

1. What is bortezomib and what is the indication?

Bortezomib is a novel, first-in-class proteasome inhibitor. It is indicated for the treatment of multiple myeloma patients who have received at least 2 prior therapies and have demonstrated disease progression on the last therapy.

Proteasome inhibitors disrupt the normal action of proteasomes, which are enzyme complexes in all cells that degrade intracellular proteins in both normal and cancer cells. Cancer cells depend on the proteasome's activity for proliferation, metastasis, and survival. The inhibition prevents the breakdown of proteins and affects multiple signaling cascades within the cells. This disruption can inhibit tumor growth and cause cancer cell death.

2. How is bortezomib administered?

Bortezomib is injected by a 3- to 5-second IV push directly into a peripheral vein or through an infusion port. The line should be flushed with normal saline. In clinical trials, extravasation was not associated with tissue damage. A small percentage of patients may experience a local skin reaction.

Bortezomib (1.3 mg/m²) is given twice weekly (Days 1, 4, 8, 11) for 2 weeks followed by a 10-day rest period (Days 12-21), comprising a 3-week cycle. Doses are typically given on Monday and Thursday or Tuesday and Friday. At least a 72-hour rest period is required between doses. Infusion reactions were rarely reported during clinical trials, and no cases of overdose were reported. In the event of an overdose, the patient's vital signs should be monitored and supportive care given to maintain body temperature and blood pressure. There is no known antidote for bortezomib overdose.

Bortezomib is cytotoxic, and caution must be taken when handling and preparing the drug. It is supplied in 10-mL single-dose vials reconstituted with 3.5 mL of normal saline. Reconstituted bortezomib should be used within 8 hours of preparation (see package insert for more details). Prior to administering bortezomib, the following procedures are recommended with each cycle:

Procedure/Test	Day 1	Day 4	Day 8	Day 11
Assess for symptom management (eg, diarrhea, vomiting, fever, etc)	XX	X	XX	X
Monitor for symptoms of peripheral neuropathy, such as burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, or pain	XX	X	XX	X
Vital signs (blood pressure, respiration rate, temperature, pulse)	XX	X	XX	X
Clinical Laboratory Tests				
Hematology (CBC and platelet count)	YY	X	YY	X
Electrolytes	YY	—	YY	—
Clinical chemistries	YY	—	YY	—
	Y		Y	
Body Surface Area (recalculate dose if weight change 8% or greater)	XX	X	XX	X

3. What are the side effects of bortezomib and how do they affect dosing or treatment schedules?

In clinical trials, the most common side effects associated with bortezomib were asthenic conditions (65%), nausea (64%), diarrhea (51%), decreased appetite including anorexia (43%), constipation (43%), thrombocytopenia (43%), peripheral neuropathy (37%), pyrexia (36%), vomiting (36%), and anemia (32%). The most commonly reported serious side effects were pyrexia (7%), pneumonia (7%), diarrhea (6%), vomiting (5%), dehydration (5%), and nausea (4%).

At the onset of Grade 3 nonhematological toxicities or Grade 4 hematological toxicities, therapy with bortezomib should be held. Once the toxicity has resolved, therapy can be restarted at a 25% reduced dose. Dose modification is different for peripheral neuropathy, in which the treatment should be modified as followed:

Severity of Peripheral Neuropathy Signs/Symptoms	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 1.0 mg/m ²
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold bortezomib therapy until toxicity resolves. When toxicity resolves, reinitiate with a reduced dose of bortezomib at 0.7mg/m ² and change treatment schedule to once per week.
Grade 4 (permanent sensory loss that interferes with function)	Discontinue bortezomib

On-study adverse events by grade in phase II clinical trials at 1.3-mg/m² dose (N=228)*

N=228	Grades 1-2 [†]	Grade 3 [†]	Grade 4 [†]
Nausea	58%	6%	0%
Diarrhea	43%	7%	<1%
Appetite decreased & anorexia	40%	3%	0%
Constipation	41%	2%	0%
Vomiting	28%	7%	<1%
Thrombocytopenia	13%	27%	3%
Anemia	23%	9%	0%
Asthenia (fatigue, malaise, weakness)	46%	18%	<1%
Peripheral neuropathy	23%	14%	0%
Pyrexia	32%	4%	0%

* Combined safety data from the SUMMIT and CREST Trials.

* AEs reported for all events, drug related or not.

† National Cancer Institute Common Toxicity Criteria (NCI CTC, Version 2.0).

4. How is peripheral neuropathy managed?

Since peripheral neuropathy can be dose limiting, patients need to 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 and tingling, burning sensation, discomfort, or pain should be evaluated prior to each treatment, and patients need to be instructed to contact the physician if symptoms develop or change.

5. How is asthenia managed?

First onset of fatigue was reported most often during Cycles 1 and 2, and most patients were able to continue therapy in spite of fatigue. At the onset of a Grade 3 nonhematologic toxicity, including fatigue, malaise, or weakness, bortezomib should be held. Once the toxicity has resolved, treatment may be restarted at a 25% reduced dose (1.3 mg/m² should be reduced to 1.0 mg/m²; 1.0 mg/m² should be reduced to 0.7mg/m²). Management is primarily by supportive care.

6. How is thrombocytopenia managed?

Thrombocytopenia is maximal at Day 11 and typically recovers by the next cycle. On average, the pattern of platelet count decrease and recovery remained consistent over the 8-cycle study period, and there was no evidence of cumulative thrombocytopenia. The mean platelet count nadir measured was approximately 40% of baseline. Platelet counts should be monitored prior to each dose of bortezomib. Bortezomib therapy should be held when the platelet count is <25,000/μL and reinitiated at a reduced dose (1.3 mg/m² should be reduced to 1.0 mg/m²; 1.0 mg/m² should be reduced to 0.7mg/m²). Platelet transfusions may be utilized at the physician's discretion. There have been reports of gastrointestinal and intracerebral hemorrhage in association with VELCADE-induced thrombocytopenia.

7. What precautions need to be taken when administering bortezomib...hypotension, gastrointestinal disturbances, and neutropenia?

Patients need to be monitored for symptoms of neuropathy and changes in blood counts, blood chemistries, and blood pressure. Bortezomib may be associated with **orthostatic hypotension** throughout therapy. Caution should be used when treating patients with a history of syncope, patients receiving medications associated with hypotension, and patients who are dehydrated. The majority of **gastrointestinal events** are mild to moderate. Patients should be advised to maintain hydration and to call the physician if they experience these side effects or symptoms of light-headedness, dizziness, or fainting. Standard antiemetics and antidiarrheals may be used, and some patients may benefit from intravenous fluid and electrolyte replacement. They should be cautious when driving cars or operating other machinery.

At the onset of any Grade 3 nonhematologic toxicities (including GI disturbances and hypotension), bortezomib should be held. Once the toxicity has resolved, treatment may resume at a 25% dose reduction (1.3 mg/m² should be reduced to 1.0 mg/m²; 1.0 mg/m² should be reduced to 0.7mg/m²).

The incidence of Grade 4 neutropenia was rare in clinical trials, and febrile neutropenia was < 1%. At the onset of Grade 4 hematologic toxicities, bortezomib should be held. Once the toxicity resolves, treatment can resume at 25% reduced dose (1.3 mg/m² should be reduced to 1.0 mg/m²; 1.0 mg/m² should be reduced to 0.7mg/m²). Blood counts should be closely watched. Use of growth factors is at the physician's discretion.

8. Is the administration of bortezomib different in patients with renal impairment? What kind of response can my patients expect from bortezomib?

There are no pharmacokinetic data in patients with impaired hepatic or renal insufficiency. Patients with creatinine clearance values < 14mL/min and those receiving dialysis should be closely monitored.

9. What kind of response can my patients expect from bortezomib?

It is impossible to predict whether an individual patient will respond or not, but, in clinical trials, 27.7% of patients who had received at least 2 prior therapies and had gotten worse on their last therapy had a partial or complete response to bortezomib treatment. Patients maintained responses over time, with a median duration of response of 12 months.

10. What are some of the early signs of peripheral neuropathy?

Some patients may start bortezomib therapy with preexisting neuropathy, particularly if they were previously treated with neurotoxic agents such as vincristine or thalidomide. Patients need to be monitored at each visit for new or worsening numbness and tingling in the hands or feet, pain in the extremities, inability to button their clothes, burning sensations, increased sensitivity to touch, neuropathic pain such as shooting pain in the legs, severe leg cramps in calves and/or thighs, or any other arthralgias or myalgias. A neurotoxicity questionnaire may increase the patient's awareness of these symptoms and establishes a method for tracking changes in symptoms. Referral to neurology, pain management, and/or psychology consultants may be appropriate.

11. Is there a standard pretreatment regimen prior to administering bortezomib?

No, the pretreatment should be specific to the individual patient's clinical history and current status. Hydration with 500 cc of normal saline may be helpful in avoiding some of the gastrointestinal side effects or in preventing hypotension. If a patient has a history of gastrointestinal reactions, such as nausea and vomiting, antiemetics may be given prior to

administering bortezomib. Allergic reactions are rare, and pretreatment with diphenhydramine or acetaminophen is not necessary.

12. How long can a patient stay on bortezomib?

This has not yet been completely determined, and individual patients should be evaluated in terms of the risks and benefits of continuing therapy within the context of their medical history and current condition. Patients in clinical trials were treated for an average of 6 cycles or 2 cycles after confirmed complete response, but patients may be treated until they progress.

13. If a patient develops a new peripheral neuropathy or a worsening of an existing peripheral neuropathy, what should be done?

Follow the recommended guidelines for dose reductions in the setting of peripheral neuropathy suggested by Millennium Pharmaceuticals, Inc. and educate the patient to the importance of reporting the signs and symptoms so they can be appropriately treated.

14. What are some of the possible symptomatic treatments for mild peripheral neuropathy?

During clinical trials at the Dana-Farber Cancer Institute, the clinicians recommended vitamin supplements such as vitamin B complex, folic acid, and vitamin E, as well as amino acid supplements such as L-carnitine. Topical creams such as capsaicin cream or cocoa butter applied to the affected area may ease discomfort. Patients complaining of nocturnal leg cramping may try drinking an 8-ounce glass of tonic water (quinine water) in the evening prior to going to bed.

If the symptoms worsen, medications such as Neurontin[®], (gabapentin), amitriptyline, or sertraline hydrochloride at bedtime may also be beneficial. Lidocaine patches have also been used.

15. Are there any nursing interventions to prevent hypotension?

Special caution should be used when treating patients at risk of hypotension, such as those with a history of syncope, patients receiving medications associated with hypotension, and patients who are dehydrated.

The nurse should monitor the patient's blood pressure and all concomitant medications including antihypertensives and instruct the patient to report any signs of hypotension such as light-headedness or dizziness. The patient should be cautioned not to drive a car or operate any machinery.

16. What are the symptom-management strategies for patients suffering from diarrhea during the treatment with bortezomib?

Patients must maintain adequate fluid intake, and in the case of mild diarrhea they should consider dietary changes, such as the introduction of the BRAT diet (**b**ananas, **r**ice, **a**pplesauce, **t**oast). If symptoms persist, a referral to a nutritionist may be necessary. More severe diarrhea may be controlled with prescription antidiarrheals such as loperamide hydrochloride or diphenoxylate hydrochloride. Additional options to alleviate symptoms include fiber supplements such as Benefiber[™] and products designed to restore the natural intestinal flora such as Culturelle[™].

17. Under what conditions would you hold treatment of bortezomib?

Holding a dose is a decision made in the context of the patient's overall medical condition, but standard dose modifications include holding the drug for any Grade 2 neuropathy with pain or

Grade 3 neuropathy, any Grade 3 nonhematologic toxicity, and any Grade 4 hematologic toxicity. Bortezomib should be discontinued for Grade 4 neuropathy.

18. What can you tell patients who want to change the treatment schedule to accommodate their schedule?

There is some flexibility in scheduling as long as there is 72 hours between doses to allow the proteasomes to recover. This is very important. Toxicities may be greatly aggravated if the proteasomes are not allowed to recover.

19. What should you do if a patient who is being treated with bortezomib develops a rash during the second cycle of therapy?

A skin rash has been a reported side effect in approximately 21% of patients in the phase II trials. Diphenhydramine or hydrocortisone creams may be administered. A few patients have experienced hives, which, if they develop, are usually seen after 3 or 4 cycles of bortezomib. Administering small doses of prednisone for a few days will usually relieve this symptom. If the rash improves or resolves, patients can continue treatment. If any rash continues to progress, bortezomib may have to be discontinued.