

Complications of Multiple Myeloma Therapy, Part 1: Risk Reduction and Management of Peripheral Neuropathy and Asthenia

Paul G. Richardson, MD; Jacob P. Laubach, MD; Robert L. Schlossman, MD; Constantine Mitsiades, MD, PhD; and Kenneth Anderson, MD; Boston, Massachusetts

Key Words

Fatigue, neurotoxicity, thalidomide, bortezomib

Abstract

Peripheral neuropathy (PN) and asthenia (fatigue) occur as both disease- and treatment-related complications in patients with multiple myeloma (MM). Risk factors for treatment-related PN, which has an estimated incidence of 37% to 83% among patients with MM, include therapy duration, dose intensity, cumulative dose, and the presence of preexisting neuropathy. Asthenia is the most common adverse effect of treatment, occurring in approximately 76% to 96% of patients receiving therapy. The severity of PN and asthenia can range from mild to potentially debilitating. These conditions can be dose limiting; they may interfere with optimizing duration of therapy and may also substantially affect patient qual-

ity of life. Regular screening and monitoring, combined with patient education and effective management strategies, can reduce the risk of these treatment-related complications, as well as their consequences. (*JNCCN* 2010;8[Suppl 1]:S4-S12)

Peripheral neuropathy (PN) and asthenia (fatigue) are among the most commonly seen complications in patients undergoing multiple myeloma (MM) therapy. These potentially debilitating adverse effects are frequently dose limiting, and they may interfere with optimal therapy and substantially affect patient quality of life as well as outcome. Effective strategies for preventing and managing these complications of MM therapy are thus critical.

Peripheral Neuropathy

Overview

PN occurs in MM both as a disease-related complication in newly diagnosed patients and as a side effect of MM therapy. The reported incidence is 1% to 20% in untreated patients with MM and 37% to 83% in previously treated individuals; neurophysiologic evidence of neuropathy may be detected in 11% to 52% and 39% to 46% of these populations, respectively.¹⁻⁶ Risk factors for PN include treatment-specific characteristics, such as therapy duration, dose intensity, and cumulative dose, and patient-specific factors, such as age, comorbidities (e.g., diabetes mellitus, alcoholism), and the presence of preexisting neuropathy.^{4,6-11}

From Harvard Medical School, Dana-Farber Cancer Institute, Boston, Massachusetts.

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Correspondence: Paul G. Richardson, MD, Harvard Medical School, Dana-Farber Cancer Institute, 44 Binney Street, Dana 1B02, Boston, MA 02115. E-mail: paul_richardson@dfci.harvard.edu

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Clinical Features

Treatment-related PN depends on the agents used, as described subsequently, and is typically a length-dependent, axonal, sensory, or mixed sensorimotor neuropathy with symmetric, distal, and progressive signs and symptoms. Clinical manifestations are usually agent-specific but range from temporary numbness, paresthesia, dysesthesia, hyperesthesia, loss of deep tendon reflexes, and muscle weakness or cramps to burning pain, muscle wasting, and paralysis. Autonomic involvement may result in orthostatic hypotension, constipation/ileus, and urinary bladder or sexual dysfunction. In the most extreme cases, the manifestations of treatment-related PN can be life-threatening but this is, fortunately, very rare.^{7,9,12}

Thalidomide-Induced PN (TiPN)

Thalidomide has been shown to produce a small- and large-fiber sensory PN with distal symmetric loss of all modalities, primarily affecting the lower limbs. Associated clinical signs and symptoms typically include tingling or painful paresthesias and numbness in the feet and sometimes the hands.^{1,5,7,9,13} Motor neuropathy occurs infrequently with thalidomide treatment; if present, it is usually mild in severity.^{9,14} Autonomic manifestations are common, and include gastrointestinal (e.g., constipation, anorexia, nausea) as well as cardiovascular (e.g., hypotension, bradycardia) effects.¹⁵⁻¹⁷ Although the symptoms of thalidomide-induced PN are usually reversible after dose reduction or treatment stoppage, some effects may be permanent.^{15,17}

The incidence of thalidomide-induced PN varies among different patient populations, treatment regimens, and diagnostic criteria, but estimates range from 37% to 83%.^{1,5,9,13,15-21} Most cases are mild to moderate, classified as grades 1 to 2 (Table 1).²² Evidence from numerous studies indicates that the risk and severity of thalidomide-induced PN increases with cumulative dose or treatment duration, particularly when therapy extends beyond 6 months,^{1,5,7,15-17,19,23} although neurotoxicity can also occur with short-term exposure.

Bortezomib-Induced PN (BiPN)

Bortezomib-induced PN is predominantly a small-fiber sensory neuropathy, characterized by distal symmetric loss of all modalities in the lower limbs.^{3,9,24,25} Clinical signs and symptoms include burning dysesthesia, numbness, hyperesthesia, and pain; effects are typically more pronounced in the lower limbs.^{9,25} Motor involvement is less likely with bortezomib than with thalidomide, but it may result in mild distal lower limb weakness.⁹ Autonomic dysfunction is frequently observed with bortezomib-induced PN; clinical manifestations include gastrointestinal adverse effects (e.g., diarrhea, nausea, constipation, vomiting, anorexia) and hypotension.^{25,26} The neurotoxic effects of bortezomib therapy are generally reversible with dose reduction or treatment discontinuation.^{3,4,11,14,24,27-31}

The distinctive clinical features of bortezomib-associated neuropathy suggest fundamental differences in its pathogenesis compared with thalidomide and other agents.^{9,24,25,28} Findings from recent *in vitro*

Table 1 National Cancer Institute Common Toxicity Criteria (Version 3) for Peripheral Neuropathy

| Adverse Event | Grade | | | | | |
|---------------------|--------|--|--|---|---|-------|
| | 0 | 1 | 2 | 3 | 4 | 5 |
| Neuropathy: motor | Normal | Asymptomatic; weakness on examination/testing only | Symptomatic; weakness interfering with function but not interfering with ADL | Weakness interfering with ADL; bracing or assistance to walk (e.g., cane or walker) indicated | Life threatening; disabling (e.g., paralysis) | Death |
| Neuropathy: sensory | Normal | Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function | Sensory alteration or paresthesia (including tingling), interfering with function but not interfering with ADL | Sensory alteration or paresthesia interfering with ADL | Disabling | Death |

Abbreviation: ADL, activities of daily living.

Adapted from National Cancer Institute. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Available at: http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae3.pdf. Accessed August 28, 2009.

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and *in vivo* studies suggest that proteasome inhibitor-induced PN may be mechanism-based (a consequence of proteasome inhibition itself), with dorsal root ganglia identified as a primary target leading to secondary peripheral nerve degeneration.³² However, a separate preclinical study suggested that the dorsal root ganglia lesions seen with bortezomib administration did not occur with carfilzomib, a second-generation proteasome inhibitor currently being investigated for the treatment of MM, although other studies have suggested carfilzomib, and agents in its class do in fact cause dorsal root ganglion abnormality.^{32,33} Further research is necessary to determine whether the mechanism underlying bortezomib-induced PN represents a class effect of proteasome inhibitors. However, clinical studies to date suggest this to be true, but with the degree of PN being less with carfilzomib.³⁴

The reported incidence of treatment-emergent PN with bortezomib is 31% to 64%, with severe (grade 3 or 4) symptoms seen in 3% to 22% of patients.^{3,4,6,11,27–31,35–37} Evidence of the dose-related and cumulative nature of bortezomib-induced neurotoxicity has been provided in several phase II and III studies, with reversibility also demonstrated in each of these.^{4,11,24,27–29,35,38}

Assessment/Monitoring

A comprehensive neuropathy assessment may involve a combination of patient history, clinical neurologic examination, and neurophysiologic testing. Diagnosis of any underlying conditions or comorbidities that may increase the risk of treatment-related PN is a critical part of this evaluation. PN severity should be characterized at each assessment to monitor neuropathy progression and determine whether a regimen change or some other type of intervention is indicated. Patient education is important for improving awareness and encouraging the reporting of symptoms. Neurotoxicity assessment tools (see an example in Figure 1) may be useful for quantifying PN severity based on patient self-reports.¹²

Patients should be evaluated for evidence of neuropathy at baseline, before initiating a change in therapeutic regimen, in conjunction with new or worsening signs or symptoms, and periodically throughout treatment. Patient- or agent-specific risk factors may necessitate more aggressive or targeted assessments. For example, because the incidence of thalidomide-induced PN has been reported to increase with longer duration of administration; monthly evaluation of patients is

recommended during the first 3 months of treatment and regularly thereafter.¹⁵ In addition, neurophysiologic testing is suggested (e.g., sensory nerve action potential amplitudes) every 6 months for the detection of asymptomatic PN.¹⁵

Management Strategies

Dose Reduction and Schedule Modification: For patients with grade 1 PN, thalidomide therapy may be continued with a 50% dose reduction, particularly if no other treatment options are available.¹⁷ For grade 2 PN, thalidomide therapy should be discontinued until neuropathy has returned to baseline or less than a grade 1 severity; treatment may subsequently be resumed with dosage levels reduced by half.¹⁷ Some recommend restricting thalidomide therapy to short-term use (e.g., < 6 months) or low-dose regimens (e.g., 50 mg/d).^{5,18} In general, a conservative PN management approach is recommended for newly diagnosed MM patients, especially when treatment alternatives exist.¹⁷ Bortezomib dose modifications should be made according to the directions in the prescribing information,²⁵ which are based on PN severity and the degree of associated neuropathic pain or impaired function (Table 2). The benefits of dose modification were shown in the pivotal phase III trial of bortezomib, with resolution or improvement of grade 2 or higher PN observed in 68% of patients who underwent a prespecified dose-reduction protocol, compared with 47% of those who did not.²⁸

Therapeutic Intervention: Nonpharmacologic management of sensory PN symptoms or neuropathic pain may involve the use of daily vitamins and nutritional supplements (e.g., multi-B complex vitamins [B₁, B₆, B₁₂], folic acid, magnesium, potassium, vitamin E, acetyl L-carnitine, α -lipoic acid, L-glutamine; see Table 3 for dosing), emollient creams (e.g., cocoa butter, menthol, and eucalyptus-based creams), and physical therapy, as well as therapeutic massage.^{12,39–43} These recommendations are largely based on anecdotal evidence, and controlled studies are needed to confirm their efficacy. Moreover, use of supplements on the day of bortezomib administration is not recommended based upon preclinical data suggesting the possibility of antagonism, although this has not been confirmed clinically.⁴⁴

If symptoms are inadequately controlled with nonpharmacologic intervention alone, pharmacologic therapy is advised. Because response is likely to vary substantially for each individual, a stepwise process may be necessary.^{41,45} Evidence of the therapeutic ben-

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Instructions for Patients

By circling one number per line, please indicate how true each statement has been for you during the past seven days using the following scale.

0 = not at all
 1 = a little bit
 2 = somewhat
 3 = quite a bit
 4 = very much

| | | | | | |
|--|---|---|---|---|---|
| I have numbness or tingling in my hands | 0 | 1 | 2 | 3 | 4 |
| I have numbness or tingling in my feet | 0 | 1 | 2 | 3 | 4 |
| I have discomfort in my hands | 0 | 1 | 2 | 3 | 4 |
| I have discomfort in my feet | 0 | 1 | 2 | 3 | 4 |
| I have joint pain or muscle cramps | 0 | 1 | 2 | 3 | 4 |
| I feel weak all over | 0 | 1 | 2 | 3 | 4 |
| I have trouble hearing | 0 | 1 | 2 | 3 | 4 |
| I get a ringing or buzzing in my ears | 0 | 1 | 2 | 3 | 4 |
| I have trouble buttoning buttons | 0 | 1 | 2 | 3 | 4 |
| I have trouble feeling the shape of small objects when they are in my hand | 0 | 1 | 2 | 3 | 4 |
| I have trouble walking | 0 | 1 | 2 | 3 | 4 |

Instructions for Healthcare Professionals

This assessment tool is provided to help you evaluate peripheral neuropathy in patients receiving chemotherapy. Healthcare professionals may find discussion of patients' responses helpful in determining the grade of neuropathy as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (<http://ctep.cancer.gov>); however, no direct correlation exist between assessment scores and toxicity grades.

Figure 1 Tool for assessing severity of peripheral neuropathy. Republished with permission from Oncology Nursing Society. Tariman JD, Love G, McCullagh E, Sandifer S. Peripheral neuropathy associated with novel therapies in patients with multiple myeloma: consensus statement of the IMF Nurse Leadership Board. Clin J Oncol Nurs 2008;12(3 Suppl):29–36; permission conveyed through Copyright Clearance Center, Inc.

efits of many pharmacologic agents used in the treatment of neuropathic pain comes primarily from short-term clinical studies, so the long-term efficacy of such therapy has not yet been established.⁴⁵

Among the pharmacologic agents recommended for the treatment of grade 1 or higher sensory PN or neuropathic pain are gabapentin, pregabalin, nortriptyline, duloxetine, and topical lidocaine. Gabapentin, an anticonvulsant approved by the FDA for the treatment of neuropathic pain associated with postherpetic neuralgia, may be administered at an initial dose of 300 mg, 3 times daily, with titration as tolerated up to 1200 mg, 3 times daily.³

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For additional symptomatic relief, the tricyclic antidepressant nortriptyline may be added at an initial dose of 25 mg every night at bedtime; dosing may be increased to 50 mg after 2 weeks, with further dose escalation of 25 mg monthly (as tolerated), up to a maximum of 100 mg every night at bedtime. If patient response remains inadequate, duloxetine, an antidepressant FDA approved for the treatment of neuropathic pain associated with diabetic peripheral neuropathy, may be prescribed at a dose of 20 to 60 mg every day. Topical lidocaine, which is FDA approved for postherpetic neuralgia, is sometimes helpful for the control of neuropathic pain in the feet and hands.

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Table 2 Bortezomib Dose Modification Based on Severity of Bortezomib-Induced Peripheral Neuropathy

| Severity of Peripheral Neuropathy | Modification of Dose and Regimen |
|---|--|
| Grade 1 (paresthesia or loss of reflex) without pain or loss of function | No action |
| Grade 1 with pain or grade 2 (interferes with function but not with activities of daily living) | Reduce bortezomib dose from 1.3 to 1.0 mg/m ² |
| Grade 2 with pain or grade 3 (interferes with activities of daily living) | Withhold until toxicity resolves, then re-initiate bortezomib at 0.7 mg/m ² once weekly |
| Grade 4 (permanent sensory loss that interferes with function) | Discontinue treatment |

From Richardson PG, Xie W, Mitsiades C, et al. **Single-agent bortezomib in previously untreated multiple myeloma: efficacy, characterization of peripheral neuropathy, and molecular correlations with response and neuropathy.** *J Clin Oncol* 2009;27:3518–3525. Reprinted with permission. ©2009 American Society of Clinical Oncology. All rights reserved.

Future Directions

The use of newer MM agents with improved neurotoxicity profiles can reduce the risk of treatment-related PN. Phase III trials have shown that with the potent thalidomide analogue lenalidomide, the incidence of grade 3 or 4 PN is less than 3%.^{46,47} The risk of treatment-emergent PN also appears to be decreased with the second-generation proteasome inhibitors carfilzomib (PR-171)⁴⁸ and salinosporamide A (NPI-0052).⁴⁹

The risk of treatment-related PN may also be reduced by combining agents that have synergistic or neuroprotective effects. For example, a number of investigations have provided evidence of the potential synergy between proteasome inhibitors and immunomodulatory agents in terms of anti-tumor effect.⁵⁰ Importantly, while neuropathy as a treatment-related side effect is a concern with this combination, the severity of PN has been less than expected. Specifically, studies have shown that the incidence of grade 3 PN is 5% to 10% with bortezomib/thalidomide/dexamethasone combination therapy.^{31,51–53} Importantly, no occurrences of grade 4 PN and only 1 case of grade 3 PN have been seen in a phase I/II study of lenalidomide/bortezomib/dexamethasone (RVD) in 66 subjects with newly diagnosed MM.⁵² In a phase II trial of RVD treatment in 64 patients with relapsed and/or refractory MM, only 1 case of grade 3 PN was seen, which occurred despite bortezomib reduction and required treatment discontinuation but subsequent improvement followed.⁵⁴ This suggests that such combinations may favorably influence at least the severity of PN, perhaps through an anti-inflammatory mechanism, as well as allowing dose reduction without loss of therapeutic effect.

Initial findings suggest that the heat shock protein inhibitor tanespimycin may exhibit both synergistic

and neuroprotective effects when combined with bortezomib for treatment of MM. In a phase I/II study, no cases of grade 3/4 treatment-emergent PN were detected in 72 patients treated with bortezomib plus tanespimycin for relapsed and refractory MM.⁵⁵

Asthenia

Asthenia, commonly referred to as fatigue, has been defined as a “distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion” that is not proportional to recent activity, interferes with usual functioning, and is not relieved by rest.^{56,57} Its symptoms can also include generalized weakness, lack of energy, and malaise. Many MM patients with asthenia have comorbidities such as depression, anxiety, and impaired psychosocial functioning, which can be exacerbated by medication effects, especially in combination with glucocorticoids.

Asthenia is a highly prevalent condition among patients with cancer in general and the most common side effect of cancer treatment.⁵⁸ Clinical trial data suggest that asthenia of any grade affects approximately 40% to 75% of patients with newly diagnosed disease, 60% to 93% of individuals treated with radiotherapy, and 76% to 96% of patients treated with chemotherapy, depending on the type of primary neoplasia and treatment regimen.^{58–62} Examples of MM-specific rates in phase III trials are grade 3/4 asthenia has been reported by 15% of newly diagnosed patients receiving thalidomide/dexamethasone,²⁰ by about 6% of patients with relapsed–refractory disease receiving bortezomib,²⁹ by 6% of patients with relapsed–refractory disease receiving bortezomib/liposomal doxorubicin,⁶³ and by 10% of newly diagnosed patients receiving lenalidomide/low-dose dexamethasone.⁶⁴ The results

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Table 3 Suggested Doses of Some Commonly Used Vitamins/Supplements for PN*

| Vitamin/Supplement | Dosing Regimen |
|---|---|
| Multi-B complex vitamins (with B1, B6, B12, folic acid and other) | B6 should be approximately 50 mg daily, not to exceed 100 mg per day. Folic acid should be 1 mg per day. |
| Vitamin E | 400 IU daily |
| Vitamin D | 400-800 IU daily |
| Fish oils (Omega-3 fatty acids [EPA and DHA]) | 1–2 capsules daily with food (1 capsule is usually 1 g) |
| Magnesium | Suggested doses include 250 mg twice a day, with prescription doses of 400 mgs daily, with dose frequency contingent on monitoring serum magnesium. May cause diarrhea in larger doses. |
| Potassium | Either as provided by the treating physician or foods that are rich in potassium (eg, bananas, oranges and potatoes); serum K should be monitored. |
| Tonic water (i.e. seltzer water with quinine) | Drink one glass in evening and any other time cramping occurs. |
| Acetyl-L-carnitine | 500 mg twice a day with food; Can take up to 2000 mg a day. |
| Alpha-lipoic acid | 300 mg to 1000 mg a day with food. |
| Glutamine | 1 g up to 3 times a day with food. |

*For either thalidomide-induced peripheral neuropathy (TiPN) or bortezomib-induced peripheral neuropathy (BiPN)

Please note: It is currently advised that patients do not take supplements on days of bortezomib infusions, and all supplements must be discussed with and approved by the treating physicians concerned. Supplements should be taken with food unless otherwise indicated.

Additional Notes and Precautions:

Nutritional supplements should be administered at low doses since there is preclinical evidence that the administration of pyridoxine (vitamin B6) and vitamin C at high doses may be harmful. Vitamin B6 can cause additional sensory neuropathy in patients with impaired renal function and in association with a protein-deficient diet. (Levine S, Saltzman A. Pyridoxine (vitamin B6) toxicity: enhancement by uremia in rats. *Food Chem Toxicol* 2002;40:1449–1451. Levine S, Saltzman A. Pyridoxine (vitamin B6) neurotoxicity: enhancement by protein-deficient diet. *J Appl Toxicol* 2004;24:497–500.)

Vitamin C may interfere with bortezomib metabolism and may also abrogate bortezomib-mediated inhibition of proteasome activity; therefore, its concomitant use with bortezomib should be avoided. (Catley L, Anderson KC. Velcade and vitamin C: too much of a good thing? *Clin Cancer Res* 2006;12:3-4. Perrone G, Hideshima T, Ikeda H, et al. Ascorbic acid inhibits antitumor activity of bortezomib in vivo. *Leukemia* 2009;23:1679–1686; Epub 2009 Apr 16.)

In preclinical studies, the anticancer activity of bortezomib has been shown to be blocked by the polyphenols. It is speculated that the vicinal diols in the polyphenols interact with the boronic acid of bortezomib and convert the active triangular boronic acid of bortezomib to an inactive tetrahedral boronate, thus inhibiting the anti-myeloma activity of bortezomib. The restriction of the intake of natural polyphenols in foods or vitamin supplements (such as in green tea) during bortezomib treatment in MM patients should be considered. (Kim TY, Park J, Oh B, et al. for the Korean Multiple Myeloma Working Party (KMMWP). Natural polyphenols antagonize the antimyeloma activity of proteasome inhibitor bortezomib by direct chemical interaction. *Br J Haematol* 2009;146:270–281.)

of patient surveys suggest that asthenia exerts a more negative and longer-lasting effect on patients than pain, nausea, or depression, but that treatment is prescribed in as few as 14% to 40% of cases.^{59,62} This is true even though asthenia may persist for months or even years after treatment is completed.

According to the NCCN Clinical Practice Guidelines in Oncology: Cancer-Related Fatigue (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org), every cancer patient should be screened for asthenia at regular intervals, in conjunction with other vital-sign monitoring.⁵⁶ During the initial screening, patients should be asked to assess their level of fatigue during the previous

7-day period, using a predefined scale. A comprehensive primary asthenia examination is recommended for all patients reporting moderate to severe fatigue. No standardized guidelines for diagnosis of asthenia have been established, but the Tenth Revision of the International Classification of Disease (ICD-10) includes a proposed set of diagnostic criteria (Table 4).⁶⁵

Management approaches for asthenia include 1) treatment of contributing factors (e.g., anemia, pain, depression/anxiety, systemic disorders, such as hypothyroidism, sleep disturbances, nutritional deficiencies, and medication side effects); 2) patient education regarding the causes of asthenia and general strategies for fatigue self-management; 3) nonpharmacologic in-

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Table 4 ICD-10 Criteria for Cancer-Related Fatigue

| | |
|-----------|--|
| A. | Six (or more) of the following symptoms have been present every day or nearly every day during the same 2-week period in the past month, with at least 1 symptom (A1) being significant fatigue: A1. Significant fatigue, diminished energy, or increased need to rest, disproportionate to any recent change in activity A2. Complaints of generalized weakness or limb heaviness A3. Diminished concentration or attention A4. Decreased motivation or interest to engage in usual activities A5. Insomnia or hypersomnia A6. Experience of sleep as unrefreshing or nonrestorative A7. Perceived need to struggle to overcome inactivity A8. Marked emotional reactivity (e.g., sadness, frustration, or irritability) to feeling fatigued A9. Difficulty completing daily tasks attributed to feeling fatigued A10. Perceived problems with short-term memory A11. Postexertional malaise lasting several hours |
| B. | The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning |
| C. | Evidence from the history, physical examination, or laboratory findings shows that the symptoms are a consequence of cancer or cancer therapy |
| D. | The symptoms are not primarily a consequence of comorbid psychiatric disorders such as major depression, somatization disorder, somatoform disorder, or delirium |

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terventions, including counseling, occupational therapy, cognitive behavioral therapy, exercise, dietary changes, and stress management; and 4) pharmacologic symptomatic therapy.⁵⁶ Clinical trial data and anecdotal evidence suggest that psychostimulants, low-dose corticosteroids, and antidepressants may be helpful,⁶⁶ but psychostimulants are investigational for this purpose and should be used with caution only after treatment- and disease-specific morbidities have been characterized or excluded. The optimal dose and schedule have not been established for use of psychostimulants in cancer patients. Specific measures in MM patients include attention to hydration, evaluation of novel-agent specific-effects (such as those seen with bortezomib, thalidomide, and lenalidomide); exclusion of important co-morbidities (e.g., thyroid deficiency, amyloidosis), and care regarding the possibility of progressive disease.⁶⁷

Conclusions

Peripheral neuropathy and asthenia are frequent complications of MM treatment. These complications interfere with optimum therapy and adversely affect patient outcomes as well as quality of life.

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Among novel therapies associated with significant PN are bortezomib and thalidomide, both agents that have transformed the MM treatment paradigm through improvements in response rates, time-to-progression, and survival. Novel combination therapies for MM have the potential to reduce side effects, as well as enhance activity, thus improving the therapeutic index.⁶⁸ In addition, effective management strategies are critical to reduce the risk of further treatment-related toxicities and improve the benefits of therapy in this otherwise incurable malignancy.

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