Bortezomib-Induced Peripheral Neuropathy in Patients With Multiple Myeloma

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Bortezomib-induced peripheral neuropathy (BIPN) often is difficult to manage or reverse once it occurs. Treatment usually involves dose-reduction, interruption, or cessation of therapy, as no other interventions have been proven effective. Oncology nurses must be vigilant and recognize BIPN early to prevent patients from experiencing symptoms and complications that may interfere with their quality of life.

Bortezomib (Velcade®) was the first approved proteasome inhibitor used predominantly for treatment of multiple myeloma, a malignant plasma cell disorder that accounts for about 10% of multiple myeloma, a malignant plasma cell disorder that accounts for about 10% of hematologic malignancies (Delforge et al., 2010). Since its approval by the U.S. Food and Drug Administration (FDA) in 2003, bortezomib has been shown to be effective at improving progression-free and overall survival in patients with multiple myeloma (Richardson et al., 2007). To date, many patients with multiple myeloma will receive bortezomib at some point during their treatment continuum, either as initial therapy or for refractory disease. However, as with many antineoplastic therapies, bortezomib has toxicities. One of the most debilitating side effects is bortezomib-induced peripheral neuropathy (BIPN). BIPN often is a dose-limiting toxicity and can significantly impact a patient’s quality of life and ability to perform activities of daily living (ADL) (Stubblefield et al., 2009).

About 55%–66% of patients with newly diagnosed multiple myeloma who receive bortezomib as initial therapy will experience BIPN, and the incidence may be higher for those previously treated with other neuropathy-inducing agents or with significant risk factors (Argyriou, Iconomou, & Kalofonos, 2008; Richardson, Lau Bach, Classman, Miltiades, & Anderson, 2010). Risk factors for developing BIPN include advanced age, poor nutritional status, preexisting neuropathy, diabetes mellitus, and alcohol abuse (Argyriou et al., 2008). In addition, multiple myeloma itself may cause neuropathy as part of the mechanism of the disease (Richardson et al., 2010). Healthcare providers must effectively assess for this debilitating toxicity so that patients do not undergo significant and incapacitating consequences when BIPN is overlooked.

Characteristics and Differential Diagnoses

BIPN is distinguishable from other types of neuropathy, such as those caused by diabetes (see Table 2), peripheral nerve disorders, and carpal tunnel syndrome. BIPN primarily affects small nerve fibers of the lower limbs and is predominantly a sensory, rather than motor, neuropathy (Richardson et al., 2010). BIPN occurs symmetrically, and patients often report feeling pain, burning, numbness, and hyperesthesia (Richardson et al., 2010; Stubblefield et al., 2009). Autonomic

Case Study

Mr. X, a 43-year-old Caucasian man, was diagnosed with immunoglobulin A lambda multiple myeloma in April 2010. Prior to his diagnosis, Mr. X had been in excellent health and was an avid athlete, participating in several triathlons. In May 2010, Mr. X initiated treatment with bortezomib and dexamethasone, a standard first-line therapy combination for patients with multiple myeloma (National Comprehensive Cancer Network [NCCN], 2011). Treatment was stopped after only three cycles because Mr. X developed grade 3 peripheral neuropathy, including significant sensory alterations and paresthesias that interfered with his ability to perform ADL (see Table 1). Subsequently, Mr. X was started on gabapentin as treatment for his BIPN. Fortunately, he had achieved a good partial response to therapy and eventually received an autologous stem cell transplantation.

Although Mr. X’s disease is controlled at present, he continues to suffer from painful paresthesias of his hands and feet related to the bortezomib he received as part of his initial therapy. He describes it as burning pain and rates it as 5 of 10 on a typical day. The pain migrates midway up his shins and partially up his forearms. He describes having trouble walking or standing on his feet for long periods of time. He also has difficulty buttoning his clothes, turning pages of a book, and picking up items.
dysfunction also has been observed, resulting in diarrhea or constipation, nausea, vomiting, urinary or sexual dysfunction, and hypotension (Delforge et al., 2010; Richardson et al., 2010). Unlike diabetic neuropathy, which often develops slowly, BIPN is a dose-dependent phenomenon, resulting from cumulative bortezomib exposure. BIPN typically peaks before the fifth cycle of treatment (Delforge et al., 2010; Farquhar-Smith, 2011). If caught early, BIPN generally subsides with dose reduction, interruption, or stopping treatment. Dosing should be adjusted as outlined in Table 1; if grade IV BIPN occurs, bortezomib should be discontinued and not rechallenged. Many patients experience improvement in their neuropathy symptoms from early intervention; however, BIPN often is difficult to manage and fully reverse once it occurs (Richardson et al., 2010; Stubblefield et al., 2009). Performing frequent neurologic and symptom assessments are crucial to the diagnosis of BIPN, particularly in patients who have underlying risk factors.

### Assessment

To date, no clinical standard exists for evaluating BIPN. Evaluation often involves a combination of history taking, physical assessment, and neurophysiologic testing (Stubblefield et al., 2009). A baseline assessment of neurologic and musculoskeletal functioning and evaluation of preexisting neuropathy is critical for all patients with multiple myeloma prior to initiating therapy with bortezomib. Establishing a strong baseline of preexisting symptoms and physiologic functioning will allow providers to recognize and diagnose BIPN early, when symptoms have the best chance of being reversible.

Patients with multiple myeloma receiving bortezomib should be evaluated for BIPN at baseline, during each clinic visit while on treatment, prior to initiating a regimen change, and with any new or worsening symptoms (Richardson et al., 2010). Patients should be asked about the presence of numbness, tingling, or pain in the hands or feet; the development of new weakness; difficulty walking; or any falls. Symptom assessment also should include questions related to ADL, such as trouble with buttoning clothing, writing, or turning the pages of a book or newspaper (Tariman, Love, McCullagh, Sandifer, & IMF Nurse Leadership Board, 2008). Evaluation for autonomic neuropathy symptoms (e.g., constipation, urinary or sexual dysfunction, orthostatic hypotension) also should be included. Physical examination of the patient includes a sensory assessment (e.g., light touch and pinprick, vibration, proprioception and temperature) measurement of deep-tendon reflexes,

### TABLE 1. Guidelines for Bortezomib Dose Modification Based on Neuropathy Grade and Severity

<table>
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<tr>
<th>Grade</th>
<th>Signs and Symptoms</th>
<th>Dose Modification</th>
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<tr>
<td>0</td>
<td>Normal</td>
<td>No action</td>
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</tbody>
</table>
| 1     | **Sensory:** Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling), but not interfering with function  
**Motor:** Asymptomatic; weakness on examination or testing only  
*Without pain:* no action  
*With pain:* Reduce dose to 1 mg/m². |
| 2     | **Sensory:** Paresthesia (including tingling) or sensory alteration interfering with function, but not ADL  
**Motor:** Symptomatic weakness interfering with function, but not ADL  
*Without pain:* Reduce dose to 1 mg/m².  
*With pain:* Withhold therapy until toxicity resolves, then reintroduce with a reduced dose at 0.7 mg/m² and change treatment schedule to once per week. |
| 3     | **Sensory:** Paresthesia or sensory alteration interfering with ADL  
**Motor:** Weakness interfering with ADL; bracing or assistance to walk (e.g., cane, walker) indicated  
Withhold therapy until toxicity resolves, then reintroduce with a reduced dose at 0.7 mg/m² and change treatment schedule to once per week. |
| 4     | Life-threatening; disabling  
ADL—activities of daily living  

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<th>Characteristic</th>
<th>BIPN</th>
<th>Diabetic Neuropathy</th>
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| Affected limbs and pathways | Predominantly affects lower limbs  
Commonly affects the fingers, hands, and arms; often described as a “glove and stocking” neuropathy |
| Development             | Predominantly a small-fiber sensory neuropathy; motor involvement less likely  
Sensory neuropathy is the most common. |
| Progression             | Typically progresses symmetrically  
Typically starts in the distal feet and progresses proximally |
| Symptoms                | Burning numbness, hyperesthesia, and pain  
Numbness, tingling, aching, electric shock-like pain, allodynia, or hyperesthesia |
|                         | Autonomic dysfunction also may occur, resulting in hypotension, diarrhea, constipation, nausea, vomiting, and anorexia  
Pain may be constant, intermittent, or worse at night; symptoms may improve with adequate glucose control. |

*Note.* Based on information from Hovaguimian & Gibbons, 2011; Richardson et al., 2010.
assessments of strength, and observation of gait (Richardson et al., 2010). Some centers also may provide neurophysiologic testing such as electromyography, nerve conduction studies, and quantitative sensory tests that allow for an objective measurement of BIPN. However, studies have found that test results may not always correlate with patient symptoms, as symptoms often are an earlier sign of BIPN development (Stubblefield et al., 2009).

Management

The most effective management of BIPN is dose reduction or interruption of bortezomib therapy (Badros et al., 2007; Cavaletti & Jakubowiak, 2010). BIPN is assigned a toxicity grade to determine whether or not treatment should be withheld, dose-reduced, or stopped, and therapy is modified to reflect the extent of toxicity. For patients experiencing more severe symptoms such as neuropathic pain, healthcare providers may prescribe adjunctive therapy, which combines nonpharmacologic interventions (e.g., nutritional supplements, emollient creams, physical therapy, massage) with pharmacologic interventions (e.g., vitamins, anticonvulsants, analgesics, selective serotonin reuptake inhibitors, tricyclic antidepressants) (Badros et al., 2007; Richardson et al., 2010) (see Figure 1). Unfortunately, the benefits of many of those treatments have been largely anecdotal and widely individualized, with most not having been substantiated in large clinical trials (Richardson et al., 2010).

Conclusion

BIPN is a dose-limiting side effect of bortezomib therapy. BIPN is difficult to reverse or manage once it occurs, often resulting in lasting pain and a compromised quality of life for patients. Patients should be educated on the signs and symptoms of BIPN before starting bortezomib therapy so they can alert healthcare providers to developing symptoms to aid with earlier recognition and diagnosis. Healthcare providers must perform a thorough baseline assessment including history and physical examination before initiating bortezomib therapy for patients with multiple myeloma. Frequent follow-up including a detailed symptom and physical assessment is paramount so that patients do not suffer from potentially irreversible consequences of prolonged bortezomib therapy.

More than a year has passed since Mr. X received bortezomib, and he believes that his symptoms are improving slowly. He has tried gabapentin at the maximum beneficial dosage (1,800 mg per day) with minimal relief, and recently was switched to pregabalin. Although he has accepted that he may be unable to participate in another triathlon, he recently began swimming. Mr. X is hopeful that staying active will not only help his neuropathy symptoms, but also will improve his overall health and quality of life.

References


