

Bortezomib, a Newly Approved Proteasome Inhibitor for the Treatment of Multiple Myeloma: Nursing Implications

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Multiple myeloma (MM) is the second most common hematologic malignancy, with more than 15,270 newly diagnosed cases and more than 11,070 deaths in the United States estimated for the year 2004 (American Cancer Society, 2004). The disease is a cancer of the antibody-forming B cells, causing uncontrolled growth of plasma cells. The malignant plasma cells invade the bone marrow as well as many other organs in the body. Myeloma cells release into the blood massive amounts of monoclonal immunoglobulin (M protein), a dysfunctional type of antibody. The spread of myeloma cells causes a variety of complications involving the bones, blood, kidneys, and nervous and immune systems (Kyle et al., 2003). The disease frequently causes a chronic condition characterized by bone pain, low levels of blood calcium, decreasing or failing kidney function, multiple recurrent infections, bone fractures, spinal cord compression, anemia, defects in the blood clotting systems, and symptoms such as peripheral neuropathy, gastrointestinal disturbances, and abnormally decreased numbers of all types of blood cells (Rice & Sheridan, 2001).

Standard treatment has included combination chemotherapy such as melphalan and

Multiple myeloma (MM), a malignancy of the plasma cells, accounts for an estimated 14% of all newly diagnosed hematologic malignancies. Advances in chemotherapy and stem cell transplantation have improved survival rates, but MM remains incurable. Bortezomib (Velcade™, Millennium Pharmaceuticals, Inc., Cambridge, MA), a first-in-class proteasome inhibitor, has been approved for patients with MM who have received at least two prior treatments and have demonstrated disease progression on the most recent one. During clinical trials, most side effects were manageable with standard interventions. The most common toxicities were asthenic conditions (fatigue, malaise, and weakness), gastrointestinal disturbances (nausea, vomiting, diarrhea, and constipation), thrombocytopenia, peripheral neuropathy, pyrexia, and anemia. Supportive therapies and strategies for side-effect management can prevent worsening of these symptoms, thereby avoiding dose reductions and treatment delays. Oncology nurses play a key role in ensuring the proper and safe administration of bortezomib and often are the first to identify the signs of side effects. Patient education about anticipated side effects and close monitoring of patients can lead to symptom management interventions that are essential to patient comfort and safety.

Key Words: multiple myeloma, peripheral neuropathies, proteasome

prednisone; vincristine, doxorubicin, and dexamethasone; or single-agent dexamethasone (Munshi, Tricot, & Barlogie, 2001).

High-dose chemotherapy supported by autologous stem cell transplantation has extended survival in selected patients but is not an option for older patients or those with serious comorbidity or poor performance status. Conventional allogeneic transplantation and miniallogeneic transplantation are associated with high mortality (Catley & Anderson, 2004).

More recently, based on its ability to reduce the formation of new blood vessels believed to promote tumor growth, thalidomide has been used. Novel therapies currently being studied include immunomodulatory drugs, arsenic compounds, and proteasome inhibitors (Tariman, 2003).

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Bortezomib is a potent, selective, reversible proteasome inhibitor. Proteasomes are enzyme complexes that are present in all cells. The interaction of bortezomib with one specific proteasome prevents the breakdown of intracellular proteins affecting multiple proteasome-regulated pathways, as shown in Figure 1, including cell growth, apoptosis (programmed cell death), and survival (Millennium Pharmaceuticals, Inc., 2003). The full extent of the activity of bortezomib still is under study. In MM, bortezomib affects the interaction of myeloma cells in bone marrow. It also has been shown to overcome drug resistance in myeloma cells in vitro (Hideshima et al., 2001; LeBlanc et al., 2002; Ma et al., 2003; Read et al., 1995).

Bortezomib is the first approved drug in the proteasome inhibitor class of anticancer drugs. Bortezomib is approved for patients with MM who have received at least two prior treatments and have demonstrated disease progression on the last therapy (Millennium Pharmaceuticals, Inc., 2003).

Bortezomib Clinical Trials

The efficacy and safety of bortezomib in patients with advanced MM have been demonstrated in two multicenter phase II clinical trials, the SUMMIT trial and CREST trial.

The SUMMIT trial enrolled 202 heavily pretreated patients with relapsed MM who were refractory to the most recent therapy. The patients had received at least two prior lines of treatment (Richardson et al., 2003a). The patients received 1.3 mg/m² of bortezomib via IV push (3–5 seconds) in 21-day cycles twice weekly on days 1, 4, 8, and 11 followed by a 10-day rest period (days 12–21). Doses must be separated by at least 72 hours to allow for normal proteasome activity to recover (Orlowski et al., 2002).

The CREST trial involved 54 patients with relapsed or refractory MM who were randomized to one of two arms comparing different bortezomib doses: 1.0 mg/m² and 1.3 mg/m². All patients were treated twice a week for two weeks followed by a 10-day rest period (Jagannath et al., 2002).

Efficacy was assessed in both trials by an independent review committee according to the criteria of the European Group for Blood and Marrow Transplantation (Blade et al., 1998). A complete response (CR) required 100% disappearance of the original myeloma protein from the blood and urine by immunofixation, less than 5% plasma cells in the bone marrow, stable bone disease, and normal calcium on at least two occasions six weeks apart. A near-CR also required stable bone disease and a normal serum calcium level but allowed for M protein seen by immunofixation but not detectable by electrophoresis. Partial response (PR) required a 50% reduction in serum protein and a 90% reduction of urine protein on at least two occasions six weeks apart, stable bone disease, and normal calcium (Richardson et al., 2003a).

The major response rate (CR and PR) was 27.7% among the patients in the SUMMIT trial who were evaluable for response. The major response rate remained consistent regardless of the type of previous therapies, including thalidomide or stem cell transplantation, or baseline patient characteristics, including performance status (PS), myeloma type, β 2-microglobulin, or chromosome 13 deletion status. Baseline predictors of decreased response were 50% plasma cells in the bone marrow and age (Richardson et al., 2003b). Median time to response was 38 days (two cycles). Median duration of response among patients with CR, PR, or minimal response to bortezomib alone was 12 months (n = 67) (Richardson et al., 2003a). The duration of response as of March 21, 2003, was reported as 14.3 months (n = 53) (Berenson et al., 2003).

In the CREST trial, overall response rates were 33% at 1.0 mg/m² and 50% at 1.3 mg/m². CR rates were 4% in each 108 study arm (Jagannath et al., 2003). Both the SUMMIT and CREST protocols permitted patients experiencing progression of their disease after at least two cycles or stable disease after the first four cycles of bortezomib to have dexamethasone added to their treatment regimen. Dexamethasone 20 mg was given on the days of and after bortezomib administration (i.e., on days 1, 2, 4, 5, 8, 9, 11, and 12 of the three-week cycle).

Eighteen percent of the patients in the SUMMIT trial and 21% of the patients in the CREST trial had a minimal or partial response and went on to receive dexamethasone with their bortezomib treatment (Jagannath et al., 2003; Richardson et al., 2003a). Experience with long-term use of bortezomib suggests that it can be administered for as many as 24 cycles (8 cycles in clinical trials followed by as many as 16 cycles in an extension trial) with a safety profile similar to that seen during the first six months of treatment (Berenson et al., 2003).

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Bortezomib and Multiple Myeloma: Nursing Considerations

Oncology nurses play a key role in ensuring the proper and safe administration of bortezomib and often are the first to identify signs of side effects. Patient education about anticipated side effects and careful patient assessment can lead to effective symptom management. Administration of all doses often is dependent on effective symptom control.

Dosing and Administration

Bortezomib should be given according to the dosage and administration schedules outlined in the prescribing information. Bortezomib is injected by IV push directly into a peripheral vein or through an infusion port over three to five seconds. The line should be flushed with normal saline. In clinical trials,

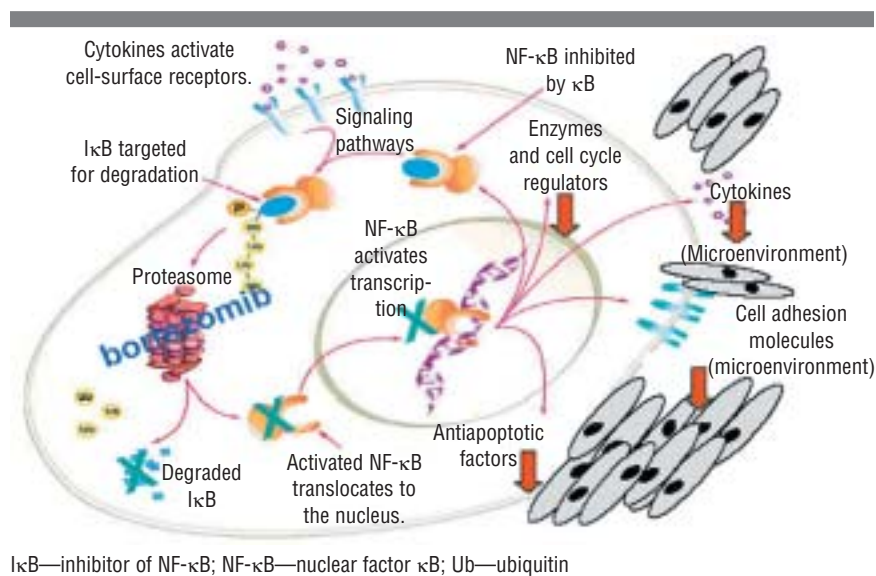


FIGURE 1. PROTEASOME INHIBITION, NF- κ B, AND MULTIPLE MYELOMA

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extravasation was not associated with tissue damage. A small percentage of patients may experience a local skin reaction. Infusion reactions were reported rarely during clinical trials, and no cases of overdose were reported (Millennium Pharmaceuticals, Inc., 2003).

Giving patients a calendar outlining the treatment schedule indicating the days of treatment and the rest period is helpful. To comply with the schedule, patients can be treated on either a Monday and Thursday, Tuesday and Friday, or Wednesday and Saturday schedule.

Prior to each dose of bortezomib, patients should be assessed to establish baseline status of vital signs, blood counts, chemistries, and neurologic assessment and then monitored throughout therapy (see Figure 2).

Dose Modifications and Treatment Delays

When necessary, dosage should be modified promptly in response to toxicity, according to product labeling. At the onset of any grade 3 nonhematologic toxicities or any grade 4 hematologic toxicities, bortezomib should be withheld. Once the symptoms of toxicity have resolved, bortezomib may be reinstated at a 25% lower dose (1.3 mg/m² dose reduced to 1.0 mg/m²; 1.0 mg/m² reduced to 0.7 mg/m²). Recommended dose modifications for bortezomib-related neuropathic pain and peripheral sensory neuropathy are presented in Table 1.

Quality of Life

In the SUMMIT trial, quality-of-life (QOL) questionnaires were administered at screening; on day 1 of cycles 3, 5, and 7; and at the end of the study (Lee et al., 2003). In addition, blood counts, number of transfusions, and Karnofsky performance status were assessed regularly. Hemoglobin, platelet counts, and Karnofsky performance status improved among patients who responded. No transfusions were required in responders after cycle 4 (Richardson et al., 2003a). In patients with CR or PR, an improvement from baseline QOL was observed. When patients able to be evaluated were included regardless of response, mean global QOL and disease symptoms improved. These data suggest that response to bortezomib in this patient population was associated with additional clinical benefit and improvement in patients' well-being (Lee et al.). As bortezomib is used more in practice, nurses have opportunities to add to this body of knowledge by evaluating QOL and measuring the efficacy of symptom management interventions.

Before Treatment

- Establish baseline profile of patient.
 - Blood counts
 - Concurrent medications, particularly antihypertensives and hypoglycemics
 - Neurologic status and preexisting neuro-pathic signs or symptoms
 - Chemistries
 - Vital signs, height and weight, and general health status, such as comorbidities including diabetes or hypertension and patient tendencies for fatigue, depression, or gastrointestinal disturbances during previous treatments
- Provide patient and family education concerning proteasome inhibition, treatment schedules, and expected response and side effects.

During Treatment

- Evaluate toxicities and response and institute nursing interventions to minimize toxicity and maximize treatment benefit.
 - Follow dose modifications as recommended and hold treatment for all grade 4 toxicities or grade 3 neuropathy.
 - Institute nursing interventions for expected side effects before each treatment.
 - Maintain schedule for treatment, allowing a 72-hour break between doses.
 - Monitor blood counts and vital signs before each treatment.
 - Monitor chemistries every two weeks or more if necessary.
 - Continue to provide education and monitoring of neuropathies.
 - Assess for adequate hydration and nutrition.
 - Assess all concurrent medications.

After Treatment

- Provide education and support to patient for continued monitoring of disease.
- Patients may be retreated if they relapse.

FIGURE 2. NURSING INTERVENTIONS

Anticipated Side Effects and Management

In the SUMMIT and CREST trials of bortezomib, the side effects that were reported most commonly were asthenic conditions (malaise, fatigue, and weakness), gastrointestinal problems, thrombocytopenia, and peripheral neuropathy, pyrexia, and anemia. All adverse events that occurred in 10% of patients receiving the 1.3 mg/m² dose of bortezomib for a maximum of eight treatment cycles are presented in Table 2 (Millennium Pharmaceuticals, Inc., 2003). Most toxicities were manageable with standard interventions, and the incidence of severe (grade 4) toxicities was rare.

Peripheral Neuropathy

Another significant adverse event was cumulative, dose-related peripheral neuropathy. Peripheral neuropathy associated with bortezomib is predominantly sensory, although rare cases of mixed sensorimotor neuropathy have been reported. During the SUMMIT and CREST trials, only one case of grade 4 neuropathy occurred, and most patients had complete resolution or improvement of symptoms with dose modification or discontinuation (Richardson et al., 2003a).

Patients with preexisting symptoms of neuropathy may experience worsening during treatment. In fact, 80% of the patients treated in the SUMMIT trial had baseline peripheral neuropathy (Richardson, Briemberg, et al., 2003). Patients with preexisting neuropathy should be treated with bortezomib only after careful risk and benefit assessment. Patients who are at higher risk for neuropathy include those with a history of treatment with other drugs that cause neuropathy, including HIV medications such as nucleoside reverse transcriptase or protease inhibitors, post-transplant immunosuppressives such as tacrolimus, and chemotherapies including cisplatin, paclitaxel, methotrexate, cytarabine, ifosfamide, suramin, and, most relevant for patients with MM, vincristine, other vinca alkaloids, and thalidomide (Dalakas, 2001; Nielsen & Brant, 2002; Peltier & Russell, 2002).

Because peripheral neuropathy can be dose limiting, patients should be monitored closely for early signs and symptoms. Dose modifications may prevent progression of neuropathy. New symptoms or changes in existing symptoms such as numbness or tingling sensations in the upper or lower extremities, burning sensations, or increased sensitivity to touch, and neuropathic pain, such as shooting pain in legs, severe leg cramps in calves or thighs, arthralgias, or myalgias, should be evaluated prior to each treatment. Patients should be instructed to contact their physicians if new symptoms develop or existing symptoms change.

Patients and their families should be educated to recognize the early signs and symptoms of neuropathy. Filling out the neurotoxicity assessment tool, which is presented in Figure 3, at each visit reinforces the importance of patient vigilance, increases awareness of symptoms, and establishes a method for tracking changes in symptoms. Referral to neurology, pain management, or psychology consultants may be appropriate.

During clinical trials at the Dana-Farber Cancer Institute (DFCI) in Boston, MA, the following recommendations, as described in Table 3, were drawn up as possible interventions to help alleviate the discomfort of

TABLE 1. RECOMMENDED BORTEZOMIB DOSE MODIFICATION FOR DRUG-RELATED NEUROPATHIC PAIN AND PERIPHERAL SENSORY NEUROPATHY

SEVERITY OF PERIPHERAL NEUROPATHY	MODIFICATION OF DOSE AND REGIMEN
Grade 1 (paresthesia and/or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or grade 2 (interfering with function but not with activities of daily living)	Reduce bortezomib to 1 mg/m ² .
Grade 2 with pain or grade 3 (interfering with activities of daily living)	Withhold bortezomib therapy until toxicity resolves. Then reinstate with a reduced dose of bortezomib at 0.7 mg/m ² and change treatment schedule to once per week.
Grade 4 (permanent sensory loss that interferes with function)	Discontinue bortezomib.

Note. Based on information from Millennium Pharmaceuticals, Inc., 2003; National Cancer Institute Cancer Therapy Evaluation Program, 1999.

peripheral neuropathies. These recommendations are based on experience and anecdotal information and are not necessarily applicable to all patients (Colson, 2003).

Any intervention must take into consideration the patient's medical history and current medical status and should be discussed with the treating physician prior to initiation.

At the onset of neuropathy, clinicians at DFCI recommend that patients take a combination of supplements, including vitamins B₆ and B₁₂, folate, magnesium, amino acids, and others. All supplements should be used with caution in these patients, taking into consideration each individual's medical history. Magnesium may cause diarrhea, and additional caution is necessary in patients with renal failure, in whom magnesium supplementation may lead to hypermagnesemia (Rude, 1998). Dietary sources of potassium,

which helps reduce cramping, include two teaspoons of apple cider vinegar, bananas, and oranges.

Amino acids are available at health food stores and, like vitamins, should be taken with food. Published reports suggest that L-carnitine ameliorates HIV-related neuropathies (Scarpini, Sacilotto, Baron, Cusini, & Scarlato, 1997). The staff at DFCI begins acetyl-L-carnitine at 500 mg twice a day and increases to as much as 2,000 mg a day, as tolerated.

Alpha-lipoic acid is an antioxidant that may improve symptoms of neuropathy in patients with diabetes (Ruhnau et al., 1999). The dosage used at DFCI is 300–1,000 mg a day with food. Several prescription drugs have shown benefit in relieving the symptoms of peripheral neuropathy. At DFCI, clinicians start gabapentin at 100 mg three times a day, gradually increasing the dose to 600 mg three times a day, as tolerated (Marrs & Newton, 2003). Amitriptyline or sertraline hydrochloride at bedtime also may be beneficial. Lidocaine patches also have been used. Topical creams, such as capsaicin cream or cocoa butter (rich in vitamin E), applied to the affected area may ease discomfort. Patients complaining of nocturnal leg cramping may try drinking 8 oz. of tonic water (quinine water) in the evening before going to bed.

Gastrointestinal Side Effects

Gastrointestinal side effects such as nausea, diarrhea, constipation, and vomiting may occur at any time during treatment with bortezomib. In clinical trials, most occurred during the first or second cycle and generally were mild to moderate. Patients should be advised to maintain hydration. At DFCI, nurses recommend drinking at least 2 quarts of fluid every day as a general practice for

patients with MM. Nausea and vomiting may occur 12–24 hours after the infusion of bortezomib and sometimes may require the use of antiemetics. Physicians at DFCI have prescribed long-acting antiemetics, such as ondansetron. Prochlorperazine or lorazepam may be prescribed as needed after bortezomib infusion (Millennium Pharmaceuticals, Inc., 2003).

Mild diarrhea may be controlled by dietary changes, such as introduction of the BRAT diet (bananas, rice, apple sauce, and toast), but if symptoms persist, referral to a nutritionist may be necessary. Generally, diarrhea may be controlled with prescription antidiarrheals such as loperamide hydrochloride or diphenoxylate hydrochloride. For acute diarrhea seen primarily in patients with previous bowel motility problems, options to alleviate symptoms include fiber supplements such as Benefiber™ (Novartis Consumer Health, Inc., Parsippany, NJ) (1 tablespoon every day in 6 oz. of liquid, increased to 2 tablespoons if necessary) and products designed to restore natural intestinal flora, such as Culturelle™ (ConAgra Food, Omaha, NE) (1 tablet a day). Medications to relieve constipation can take a few days to a week to begin working. DFCI uses a stepwise approach, beginning with docusate sodium, adding a senna-based laxative and then flaxseed meal, a high-fiber supplement available in health-food stores.

Asthenia

First onset of fatigue was reported most often during cycles 1 and 2, and most patients were able to continue therapy despite it. Individual patients should be evaluated for possible causes of fatigue, and nurses can recommend proper hydration and nutrition, vitamin supplements, and lifestyle changes; in some cases, antidepressants or counseling may be appropriate.

Thrombocytopenia

Platelet counts generally drop during the dosing period (days 1–11), with a return to baseline during the rest period (days 12–21). Onset of thrombocytopenia is most common in cycles 1 and 2, but it can continue throughout therapy. All patients developed about a 60% reduction in their platelet counts, although grade 4 thrombocytopenia was uncommon in patients with baseline platelet counts higher than 70,000 (Lonial et al., 2003). Some reports have been made of gastrointestinal and intracerebral hemorrhage in association with bortezomib-induced thrombocytopenia (Millennium Pharmaceuticals, Inc., 2003). Grade 4 thrombocytopenia may be managed by temporarily

TABLE 2. MOST COMMON ADVERSE EVENTS BY GRADE REPORTED IN THE SUMMIT TRIAL

ADVERSE EVENT	GRADE 1–2 (%)	GRADE 3 (%)	GRADE 4 (%)
Nausea	58	6	0
Diarrhea	41	7	1
Fatigue	37	12	0
Thrombocytopenia	13	28	3
Constipation	41	2	0
Vomiting	27	8	1
Anorexia	32	2	0
Peripheral neuropathy	22	12	0
Pyrexia	30	4	0
Anemia	23	8	0

N = 202

Note. Based on information from Millennium Pharmaceuticals, Inc., 2003.

Instructions for Patients

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

	Not at all	A little bit	Somewhat	Quite a bit	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 feel discomfort in my hands.	0	1	2	3	4
I feel 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 (NCI) Common Toxicity Criteria (CTC) listed below; there is no direct correlation between assessment scores and toxicity grades.

NCI CTC for Peripheral Neuropathy and Neuropathic Pain

Peripheral sensory neuropathy (NCI CTC grade)

- 1 Normal
- 2 Loss of deep tendon reflexes or paresthesia but not interfering with function
- 3 Objective sensory loss or paresthesia, interfering with function, but not with activities of daily living (ADLs)
- 4 Sensory loss or paresthesia interfering with ADLs
- 5 Permanent sensory loss that interferes with ADLs

Neuropathic pain (NCI CTC grade)

- 0 None
- 1 Mild pain not interfering with function
- 2 Moderate pain: pain or analgesics interfering with function but not ADLs
- 3 Severe pain: pain or analgesics severely interfering with ADLs
- 4 Disabling

FIGURE 3. NEUROTOXICITY ASSESSMENT TOOL

Note. Based on information from Calhoun et al., 2000; Cella et al., 1993; National Cancer Institute Cancer Therapy Evaluation Program, 1999.

withholding bortezomib treatment or with platelet infusion. Treatment may be started at a 25% reduced dose when toxicity is resolved. Platelet counts should be checked prior to each dose of bortezomib for the first two cycles of therapy and as clinically indicated thereafter.

Neutropenia

The incidence of grade 4 neutropenia was rare in clinical trials, and febrile neutropenia was reported in fewer than 1% of patients (Millennium Pharmaceuticals, Inc., 2003).

Orthostatic Hypotension

Bortezomib may be associated with orthostatic hypotension throughout therapy. Caution should be used when treating patients at risk for hypotension, such as those with a history of syncope, those receiving medications associated with hypotension,

and those who are dehydrated. Patients should be instructed to call their physicians if they experience these side effects or symptoms of lightheadedness, dizziness, or fainting. They should be cautious when driving cars or operating other machinery.

Electrolyte Imbalances

Hyponatremia may occur during treatment with bortezomib. Decreases in sodium levels have been reported after several cycles of treatment. Signs and symptoms include confusion, weakness, and seizures. Sodium levels should be kept above 130 nmol/L, and electrolytes should be checked prior to treatment. Patients can be encouraged to drink tomato juice prior to clinic visits or to increase the intake of sodium-rich foods. Frequent monitoring of serum electrolytes and early interventions can prevent worsening of these conditions and provide improved comfort for patients.

Rashes, Hives, and Pyrexia

Rashes were a reported side effect in about 21% of patients in the phase II trials and were primarily grade 1 or 2 (Millennium Pharmaceuticals, Inc., 2003). Diphenhydramine or hydrocortisone creams may be administered. Pyrexia also has occurred and may be treated with acetaminophen. A few patients have experienced hives, which, if they develop, usually are seen after three or four cycles of bortezomib. Administering small doses of prednisone for a few days usually relieves this symptom. If any rash continues to progress, bortezomib may have to be discontinued.

Additional Precautions for Comorbidity and Concurrent Medications

Patients with comorbidities and preexisting chronic conditions should be monitored closely. In addition to the adverse events reported in clinical trials, risks associated with bortezomib administration include congestive heart failure and tumor lysis syndrome (Millennium Pharmaceuticals, Inc., 2003). Patients with existing cardiac disease or risk factors for cardiac disease should be watched closely. Patients with high tumor burden should be followed, and appropriate precautions should be taken for tumor lysis syndrome. Diabetics and patients receiving oral hypoglycemics should have blood gluces monitored, and adjustments to their medications may be necessary (Millennium Pharmaceuticals, Inc.).

Pharmacokinetic studies in patients with renal or hepatic dysfunction are ongoing. Patients with hepatic or renal impairment should be monitored closely for toxicities when treated with bortezomib (Millennium Pharmaceuticals, Inc., 2003). For patients on dialysis, the timing of dosing has not been studied formally. Some have suggested that dosing should occur on days when dialysis is not performed to minimize the possibility of interfering with the concentrations of bortezomib.

Conclusions

Bortezomib is a new, first-in-class treatment for MM that offers new hope to patients with the disease. Administering this new therapy offers nurses many opportunities for educating patients and their families about the mechanism of action of the drug, how it differs from other chemotherapies, and what to expect during treatment.

TABLE 3. SIDE EFFECTS AND NURSING CONSIDERATIONS FOR PATIENT MANAGEMENT

SIDE EFFECT	POSSIBLE INTERVENTIONS
Peripheral neuropathy	<p>Patient education for signs and symptoms</p> <p>Establish baseline neurologic assessment and monitor throughout treatment.</p> <p>Vitamin supplements, including multi-B complex with B₁, B₆, B₁₂ (at least 400 mcg), folic acid, 1–2 mg folate, and vitamin E, 400 IU daily</p> <p>Magnesium supplement, 250 mg twice a day</p> <p>Dietary considerations (e.g., increased potassium intake, such as 2 teaspoons of apple cider vinegar, bananas, and oranges)</p> <p>Amino acid supplements (e.g., L-carnitine [start with 500 mg twice a day with food, up to 2,000 mg a day], L-glutamine [10 g a day for one week followed by 1 g twice a day], alpha-lipoic acid [400–600 mg a day with food])</p> <p>Tonic water (quinine or seltzer water) for cramping</p> <p>Topical creams such as capsaicin cream or cocoa butter</p> <p>Medications as indicated</p> <ul style="list-style-type: none"> • Gabapentin (start with 100 mg three times a day and gradually work up to 600 mg three times a day; can dose as high as 2,700 mg with physician permission) • Amitriptyline (25–50 mg at bedtime) • Sertraline (50–100 mg at bedtime) • Lidoderm patch 5% (1.5 patches to each area of pain; remove after 12 hours each day) <p>Referral to neurology or pain management</p>
Gastrointestinal	
Diarrhea	<p>Dietary considerations such as BRAT diet (bananas, rice, apple sauce, and toast)</p> <p>Adequate fluid intake (at least 2 quarts every day)</p> <p>Fiber supplements or natural bacterial flora supplements, such as</p> <ul style="list-style-type: none"> • Benefiber™ (1 tablespoon every day in 6 oz of liquid, increased to 2 tablespoons twice a day if needed) • Culturelle™ (1 tablet a day) • Glutamine (15 g twice a day) <p>Antidiarrheals (e.g., loperamide [1–2 tablets before each dose of bortezomib and 1 after every loose stool for 36 hours, not to exceed 8 tablets per day])</p> <p>Referral to nutritionist</p>
Constipation	<p>Dietary considerations such as high-fiber foods (e.g., flaxseed meal, prunes or prune juice every morning)</p> <p>Start with stool softeners (docusate sodium twice a day then three times a day). If needed, add senna-based laxatives, flaxseed oil (2 tablespoons a day), or milk of magnesia every other night at bedtime.</p> <p>If no stool in three days, try magnesium citrate, but not more than once a week.</p> <p>Referral to nutritionist</p>
Nausea and vomiting	Consider antiemetics as premedications as needed.
Anorexia	Appetite stimulants
Asthenia and fatigue	<p>Recommend proper rest, nutrition, hydration, and exercise.</p> <p>Antidepressants or psychiatric referral when indicated</p>
Thrombocytopenia	<p>Frequent monitoring of blood counts</p> <p>Platelet transfusion at the discretion of physician</p> <p>Patient education on signs and symptoms of bleeding, such as easy bruising or nose bleeds</p>
Neutropenia and anemia	<p>Monitor blood counts</p> <p>Transfusions and growth factors at physician's discretion</p>
Hypotension	<p>Determine whether patient has history of hypertension or syncope.</p> <p>Monitor all concomitant medications (hypertensive medications).</p> <p>Instruct patient to report symptoms such as lightheadedness and dizziness and to be cautious when driving.</p> <p>Monitor blood pressure.</p>
Electrolyte imbalances	<p>Monitor blood chemistries.</p> <p>Magnesium and potassium supplements as needed</p> <p>Dietary considerations, including high-sodium foods (e.g., canned soups, tomato juice) and potassium-rich foods (e.g., bananas)</p> <p>Adequate fluid intake</p>
Rash and pyrexia	Medications such as diphenhydramine and cortisone creams or acetaminophen as indicated

Note. These interventions have been used in bortezomib phase II trials, but experience with them is anecdotal. A formal evaluation has not been conducted.

Note. Based on information from Colson, 2003.

Early intervention with symptom management strategies can prevent side effects from developing or worsening. Oncology nurses are in a key position to identify these signs and to initiate appropriate treatment measures. In addition to monitoring laboratory values and following other standard clinic practices for treating MM, nurses are able to assess changes in patients' conditions, initiate interventions, evaluate the efficacy of supportive interventions, and further refine symptom management strategies. The management of some of the side effects associated with the administration of bortezomib, such as fatigue, hypotension, and gastrointestinal disturbances, may be affected by hydration regimes. Dietary supplements, including vitamins, minerals, and other supplements including amino acids, may ameliorate symptoms associated with peripheral neuropathies, but research is needed to support these interventions. Tools, such as the neurotoxicity assessment form, calendars, and information on symptom management can increase patients' awareness of important aspects of their care, minimize discomforts, and prevent unnecessary interruptions in treatment.

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References

- American Cancer Society. (2004). Cancer facts and figures 2004. Retrieved September 14, 2004, http://www.cancer.org/downloads/STT/CAFF_finalPWsecured.pdf
- Berenson, J.R., Jagannath, B., Barlogie, B., Siegel, R., Alexanian, D., Irwin, D., et al. (2003). Data on file at Millennium Pharmaceuticals, Inc.
- Blade, J., Samson, D., Reece, D., Apperley, J., Bjorkstrand, B., Gahrton, G., et al. (1998). Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haematopoietic stem cell transplantation. *British Journal of Haematology*, *102*, 1115–1123.
- Calhoun, E.A., Fishman, A., Roland, P.Y., Lurain, J.R., Chang, C.H., & Cella, D. (2000). Validity and selective sensitivity of the FACT/GOG-Ntx [Abstract 1751]. 36th Annual Meeting of the American Society of Clinical Oncology. Retrieved January 20, 2004, from http://www.asco.org/ac/1,1003,_12-002489-00_18-002000-00_19-00202320-00_28-00RESULTPAGE,00.asp
- Catley, L., & Anderson, K. (2004). Strategies to improve the outcome of stem cell transplantation in multiple myeloma. *Hematology Journal*, *5*, 9–23.
- Cella, D.F., Tulskey, D.S., Gray, G., Sarafian, B., Linn, E., Bonomi, A., et al. (1993). The Functional Assessment of Cancer Therapy scale: Development and validation of the general measure. *Journal of Clinical Oncology*, *11*, 570–579.
- Colson, K. (2003, November). *Proteasome inhibition: Patient management considerations for multiple myeloma patients*. Presented at the Oncology Nursing Society Institutes of Learning, Philadelphia, PA.
- Dalakas, M.C. (2001). Peripheral neuropathy and antiretroviral drugs. *Journal of the Peripheral Nervous System*, *6*, 14–20.
- Hideshima, T., Richardson, P., Chauhan, D., Palombella, V.J., Elliott, P.J., Adams, J., et al. (2001). The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells. *Cancer Research*, *61*, 3071–3076.
- Jagannath, S., Barlogie, B., Berenson, J., Siegel, D., Irwin, D., Richardson, P.G., et al. (2002). A phase II multicenter randomized study of proteasome inhibitor bortezomib (Velcade™ formerly PS-341) in multiple myeloma patients relapsed after front line therapy [Abstract 3207]. *Blood*, *100*, 812a.
- Jagannath, S., Richardson, P.G., Barlogie, B., Berenson, J., Singhal, S., Irwin, D., et al. (2003). Phase II trials of bortezomib in combination with dexamethasone in multiple myeloma (MM): Assessment of additional benefits to combination in patients with sub-optimal responses to bortezomib alone [Abstract 2341]. *Proceedings of the American Society of Clinical Oncology*, *22*, 582.
- Kyle, R.A., Gertz, M.A., Witzig, T.E., Lust, J.A., Lacy, M.O., Dispenzieri, A., et al. (2003). Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clinic Proceedings*, *78*, 21–33.
- LeBlanc, R., Catley, L.P., Hideshima, T., Lentzsch, S., Mitsiades, C.S., Mitsiades, N., et al. (2002). Proteasome inhibitor PS-341 inhibits human myeloma cell growth in vivo and prolongs survival in a murine model. *Cancer Research*, *62*, 4996–5000.
- Lee, S., Richardson, P.G., Barlogie, B., Berenson, J.R., Singhal, S., Jagannath, S., et al. (2003). Quality-of-life (QOL) and clinical benefit assessment in patients with relapsed and refractory multiple myeloma (MM) treated with bortezomib [Abstract 2339]. *Proceedings of the American Society of Clinical Oncology*, *22*, 582.
- Lonial, S., Waller, E.K., Richardson, P.G., Jagannath, S., Francis, D., Lehman, M., et al. (2003). Evaluation of the degree of thrombocytopenia and associated risk factors following bortezomib therapy for relapsed multiple myeloma [Abstract 1632]. *Blood*, *102*, 447a.
- Ma, M.M., Yang, H.H., Parker, K., Manyak, S., Friedman, J.M., Altamirano, C., et al. (2003). The proteasome inhibitor PS-341 markedly enhances sensitivity of multiple myeloma tumor cells to chemotherapeutic agents. *Clinical Cancer Research*, *9*, 1136–1144.
- Marrs, J., & Newton, S. (2003). Updating your peripheral neuropathy “know-how.” *Clinical Journal of Oncology Nursing*, *7*, 299–303.
- Millennium Pharmaceuticals, Inc. (2003). Velcade™ (bortezomib) prescribing information. Cambridge, MA: Author.
- Munshi, N.C., Tricot, G., & Barlogie, B. (2001). Plasma cell neoplasms. In V.T. DeVita, S. Hellman, & S.A. Rosenberg (Eds.), *Cancer: Principles and practices of oncology* (6th ed., pp. 2483–2485). Philadelphia: Lippincott Williams and Wilkins.
- National Cancer Institute Cancer Therapy Evaluation Program. (1999). *Common toxicity criteria* (Version 2.0). Retrieved December 8, 2003, from <http://ctep.info.nih.gov/reporting/CTC-3.html>
- Nielsen, E., & Brant, J. (2002). Chemotherapy-induced neurotoxicity: Assessment and interventions for patients at risk. *American Journal of Nursing*, *102*(Suppl. 4), 16–19.
- Orlowski, R.Z., Stinchcombe, T.E., Mitchell, B.S., Shea, T.C., Baldwin, A.S., Stahl, S., et al. (2002). Phase I trial of the proteasome inhibitor PS-341 in patients with refractory hematologic malignancies. *Journal of Clinical Oncology*, *20*, 4420–4427.
- Peltier, A.C., & Russell, J.W. (2002). Recent advances in drug-induced neuropathies. *Current Opinion in Neurology*, *15*, 633–638.
- Read, M.A., Neish, A.S., Luscinikas, F.W., Palombella, V.J., Maniatis, T., Collins, T., et al. (1995). The proteasome pathway is required for cytokine-induced endothelial-leukocyte adhesion molecule expression. *Immunity*, *2*, 493–506.
- Rice, D., & Sheridan, C.A. (2001). Nursing care of patients with multiple myeloma: A paradigm for the needs of special populations. *Clinical Journal of Oncology Nursing*, *5*, 89–93.
- Richardson, P.G., Barlogie, B., Berenson, J., Singhal, S., Jagannath, S., Irwin, D., et al. (2003a). A phase 2 study of bortezomib in relapsed, refractory myeloma. *New England Journal of Medicine*, *348*, 2609–2617.
- Richardson, P.G., Barlogie, B., Berenson, J.R., Singhal, S., Jagannath, S., Irwin, D., et al. (2003b). Prognostic factors for response parameters and overall survival in patients with multiple myeloma (MM) following treatment with bortezomib [Abstract 1629]. *Blood*, *102*, 446a.
- Richardson, P.G., Briemberg, H., Jagannath, S., Barlogie, B., Berenson, J., Singhal, S., et al. (2003). Peripheral neuropathy following bortezomib (Velcade™, formerly PS-341) therapy in patients with advanced multiple myeloma (MM): Characterization and reversibility [Abstract 512]. *Blood*, *102*, 149a.

Rude, R.K. (1998). Magnesium deficiency: A cause of heterogeneous disease in humans. *Journal of Bone and Mineral Research*, 13, 749–758.

Ruhnau, K.J.L., Meissner, H.P., Finn, J.R., Reljanovic, M., Lobisch, M., Schutte, K., et al. (1999). Effects of 3-week oral treatment with the antioxidant thioctic acid (α -lipoic acid) in symptomatic diabetic polyneuropathy. *Dia-*

betic Medicine, 16, 1040–1043.

Scarpini, E., Sacilotto, G., Baron, P., Cusini, M., & Scarlato, G. (1997). Effect of acetyl-L-carnitine in the treatment of painful peripheral neuropathies in HIV+ patients. *Journal of the Peripheral Nervous System*, 2, 250–252.

Tariman, J.D. (2003). Understanding novel therapeutic agents for multiple myeloma. *Clinical Journal of Oncology Nursing*, 7, 521–528.

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Rapid Recap

Bortezomib, a Newly Approved Proteasome Inhibitor for the Treatment of Multiple Myeloma: Nursing Implications

- Multiple myeloma (MM), the second most common hematologic malignancy, remains incurable, stimulating interest in novel therapies.
- Bortezomib is the first in a new class of anticancer drugs known as proteasome inhibitors. Its mechanism of action disrupts multiple signaling cascades involved in tumor cell proliferation, survival, and spread.
- Bortezomib has been approved to treat patients with MM who have received at least two prior therapies and have progressed on the most recent one.
- The most common side effects of asthenic conditions (including fatigue, malaise, and weakness), gastrointestinal events (including nausea, vomiting, diarrhea, anorexia, and constipation), thrombocytopenia, peripheral neuropathy, pyrexia, and anemia usually can be managed by standard interventions.
- Pretreatment assessments, patient education, and early identification of side effects by oncology nurses minimize treatment delays and interruptions and the worsening of symptoms.
- Nurses play a vital role in developing and implementing management strategies for side effects that can guide nursing interventions in the future in this new class of drugs.

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