

ROWENA SCHWARTZ, PharmD, BCOP
Associate Professor of Pharmacy
and Therapeutics
University of Pittsburgh
School of Pharmacy
Coordinator, University of
Pittsburgh Cancer Institute
Pittsburgh, Pennsylvania

TERRI DAVIDSON, PharmD, BCOP
Chief Executive Officer
Syntaxx Communications, Inc.
Atlanta, Georgia

Pharmacology, Pharmacokinetics, and Practical Applications of Bortezomib

Normal cellular function and homeostasis depend on precisely controlled intracellular processes, including the systematic and highly regulated degradation of proteins that control cellular division, growth, function, and death.[1-3] For example, regulation of the cell cycle depends on the orderly degradation of cyclins and inhibitors of the cyclin-dependent kinases.[1] If the systematic degradation of proteins is interrupted, regulatory proteins accumulate within the cell, creating an imbalance in the number of proteins required to elicit certain cellular functions, such as progression from the G₁ to the S phase of the cell cycle or activation of signal transduction pathways.[4,5]

In eukaryotic cells, the ubiquitin-proteasome pathway (UPP), comprising a ubiquitin-conjugating system and the proteasome, is primarily responsible for the degradation of cellular proteins and plays an important role in many basic cellular processes.[5-7] The list of cellular proteins controlled by the UPP is growing rapidly and includes, in addition to the

— One or two copies of this article for personal or internal use may be made at no charge. Copies beyond that number require that a 9¢ per page per copy fee be paid to the Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01970. Specify ISSN 0890-9091. For further information, contact the CCC at 508-750-8400. Write publisher for bulk quantities.

ABSTRACT

Bortezomib (PS-341, Velcade) is a novel, first-in-class proteasome inhibitor with antitumor activity against a number of hematologic and nonhematologic malignancies. Based on the results of phase II clinical trials, bortezomib received accelerated US Food and Drug Administration approval on May 13, 2003, for the treatment of multiple myeloma patients whose disease has progressed after they have received at least two prior conventional therapies. The results of phase III studies evaluating bortezomib as first- or second-line therapy, or in combination with other commonly prescribed therapies in multiple myeloma patients, are eagerly awaited. Studies assessing the antitumor effects of bortezomib in other hematologic malignancies and solid tumors are also under way. A thorough understanding of the pharmacology, pharmacodynamics, and pharmacokinetics of this novel compound is essential for appropriate prescribing and monitoring of bortezomib therapy. Bortezomib is rapidly distributed into tissues after administration of a single dose, with an initial plasma distribution half-life of less than 10 minutes, followed by a terminal elimination half-life of more than 40 hours. Maximum proteasome inhibition occurs within 1 hour and recovers close to baseline within 72 to 96 hours after administration. Bortezomib is primarily metabolized by oxidative deboronation to one of two inactive enantiomers that are further processed and eliminated, both renally and in bile. Bortezomib has been shown to be a substrate of several cytochrome P450 isoenzymes using in vitro systems. Adverse effects of bortezomib are generally mild and effectively managed with supportive care. Bortezomib should be administered with caution to patients with preexisting fluid retention and patients with baseline platelet counts of less than 70,000/ μ L. Dose reductions are recommended for patients experiencing peripheral neuropathy, grade 3 or higher nonhematologic toxicities, or grade 4 hematologic toxicities. Formal drug interaction studies have not been performed, but bortezomib has been administered in combination with a variety of antitumor agents without significant alterations to its pharmacokinetic or pharmacodynamic profile.

cell-cycle regulatory proteins (eg, cyclins, cyclin-dependent kinase inhibitors), proteins involved in chromatid separation, oncogenes and tumor suppressor genes, and transcriptional activators and inhibitors.[5,7-10] Another important function of the UPP is the selective removal of mutated and denatured or misfolded proteins, as well as proteins damaged by stress, oxidation, chemicals, or viral infection.[1,8,10]

Aberrations in the UPP have been implicated in the pathogenesis of many diseases, including certain malignancies. For example, degradation of the p53 tumor suppressor gene or p27 inhibitor of cyclin-dependent kinases can promote tumorigenesis of various malignancies, including uterine, colon, breast, and prostate cancers.[1,7,8]

Inhibiting the activity of the proteasome, one of the key constituents of the UPP, can block cellular growth and division, ultimately leading to cell death. Because the proteasome is responsible for degrading more than 80% of cellular proteins in eukaryotic cells, its inhibition would seem incompatible with life.[5] However, the results of preclinical and early-phase clinical studies show that proteasome inhibition (PI) can arrest the growth of tumor cells, induce apoptosis, inhibit angiogenesis, and increase the sensitivity of tumor cells to chemotherapy or radiation therapy, without having a major deleterious effect on nontumor cells.[3,11-13]

Based on these results, a number of synthetic PIs have been developed and evaluated as antitumor agents. Bortezomib (PS-341, Velcade), the first proteasome inhibitor to be evaluated in humans, received US Food and Drug Administration (FDA) approval for the treatment of patients with multiple myeloma previously treated with two or more therapies

Address all correspondence to:
Rowena Schwartz, PharmD, BCOP
Associate Professor of Pharmacy
and Therapeutics
University of Pittsburgh School of Pharmacy
9th Floor, Salk Hall
3501 Terrace St
Pittsburgh, PA 15261
e-mail: schwartzrn@upmc.edu

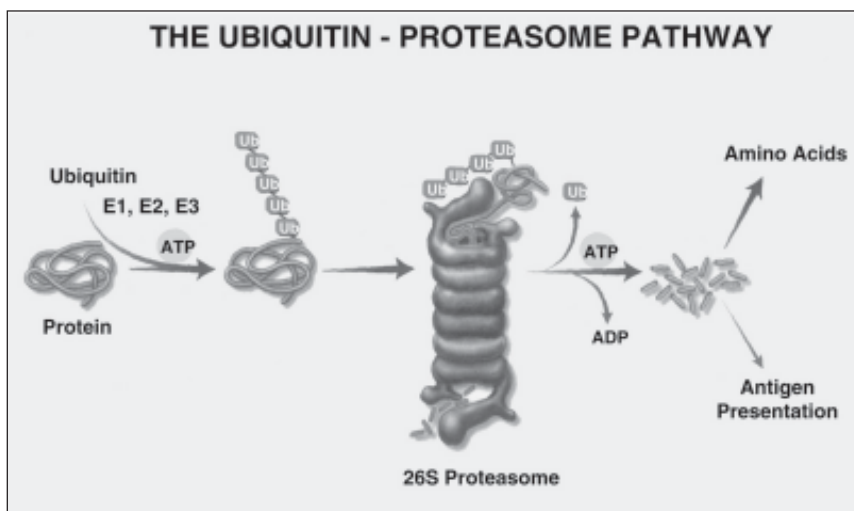


Figure 1: Mechanism of Action of Bortezomib—ADP = adenosine 5'-diphosphate; ATP = adenosine 5'-triphosphate; E1 = ubiquitin-activating enzyme; E2 = ubiquitin-conjugating enzyme; E3 = ubiquitin protein ligase; Ub = ubiquitin. Reprinted, with permission, from Elsevier © 2001.[1]

and with disease progression on the last therapy.[5,14-17] This article summarizes the pharmacology, pharmacokinetics, and current practical applications of bortezomib.

Proteasome Inhibition

To understand more clearly the mechanism of action of bortezomib (Figure 1), a basic understanding of the proteasome's role in the UPP and the consequences of PI are required.[1,18]

Ubiquitin-Proteasome Pathway

Protein degradation by the UPP involves two discrete and successive steps: (1) tagging of the substrate (protein to be destroyed) by covalent attachment of multiple ubiquitin molecules, and (2) degradation of the tagged protein by the 26S proteasome.[7,8] Ubiquitin molecules are attached to the target protein by the sequential activity of three enzymes: E1, E2, and E3. E1, the ubiquitin-activating enzyme, activates the ubiquitin molecule through an adenosine 5'-triphosphate (ATP)-dependent reaction and transfers it to one of many different E2 or ubiquitin-conjugating enzymes. The ubiquitin molecule is then transferred to the target protein in a step that requires the E3 enzyme (ubiquitin protein ligase). Eukaryotic

cells contain hundreds of E3 enzymes, each with the ability to recognize different degradation signals on proteins. Ubiquitinated proteins are then recognized and degraded by the 26S proteasome.[1,6-9]

The 26S proteasome is a multifunctional proteolytic complex that consists of a proteolytic core particle, the 20S proteasome, and two 19S regulatory particles.[7] The 20S core particle consists of four stacked rings: two identical outer rings (α rings) and two identical inner rings (β rings). The α and β rings are composed of seven distinct subunits, giving the 20S complex the general structure of $\alpha_{1-7}\beta_{1-7}\beta_{1-7}\alpha_{1-7}$. The proteolytic sites are localized on the β_1 , β_2 , and β_5 subunits of the two inner β rings. Each end of the 20S core is capped with a 19S regulatory particle, which recognizes polyubiquitinated proteins, cleaves the polyubiquitin chain from the target protein (the polyubiquitin chain can then be disassembled by deubiquitinating enzymes and recycled into the UPP), unfolds proteins that would be unable to fit through the narrow proteasomal channel, and opens the channel in the α ring to permit entry of the target protein into the proteolytic chamber. The opening of the channel requires metabolic energy, and each 19S regulatory particle contains six different ATPase subunits that pro-

vide energy upon hydrolysis by ATP. After the protein is degraded by the 20S core particle, short peptides are released into the cytosol of the cell. Because the active sites (β subunits) of the proteasome are confined to the inner cavity of the 20S core particle, uncontrolled degradation of cellular proteins cannot occur.[1,2,6-9]

The beta subunits of the 20S core particle contain three types of proteolytic sites: chymotrypsin-like sites, trypsin-like sites, and caspase-like sites.[1,6,9] These sites differ in their specificity for the types of protein residues (eg, hydrophobic residues and acidic residues) at which they cleave. Although the 26S proteasome has several active sites, inhibition of all three sites is not required to significantly reduce protein processing. Specific inhibition of the chymotrypsin-like site by bortezomib significantly reduces protein processing ($K_i = 0.6$ nM). Most inhibitors of chymotrypsin-like sites are more highly hydrophobic and cell-permeable than inhibitors of the trypsin- or caspase-like sites, which contain charged residues; therefore, most proteasome inhibitors act predominantly on the chymotrypsin-like sites and to a much lesser degree on the other two sites.[1]

Proteasome Inhibition

Various natural and synthetic proteasome inhibitors—all of which bind to and directly inhibit the active sites within the 20S core particle of the proteasome—have been identified.[1,5,11-13] Impeding the degradation of regulatory proteins through PI results in accumulation of several important regulatory proteins, including the inhibitor of nuclear factor- κ B (NF- κ B), I κ B, the p53 tumor suppressor gene, the p21 and p27 cyclin-dependent kinase inhibitors, and the bax protein.[1,5,13,19-22] Accumulation of these proteins leads to decreased NF- κ B activity, increased p53-mediated transcription of genes important in apoptosis and dysregulation of the cell cycle, increased p21- and p27-mediated induction of cell cycle arrest, and promotion of apoptosis by inhibition of Bcl-2 by bax.[1,5,13,19-22] Proteasome inhibition also downregulates the p44/42

mitogen-activated protein kinase (MAPK)-induced signals required for tumorigenesis.[1,5] As a result of these and other incompletely understood effects of PI, proteasome inhibitors inhibit tumor cell proliferation, induce apoptosis, and inhibit angiogenesis.

As mentioned previously, the results of several preclinical studies have shown cancer cells to be more sensitive to the effects of PI than are normal cells. For example, patient-derived chronic lymphocytic leukemia cells are about 10 times more sensitive to PI than are normal human lymphocytes.[20] Although the biologic basis for the enhanced susceptibility of cancer cells to PI has not been fully elucidated, several hypotheses exist, including a greater sensitivity of rapidly proliferating cells (eg, tumor cells) to PI and more efficient uptake and slower inactivation of proteasome inhibitors by tumor cells.[1,5] Other theories focus on the deregulation of various UPP functions during the malignant transformation of a cell. For example, low levels of the bax proapoptotic protein resulting from an upregulation of UPP activity have been associated with higher Gleason scores in prostate cancer patients.[22] Proteasome inhibition blocks the degradation of this protein, resulting in higher intracellular levels and increased apoptosis.[22]

In addition to producing antitumor effects, proteasome inhibitors sensitize both chemosensitive and chemoresistant cancer cells to conventional chemotherapy.[5,12,13,18,19,23,24] For example, the combination of bortezomib with irinotecan (Camptosar) was more effective in inhibiting tumor growth in mice than either irinotecan or bortezomib alone.[23] Combined with subtoxic doses of bortezomib, melphalan (Alkeran), doxorubicin, and mitoxantrone (Novantrone) exhibit cytotoxic effects on chemoresistant multiple myeloma cell lines at drug concentrations 100,000- to 1,000,000-fold lower than concentrations required for cytotoxicity in the absence of bortezomib.[24]

Proteasome inhibitors also play a role as radiation therapy sensitizers. In a mouse colon cancer model, a single dose of radiation therapy and

bortezomib produced significantly lower tumor volumes and increased apoptosis rates compared with radiation therapy alone.[25] These combination therapies did not increase cytotoxic or radiotoxic effects on normal bone marrow cells in healthy, cancer-free individuals.

The mechanisms by which proteasome inhibitors reverse chemotherapy or radiation therapy resistance are not completely understood, although downregulation of NF- κ B has been shown to play an important role in abrogating drug resistance.[5,23] For example, NF- κ B activity in multiple myeloma cell lines resistant to melphalan, mitoxantrone, and doxorubicin is greater than NF- κ B activity in nonresistant multiple myeloma cell lines; treatment with subtoxic doses of bortezomib attenuated NF- κ B activity, sensitizing the resistant cells to treatment with these agents.[22] Proteasome inhibitors may also downregulate other resistance pathways, including the p44/42 MAPK pathway, which is activated by certain chemotherapy agents, such as the taxanes and anthracyclines. In a murine xenograft model of breast cancer, proteasome inhibitors have been shown to block doxorubicin-mediated activation of the p44/42 MAPK pathway, which correlates with increased apoptosis and antitumor efficacy.[5]

Proteasome inhibitors have shown a broad spectrum of activity in preclinical models. The dipeptide boronic acid bortezomib is a specific and reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome. While many other proteasome inhibitors have been synthesized and tested in preclinical models, bortezomib is the only one to be clinically evaluated in cancer patients and approved for clinical use.[1,5,13-17]

Pharmacology of Bortezomib

Bortezomib is a potent, selective, and reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome (see Figure 1). Preclinical and early-phase study results revealed that bortezomib was active against a broad range of hematologic and solid tumors, with tolerable effects on nor-

mal tissues.[3-5,11-14] The results of a phase I dose-determining study by Aghajanian and colleagues[3] showed that PI increases with increasing doses of bortezomib, with approximately 65% PI occurring after administration of the manufacturer-recommended dose of 1.3 mg/m². Maximum inhibition of 20S activity occurs within 1 hour after bortezomib administration; 20S activity returns toward baseline within 72 to 96 hours.[26,27] No significant difference in the mean percentage of PI was observed with administration of subsequent doses on days 4, 8, and 11, suggesting that 72 hours between administration is sufficient for recovery of proteasome function in normal tissues.[3]

Pharmacokinetics

The pharmacokinetics of bortezomib have not been fully characterized in multiple myeloma patients.[16] The pharmacokinetics have been investigated in two phase I studies in patients with solid tumors receiving combination therapy of bortezomib and irinotecan or gemcitabine (Gemzar).[28,29]

After intravenous (IV) bolus administration, bortezomib quickly distributes into tissues from the plasma.[17,27,28,30] The distribution half-life is less than 10 minutes, followed by a long elimination half-life (> 40 hours).[27] In animal studies using radiolabeled bortezomib, bortezomib was rapidly distributed into nearly all tissues, with the exception of adipose tissue and certain tissues in the brain protected by the blood-brain barrier.[30] Following extensive tissue distribution of radiolabeled bortezomib, a slow terminal elimination rate was observed, with only 65% (females) to 85% (males) of the total dose recovered from monkeys after 144 hours.[30] Plasma protein binding of bortezomib is considered moderate (approximately 83%) and was not shown to be concentration dependent over the concentration range studied (100 to 1,000 ng/mL).[17]

The results of *in vitro* studies suggest that bortezomib is metabolized primarily through oxidative deboronation (the removal of boronic acid from

the parent compound), which can be mediated by multiple cytochrome P450 system isoenzymes, including 3A4, 2C19, 1A2, 2D6, and 2C9.[16,17,31] Deboronation produces two inactive enantiomers that subsequently undergo further metabolic processing and are eliminated by both renal and hepatic routes.[30,32] More than 30 inactive metabolites have been identified in animal and human studies.

Pharmacokinetics studies of bortezomib in patients with renal or hepatic insufficiency have not been completed; however, studies evaluating bortezomib in these patient populations are under way with the National Cancer Institute's Organ Dysfunction Group.[17,33] Clinical trials included patients with creatinine clearance values ranging from 13.8 to 220 mL/min.[17] No correlation between creatinine clearance and maximum PI at 1 hour, the incidence of grade 3 or 4 adverse effects, or discontinuation rates have been observed.[33] Patients with reduced renal function have displayed response and treatment discontinuation rates comparable to those in patients with more normal renal function and were able to receive a comparable number of bortezomib doses.[33] The pharmacokinetics in patients either undergoing hemodialysis or with a creatinine clearance value less than 13 mL/min have not been completely described.[17]

The appropriate dosage of bortezomib in patients who were more than 30% above their ideal body weight was calculated based on average body weight ([actual body weight - ideal body weight]/2); however, the effectiveness of this method for determining an appropriate dose in obese patients is unknown.[34] Bortezomib use has not been evaluated in pediatric patients, although a pharmacokinetics study of bortezomib administered to pediatric patients is under way.[17]

Practical Applications

Based on the results of two phase II clinical trials, the SUMMIT and CREST trials, bortezomib received

accelerated FDA approval on May 13, 2003, for the treatment of multiple myeloma patients whose disease has progressed after they have received at least two prior conventional therapies.[16,17,35] Studies evaluating bortezomib as first- and second-line therapy for multiple myeloma patients, including a phase III, multicenter, randomized trial comparing bortezomib with high-dose dexamethasone in relapsed multiple myeloma patients, are under way.[14,16,35] Additional phase I or II studies evaluating bortezomib alone or combined with standard chemotherapy agents as multiple myeloma treatment and as treatment of solid tumor and other hematologic malignancies have shown promising results.[36-42] For a more in-depth discussion of the clinical uses of bortezomib, refer to the article entitled "Discovery, Development, and Clinical Applications of Bortezomib" found in this supplement.

Because bortezomib is a novel, first-in-class proteasome inhibitor approved for use in relapsed or refractory multiple myeloma, clinicians prescribing or monitoring bortezomib therapy should be educated about its effects in humans. Although additional studies are needed to define more clearly the effects of bortezomib administered either alone or in combination with other antitumor agents for various cancers, the results of phase I and II studies have provided useful information about monitoring the toxicity of bortezomib in relapsed or refractory multiple myeloma patients whose disease has relapsed or whose disease is refractory to conventional therapies.

Adverse Effects

In the SUMMIT and CREST phase II trials, the most common adverse effects in multiple myeloma patients receiving bortezomib 1.3 mg/m², included fatigue (65%), nausea (64%), diarrhea (51%), thrombocytopenia (43%), anorexia (43%), peripheral neuropathy (37%), vomiting (36%), pyrexia (36%), anemia (32%), periph-

Financial Disclosure: Dr. Schwartz has acted as a speaker for Millennium Pharmaceuticals, Inc.

Table 1

Grades 3 and 4 Adverse Events in the SUMMIT and CREST Phase II Clinical Trials^a

Adverse Event	Grade 3	Grade 4
Thrombocytopenia	27%	3%
Asthenia	18%	< 1%
Peripheral neuropathy	14%	0%
Neutropenia	13%	3%
Anemia	9%	0%
Diarrhea	7%	< 1%
Vomiting	7%	< 1%
Limb pain	7%	0%
Nausea	6%	0%
Arthralgia	5%	0%
Headache	4%	0%
Pyrexia	4%	0%
Anorexia	3%	0%
Paresthesia and dysesthesia	3%	0%
Dyspnea	3%	< 1%
Constipation	2%	0%
Insomnia	1%	0%
Edema	1%	0%
Dizziness	1%	0%

^an = 228.

eral edema (25%), and dyspnea (22%).^[16,17] Table 1 lists the severe (grades 3 and 4) adverse effects observed in these trials.^[16,17] Most toxicities were mild to moderate in severity (grades 1 or 2) and did not require discontinuation or delay of bortezomib therapy.

Treatment was withheld in patients experiencing grade 3 or higher non-hematologic toxicities or grade 4 hematologic toxicities.^[14] Retreatment with a 25% dose reduction (ie, reduced from 1.3 to 1.0 mg/m² or from 1.0 to 0.7 mg/m²; doses below 0.7 mg/m² were not permitted) was allowed in patients who experienced a lessening in the severity of the adverse effect to a grade 1 or lower level.^[14] Bortezomib-related toxicities that required treatment discontinuation, including peripheral neuropathy (5%), thrombocytopenia (4%), fatigue (2%), and diarrhea (2%), developed in 18% of patients.^[17]

In another phase II trial in mantle cell lymphoma patients receiving bortezomib, Assouline and colleagues^[43] reported five cases of severe fluid retention in patients with baseline dyspnea or peripheral edema. Two patients died: one died of grade 4 acute vascular leak syndrome and the other died of progressive disease with severe edema. The other three patients experienced dyspnea and peripheral edema or hypoxia and peripheral edema. Based on these results, the authors amended their study to exclude patients with baseline dyspnea or fluid retention. Interestingly, less than 5% of multiple myeloma

patients enrolled in the SUMMIT and CREST trials experienced grade 3 or 4 dyspnea or edema; presumably these patients showed no signs of fluid retention at study entry.^[17] Nevertheless, patients with preexisting fluid retention, especially in the presence of dyspnea or hypoxia, should not receive bortezomib therapy, and patients should be instructed to report any signs of fluid retention promptly to their caretaker.

Because of the potential need for dosage adjustment or requirement for premedication, several adverse events associated with bortezomib merit further discussion, including peripheral neuropathy, hypotension, thrombocytopenia, and gastrointestinal effects.

• Peripheral Neuropathy—Based on pooled data from the SUMMIT and CREST trials, treatment-emergent peripheral neuropathy—primarily sensory neuropathy characterized by burning or painful dysesthesias, paresthesias, or numbness—was observed in 35% of patients receiving bortezomib therapy.^[44] Of the patients who experienced bortezomib-induced peripheral neuropathy, more than 70% had previously received neurotoxic therapies; additionally, more than 80% of patients reported symptoms of peripheral neuropathy at baseline.^[17,44] Patients with these baseline symptoms were at greater risk of developing grade 3 or 4 peripheral neuropathy during bortezomib therapy.^[44] Only two patients without baseline peripheral neuropathy symptoms developed grade 3 peripheral neuropathy, suggesting that the incidence of peripheral neuropathy may be lower in ongoing and future studies evaluating patients with earlier-stage disease and who have received no or minimal previous neurotoxic therapies.^[44]

In patients experiencing grade 3 or 4 peripheral neuropathy requiring treatment discontinuation, symptoms disappeared or lessened in 37% of patients during treatment; however, the remaining patients experienced symptoms throughout and after discontinuing bortezomib therapy. Partial or complete reversal of symptoms occurred in 71% of patients; in 40%,

symptoms resolved during bortezomib therapy and in 32% after therapy discontinuation. For patients who experienced resolution or improvement in peripheral neuropathy after completing therapy, the median time to resolution was 47 days (range: 1–529 days) after the last dose of bortezomib. Treatment-emergent peripheral neuropathy required therapy discontinuation or dosage reductions in only 5% and 12% of patients, respectively.[44]

In an open-label extension study, patients from the SUMMIT and CREST trials who benefitted from bortezomib therapy were allowed to continue receiving bortezomib and were assessed for an average of 24.4 additional weeks (patients were assessed for 8 cycles, or 24 weeks, during the SUMMIT and CREST trials).[45] Evidence of cumulative or permanent toxicity, including peripheral neuropathy, after prolonged bortezomib exposure (median, 45 weeks; maximum, 99.9 weeks) did not exist.

Early diagnosis of bortezomib-induced peripheral neuropathy and bortezomib dosage adjustments may prevent development of severe neuropathies; therefore, patients should be closely monitored for and instructed to report new or worsening symptoms of neuropathy (eg, increasing pain, numbness).[17] Additionally, the dosage should be adjusted in most patients experiencing painful peripheral neuropathy during bortezomib therapy (Table 2).[17] Data regarding the outcome of peripheral neuropathy in patients receiving bortezomib are limited, but analyses of follow-up data will be used to determine the pathophysiology and reversibility of peripheral neuropathy in these patients.[17,44]

• **Hypotension**—Orthostatic/postural hypotension occurred in 12% of multiple myeloma patients enrolled in the SUMMIT and CREST trials.[17] Grade 3 hypotension occurred in 4% of patients; grade 4 hypotension was not observed. None of these patients

Acknowledgments: The authors acknowledge the assistance of Stephanie Butler and Alison Shore in the manuscript preparation and editing, respectively. Development of the manuscript was supported through an unrestricted educational grant from Millennium Pharmaceuticals, Inc.

Table 2

Dose Modifications for Patients Experiencing Peripheral Neuropathy, Grade 3 Nonhematologic Toxicities, and/or Grade 4 Hematologic Toxicities[17]

Type and Severity of Adverse Event ^a	Dose Modification Recommendation
Peripheral neuropathy	
Grade 1 without pain ^b	No modification required
Grade 1 with pain or grade 2 without pain ^c	Reduce by 25% ^d
Grade 2 with pain or grade 3 ^e	Discontinue bortezomib until resolution of peripheral neuropathy, reinstate at 0.7 mg/m ² and change frequency to once weekly
Grade 4 ^f	Discontinue bortezomib
Grade 3 nonhematologic toxicity (excluding peripheral neuropathy)	Discontinue bortezomib until symptoms resolve; reinstate therapy with 25%-reduced dose ^d
Grade 4 hematologic toxicity	Discontinue bortezomib until symptoms resolve; reinstate therapy with 25%-reduced dose ^d

^aBased on National Cancer Institute Common Toxicity Criteria. Available at <http://ctep.info.nih.gov/reporting/ctc.html>

^bParesthesias and/or loss of reflexes without loss of function.

^cInterferes with function, but not with activities of daily living.

^dReduce to 1 mg/m² if original dose = 1.3 mg/m²; reduce to 0.7 mg/m² if original dose = 1.0 mg/m².

^eInterferes with activities of daily living.

^fPermanent sensory loss that interferes with function.

had evidence of orthostatic hypotension at baseline; however, approximately 50% had preexisting hypertension and 33% had symptoms of peripheral neuropathy. Four percent of patients experienced hypotension and a concurrent syncopal episode.[17]

Risk factors for the development of hypotension after bortezomib therapy include (1) history of syncope, (2) concomitant use of medications known to lower blood pressure (ie, antihypertensive agents), and (3) dehydration.[17] Hydration status should be assessed and corrected, if necessary, before and throughout bortezomib therapy, especially in patients experiencing nausea and/or vomiting. Additionally, patients receiving antihypertensive medications should be closely monitored to determine if antihypertensive medication dosage adjustment is necessary. Mineralocorticoids were effective in minimizing the hypotensive effects of bortezomib therapy

in some patients.[17]

Finally, patients and/or caregivers should be instructed to report signs or symptoms of hypotension (eg, lightheadedness, dizziness, syncope) immediately to a healthcare professional, maintain adequate hydration, and exercise caution when operating machinery, including automobiles. In patients experiencing grade 3 hypotension, the bortezomib dose should be discontinued until symptoms resolve, at which time a 25%-reduced dose of bortezomib may be implemented (see Table 2).[17]

• **Thrombocytopenia**—Patients receiving bortezomib 1.3 mg/m² in these trials experienced a median 60% decrease in their baseline platelet count during therapy regardless of initial baseline platelet count, baseline serum myeloma paraprotein (M-protein) level, or degree of multiple myeloma bone marrow involvement.[46] The onset of thrombo-

cytopenia most commonly occurred after cycles 1 or 2 and continued throughout therapy.[17] Platelet counts typically reached a nadir on day 11 and rose to a normal count by day 21. Cerebral and gastrointestinal hemorrhages secondary to bortezomib-induced thrombocytopenia were rarely reported.[17] Patients with a baseline platelet count of less than 70,000/ μ L had an increased risk of developing grade 4 thrombocytopenia.[46] Furthermore, patients with greater bone marrow involvement (ie, > 50% plasma cells) or higher M-protein levels (> 31 g/L) usually had lower baseline platelet counts and lower platelet count nadirs. Thrombocytopenia caused by bortezomib therapy presumably results from an inhibition of thrombopoiesis, an NF- κ B-dependent process, rather than direct bone marrow toxicity; therefore, supportive care, rather than discontinuation of bortezomib therapy, may be adequate for controlling bortezomib's effects on platelet production.[46]

Platelet counts should be monitored throughout bortezomib therapy, and therapy should be discontinued in patients with platelet counts less than 25,000/ μ L (grade 4 thrombocytopenia) until the platelet count returns to normal.[17] Bortezomib can be reinitiated at a 25%-reduced dose when platelet counts return to baseline levels. Patients and/or caregivers should be educated about the risks of bleeding and instructed how to manage a bleeding episode.

• **Gastrointestinal Effects**—Gastrointestinal adverse effects, including nausea, vomiting, diarrhea, constipation, and/or anorexia, are common in patients receiving bortezomib therapy. Nausea, vomiting, and diarrhea should be anticipated and may warrant premedication with antiemetics or antidiarrheals.[16] Ensuring adequate hydration and electrolyte levels in patients experiencing nausea, vomiting, diarrhea, or constipation helps to reduce the consequences of these adverse effects. Although therapy discontinuation due to gastrointestinal adverse effects was required in only 5% of patients, grade 3 or 4 events occurred in 21% of patients.[17]

Dose Modifications Due to Adverse Effects

The recommended bortezomib dose for multiple myeloma is 1.3 mg/m² administered as a 3- to 5-second IV bolus.[14,17] Administration is repeated twice weekly for 2 weeks, with a minimum of 72 hours between doses to allow for restoration of proteasome function in normal cells.[17] Each cycle of four doses is followed by a 10-day rest (ie, bortezomib is administered on days 1, 4, 8, and 11, followed by no administration on days 12 through 21). Dose modifications are recommended to manage peripheral neuropathy, grade 3 nonhematologic toxicities, and grade 4 hematologic toxicities (see Table 2).[17]

Drug Interactions

Although formal drug interaction studies of bortezomib have not been conducted, the results of phase I or II clinical trials evaluating bortezomib in combination with other chemotherapy agents, including docetaxel (Taxotere), gemcitabine, or irinotecan (Camptosar), have shown no alteration in the pharmacokinetics or pharmacodynamics (ie, degree of 20S PI) of any of these drugs when concurrently administered.[17,28,47-50] Additionally, toxicities associated with the combination of bortezomib and dexamethasone were similar to toxicities of bortezomib or dexamethasone alone, suggesting that no interaction occurs with concomitant administration of these agents.[51] Results of in vitro studies demonstrate that bortezomib is a substrate of several isoenzymes in the cytochrome P450 system.[17] Further studies are warranted to characterize the disposition of bortezomib when administered with other substrates or inhibitors of the P450 metabolic system.

Conclusions

Proteasome inhibition is a promising new anticancer therapy that inhibits one target, but affects multiple pathways. Bortezomib, which possesses highly selective and reversible PI activity, is the first commercially available proteasome inhibitor. The adverse effects of bortezomib are gen-

erally well tolerated and, with standard supportive care measures, manageable. The most common severe adverse effects include peripheral neuropathy, fluid retention, thrombocytopenia, fatigue, nausea, vomiting, and diarrhea. Bortezomib is currently approved for the treatment of multiple myeloma in patients whose disease has progressed after they have received at least two prior therapies. Ongoing studies are evaluating the efficacy and safety of bortezomib as first- or second-line treatment of multiple myeloma and in the treatment of other malignancies.

References

1. Kisselev AF, Goldberg AL: Proteasome inhibitors: From research tools to drug candidates. *Chem Biol* 8:739-758, 2001.
2. Zwickl P, Voges D, Baumeister W: The proteasome: A macromolecular assembly designed for controlled proteolysis. *Philos Trans R Soc Lond B Biol Sci* 354:1501-1511, 1999.
3. Aghajanian C, Soignet S, Dizon DS, et al: A phase I trial of the novel proteasome inhibitor PS341 in advanced solid tumor malignancies. *Clin Cancer Res* 8:2505-2511, 2002.
4. Mitsiades N, Mitsiades CS, Poulaki V, et al: Molecular sequelae of proteasome inhibition in human multiple myeloma cells. *Proc Natl Acad Sci U S A* 99:14374-14379, 2002.
5. Voorhees PM, Dees EC, O'Neil B, et al: The proteasome as a target for cancer therapy. *Clin Cancer Res* 9:6316-6325, 2003.
6. DeMartino GN, Slaughter CA: The proteasome, a novel protease regulated by multiple mechanisms. *J Biol Chem* 274:22123-22126, 1999.
7. Glickman MH, Ciechanover A: The ubiquitin-proteasome proteolytic pathway: Destruction for the sake of construction. *Physiol Rev* 82:373-428, 2002.
8. Ciechanover A, Orian A, Schwartz AL: Ubiquitin-mediated proteolysis: Biological regulation via destruction. *BioEssays* 22:442-451, 2000.
9. Hershko A, Ciechanover A: The ubiquitin system. *Annu Rev Biochem* 67:425-479, 1998.
10. Wilkinson KD: Ubiquitin-dependent signaling: The role of ubiquitination in the response of cells to their environment. *J Nutr* 129:1933-1936, 1999.
11. Adams J, Palombella VJ, Sausville EA, et al: Proteasome inhibitors: A novel class of potent and effective antitumor agents. *Cancer Res* 59:2615-2622, 1999.
12. Hideshima T, Richardson P, Chauhan D, et al: The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells. *Cancer Res* 61:3071-3076, 2001.
13. Richardson PG, Hideshima T, Anderson KC: Bortezomib (PS-341): A novel, first-in-class proteasome inhibitor for the treatment of

- multiple myeloma and other cancers. *Cancer Control* 10:361-369, 2003.
14. Richardson PG, Barlogie B, Berenson J, et al: A phase 2 study of bortezomib in relapsed, refractory myeloma. *N Engl J Med* 348:2609-2617, 2003.
 15. Adams J: Development of the proteasome inhibitor PS-341. *The Oncologist* 7:9-16, 2002.
 16. Kane RC, Bross PF, Farrell AT, et al: Velcade: US FDA approval for the treatment of multiple myeloma progressing on prior therapy. *The Oncologist* 8:508-513, 2003.
 17. Velcade [package insert]. Cambridge, Mass, Millennium Pharmaceuticals, Inc., 2003.
 18. Mitchell BS: The proteasome—An emerging therapeutic target in cancer. *N Engl J Med* 348:2597-2598, 2003.
 19. O'Connor O, Wright J, Moskowitz CH, et al: Promising activity of the proteasome inhibitor bortezomib (Velcade) in the treatment of indolent non-Hodgkin's lymphoma and mantle cell lymphoma (abstract 2346). Paper presented at the Annual Meeting of the American Society of Hematology, December 6-9, 2003, San Diego.
 20. Masdehors P, Merle-Béral H, Maloum K, et al: Deregulation of the ubiquitin system and p53 proteolysis modify the apoptotic response in B-CLL lymphocytes. *Blood* 96:269-274, 2000.
 21. Chiarle R, Budel LM, Skolnik J, et al: Increased proteasome degradation of cyclin-dependent kinase inhibitor p27 is associated with a decreased overall survival in mantle cell lymphoma. *Blood* 95:619-626, 2000.
 22. Li B, Dou QP: Bax degradation by the ubiquitin/proteasome-dependent pathway: Involvement in tumor survival and progression. *Proc Natl Acad Sci U S A* 97:3850-3855, 2000.
 23. Cusack JC, Liu R, Houston M, et al: Enhanced chemosensitivity to CPT-11 with proteasome inhibitor PS-341: Implications for systemic nuclear factor- κ B inhibition. *Cancer Res* 61:3535-3540, 2001.
 24. Ma MH, Yang HH, Parker K, et al: The proteasome inhibitor PS-341 markedly enhances sensitivity of multiple myeloma tumor cells to chemotherapeutic agents. *Clin Cancer Res* 9:1136-1144, 2003.
 25. Russo SM, Tepper JE, Baldwin AS, et al: Enhancement of radiosensitivity by proteasome inhibition: Implications for a role of NF- κ B. *Int J Radiat Oncol Biol Phys* 50:183-193, 2001.
 26. Nix D, Pien C, Newman R, et al: Clinical development of a proteasome inhibitor, PS-341, for the treatment of cancer (abstract 339). *Proc Am Soc Clin Oncol* 20:86a, 2001.
 27. Nix D, Milton M, Pligavko C, et al: Pharmacokinetics of the proteasome inhibitor bortezomib (Velcade) in male cynomolgus monkeys (abstract C245). Paper presented at the 2003 American Association for Cancer Research—National Cancer Institute—European Organization for Research and Treatment of Cancer Molecular Targets and Cancer Therapeutics Discovery, Biology, and Clinical Applications meeting. November 17-21, 2003, Boston.
 28. Supko JG, Eder JP, Lynch TJ, et al: Pharmacokinetics of irinotecan and the proteasome inhibitor bortezomib in adult patients with solid malignancies (abstract/poster 544). *Proc Am Soc Clin Oncol* 22:136, 2003.
 29. Appleman LJ, Ryan DP, Clark JW, et al: Phase I dose escalation study of bortezomib and gemcitabine safety and tolerability in patients with advanced solid tumors (abstract 839). *Proc Am Soc Clin Oncol* 22:209, 2003.
 30. Nix D, Press R, Wehrman T, et al: Tissue distribution and mass balance of bortezomib (Velcade) in non-human primates (abstract M1336). Paper presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, October 26-30, 2003, Salt Lake City.
 31. Lu C, Gallegos R, Xia C, et al: CYP induction potential of bortezomib (Velcade) in vivo in Sprague-Dawley rats and in vitro in human hepatocytes and HEPG2 cells (abstract 264). Paper presented at 12th North American Meeting of the International Society for the Study of Xenobiotics, October 12-16, 2003, Providence, RI.
 32. LaButti J, Pekol T, Wang R, et al: Metabolism of the peptide boronic acid proteasome inhibitor bortezomib (Velcade) in multiple species (abstract 82). Paper presented at the 12th North American Meeting of the International Society for the Study of Xenobiotics, October 12-16, 2003, Providence, RI.
 33. Jagannath S, Barlogie B, Berenson J, et al: Limited experience from 2 phase 2 trials suggest bortezomib can be given safely in multiple myeloma (MM) patients (pts) with severe renal impairment with comparable responses and toxicities (abstract 828). Paper presented at the Annual Meeting of the American Society of Hematology, December 6-9, 2003, San Diego.
 34. Orlowski RZ, Stinchcombe TE, Mitchell BS, et al: Phase I trial of the proteasome inhibitor PS-341 in patients with refractory hematologic malignancies. *J Clin Oncol* 20:4420-4427, 2002.
 35. Paramore A, Frantz S: Bortezomib. *Nat Rev* 2:611-612, 2003.
 36. Orlowski RZ, Voorhees P, Garcia R, et al: Phase I study of the proteasome inhibitor bortezomib in combination with pegylated liposomal doxorubicin in patients with refractory hematological malignancies (abstract 1639). Paper presented at the Annual Meeting of the American Society of Hematology, December 6-9, 2003, San Diego.
 37. Cavenagh JD, Curry N, Stec J, et al: PAD therapy (bortezomib, doxorubicin, and dexamethasone) for untreated multiple myeloma (MM) (abstract/poster 6550). *Proc Am Soc Clin Oncol* 23:568, 2004.
 38. Dreicer R, Roth B, Petrylak D, et al: Phase I/II trial of bortezomib plus docetaxel in patients with advanced androgen-independent prostate cancer (abstract/poster 4654). *Proc Am Soc Clin Oncol* 23:418, 2004.
 39. Fanucchi M, Belt R, Fossella F, et al: Phase (Ph) 2 study of bortezomib \pm docetaxel in previously treated patients with advanced non-small cell lung cancer: Preliminary results (abstract/poster 7107). *Proc Am Soc Clin Oncol* 23:640, 2004.
 40. Goy A, Younes A, McLaughlin P, et al: Update on a phase (Ph) 2 study of bortezomib in patients (pts) with relapsed or refractory indolent or aggressive non-Hodgkin's lymphoma (abstract/poster 6581). *Proc Am Soc Clin Oncol* 23:575, 2004.
 41. Hegewisch-Becker S, Sterneck M, et al: Phase I/II trial of bortezomib in patients with unresectable hepatocellular carcinoma (HHC) (abstract/poster 4089). *Proc Am Soc Clin Oncol* 23:334, 2004.
 42. Iqbal S, Cole S, Yang D, et al: Phase I study of PS-341 (bortezomib) with 5-fluorouracil/leucovorin (5-FU/LV) in advanced solid tumors: A California Cancer Consortium study (abstract/poster 2057). *Proc Am Soc Clin Oncol* 23:141, 2004.
 43. Assouline S, Belch A, Sehn L, et al: A phase II study of bortezomib in patients with mantle cell lymphoma (abstract 3358). Paper presented at the Annual Meeting of the American Society of Hematology, December 6-9, 2003, San Diego.
 44. Richardson P, Briemberg H, Jagannath S, et al: Characterization and reversibility of peripheral neuropathy in patients with advanced multiple myeloma treated with bortezomib (Velcade). The SUMMIT and CREST Study Group (abstract 368). Paper presented at the Annual Meeting of the European Hematology Association, June 12, 2004, Geneva Palexpo, Switzerland.
 45. Berenson JR, Jagannath S, Barlogie B, et al: Proteasome inhibitor bortezomib (Velcade) in relapsed and/or refractory multiple myeloma (MM) (abstract 367). Paper presented at the Annual Meeting of the European Hematology Association, June 12, 2004, Geneva Palexpo, Switzerland.
 46. Lonial S, Waller EK, Richardson PG, et al: Evaluation of the degree of thrombocytopenia and associated risk factors following bortezomib therapy for relapsed and/or refractory multiple myeloma (abstract 1632). Paper presented at the Annual Meeting of the American Society of Hematology, December 6-9, 2003, San Diego.
 47. Ryan DP, O'Neil B, Lima CR, et al: Phase I dose-escalation study of the proteasome inhibitor, bortezomib, plus irinotecan in patients with advanced solid tumors (abstract/poster 915). *Proc Am Soc Clin Oncol* 22:228, 2003.
 48. Roth BJ, Dreicer R, Berg W, et al: Phase I/II trial of bortezomib (PS-341) plus docetaxel in patients with advanced androgen-independent prostate cancer (abstract/poster 1705). *Proc Am Soc Clin Oncol* 22:424, 2003.
 49. Appleman LJ, Ryan DP, Clark JW, et al: Phase I dose escalation study of bortezomib and gemcitabine safety and tolerability in patients with advanced solid tumors (abstract/poster 839). *Proc Am Soc Clin Oncol* 22:209, 2003.
 50. Messersmith WA, Baker SD, Dinh K, et al: Phase I trial of bortezomib (PS-341) in combination with docetaxel in patients with advanced solid tumors (abstract/poster 3052). *Proc Am Soc Clin Oncol* 23:208, 2004.
 51. Jagannath S, Richardson P, Barlogie B, et al: 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/poster 2341). *Proc Am Soc Clin Oncol* 22:582, 2003.