Pharmacology, Pharmacokinetics, and Practical Applications of Bortezomib

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Bortezomib (PS-341, Velcade) is a novel, first-in-class proteasome inhibitor with antitumor activity against a number of hematologic and nonhematologic malignancies.

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 ubiquitinproteasome 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 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 and with disease progression on the last therapy.[5,14-17] This article summarizes the pharmacology, pharmacokinetics, and current practical applications of...
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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. Ubiquinated 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 α₁₋₇ β₁₋₇ β₁₋₇ α₁₋₇. The proteolytic sites are localized on the β1, β2, and β5 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 provide 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 (Ki = 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 kappa beta (NF-kB), IkB, 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-kB 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 chemotheraphy or radiation therapy resistance are not completely understood, although downregulation of NF-kB has been shown to play an important role in abrogating drug resistance.[5,23] For example, NF-kB activity in multiple myeloma cell lines resistant to melphalan, mitoxantrone, and doxorubicin is greater than NF-kB activity in nonresistant multiple myeloma cell lines; treatment with subtoxic doses of bortezomib attenuated NF-kB 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 normal 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 indepth 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%), peripheral 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 nonhematologic toxicities or grade 4 hematologic toxicities.[14] Retreatment with a 25% dose reduction (ie, reduced from 1.3 to 1.0 mg/m$^2$ or from 1.0 to 0.7 mg/m$^2$; doses below 0.7 mg/m$^2$ 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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 3</th>
<th>Grade 4</th>
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<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>27%</td>
<td>3%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>18%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>14%</td>
<td>0%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>13%</td>
<td>3%</td>
</tr>
<tr>
<td>Anemia</td>
<td>9%</td>
<td>0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Limb pain</td>
<td>7%</td>
<td>0%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Headache</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Paresthesia and dysesthesia</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Constipation</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Edema</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

* *n = 228.*
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.

### Table 2

<table>
<thead>
<tr>
<th>Type and Severity of Adverse Event</th>
<th>Dose Modification Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral neuropathy</td>
<td></td>
</tr>
<tr>
<td>Grade 1 without pain</td>
<td>No modification required</td>
</tr>
<tr>
<td>Grade 1 with pain or grade 2 without pain</td>
<td>Reduce by 25%</td>
</tr>
<tr>
<td>Grade 2 with pain or grade 3</td>
<td>Discontinue bortezomib until resolution of peripheral neuropathy, reinitiate at 0.7 mg/m² and change frequency to once weekly</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Discontinue bortezomib</td>
</tr>
<tr>
<td>Grade 3 nonhematologic toxicity (excluding peripheral neuropathy)</td>
<td>Discontinue bortezomib until symptoms resolve; reinitiate therapy with 25%-reduced dose</td>
</tr>
<tr>
<td>Grade 4 hematologic toxicity</td>
<td>Discontinue bortezomib until symptoms resolve; reinitiate therapy with 25%-reduced dose</td>
</tr>
</tbody>
</table>

*Based on National Cancer Institute Common Toxicity Criteria. Available at http://ctep.info.nih.gov/reporting/ctc.html
*Paresthesias and/or loss of reflexes without loss of function.
*Interferes with function, but not with activities of daily living.
*Reduce to 1 mg/m² if original dose = 1.3 mg/m²; reduce to 0.7 mg/m² if original dose = 1.0 mg/m².
*Interferes with activities of daily living.

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 (i.e., 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 (e.g., 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 thrombocytopenia 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/μL 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-κB-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/μL (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 generally 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.

**Disclosures:**

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

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