

# Managing and avoiding bortezomib toxicity

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Bortezomib, the only currently approved proteasome inhibitor, is used in the treatment of relapsed/refractory multiple myeloma and mantle cell lymphoma. The most frequent toxicities of bortezomib are gastrointestinal symptoms, thrombocytopenia, asthenia (fatigue, malaise, and weakness), and peripheral neuropathy. Thrombocytopenia, the most common grade 3/4 toxicity, usually resolves before the next cycle of bortezomib therapy begins. Peripheral neuropathy may be managed by modifying the dose and schedule of bortezomib administration. Gastrointestinal complaints (nausea, vomiting, diarrhea, and constipation) are managed symptomatically. Careful attention to avoiding dehydration and hypotension has a role in mitigating fatigue, and adjustments in the patient's other medications may be needed. Modifications in the dose and scheduling of bortezomib, now being investigated, promise to improve the therapeutic ratio of this valuable drug.

**B**ortezomib (Velcade) is the first of a group of compounds known as proteasome inhibitors to be approved for use in the treatment of neoplastic disease. The US Food and Drug Administration approved the use of bortezomib in 2003 to treat relapsed/refractory multiple myeloma and more recently (December 2006) for the management of relapsed/refractory mantle cell lymphoma. In addition, bortezomib has shown promising results as first-line therapy of myeloma and lymphoma, as well as other neoplasms.<sup>1</sup> As the use of proteasome inhibitor therapy in oncology increases, knowledge of the ubiquitin proteasome system

(UPS) and the drugs that affect it will become more important. This brief review focuses on the toxicity associated with bortezomib therapy and discusses the appropriate medical management of bortezomib's side effects.

## Mechanism of action and pharmacokinetics

Bortezomib, a boronic acid dipeptide, is a reversible proteasome inhibitor. The ubiquitin-proteasome degradation pathway modulates intracellular levels of key regulatory proteins that orchestrate cell-cycle progression in a highly selective and specific fashion. Protein degradation is initiated by ubiquitin-substrate conjugation, which is catalyzed by three enzymes (E1, E2, and E3). Degradation of the ubiquitin-tagged substrate by the 26S proteasome then occurs. Diseases linked to mutations of the UPS include juvenile Parkinson's disease and breast and ovarian cancers associated with *BRCA1* mutations.<sup>2</sup>

For reasons that are unclear, neoplastic cells are more sensitive to pharmacologic proteasome inhibition than are normal cells. In the case of bortezomib, the main mechanism of action seems to be induction of apoptosis via inhibition of abnormal protein (immunoglobulin chain) degradation

### KEY POINTS

Asthenia, nausea, and diarrhea are the most frequent toxicities of bortezomib monotherapy.

Thrombocytopenia, the most common severe toxicity, usually resolves before the next cycle of bortezomib therapy begins.

Peripheral neuropathy is also common and may be managed by lowering the dose of bortezomib and/or giving it less frequently.

Fatigue is common with bortezomib but usually improves with continued therapy; steps should be taken to avoid dehydration and hypotension.

Gastrointestinal complaints are managed symptomatically.

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and inactivation of nuclear factor- $\kappa$ B (a potent anti-apoptotic protein) by degradation of its inhibitory component,  $\kappa$ B (Figure 1).<sup>3,4</sup>

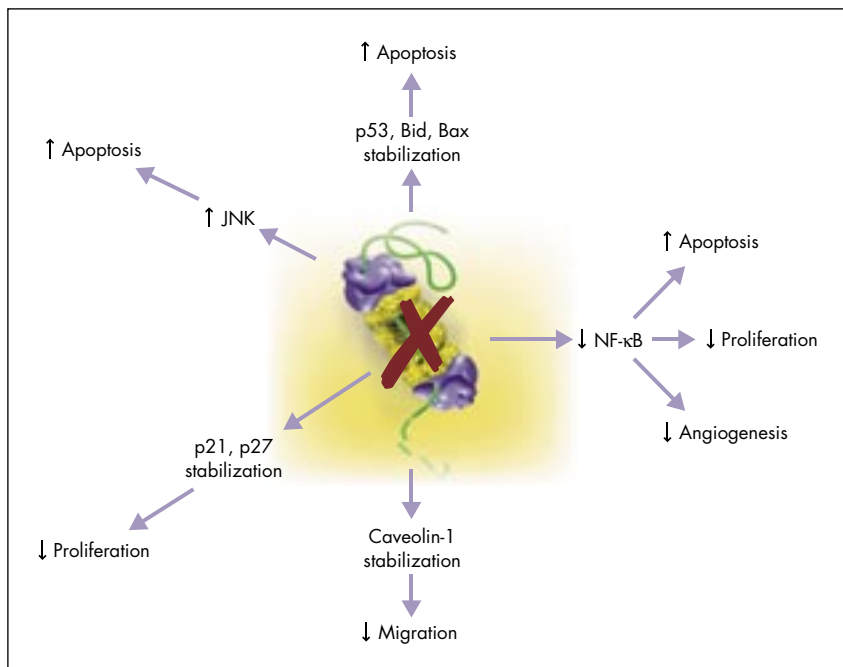
Bortezomib is largely cleared from the plasma within minutes following intravenous administration. Standard monotherapy is given at a dose of 1.3 mg/m<sup>2</sup> on days 1, 4, 8, and 11 of a 21-day cycle, for a maximum of 8 cycles.<sup>5,6</sup> For extended therapy beyond 8 cycles, bortezomib may be given in once-weekly doses of 1.3 mg/m<sup>2</sup> for 4 consecutive weeks out of a 5-week cycle.<sup>5,6</sup>

Bortezomib is metabolized in the liver by cytochrome P450 microsomes. Clearance may be reduced in patients taking inhibitors of the P450 enzymes 3A4, 2C19, and 1A2, such as erythromycin or ketoconazole, and in patients with hepatic impairment.<sup>6</sup>

### Bortezomib toxicity

The most common toxicities of bortezomib monotherapy reported in clinical trials were gastrointestinal symptoms, cytopenias (notably thrombocytopenia), asthenia (fatigue, malaise, and weakness), and peripheral neuropathy (Table 1).<sup>7,8</sup> Thrombocytopenia was the most commonly reported grade 3/4 toxicity (30%) but usually resolved during the rest period (days 12–21) of the treatment cycle. Asthenia, nausea, and diarrhea were the most common overall toxicities.

In patients with multiple myeloma who were treated on an extension of the phase II SUMMIT trial, there was no apparent cumulative toxicity (neurologic or hematologic) among those receiving conventional bortezomib monotherapy for a median duration of 45 weeks or, in some patients, up to 32 cycles.<sup>5</sup> In another phase II trial, the CREST trial, toxicity was lessened significantly in patients receiving 1.0 mg/m<sup>2</sup> of bortezomib twice weekly.<sup>7</sup> Bortezomib may cause rapid tumor cell death, and clinicians should be alert to the development of tumor lysis syndrome in patients with



**FIGURE 1** Bortezomib inhibition of the 26S proteasome results in activation of JNK and stabilization of p53, Bid, Bax, p21, p27, caveolin-1, and inhibitor kappaB-alpha, with consequent inhibition of nuclear factor kappaB (NF- $\kappa$ B). Alteration of the levels of these cellular proteins leads to inhibition of proliferation, migration, and angiogenesis and promotion of apoptosis of cancer cells. Adapted from Boccadoro et al.<sup>4</sup>

**TABLE 1**

Most commonly reported adverse events in phase II trials of bortezomib in relapsed/refractory multiple myeloma

Adverse event	All grades, %	Grade 3, %	Grade 4, %
<b>Gastrointestinal</b>			
Nausea	64	6	0
Diarrhea	51	7	< 1
Decreased appetite	43	3	0
Constipation	43	2	0
Vomiting	36	7	< 1
<b>Hematologic</b>			
Thrombocytopenia	43	27	3
Anemia	32	9	0
<b>Neurologic and other</b>			
Asthenia (fatigue, malaise, weakness)	65	18	< 1
Peripheral neuropathy	37	14	0
Pyrexia	36	4	0
Headache	28	4	0
Insomnia	27	1	0
Arthralgia	26	5	0
Limb pain	26	7	0
Edema	25	1	0

Source: Jagannath et al<sup>7</sup> and Richardson et al<sup>8</sup>

**TABLE 2**  
Management of bortezomib-related peripheral neuropathy

Severity of peripheral neuropathy signs and symptoms	Recommended modification of bortezomib dose and regimen
Grade 1 (paresthesia and/or loss of reflexes) without pain or loss of function	No action needed
Grade 1 with pain or grade 2 (interfering with function but not with activities of daily living)	Reduce dose to 1.0 mg/m <sup>2</sup>
Grade 2 with pain or grade 3 (interfering with activities of daily living)	<ul style="list-style-type: none"> <li>• Withhold bortezomib until toxicity resolves</li> <li>• When toxicity resolves, reinstitute bortezomib therapy at a reduced dose of 0.7 mg/m<sup>2</sup></li> <li>• Change treatment schedule to once per week</li> </ul>
Grade 4 (disabling)	Discontinue bortezomib therapy

Adapted from San Miguel et al<sup>14</sup>

a high tumor burden.<sup>9</sup>

Bortezomib appears to act synergistically with dexamethasone. Possible synergy has also been observed when bortezomib was combined with melphalan (Alkeran) and doxorubicin in myeloma therapy. In combination with melphalan, toxicity was manageable, with grade 3 hematologic toxicity occurring only in patients with baseline cytopenias.<sup>10</sup> In a phase I/II trial of VMPT (bortezomib, melphalan, prednisone, and thalidomide [Thalomid]), decreased-intensity bortezomib (1.3 mg/m<sup>2</sup> on days 1, 4, 15, and 22 in a 35-day cycle) and thalidomide (50 mg/d) did not result in severe (grade 3/4) neurotoxicity. Notably, neutropenia was more common than thrombocytopenia in this treatment scheme compared with 21-day bortezomib cycles.<sup>11</sup> When bortezomib was combined with thalidomide and dexamethasone as first-line therapy of multiple myeloma, no grade 3/4 neuropathy was evident after short-term therapy.<sup>12</sup>

**Managing bortezomib toxicity**

The clinical management of toxicities arising as a result of bortezomib therapy allows for the provision of ongoing effective therapy while minimizing acute and chronic toxicities

that decrease the patient’s quality of life.

*Patients with hepatic or renal impairment*

Since bortezomib is cleared by the liver, care should be taken in treating patients with hepatic insufficiency with this agent. Patients with mild-to-moderate hepatic impairment (ie, serum bilirubin or transaminase levels two to three times normal) can usually be treated safely with careful monitoring for toxicity and rapid dose adjustments, if needed. Patients with more severe liver disease should probably not be treated with bortezomib.

Patients with renal insufficiency who are receiving hemodialysis may be treated successfully with bortezomib. In phase II trials, the incidence of serious adverse effects (≥ grade 3) was apparently increased in patients with a creatinine clearance < 50 mL/min, but the only statistically significant increased toxicity was dyspnea.<sup>13</sup> Vigilant monitoring for toxicity and dose reduction to 0.7–1.0 mg/m<sup>2</sup>, where appropriate, can allow for successful therapy. Because of its small molecular size, bortezomib is potentially dialyzable; therefore, it is usually given on non-dialysis days in renally impaired patients receiving hemodialysis. There are no formal dos-

ing guidelines for these patients, but some investigators have used a starting dose of 1 mg/m<sup>2</sup> of bortezomib, with the usual precaution of spacing doses 72 hours or more apart.

*Peripheral neuropathy*

Peripheral neuropathy is common in myeloma as a result of the disease itself, as well as in patients being treated with thalidomide. In phase II trials of bortezomib, 37% of patients developed peripheral neuropathy during therapy.<sup>7,8</sup> The peripheral neuropathy that develops is primarily a sensory neuropathy, with predominant involvement of the feet and hands. Pain, dysesthesias, and numbness are common; 14% of patients developed grade 3 or higher neuropathy. In these patients, 71% showed improvement on discontinuation of therapy or dose modification, with a median time to improvement in peripheral neuropathy of 47 days. In patients treated on the extension protocol of phase II bortezomib, only 12% noted new-onset peripheral neuropathy with extended bortezomib therapy. Patients with pre-existing peripheral neuropathy had a 27% incidence of progressive peripheral neuropathy on the extension trial.<sup>5,7</sup>

Managing the peripheral neuropathy associated with bortezomib requires sensitivity to the presentation of neuropathic signs and symptoms.<sup>14</sup> For patients experiencing moderate pain or decreased functional ability (eg, in writing or dressing) attributable to peripheral neuropathy, dose modification should be rapidly instituted. The utility of managing peripheral neuropathy using patient-reported symptoms in a standard dose-adjustment algorithm was documented in an updated analysis of the phase III APEX trial. In this evaluation, the incidence of severe neuropathy was less than that reported in earlier bortezomib trials.<sup>15</sup>

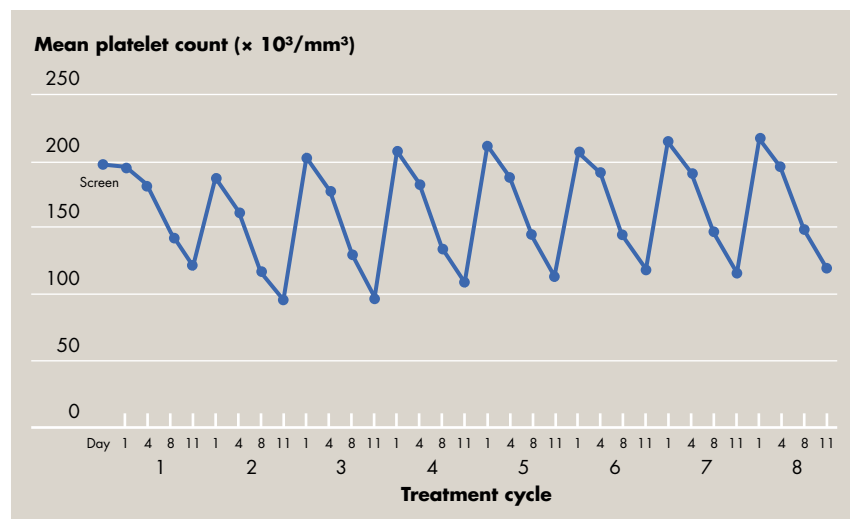
Consideration should be given to the possibility of cobalamin deficiency, which could be palliated with vita-

min B<sub>12</sub> repletion. Drug therapy with gabapentin or duloxetine (Cymbalta) may be beneficial in palliating painful neuropathy, but the benefit of using these agents or, alternatively, pyridoxine or glutamine is uncertain in terms of improving the duration and severity of the neuropathy; hence, the primacy of dose modification in managing this toxicity.

### Thrombocytopenia

The thrombocytopenia associated with bortezomib is common and has a characteristic temporal pattern (Figure 2).<sup>5</sup>

Bortezomib does not appear to destroy stem cells or megakaryocytes. However, due to NF- $\kappa$ B inhibition, platelet budding from megakaryocytes is compromised in patients receiving bortezomib.<sup>16</sup> Thrombopoietin levels are not decreased, and recovery to the baseline platelet count is usual after a rest period of 7–11 days. The temporal pattern and proportional decrease in the platelet count (approximately 55%–65% from baseline to nadir in all patients) are not affected by the extent of bone marrow involvement. Serious bleeding or a requirement for platelet transfusion support is therefore unusual in these patients, unless the baseline platelet count falls below 65,000/ $\mu$ L. Because the thrombocytopenic effect of bortezomib is generally predictable, monitoring the platelet count prior to each dose of bortezomib is recommended for the first 2 cycles of therapy for patients with normal baseline platelet counts. Less frequent monitoring can be applied in subsequent cycles of treatment. For patients with baseline thrombocytopenia, more frequent monitoring is warranted. In general, treatment with bortezomib should be deferred if the baseline platelet count is severely depressed (< 30,000/ $\mu$ L), although clinical judgment will dictate whether dosage reduction and/or platelet transfusion support is appropriate. Persistent thrombocytopenia is



**FIGURE 2** Cycle-to-cycle variation in mean platelet count observed in 331 myeloma patients treated with bortezomib. The platelet counts decreased during the treatment phase of each 3-week cycle and returned to the baseline value during the rest period of the cycle. Adapted from Richardson et al.<sup>5</sup>

more indicative of refractory disease than it is of bortezomib toxicity.

### Other cytopenias

Severe neutropenia and anemia were unusual in the phase II bortezomib trials. In the SUMMIT trial, there was a < 1% incidence of febrile neutropenia, and there were no cases of grade 4 anemia.<sup>8</sup> If anemia is noted, evaluations are mandated to direct decisions regarding appropriate therapy. Significant neutropenia may require growth-factor support (either filgrastim [Neupogen] or pegfilgrastim [Neulasta]).

### Fatigue

In the SUMMIT and CREST trials, 8%–12% of patients developed grade 3 fatigue (fatigue sufficient to interfere with activities of daily living), and less severe fatigue was common.<sup>7,8</sup> The usual onset of fatigue is in the first 2 cycles of bortezomib therapy, and typically the condition improves over subsequent cycles of therapy.<sup>17</sup> Careful attention to avoiding dehydration and hypotension has a role in mitigating fatigue. Adjustment of antihypertensive drug therapy, mineralocorticoid therapy, and intrave-

nous hydration at the time of bortezomib administration may benefit patients suffering fatigue, as well as patients with postural hypotension. Modafinil (Provigil) or methylphenidate may lessen fatigue attributable to therapy, but if fatigue is significant, bortezomib should be withheld temporarily and then restarted at a lower dose, when the patient's energy level has improved.

### Gastrointestinal toxicities

Nausea, vomiting, diarrhea, and constipation were commonly reported in phase II clinical studies but were rarely severe.<sup>6–8</sup> Symptomatic treatment of these toxicities with antiemetics, antidiarrheal medications, or laxatives may be required; special care should be taken to prevent dehydration in patients who are vomiting or suffering diarrhea.

### Conclusion

As the treatment paradigm for multiple myeloma continues to evolve, it is likely that bortezomib will be used for longer periods and in novel combinations with other drugs that are active against myeloma. New dose and administration schedules

for bortezomib that may increase the therapeutic ratio have been reported.<sup>18</sup> It is likely, too, that new, more selective proteasome inhibitors will enter the clinical arena. Caregivers will need to remain dutiful in observing their patients for new and varying treatment-related toxicities to ensure that patients benefit maximally from these therapies.

#### References

1. Aghajanian C, Soignet S, Dixon DS, et al. A phase I trial of the novel proteasome inhibitor PS341 in advanced solid tumor malignancies. *J Clin Oncol* 2002;8:2505–2511.
2. Reinstein E, Ciechanover A. Protein degradation and human diseases: the ubiquitin connection [review]. *Ann Intern Med* 2006;145:676–684.
3. Hideshima T, Mitsiades C, Akiyama M, et al. Molecular mechanisms mediating anti-multiple myeloma activity of proteasome inhibitor PS-341. *Blood* 2003;101:2377–2380.
4. Boccadoro M, Morgan G, Cavenagh J. Preclinical evaluation of the proteasome inhibitor bortezomib in cancer therapy. *Cancer Cell Int* 2005;5:18 (epub doi: 10.1186/1475-2867-5-18).
5. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med* 2005;352:2487–2498.
6. Velcade [prescribing information]. Cambridge, Mass: Millennium Pharmaceuticals, Inc; 2004.
7. Jagannath S, Barlogie B, Berenson J, et al. A phase 2 study of two doses of bortezomib in relapsed or refractory multiple myeloma. *Br J Haematol* 2004;127:165–172.
8. Richardson PG, Barlogie B, Berenson J, et al. A phase 2 study of bortezomib in relapsed, refractory multiple myeloma. *N Engl J Med* 2003;348:2609–2617.
9. Sezer O, Vesole D, Singhal S, et al. Bortezomib-induced tumor lysis syndrome in multiple myeloma. *Clin Lymphoma Myeloma* 2006;7:233–235.
10. Berenson J, Yang H, Swift R, et al. Bortezomib in combination with melphalan in the treatment of relapsed or refractory multiple myeloma: a phase I/II study. *Blood* 2004;104(11):209.
11. Palumbo A, Ambrosini M, Benevolo G, et al. Bortezomib, melphalan, prednisone, and thalidomide for relapsed multiple myeloma. *Blood* 2007;109(11):2767.
12. Alexanian R, Wang L, Weber D, et al. VTD as primary therapy for newly diagnosed multiple myeloma. *Blood* 2004;104(11):210.
13. Jagannath S, Barlogie B, Berenson J, et al. Bortezomib in recurrent and/or refractory multiple myeloma: initial clinical experience in patients with impaired renal function. *Cancer* 2005;103:1195–1200.
14. San Miguel JF, Richardson P, Sonneveld P, et al. Frequency, characteristics, and reversibility of peripheral neuropathy (PN) in the APEX trial. *Blood* 2005;106:366.
15. Richardson PG, Briemberg H, Jagannath S, et al. Frequency, characteristics and reversibility of peripheral neuropathy during treatment of advanced multiple myeloma with bortezomib. *J Clin Oncol* 2006;24:3113–3120.
16. Lonial S, Waller EK, Richardson PG, et al. Evaluation of the degree of thrombocytopenia and associated risk factors following bortezomib therapy for relapsed multiple myeloma. *Blood* 2003;102(11):1632.
17. Lee S, Richardson PG, Barlogie B, et al. Quality of life (QOL) and clinical benefit assessment in patients with relapsed and refractory multiple myeloma (MM) treated with bortezomib. *Proc Am Soc Clin Oncol* 2003;22:2339.
18. Suvannasankah A, Smith G, Juliar B, et al. Weekly bortezomib/methylprednisolone is effective and well tolerated in relapsed multiple myeloma. *Clin Lymphoma Myeloma* 2006;7:131–134.

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