortezomib on day 1 and day 4 of the first treatment cycle. Results of this pilot study provided in vivo evidence that bortezomib exerts antithrombotic actions mainly by its effects on platelet function. The study authors concluded that even a short bortezomib exposure in vivo can significantly impair platelet number and function, which may explain the low incidence of thromboembolic events observed with bortezomib treatment.
325 mg). Fourteen (58%) of the 24 events occurred in patients not receiving VTE prophylaxis; 7 of these occurred in patients on various MM regimens, including 2 on melphalan/ASCT and 1 each on bortezomib, thalidomide, dexamethasone, denosumab, and cyclophosphamide plus dexamethasone. In this study, VTE events occurred during treatment with lenalidomide plus dexamethasone despite the ASA prophylaxis, suggesting that ASA alone may not adequately prevent VTE in MM patients with multiple risk factors for VTE.44

Myelosuppression

Myelosuppression, another common side effect of MM therapy, can result in anemia, neutropenia, and thrombocytopenia. Depending on the severity, these side effects can have a negative impact on clinical outcomes and quality of life by interrupting or reducing therapy and causing life-threatening complications.45

The hematologic toxicities associated with bortezomib are well characterized and have been shown to be generally predictable and manageable. Bortezomib-related thrombocytopenia and neutropenia are transient and cyclical; in patients experiencing thrombocytopenia, platelet counts decrease and recover predictably during each bortezomib treatment cycle with no evidence of cumulative toxicity.46,47 Notably, despite a higher incidence of grade ≥3 thrombocytopenia with bortezomib compared with dexamethasone in the APEX trial, the incidence of significant bleeding events (including grade ≥3 bleeding events, serious bleeding, and cerebral hemorrhage) was similar between the 2 arms (Figure 2).46 Not surprisingly, patients with low platelet counts at baseline (<70 x 10^9/L) have been shown to be at a higher risk for grade ≥3 thrombocytopenia; thus, bortezomib use in such patients warrants caution but is feasible and can be effective.47

Neutropenia and thrombocytopenia are also common grade ≥3 side effects associated with lenalidomide. Rates of these toxicities vary depending on the trial and the population of patients. In general, neutropenia occurs in approximately 40% to 60% of patients and thrombocytopenia in about 20% to 30% of patients. These toxicities are usually manageable with dose reduction and growth factor support.46,47

At ASH 2007, Quach and colleagues presented the results of a retrospective analysis of 41 relapsed or refractory MM patients treated with bortezomib either with or without dexamethasone.48 The study investigated whether corticosteroid use could modulate the risk of bortezomib-induced thrombocytopenia by impacting platelet budding, release, or survival. Patients receiving dexamethasone had a higher mean platelet count at the start of each new cycle (P=.002), a higher nadir platelet count (P<.001), and a lower mean platelet reduction (P<.001) per treatment cycle versus patients not receiving dexamethasone, who required more platelet transfusions (P=.004). Those requiring transfusions had lower baseline platelets at the beginning of cycle 1. The study authors concluded that, through anti-apoptotic mechanisms at the megakaryocyte or platelet level, dexamethasone may affect either platelet release or platelet survival.48

Orlowski and colleagues reported results of a phase 1 dose-escalation trial investigating the proteasome inhibitor carfilzomib (PR-171) in 29 subjects with various hematologic malignancies, including MM. Patients in the study experienced grade 3 (25%) or 4 events (8%) that were primarily hematologic; dose-limiting toxicities included reversible febrile neutropenia and grade 4 thrombocytopenia.49

Viral Infections

Herpes zoster is the most common infection in patients receiving immunosuppressive agents, such as corticosteroids, and in those undergoing ASCT for MM.50 Characterized by a localized painful vesicular rash, herpes zoster results from reactivation of latent varicella-zoster virus (VZV). Cell-mediated immunity is believed to play a larger role than humoral immunity in prevention of reactivation.51 Because MM is associated with defects in humoral immunity rather than in cell-mediated immunity, patients with MM are not at increased risk of recurrent herpes and herpes zoster infections.52 However, because bortezomib...
interferes with cell-mediated immunity, the investigators in the phase 2 CREST and SUMMIT trials hypothesized that bortezomib may increase the incidence of herpes zoster infections, which were reported in 11% (22/202) of patients in SUMMIT and 13% (7/54) of patients in CREST. They reported that bortezomib monotherapy was associated with a significantly higher incidence of herpes zoster (13%, 42/332 patients) compared with high-dose dexamethasone treatment (5%, 15/332 patients; P = .0002). Most herpes zoster infections were grade 1 or 2; the incidence of grade 3/4 events and infections considered to be serious adverse events was similar between treatment arms, and no herpes zoster-related deaths occurred. The sole herpes viral event that was significantly higher in the bortezomib group than in the dexamethasone group was VZV reactivation (P = .0002), but both arms had similar rates of non–VZV-related herpes viral infections.

At ASH 2007, Kim and colleagues reported results of a study of the incidence of VZV reactivation among 267 relapsed or refractory MM patients treated with bortezomib. All patients had been treated with at least 1 other therapy before receiving bortezomib. VZV reactivation was observed in 22% (58/267) of patients during or after bortezomib treatment and in 9% (25/267) of patients during other treatments, such as vincristine-doxorubicin-dexamethasone or melphalan-prednisone. The incidence of VZV reactivation did not vary with type of regimen (23% with bortezomib monotherapy and 23% with bortezomib plus dexamethasone, alkylating agents, or thalidomide), nor was it related to disease stage, health status, or incidence of other toxicities. VZV reactivation occurred at a median of 46 days (range, 7–560 days) and 2.58 ± 1.97 cycles after the first infusion of bortezomib. The most common form of VZV seen was localized herpes zoster, with most cases responding well to antiviral therapeutics without significant sequelae.

DePaolo and colleagues reported the results of a prospective study of the efficacy of oral acyclovir as prophylaxis for bortezomib-associated herpes zoster. The study included 51 MM patients receiving bortezomib or bortezomib-based regimens for either frontline use or for relapsed or refractory disease, along with oral acyclovir 400 mg twice daily, compared with historical control. The overall incidence of herpes zoster among patients receiving the acyclovir prophylaxis was 0% compared with 13% in the historical control (P = .0026). The study authors concluded that bortezomib-associated herpes zoster in MM patients can be effectively prevented by adding oral acyclovir to the regimen.

References
SIDE EFFECT MANAGEMENT

MANAGING THE TOXICITIES OF MULTIPLE MYELOMA THERAPIES

Lillian Chou, PharmD; Cindy Ippoliti, PharmD
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Introduction
Multiple myeloma (MM) accounts for 10% of all hematologic malignancies, with approximately 20,000 new cases estimated to be diagnosed in 2008.1,2 Recent pharmacologic advancements, including the use of thalidomide, lenalidomide, and bortezomib, have significantly improved response rates and survival. Unfortunately, like most therapies, these agents cause predictable side effects that can increase morbidity and mortality and negatively impact quality of life. This review will discuss the toxicities associated with these agents and their subsequent management.

Thalidomide and Lenalidomide
Thalidomide was originally developed as an antiemetic and sedative agent. However, this agent was withdrawn from the market in 1961 secondary to severe congenital birth defects. Since that time, thalidomide’s unique anti-inflammatory, antiangiogenic, and immunomodulatory properties have provided a rationale for exploring its utility as an agent for the treatment of MM. Unfortunately, therapy with thalidomide is often complicated by serious adverse effects, namely, peripheral neuropathy (PN) and venous thromboembolism (VTE). In an effort to enhance thalidomide’s antineoplastic properties while minimizing its side effects, scientists developed lenalidomide, an amino-substituted analogue of thalidomide with 2000 times greater potency in inhibiting tumor necrosis factor-alpha, a cytokine that promotes angiogenesis and MM cell growth.1

PN remains one of the most challenging and dose-limiting toxicities of thalidomide. This toxicity occurs as a result of thalidomide-induced injury, inflammation, or degeneration of peripheral nerve fibers. The development of neuropathy is related to duration of treatment and cumulative dosing. The incidence of all-grade and grade 3/4 sensory neuropathy in the registration trial of thalidomide plus dexamethasone for MM was 54% and 4%, respectively, and the incidence of all-grade and grade 3/4 motor neuropathy was 22% and 8%, respectively.1 In contrast, the incidence of grade 3/4 neuropathy with lenalidomide plus dexamethasone is only 2%.5

Typically, thalidomide discontinuation will lead to recovery within 3 weeks. If thalidomide therapy is continued, then the neuropathy may progress and become irreversible. All patients should be counseled to recognize the signs and symptoms of PN (most often described as painless numbness, tingling, paresthesias, and/or muscle weakness). As a general guideline, if grade 2 (moderate) neuropathy develops, the thalidomide dose should be halved. Thalidomide should be discontinued if grade 3 (severe) neuropathy is experienced and may be resumed at a reduced dose once symptoms have resolved to grade ≤ 2. Should grade 4 (life-threatening or disabling) neuropathy occur, thalidomide should be discontinued permanently. Table 1 lists adjunctive therapies that can be administered for symptomatic treatment of neuropathy.3

Both thalidomide and lenalidomide are associated with an increased risk of VTE, such as deep vein thrombosis (DVT) and pulmonary embolism (PE). The pathogenic mechanism by which these agents cause thromboembolism is not fully understood. VTE risk is especially great when either thalidomide or lenalidomide are coadministered with high-dose dexamethasone. For example, in one trial, the rate of VTE was 23% in patients receiving thalidomide plus dexamethasone, compared with 5% with dexamethasone alone.4 Similarly, the rate of VTE was 10% to 15% in patients receiving lenalidomide plus dexamethasone, compared with 4% to 5% with dexamethasone alone.5

 Patients should be counseled on how to recognize

<table>
<thead>
<tr>
<th>Table 1. Therapies for the Symptomatic Treatment of Neuropathy4</th>
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<tbody>
<tr>
<td>• Opioids (eg, oxycodone, morphine)</td>
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<tr>
<td>• Tricyclic antidepressants (eg, amitriptyline, nortriptyline)</td>
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<tr>
<td>• Anticonvulsants (eg, gabapentin, pregabalin)</td>
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<tr>
<td>• Serotonin-norepinephrine reuptake inhibitors (eg, duloxetine hydrochloride)</td>
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<tr>
<td>• Nonsteroidal anti-inflammatory drugs and COX-2 inhibitors (eg, ibuprofen and celecoxib)</td>
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<tr>
<td>• Nutritional supplements (eg, vitamin B6, L-glutamine, L-carnitine)</td>
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<tr>
<td>• Topical anesthetics (eg, transdermal lidocaine 5% patch)</td>
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the signs and symptoms of DVT (swollen/erythematous extremity, ache/tightness/pain surrounding the area) and PE (sudden-onset dyspnea/tachypnea, fever, chest discomfort, tachycardia) and should be encouraged to seek prompt medical attention should any of these symptoms arise. Risk-minimizing strategies include modifying the schedule of administration for dexamethasone. For example, consider administering dexamethasone 20-40 mg once weekly or 20 mg on days 1-4 of every 28-day cycle instead of the standard 4-day pulse schedule (days 1-4, 9-12, and 17-20).9

The National Comprehensive Cancer Network (NCCN) Venous Thromboembolic Disease Guidelines recommend prophylactic anticoagulation in patients treated with thalidomide or lenalidomide in combination with dexamethasone.10 The decision to prescribe thromboprophylaxis should be based on the presence of baseline risk factors, including patient-related factors (obesity, history of VTE, comorbidities) and treatment-related factors (concomitant high-dose dexamethasone, doxorubicin, or recombinant erythropoietin products). Some recommendations include aspirin (81-325 mg daily) as thromboprophylaxis for patients with low risk of VTE, and low-molecular-weight heparin (enoxaparin 40 mg subcutaneously daily) or full-dose warfarin (to maintain an international normalized ratio of 2.0-3.0) as thromboprophylaxis for high-risk VTE patients.11 Since most cases of VTE are reported within the first 6 months of initiating therapy, it is recommended that anticoagulant prophylaxis be administered for approximately 6 months and then continued if additional risk factors are present.11

Myelosuppression is the dose-limiting toxicity of lenalidomide. In the registration trials of lenalidomide plus dexamethasone in relapsed MM, the incidence of grade 3/4 neutropenia ranged from 30% to 41%, and grade 3/4 thrombocytopenia ranged from 10% to 15%.9 Increased incidence of grade 3/4 myelosuppression has been linked to patients who have received a prior autologous stem cell transplant and who have impaired renal function.12 Therefore,
lenalidomide should be dosed appropriately for renal dysfunction. Myelosuppression during lenalidomide therapy may be effectively managed through dose reductions or interruptions (Table 2).14

Bortezomib

Bortezomib is a proteasome inhibitor FDA-approved for the treatment of MM.15 This agent targets the 26S proteasome, and its effectiveness is the result of this mechanism. The inhibition of the 26S proteasome leads to dysregulation of cellular function, ultimately resulting in apoptosis. Other possible mechanisms of action of bortezomib include inhibition of NF-κB activation, inhibition of the binding of myeloma cells to bone marrow stromal cells, and inhibition of angiogenesis. Bortezomib is administered twice weekly (days 1, 4, 8, and 11) at a dose of 1.3 mg/m2 every 21 days.16 Dosage adjustment is not required in patients with severe renal dysfunction, including those with end-stage disease and those requiring dialysis.17,18 The most commonly reported side effects of bortezomib include PN, thrombocytopenia, and hypotension.16

Hypotension was reported in up to 12% of patients treated in phase 2 and 3 trials of bortezomib. The manufacturer recommends caution in treating patients with a history of syncope or patients who are dehydrated.16 Adjustments in antihypertensive medications may be necessary during therapy with bortezomib.

Thrombocytopenia occurs in up to 38% of patients treated with bortezomib, although drug discontinuation is rarely necessary.16 The platelet count predictably nadirs on day 11 of treatment and typically recovers by the start of the next treatment cycle. The thrombocytopenia does not appear to be cumulative and is more frequent and severe in patients who start with a pretreatment platelet count <75,000/mcL. Platelet counts should be checked prior to each dose of bortezomib and the dose held for platelets <25,000/mcL; subsequent doses should be reduced.16

Bortezomib-induced PN (BIPN) is a frequent and severe dose-limiting toxicity. It is characterized by neuropathic pain in the fingertips and toes, distal sensory loss, suppression of deep tendon reflexes, and changes in proprioception. It typically occurs during the first treatment cycle and peaks by the 5th cycle. A recent comprehensive review on BIPN discusses this topic in detail, including possible pathogenesis and diagnosis.1 The incidence of this toxicity can be as high as 60%, with more than 15% of patients experiencing grade 3/4 PN. Dose adjustment and drug discontinuation has been warranted in 12% and 5% of patients, respectively. These measures have improved the symptoms of BIPN in the majority of patients, and strict adherence to dose modification guidelines is strongly recommended (Table 3).16 Management of BIPN is similar to other neuropathies and is largely aimed at symptomatic control of pain (Table 1).

Summary

Significant advances in the treatment of MM have positively impacted patient survival. Although some therapies are associated with serious toxicities, careful monitoring and early intervention can greatly reduce the morbidity and mortality associated with these treatments.

References

**Introduction**

Multiple myeloma (MM) is the second most prevalent hematologic cancer after non-Hodgkin’s lymphoma. The disease is characterized by bone lesions, hypercalcemia, anemia, renal impairment, and increased serum total protein concentration. Although MM remains incurable, new treatment options based on the biology of the disease have improved patient response rates and increased overall survival. Nurses, as integral members of the healthcare team, play a critical role in identifying supportive care needs and managing side effects related to MM treatments.

**Supportive Care Issues**

Bone lesions are a hallmark presenting symptom of MM. The pathobiology of this condition involves malignant cells, which produce osteoclast-activating factors that destroy bone cells and lead to osteolytic lesions, severe bone pain, and pathologic fractures. The most commonly involved areas include lumbar and thoracic vertebrae, as well as ribs, skull, pelvis, and proximal long bones. Spinal cord compression may occur, and if it does, it is considered an oncologic emergency. Management of bone lesions includes treatment of the myeloma, bisphosphonate therapy, physical therapy, radiation therapy, pain medication, kyphoplasty, and vertebroplasty.

Bisphosphonates, including pamidronate and zoledronic acid, are recommended for all myeloma patients with bone disease. These agents are also used to treat hypercalcemia of malignancy. Patients receiving bisphosphonates must be monitored for renal dysfunction and osteonecrosis of the jaw (ONJ). Updated clinical practice guidelines published by the American Society of Clinical Oncology (ASCO) recommend that patients with preexisting mild to moderate renal impairment (creatinine clearance 30-60 mL/min) receive a reduced dose of zoledronic acid. For patients with extensive bone disease and existing severe renal impairment (creatinine clearance <30 mL/min), pamidronate 90 mg given over 4 to 6 hours is recommended.

Nurses, as integral members of the healthcare team, play a critical role in identifying supportive care needs and managing side effects related to multiple myeloma treatments.

**ONJ is an uncommon complication that causes avascular necrosis of the maxilla or mandible. Symptoms of ONJ, including tooth or jaw pain or exposed bone, may be related to the duration of bisphosphonate therapy. The ASCO guidelines recommend that all cancer patients receive a comprehensive dental evaluation and preventive dentistry prior to beginning bisphosphonate therapy. Patients should also be treated for any active oral infections, and sites at high risk for infection should be eliminated. While receiving bisphosphonate therapy, patients should be urged to maintain excellent dental hygiene and avoid invasive dental procedures.

Anemia is often the most common presenting symptom of MM. The cause of anemia is multifactorial: it can be the result of bone marrow replacement by plasma cells, erythropoietin (EPO) deficiency, renal failure, chemotherapy or radiation therapy, and/or unregulated cell apoptosis. Patients with MM may require transfusions of packed red blood cells, and once treatment is initiated, the anemia often improves.

Recombinant human EPO (rHuEPO) and darbepoetin alfa have shown beneficial effects in the treatment of anemia. However, there are several factors to consider when administering these agents, including dose, schedule, and type of EPO; baseline EPO levels; predictors of response; and the role of iron repletion. In myeloma patients, another important consideration is the increased risk of thrombosis associated with the disease, especially for patients who are treated with the immunomodulatory agents thalidomide and lenalidomide.

Renal failure is another common and significant complication of MM. Primary causes of this condition are hypercalcemia and precipitation of monoclonal light chains in distal and collecting renal tubules. Other contributing factors include dehydration, use of nonsteroidal anti-inflammatory agents, and radiographic contrast media, which can exacerbate the formation of precipitate within the renal tubules.

Reversibility of renal failure in MM patients is highly variable. Factors associated with renal function recovery include a serum creatinine level lower than 4 mg/dL, a 24-hour urine protein excretion lower than 1 g/24 hr, and a serum calcium level higher than 11.5 mg/dL.

**Treatment-Related Side Effects**

For the purpose of this discussion, treatment-related side effects will focus on the use of novel therapies in MM, including the immunomodulatory drugs...
thalidomide and lenalidomide and the proteasome inhibitor bortezomib.

Peripheral neuropathy

Peripheral neuropathy (PN) is an injury, inflammation, or degeneration of the peripheral nerve fibers. This condition often causes symptoms such as numbness and tingling, sensitivity to touch, paresthesias, burning pain, muscle weakness, and lack of coordination. In rare cases, severe PN may result in muscle paralysis, breathing difficulties, and organ failure. In one study, neuropathy was present in approximately 80% of previously treated MM patients. In the registration trial of thalidomide in newly diagnosed patients with MM, the incidence of treatment-induced PN was 54% for all grades. Baseline assessment and monitoring at each visit is crucial and includes identification of risk factors, review of current medications and previous chemotherapy regimens with neurotoxic agents, and presence of PN-associated symptoms. Risk factors for PN include nutritional diseases such as vitamin B12 deficiency, endocrine diseases such as diabetes and hypothyroidism, hereditary diseases such as Charcot-Marie-Tooth syndrome, and infectious diseases such as HIV or Lyme disease. Specific dosing adjustments are recommended for PN occurring with thalidomide or bortezomib therapy. Symptom control includes treatment with vitamins/minerals (B, folic acid, E, magnesium, potassium), amino acids (acetyl-t-carnitine, alpha-lipoic acid), and topical creams.

FDA-approved agents for the treatment of diabetic neuropathy include duloxetine 60 mg daily and pregabalin 50-100 mg 3 times daily, both of which have been used to decrease painful chemotherapy-induced neuropathy. Pregabalin needs to be adjusted for renal insufficiency.

Venous thromboembolism

Venous thromboembolism (VTE) is a significant risk for MM patients for several reasons, including the biology of the disease, inactivity caused by fatigue or pain, and the effects of novel agents such as thalidomide and lenalidomide. Prophylactic strategies are not yet standardized, but several have been effective in lowering the risk of developing VTE, including daily aspirin (81-325 mg/day), therapeutic warfarin to target international normalized ratio of 2 to 3, and prophylactic enoxaparin 40 mg/day subcutaneously. It is recommended that patients be screened for the risk of developing a VTE event before starting immunomodulatory therapy. Risk factors include (but are not limited to) use of certain drugs (EPO, high-dose dexamethasone, doxorubicin), history of thromboembolic event, obesity, concurrent cardiac or renal disease, diabetes, acute infection, and surgery.

Nurses need to educate patients regarding the possibility of VTE and which prevention strategies to follow, including maintaining activity and oral hydration and monitoring for symptoms of blood clots such as calf tenderness and unilateral extremity swelling. If patients are taking warfarin, they need to be apprised of potential dietary and drug interactions.

Myelosuppression

Myelosuppression is another side effect seen with the use of novel therapies. The hematologic toxicities associated with lenalidomide include anemia, leukopenia, and thrombocytopenia, and it is recommended that blood counts be monitored every 2 weeks. Growth factors such as granulocyte colony-stimulating factor can be administered for neutropenia, and EPO-stimulating agents may be given to patients to maintain their hemoglobin at 12 g/dL. Thrombocytopenia is the most common hematologic toxicity associated with bortezomib. Platelets are lowest at day 11, but in the presence of normal bone marrow function they will recover by the next cycle. It is recommended to hold treatment at the onset of thrombocytopenia if a patient's platelet count is less than 25,000/mL; therapy may be reinitiated at a 25% dose reduction with platelet recovery.

Gastrointestinal side effects, including constipation, diarrhea, nausea, and vomiting, may occur with novel therapies. Management of nausea and vomiting includes use of antiemetics, assessment for dehydration, and replacement of electrolytes. Constipation can be addressed with dietary changes, increased activity, and a bowel regimen. Diarrhea may require increased fluid replacement, antidiarrheals, and dietary changes. For any grade 3 nonhematologic toxicity, treatment should be held until the toxicity resolves, and then a dose reduction may be required.

Conclusion

Novel agents and treatment regimens for MM have led to increased response rates and longer survival times compared with conventional chemotherapy. However, the toxicities associated with these agents have the potential to seriously affect patient quality of life and interfere with optimal treatment. Oncology nurses must assume an active role in the identification and management of side effects associated with these therapies. Patients should be educated regarding the specific toxicities that may occur with various agents and regimens, and must be made aware of the importance of early reporting of symptoms.
NURSING IMPLICATIONS

References

CASE STUDY

Case Study: A 46-Year-Old Woman Diagnosed With Multiple Myeloma

Charise Gleason, MSN, ANP-BC, AOCNP, Emory University, Atlanta, GA

Patient History
A 46-year-old previously healthy woman initially presented to her physician with left rib pain of 2 to 3 weeks' duration. This pain then progressed to the right rib and lower back with spasm. She initially received symptomatic care and was subsequently referred for a more extensive evaluation that demonstrated the presence of an IgA paraprotein of 4.9 g/dL.

Bone marrow biopsy demonstrated infiltration of clonal plasma cells with lambda light chain restriction, comprising approximately 40% to 50% of the aspirate smear. Conventional cytogenetics were normal, and fluorescence in-situ hybridization was negative for t(4;14), t(11;14), and loss of P53 and positive for deletion (13)(14), and gain of CCND1.

Axial skeletal survey revealed diffuse lytic disease throughout, with osteopenia and multiple compression fractures of the spine. MRI revealed end plate compression fractures of the T11, T12, L1, L3, and L4 vertebrae.

Diagnosis
The patient was diagnosed with International Staging System stage II symptomatic multiple myeloma, with anemia, hypercalcemia, and significant bone involvement.

Treatment
The patient was initiated on combination therapy with lenalidomide 25 mg po on days 1 to 14 of a 21-day cycle; bortezomib 1.3 mg/m² IV on days 1, 4, 8, and 11 of a 21-day cycle; and dexamethasone 20 mg po on the day of and day after bortezomib. She was also referred for vertebroplasty and went on to have the procedure performed at L3, L4, and L5, which resulted in significant pain improvement.
CASE STUDY

After 1 cycle of combination therapy and supportive care, the patient was once again ambulating and no longer used the wheelchair. She also remained on bisphosphonate treatment monthly and started on prophylactic antimicrobials with trimethoprim/sulfamethoxazole 3 times weekly, antiviral with acyclovir 400 mg po every 12 hours, and deep vein thrombosis prophylaxis with aspirin, 325-mg enteric-coated tablet daily.

Following 4 cycles of induction therapy, autologous peripheral blood stem cells were collected using granulocyte colony-stimulating factor mobilization. The patient achieved a very good partial remission following 3 cycles of treatment, and a complete response following 5 cycles of treatment. She tolerated therapy without significant side effects and achieved normalization of her CA and blood counts. At the start of cycle 5 of treatment, she did develop grade 1 peripheral neuropathy (PN) with mild pain in both lower extremities with decreased reflexes as well as decreased sensation to pinprick touch to both mid-feet. The bortezomib dose was modified per protocol to 1 mg/m² on days 1, 4, 8, and 11. The patient was also initiated on vitamin supplements and pregabalin 5 times daily, with complete resolution of her symptoms.

The patient completed 8 cycles of therapy and is currently on maintenance therapy with single-agent lenalidomide. She remains in remission and is tolerating therapy with minimal side effects.

The patient achieved a very good partial remission following 3 cycles of treatment, and a complete response following 5 cycles of treatment.

Peripheral Neuropathy

PN is one of the key toxicities associated with bortezomib, and approximately one third of patients receiving this agent will experience some form of neurotoxicity. It is important to aggressively monitor for PN and use established dose modification guidelines to minimize the development of worsening toxicity. Use of a neurotoxicity assessment tool can assist the healthcare team in identifying and grading the neuropathy.

Bortezomib-associated PN is usually sensory related, and patients may report symptoms such as numbness, tingling, burning, cramping, or weakness. Appropriate symptom management may include oral supplements with B vitamins, amino acids, and dietary changes. The use of medications such as pregabalin, gabapentin, and duloxetine may provide benefit, but these drugs are currently not FDA-approved for treatment-associated neuropathy and patients receiving them need to be monitored closely.

References

POSTTEST

Considerations in Multiple Myeloma: Side Effect Management

For each question, select the one statement that provides the best answer. Please enter your answers on the Posttest Answer Key.

1. Which of the following is among the most common side effects associated with thalidomide treatment?
   - a. Peripheral neuropathy
   - b. Neutropenia
   - c. Thrombocytopenia
   - d. All of the above

2. Which of the following treatment-related side effects are more common with lenalidomide than thalidomide?
   - a. Somnolence
   - b. Constipation
   - c. Myelosuppression
   - d. None of the above

3. Which of the following is among the most common side effects associated with bortezomib treatment?
   - a. Gastrointestinal events
   - b. Peripheral neuropathy
   - c. Rash
   - d. Both a and b

4. In the study by Bibas and colleagues, patients with advanced/relapsed multiple myeloma (MM) received low-dose thalidomide maintenance therapy in an effort to reduce which treatment-related toxicity?
   - a. Venous thromboembolism
   - b. Myelosuppression
   - c. Peripheral neuropathy
   - d. None of the above

5. According to recommendations set forth by the National Comprehensive Cancer Network, thalidomide should be added to dexamethasone for the treatment of MM patients with low tumor load only if no response is seen with dexamethasone alone.
   - a. True
   - b. False

6. Which of the following statements is FALSE regarding safety data from studies of regimens involving bortezomib in combination with thalidomide or lenalidomide?
   - a. There is no indication of an elevated thromboembolic risk with these combinations.
   - b. A low incidence of deep vein thrombosis (DVT) was seen during the induction phase of a study combining bortezomib, thalidomide, and dexamethasone.
   - c. Despite the absence of any anticoagulant prophylaxis, no thromboembolic events were observed in a group of 30 patients with relapsed MM who were treated with bortezomib plus melphalan, prednisone, and thalidomide (MPT).
   - d. The incidence of venous thromboembolism was significantly lower when MPT was given without bortezomib.

7. Warfarin, low-molecular-weight heparin, and aspirin are used for the prevention of which treatment-related toxicity?
   - a. Myelosuppression
   - b. DVT
   - c. Gastrointestinal events
   - d. None of the above

8. In general, patients treated with lenalidomide are more likely to experience neutropenia than thrombocytopenia.
   - a. True
   - b. False

9. Which of the following statements is TRUE regarding hematologic toxicities observed in the APEX trial?
   - a. The incidence of grade ≥3 thrombocytopenia was higher in the bortezomib arm compared with the dexamethasone arm.
   - b. The incidence of grade ≥3 thrombocytopenia was higher in the dexamethasone arm compared with the bortezomib arm.
   - c. The incidence of grade ≥3 bleeding events was higher in the bortezomib arm compared with the dexamethasone arm.
   - d. None of the above

10. Which of the following statements is FALSE regarding the results of a study by DePaolo and colleagues investigating bortezomib-associated herpes zoster?
    - a. None of the patients who received acyclovir prophylaxis experienced bortezomib-associated herpes zoster infections.
    - b. Bortezomib-associated herpes zoster in MM patients can be effectively prevented by adding oral acyclovir to the regimen.
    - c. Oral acyclovir is relatively ineffective in preventing bortezomib-associated herpes zoster in MM patients.
    - d. None of the above
**EVALUATION FORM**

**Considerations in Multiple Myeloma: Side Effect Management**

Project ID: JE8027515

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. *You must complete this evaluation form to receive acknowledgment for completing this activity.*

**Please answer the following questions by circling the appropriate rating:**

1 = Strongly Disagree  2 = Disagree  3 = Neutral  4 = Agree  5 = Strongly Agree

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### Extent to Which Program Activities Met the Identified Objectives

*After completing this activity, I am now better able to:*

<table>
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<th>Objective</th>
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<tbody>
<tr>
<td>Summarize the most common side effects associated with novel agents used in the treatment of multiple myeloma (MM)</td>
<td>![Rating Options]</td>
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<tr>
<td>Identify the side effects associated with these agents in various combination regimens</td>
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<tr>
<td>Discuss appropriate management strategies for MM patients experiencing treatment-related side effects and disease-related complications</td>
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### Overall Effectiveness of the Activity

*The content presented:*

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### Impact of the Activity

Name one thing you intend to change in your practice as a result of completing this activity:

___________________________________________________________________________________________________________

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Please list any topics you would like to see addressed in future educational activities:

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EVALUATION FORM

Considerations in Multiple Myeloma: Side Effect Management
Project ID: JE8027515

Additional comments about this activity:
___________________________________________________________________________________________________________
___________________________________________________________________________________________________________

Follow-up
As part of our continuous quality improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate if you would be willing to participate in such a survey:

☐ Yes, I would be interested in participating in a follow-up survey.
☐ No, I’m not interested in participating in a follow-up survey.

If you wish to receive acknowledgment for completing this activity, please complete the posttest by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876.

You may also complete the posttest online at www.cmeuniversity.com. Click on “Find Posttest/Evaluation by Course” on the navigation menu, and search by project ID JE8027515. Upon successfully completing the posttest and evaluation, your certificate will be made available immediately.

Posttest Answer Key

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Request for Credit (check box):  MD ☐  RN ☐  Pharm ☐  Other ☐

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For Physicians Only
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☐ I participated in the entire activity and claim 1.0 credits.
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