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Discovery, Development, and Clinical Applications of Bortezomib

A greater understanding of cancer molecular biology has led to the development of several agents that target specific intracellular signal transduction pathways involved in cancer cell development and progression.[1] One pathway, the ubiquitin-proteasome pathway (UPP), is primarily responsible for the systematic degradation of cell cycle regulatory proteins and has recently received considerable attention.[2,3] In cancer cells, the UPP is essential to the mechanisms underlying tumorigenesis and metastasis, including cell cycle arrest, apoptosis, and angiogenesis.[2] Disruption of the UPP, particularly in rapidly dividing cancer cells, can potentially arrest or retard cancer progression by interfering with mechanisms that confer malignant properties to the cell.[4-6] Furthermore, disruption of the UPP may interrupt and potentially reverse mechanisms of de novo and acquired resistance to chemotherapy or radiation therapy.[6]

A variety of proteasome inhibitors,

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ABSTRACT

Proteasome inhibition is a novel, targeted approach in cancer therapy. Both natural and synthetic proteasome inhibitors selectively penetrate cancer cells, disrupting the orderly destruction of key regulatory proteins involved in tumorigenesis and metastasis. Disrupting the orderly destruction of regulatory proteins causes an imbalance of these proteins within the cell, which interferes with the systematic activation of signaling pathways required to maintain tumor cell growth and survival; therefore, cellular replication is inhibited and apoptosis ensues. Bortezomib (PS-341, Velcade), the first proteasome inhibitor evaluated in human clinical trials, has been approved by the US Food and Drug Administration for use in patients with refractory or relapsed multiple myeloma. Preclinical study results show that bortezomib suppresses tumor cell growth, induces apoptosis, overcomes resistance to standard chemotherapy agents and radiation therapy, and inhibits angiogenesis. Phase I study results established the antitumor activity of bortezomib, administered alone or in combination with standard chemotherapy agents, in patients with advanced hematologic malignancies or solid tumors, usually without additive toxicities. The results of phase II studies further supported the antitumor activity of bortezomib in patients with refractory or relapsed multiple myeloma and non-Hodgkin's lymphoma; less impressive results were observed in patients with stage IV renal cell cancer. Studies evaluating bortezomib in earlier stages of multiple myeloma, including first-line therapy, are under way. Evidence suggests that certain prognostic factors, such as older age and bone marrow containing more than 50% plasma cells, may be useful in predicting response and survival time in multiple myeloma patients receiving bortezomib. Further studies of bortezomib are needed to establish its full spectrum of activity, the ideal regimens for various tumor types, and clinically useful prognostic indicators that predict successful outcomes.

both natural and synthetic, have been shown to disrupt the UPP pathway.[4-6] In 2003, the first proteasome inhib-

itor, bortezomib (PS-341, Velcade), was approved by the US Food and Drug Administration (FDA) for the treat-

ment of recurrent and/or refractory multiple myeloma. In 2004, the European Commission also approved the use of bortezomib for this indication in European Union member countries.[7]

This article reviews proteasome function and inhibition, the results of preclinical studies demonstrating tumoricidal effects of proteasome inhibition (PI), and the results of phase I and II clinical trials evaluating bortezomib in the treatment of various hematologic malignancies and solid tumors.

Proteasome Function and Inhibitors

Cellular homeostasis and the ability of cells to function in their environment depend on the systematic degradation of regulatory proteins and their inhibitors.[4] The majority of proteins in eukaryotic cells are degraded by the UPP, which consists of a ubiquitin-conjugating system and proteasome.[6,8] For a protein to be recognized by a proteasome, several ubiquitin molecules must first attach to the side of the target protein, a process carried out by a cascade of enzymes; this polyubiquitinated sidechain flags the protein for destruction by a proteasome.[5] Proteasomes are responsible for degrading more than 80% of all cellular proteins—including several important proteins that regulate tumor cell survival, proliferation, invasion and metastasis, angiogenesis, and apoptosis—such as the cyclin B1 cell-cycle regulatory protein; the p53 tumor suppressor gene; the p21 and p27 cyclin-dependent kinase inhibitors; $\text{I}\kappa\text{B}$, an inhibitor of nuclear factor-kappa beta (NF- κB); the p44/42 mitogen-activated protein kinase (MAPK); and the bax proapoptotic protein.[4-6] Proteasome inhibition results in accumulation of these cellular proteins, resulting in antitu-

mor effects, such as cell-cycle arrest, apoptosis, and downregulation of angiogenesis.[6]

Because proteasomes are essential components of eukaryotic cell protein degradation, PI would seemingly kill both normal and malignant cells. However, all cells do not respond similarly to PI. The results of several preclinical studies suggest that malignant cells are more susceptible to PI than are normal cells.[9,10] The molecular basis for this differential susceptibility of cells to PI remains undetermined, although several interesting theories are being investigated.[5,6,9] For a more in-depth discussion of UPP and PI, refer to the article entitled “Pharmacology, Pharmacokinetics, and Practical Applications of Bortezomib” in this supplement.

Numerous natural and synthetic compounds inhibit the activity of proteasomes. Many of these compounds bind to and interfere with the chymotrypsin-like activity (one of three types of proteolytic activity within the proteasome) of the proteasome.[4,9] However, many of these inhibitors also lack specificity for the proteasome, have poor metabolic stability, or bind irreversibly to the proteasome.[4,5] An ideal proteasome inhibitor would exhibit metabolic stability, enzyme specificity, reversible binding to the proteasome, and selective cytotoxicity toward malignant cells.[2]

The natural proteasome inhibitors include lactacystin, epoxyketones (epoxomicin and eponemycin), and TMC-95 cyclic peptides. The synthetic compounds include the peptide vinyl sulfones, peptide aldehydes (MG132 and PSI), and the peptide boronic acids.[4,5] The peptide aldehydes were one of the first groups of proteasome inhibitors discovered. However, their fast dissociation rate from the proteasome and their rapid transportation out of the cell by the multidrug resistance (MDR) transporter limited their usefulness as a therapeutic strategy.[9] Because of these limitations, the peptide boronic acids, were developed by replacing an aldehyde group with boronic acid; peptide boronic acids have a slower dissociation rate and up to 1,000-fold

higher potency than those of the peptide aldehydes.[4,5] The peptide boronic acids are selective for proteasomes and form covalent and reversible complexes within the chymotrypsin-like site of proteasomes, thereby inhibiting proteasome activity.[5,11]

Bortezomib

Bortezomib is a peptide boronic acid and the first proteasome inhibitor to be approved for use in humans. The results of a preclinical study by the National Cancer Institute (NCI) in 60 cancer cell lines determined that bortezomib had substantial in vitro cytotoxicity against multiple human tumors.[11] The NCI also compared the mechanism of cytotoxicity of bortezomib with that of 60,000 compounds and determined bortezomib’s mechanism to be unique.[11] Although the exact mechanism of cytotoxicity of bortezomib and other proteasome inhibitors has yet to be fully elucidated, inhibition of proteasomes by these agents affects numerous cellular pathways, all of which result in increased apoptosis of affected cells.[11]

Preclinical Data

The NCI study results showing the cytotoxic activity of bortezomib led to the evaluation of this agent in numerous murine xenograft models, representing a wide variety of malignancies (eg, multiple myeloma and colorectal, pancreatic, prostate, and ovarian cancers).[10-14] In these models, bortezomib decreased tumor volume, confirming its in vivo effectiveness as an antineoplastic agent. Bortezomib also demonstrated an increased tumoricidal effect in human xenografts when combined with various standard chemotherapy agents, including cisplatin, docetaxel (Taxotere), fluorouracil (5-FU), gemcitabine (Gemzar), irinotecan (Camptosar), and paclitaxel.[12-15]

Results of preclinical studies of multiple myeloma cell lines have also demonstrated the ability of bortezomib to circumvent chemotherapy or radiation resistance and inhibit angiogenesis.[16-22] The primary mechanism

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Table 1

Phase I Clinical Studies Evaluating Bortezomib in Combination Therapy

Cancer Type	No. Enrolled/ Assessable ^a	Regimen	MTD	End Point: No. of Patients	Grade 3/4 Toxicities at MTD
Refractory hematologic malignancies[29] ^b	41/39	Bortezomib 0.9–1.5 mg/m ² twice weekly × 2 wk, q3wk, and liposomal doxorubicin 30 mg/m ² day 4, q3wk	1.5 mg/m ² ^c 30 mg/m ²	CR: 6 (5 MM, 1 T-cell NHL) Near CR: 3 (MM) PR: 12 (8 MM, 3 AML, 1 B-cell NHL) MR: 1 (MM) SD: 9 (4 MM, 2 HD, 1 MDS, 2 CLL)	Constipation Hyperglycemia Neuropathy Thrombocytopenia
Advanced solid tumors[30] ^d	31/31	Bortezomib 1–1.3 mg/m ² twice weekly × 2 wk, q3wk, and gemcitabine 500–1,000 mg/m ² once weekly × 2 wk, q3wk	1 mg/m ² 1,000 mg/m ²	PR: 1 (NSCLC)	Leukopenia, 7% Thrombocytopenia, 13%
Advanced NSCLC[31]	16/12	Bortezomib 1–1.3 mg/m ² twice weekly × 2 wk, q3wk, and gemcitabine 800–1,000 mg/m ² once weekly × 2 wk, q3wk, and carboplatin AUC 5–5.5 q3wk	1 mg/m ² 1,000 mg/m ² AUC 5	PR: 4 SD: 7	Thrombocytopenia, 17% ^e
Advanced solid tumors[32]	51/51	Bortezomib 1–1.5 mg/m ² twice weekly × 2 wk, q3wk, and irinotecan 50–125 mg/m ² over 90 min once weekly × 2 wk, q3wk	1.3 mg/m ² 125 mg/m ²	Response: 2 (1 GI, ^f 1 ovarian cancer) ^g	None ^h
Advanced solid tumors[33]	21/21	Bortezomib 0.5–1.3 mg/m ² twice weekly × 4 wk, q6wk and fluorouracil 500 mg/m ² and leucovorin 20 mg/m ² /wk × 4 wk q6wk	0.7 mg/m ² 500 mg/m ² 20 mg/m ²	PR: 1 (esophageal cancer) SD: 8 (7 colorectal, 1 anal)	Constitutional symptoms, 17% ⁱ GI symptoms, 33% ⁱ Neutropenia/granulocytopenia, 17% ⁱ Pain, 33% ⁱ

^aAssessable for efficacy.

^bToxicities reported for 61 patients in cycle 1 at MTD. Incidence of each toxicity not provided.

^cMTD of bortezomib was reported as 1.5 mg/m²; however, the recommended phase II trial dose was 1.3 mg/m², because later cycles with bortezomib 1.4 and 1.5 mg/m² necessitated dose reductions and treatment delays.[29]

^dToxicities reported for 15 patients at the MTD.

^eOnly dose-limiting toxicity at MTD in 6 patients.

^fUnconfirmed gastroesophageal junction adenocarcinoma.

^gResponses not specified as CR, PR, or SD.

^hNo grade 3 or 4 dose-limiting toxicities at MTD.

ⁱToxicities are with cycle 1.

AML = acute myelogenous leukemia; AUC = area under the concentration-time curve; CLL = chronic lymphocytic leukemia; CR = complete response; GI = gastrointestinal; HD = Hodgkin's disease; MDS = myelodysplastic syndrome; MM = multiple myeloma; MR = minor response; MTD = maximum tolerated dose; NHL = non-Hodgkin's lymphoma; NSCLC = non-small-cell lung cancer; PR = partial response; SD = stable disease.

by which bortezomib overcomes drug resistance may be the downregulation of NF-κB.[16,18–21] NF-κB activity in resistant myeloma cell lines is higher than that in nonresistant cell lines.[16] Bortezomib also downregulates or disrupts other resistance pathways or mechanisms, such as the p44/42 MAPK pathway, topoisomerase II-α, Bcl-2, or the transcription of genes involved in DNA damage repair.[18,19] Furthermore, bortezomib is not a substrate for the

multidrug resistance protein, a protein that is overexpressed in tumors resistant to a variety of chemotherapy agents.[19]

Bortezomib's effects on the tumor microenvironment include disruption of cellular adhesion of cancer cells to bone marrow stromal cells; this adhesion is recognized as a principal promoter of tumor cell growth and survival. Cell-cell adhesion initiates the production of growth factors (eg, interleukin-6) that stimulate tumor re-

sistance to chemotherapy.[17,18] Finally, bortezomib has been shown to inhibit tumor angiogenesis, probably as a result of decreased vascular endothelial cell growth factor secretion and high levels of endothelial cell apoptosis. In preclinical models, bortezomib markedly decreased microvessel density and inhibited the activity of proangiogenic cytokines (eg, vascular endothelial growth factor [VEGF]).[16,22] The ability of bortezomib to inhibit tumor cell pro-

liferation, selectively induce apoptosis in proliferating cells, alter the tumor microenvironment, inhibit angiogenesis, and overcome resistance to standard therapies encouraged investigators to initiate clinical trials with this agent.

Phase I Clinical Studies

• **Single-Agent Bortezomib**—Two phase I trials have evaluated single-agent bortezomib for the treatment of refractory and/or relapsed hematologic malignancies and solid tumors.[23-25] Orłowski and colleagues[23] evaluated a twice-weekly regimen of bortezomib in patients with refractory hematologic malignancies; the maximum tolerated dose was 1.04 mg/m² administered twice weekly for 4 weeks of a 6-week cycle. Proteasome inhibition was dose-dependent, with the maximum tolerated dose providing 60% ± 1% inhibition; proteasome activity returned toward baseline within 72 hours. Electrolyte disturbances, particularly hyponatremia and hypokalemia, and cytopenias were common at the maximum tolerated dose; thrombocytopenia was the most common maximum tolerated dose-related cytopenia, but patients experienced a recovery of their platelet counts to their baseline level or higher before starting the next cycle. Evidence of antitumor activity was noted for 9 of 9 assessable patients with multiple myeloma, with 1 patient obtaining a complete response.

Twice-weekly bortezomib was also evaluated in patients with advanced solid tumors.[24] The original publication of this study suggested a maximum tolerated dose of 1.56 mg/m² administered twice weekly for 2 weeks of a 3-week cycle; however, the dose recommended for further clinical study by the principal investigator was 1.3 mg/m². [25] Again, PI was dose dependent, with the 1.3 mg/m² maximum tolerated dose providing 65% inhibition and the 1.56 mg/m² maxi-

um tolerated dose producing 68% inhibition.[24] Cytopenias were less common with this regimen, with only one episode of grade 3 anemia reported with bortezomib 1.3 mg/m². [24] Although grades 3/4 neutropenia and thrombocytopenia were not reported at this dose, bortezomib 1.56 mg/m² was associated with the development of these hematologic toxicities as well as dose-limiting toxicities of grade 3 diarrhea and grade 3 sensory neuropathy. Diarrhea and sensory neuropathy may also have been dose related. In this heavily pretreated patient population, one patient with non-small-cell lung cancer (NSCLC) had a partial response and three patients (nasopharyngeal carcinoma, malignant melanoma, and renal cell carcinoma, one each) experienced stable disease. The median duration of stable disease was 4 months (range: 2.5–5 months).

Several ongoing phase I or I/II studies are evaluating different regimens in both hematologic malignancies and solid tumors, including bortezomib once weekly for 4 weeks repeated every 6 weeks and twice weekly every other week.[26-28]

• Bortezomib in Combination With Chemotherapy

—Several phase I studies have evaluated bortezomib combined with various chemotherapy agents for the treatment of hematologic malignancies and solid tumors (Table 1).[29-33] For example, bortezomib combined with liposomal doxorubicin (Doxil) was evaluated in 41 patients with refractory hematologic malignancies.[29] This combination was selected because preclinical study results suggested that PI by bortezomib may enhance tumor sensitivity to anthracyclines by downregulating the activation of the NF-κB and p44/42 MAPK pathways.[6]

During cycle 1, grade 3 or 4 adverse events at the maximum tolerated dose included thrombocytopenia, constipation, neuropathy, and hyperglycemia; however, repeated administration of the first-cycle maximum tolerated dose necessitated dose reductions and delays.[29] Therefore, the dose recommended for phase II trials (ie, bortezomib 1.3 mg/m² twice weekly for 2 weeks and liposomal

doxorubicin 30 mg/m² on day 4, with cycles repeated every 3 weeks) was lower than the maximum tolerated dose reported during cycle 1. This combination displayed disease activity not only in patients with multiple myeloma, but also in patients with acute myelogenous leukemia, non-Hodgkin's lymphoma (NHL), Hodgkin's disease, myelodysplastic syndromes, and chronic lymphocytic leukemia. As in phase I studies evaluating bortezomib alone, PI was dose dependent and did not increase with the use of liposomal doxorubicin.[29]

Phase I studies assessed bortezomib combined with either gemcitabine, gemcitabine and carboplatin (Paraplatin), irinotecan, or 5-FU/leucovorin, in patients with solid tumors (see Table 1).[30-33] Various doses of bortezomib and gemcitabine were evaluated; the maximum tolerated dose was bortezomib 1 mg/m² and gemcitabine 1,000 mg/m². [30] Table 1 lists the toxicities at the maximum tolerated dose. One patient with relapsed metastatic NSCLC experienced a partial response despite previous treatment with numerous chemotherapy agents, including gemcitabine.

Activity of bortezomib in NSCLC was also reported with gemcitabine and carboplatin.[31] The maximum tolerated dose in this trial was bortezomib 1 mg/m², gemcitabine 1,000 mg/m², and carboplatin at an area under the concentration-time curve of 5 (see Table 1). Four patients experienced a partial response and seven patients experienced stable disease.[31] In the irinotecan-bortezomib trial, the maximum tolerated dose was bortezomib 1.3 mg/m² and irinotecan 125 mg/m². [32] Although concern about additive toxicities, particularly diarrhea, exists with this combination, no grade 3 or 4 adverse events were reported at the maximum tolerated dose. Two patients, one with gastroesophageal junction adenocarcinoma (unconfirmed) and one with ovarian cancer, achieved a response (unspecified).

Weekly 5-FU/leucovorin has also been evaluated with bortezomib (see Table 1).[33] The maximum tolerated dose was bortezomib 0.7 mg/m² with 5-FU 500 mg/m², and leucovorin

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in 20 mg/m². One patient with esophageal cancer experienced a partial response and eight patients with either colorectal cancer or anal cancer experienced stable disease.[33]

Several other phase I or I/II studies are evaluating bortezomib in combination with chemotherapy agents, including liposomal doxorubicin, docetaxel, and carboplatin.[34-37] The results of these and ongoing phase I trials evaluating single-agent bortezomib are eagerly awaited and may define the optimal regimen of bortezomib as a single agent or in combination with other agents.

Phase II Clinical Studies

Phase II clinical trials have evaluated bortezomib administered twice weekly for 2 weeks, with cycles repeated every 3 weeks, as treatment of solid tumors (bortezomib alone) or hematologic malignancies (bortezomib alone or in combination with dexamethasone) (Table 2).[25,38-44] The largest study, the SUMMIT trial, evaluated bortezomib in 202 patients with multiple myeloma who had received a median of six prior therapies (see Table 2).[25,38] Of 193 assessable patients, 7 patients (4%) achieved a complete response, 12 (6%) achieved a near complete response, and 34 (18%) achieved a partial response; responses occurred independent of the number and type of previous therapies.[38] Additionally, response rates in patients with a chromosome 13 abnormality, a poor prognostic indicator, and patients without this abnormality did not differ.[25] The median time to disease progression in all 202 patients receiving bortezomib was 7 months, which was significantly longer than the median time to disease progression (3 months) with the last prior treatment patients had received before study entry ($P = .01$).[38] Table 2 lists the grade 3 and 4 toxicities associated with bortezomib administration.

A smaller study (the CREST trial) evaluated bortezomib in 54 patients with relapsed or refractory multiple myeloma who had received a median of three prior therapies.[39] Bortezomib 1 or 1.3 mg/m² was administered using the same schedule as that

in the SUMMIT trial (see Table 2).[39] The overall response rate (complete plus partial response) in 53 assessable patients was 30% and 38% for the 1- and 1.3-mg/m² groups, respectively, with one complete response observed at each dose level.[39] The median time to disease progression was 212 days for the 1-mg/m² group and 333 days for the 1.3-mg/m² group.[39]

In both the SUMMIT and CREST trials, patients with disease progression or stable disease after two and four cycles, respectively, could receive dexamethasone 20 mg orally on the day of and the day after bortezomib administration; 78 patients in the SUMMIT trial and 28 patients in the CREST trial received dexamethasone.[40] The addition of dexamethasone improved response rates in 18% and 33% of patients in the SUMMIT and CREST trials, respectively, including patients refractory to dexamethasone alone. The median time to disease progression for these patients was 5.7 months (SUMMIT) and 6.8 months (CREST). Importantly, the addition of dexamethasone did not increase toxicities associated with single-agent bortezomib.[40]

A phase II study evaluated bortezomib 1.3 mg/m² in patients with mantle cell lymphoma (MCL) who had received 0 to 2 prior therapies.[41] Of 13 assessable patients, 5 patients (38.5%) experienced a partial response and 5 patients (38.5%) experienced stable disease. Five patients experienced treatment-limiting fluid retention and/or dyspnea. Therefore, the investigators modified the protocol to exclude patients with preexisting fluid retention or dyspnea.[41]

Two additional phase II studies have evaluated 1.5 mg/m² bortezomib in patients with relapsed or refractory NHL.[42,43] In one study, patients with MCL experienced a 48% response rate (complete, 26%; partial, 22%). Responses were also observed in other B-cell lymphomas, including one complete response (follicular lymphoma) and two partial responses (one diffuse large cell lymphoma, one Waldenström's macroglobulinemia).[42] A second study produced similar results, with an overall re-

sponse rate of 55%, including a 7% complete response rate (follicular lymphoma) and 48% partial response rate (17% follicular lymphoma, 21% MCL, 3% small-cell lymphocytic lymphoma–chronic lymphocytic leukemia, 7% marginal zone lymphoma).[43] Toxicities in both studies were manageable, with the most common grade 3 or 4 toxicities being thrombocytopenia and lymphopenia, respectively (see Table 2).[42,43]

Bortezomib 1.5 mg/m² has also been evaluated in patients with stage 4 renal cell carcinoma who had received minimal pretreatment (median: 1 prior therapy).[44] Dose escalation to 1.7 mg/m² was permitted beginning with cycle 2 in patients who developed less than or equal to grade 2 toxicities during cycle 1. Twenty-one patients received a total of 74 treatment cycles: 34 cycles at 1.7 mg/m², 36 at 1.5 mg/m², and 4 at 1.3 mg/m². One patient had a partial response, and six patients had stable disease; enrollment in this study was ceased because of a lack of response. Toxicities reported were similar to toxicities reported in other trials (see Table 2). Although 10% of patients experienced grades 3 or 4 neuropathy, the incidence for all grades of neuropathy was 47%. A correlation between the number of doses given or the cumulative dose of bortezomib and the development of neuropathy was not observed.

Kondagunta and colleagues[45] conducted a similar study in 37 metastatic renal cell cancer patients who had either received no prior therapy (49%) or cytokine therapy alone (51%). Bortezomib 1.5 mg/m² was administered to the first 25 patients enrolled in the study; however, the dose was decreased to 1.3 mg/m² for the subsequent 12 patients, because more than 50% of the patients receiving bortezomib 1.5 mg/m² required toxicity-related dose reductions, primarily due to grade 2 or 3 peripheral neuropathy, fatigue, thrombocytopenia, and anemia. A partial response was observed in 4 patients (11%) and stable disease in 14 patients (38%). In the four patients with a partial response, durations of response ranged from 8 to more than 20 months. The median time to disease progression

Table 2

Phase II Clinical Trials Evaluating Bortezomib

Cancer Type	No. Enrolled/ Assessable ^a	Regimen	End Point	Grade 3/4 Toxicities	Comments
Relapsed, refractory MM (SUMMIT trial)[25,38]	202/193	Bortezomib 1.3 mg/m ² twice weekly × 2 wk q3wk ^b	CR: 4% NCR: 6% PR: 18%	Anemia: 8% Diarrhea: 8% Fatigue: 12% Neuropathy: 12% Neutropenia: 14% Thrombocytopenia: 31% Vomiting: 8%	<ul style="list-style-type: none"> • Patients received a median of 6 prior therapies (eg, corticosteroids, alkylating agents, anthracyclines, thalidomide, PBSCT, investigational therapy) • Overall median TTP, 7 mo; median TTP for responders, 13 mo • Median OST, 16 mo • Median duration of response, 12 mo • Responses associated with increase of Hgb by 1–2 g/dL and reduction in PRBC transfusions after 4 cycles in patients with CR or PR • 80% of patients had peripheral neuropathy at enrollment; 34% experienced new or worsening peripheral neuropathy during study
Relapsed, refractory MM (CREST trial)[39]	54/53	Bortezomib 1 or 1.3 mg/m ² twice weekly × 2 wk, q3wk ^b	1 mg/m ² CR: 4% NCR: 7% PR: 19% MR: 4% SD: 26% 1.3 mg/m ² CR: 4% NCR: 0% PR: 35% MR: 12% SD: 19%	Lymphopenia: 11%-12% Neuropathy: 8%-15% Neutropenia: 11%-23% Thrombocytopenia: 23%-29%	<ul style="list-style-type: none"> • Patients received a median of 3 prior therapies (eg, corticosteroids, alkylating agents, anthracyclines, thalidomide, PBSCT, radiation therapy, other therapies) • Median TTP, 212 d and 333 d for 1- and 1.3-mg/m² groups, respectively • Median OST, 26.7 mo and NR for 1- and 1.3-mg/m² groups, respectively • Median duration of response 288 and 417 d in the 1- and 1.3-mg/m² groups, respectively • 71% of patients had peripheral neuropathy at baseline; 28% reported new-onset symptoms
Mantle cell lymphoma[41]	14/13	1.3 mg/m ² twice weekly × 2 wk q3wk	PR: 38.5% SD: 38.5%	Death secondary to acute vascular leak syndrome or severe edema: 23%	<ul style="list-style-type: none"> • All patients enrolled had stage IV disease • Treatment-limiting fluid retention and/or dyspnea reported in 5 patients; death resulted in 3 patients. All 5 patients had symptoms of fluid retention and/or dyspnea at baseline
Relapsed, refractory NHL[42]	MCL 29/23 Other B-cell lymphomas 22/19	1.5 mg/m ² twice weekly × 2 wk, q3wk	MCL CR: 26% PR: 22% SD: 16% Other B-cell lymphomas CR: 5% PR: 11% SD: 26%	Diarrhea: 4% Fatigue: 18% Hypotension: 4% Nausea: 8% Neuropathy: 6% Neutropenia: 14% Thrombocytopenia: 46% Vomiting: 4%	<ul style="list-style-type: none"> • Patients with MCL and other B-cell lymphomas received median of 3 or 4 prior therapies, respectively • No disease progression in 73% of patients with MCL after median follow-up of 5.6 mo (range: 1.5–19 mo) • Median TTP not reached

Table 2 continued

Cancer Type	No. Enrolled/Assessable ^a	Regimen	End Point	Grade 3/4 Toxicities	Comments
Relapsed, follicular lymphoma and MCL[43]	Follicular: 15/12 MCL: 17/11 SLL/CLL: 4/4 Marginal zone: 3/2	1.5 mg/m ² twice weekly × 2 wk, q3wk	CR: 7% (follicular lymphoma) PR: 48% (17% follicular lymphoma, 21% MCL, 3% SLL/CLL, 7% marginal zone lymphoma) SD: 41% (14% follicular lymphoma, 17% MCL, 10% SLL/CLL)	Lymphopenia: 38% Motor neuropathy: 3% Sensory neuropathy: 5% Thrombocytopenia: 13%	<ul style="list-style-type: none"> • Patients received < 3 prior cytotoxic therapies (eg, alkylating agents, purine analogs, monoclonal antibodies, HDC/PBSCT) • 54% of patients received rituximab once • 26% of patients received rituximab 2 or more times
Renal cell carcinoma[44]	23/21	1.5 mg/m ² twice weekly × 2 wk, q3wk ^c	PR: 5% SD: 29%	Anemia: 10% Diarrhea: 24% Fatigue: 14% Fluid/electrolyte toxicity: 29% Nausea: 19% Neuropathy: 10% Thrombocytopenia: 24% Vomiting: 14%	<ul style="list-style-type: none"> • Patients received median of 1 prior therapy, excluding radiation therapy (eg, immunotherapy, other therapy) • 43% of patients had no prior systemic therapy • 90% of patients had no prior nephrectomy • Enrollment ceased after 21 patients had been assessed because of lack of efficacy
Renal cell carcinoma[45]	37/27	1.3–1.5 mg/m ² twice weekly × 2 wk, q3wk	PR: 11% SD: 38%	Anemia: 17% Diarrhea: 10% Fatigue: 49% Hyperkalemia: 24% Nausea: 27% Neuropathy: 27% Thrombocytopenia: 19% Vomiting: 5%	<ul style="list-style-type: none"> • 49% of patients had no prior systemic therapy • 51% of patients had prior cytokine therapy (eg, IFN, IL-2) • 62% of patients had prior nephrectomy

^aAssessable for efficacy.

^bDexamethasone 20 mg po on day of and day after each dose of bortezomib permitted in patients with SD or progressive disease after 2 or 4 cycles; however, end point data reported with bortezomib only.[40]

^cEscalation of dose to 1.7 mg/m² permitted beginning in cycle 2 if patients experienced ≤ grade 2 toxicity in cycle 1.

CLL = chronic lymphocytic leukemia; CR = complete response; HDC = high-dose chemotherapy; Hgb = hemoglobin; IFN = interferon; IL-2 = interleukin-2; MCL = mantle cell lymphoma; MM = multiple myeloma; MR = minor response; NA = not available; NCR = near complete response; NHL = non-Hodgkin's lymphoma; NR = not reached; OST = overall survival time; PBSCT = peripheral blood stem cell transplantation; PR = partial response; PRBC = packed red blood cell; SD = stable disease; SLL = small lymphocytic lymphoma; TTP = time to disease progression.

was 1.4 months and the median survival time was 7.5 months (median follow-up: 11.7 months [range: 3.7–20.9 months]). Peripheral neuropathy occurred in 27% of all patients, 28% of patients receiving bortezomib 1.5 mg/m², and 25% of patients receiving 1.3 mg/m². The authors concluded that only a small portion of patients with renal cell carcinoma are likely to respond to bortezomib therapy and do not recommend routine use of bortezomib in this patient population.[45]

Bortezomib has also been evaluated in patients with hepatocellular carcinoma, soft tissue sarcoma, and NSCLC.[46–49] Preliminary results of these studies suggest promising activity of bortezomib in patients with metastatic or recurrent sarcomas and advanced NSCLC.[46–49]

Predictors of Response

The results of a retrospective multivariate analysis have reported predictors of response to bortezomib in patients with refractory or relapsed multiple myeloma.[50] Older age (ie, ≥ 65 years) was associated with a low-

er response rate and longer time to treatment response; however, age was not predictive of duration of response, time to disease progression, or overall survival time.[50] Elevated levels of C-reactive protein and the presence of more than 50% plasma cells in the bone marrow were predictive of a longer time to treatment response.

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Low albumin levels and Karnofsky performance scale scores were predictors of shorter response duration and overall survival time. Additionally, elevated levels of C-reactive protein and abnormal cytogenetics were found to be predictors of shorter time to disease progression, and the presence of more than 50% plasma cells in bone marrow and low platelet counts were associated with a decreased overall survival time.[50]

Another predictor of response may be an increase in bone alkaline phosphatase level without an increase in gamma glutaryl transferase level, which occurred in patients with multiple myeloma who responded to combination therapy with bortezomib, thalidomide (Thalomid), and dexamethasone.[51] Finally, pharmacogenomics may predict time to disease progression after treatment with bortezomib; preliminary results indicate that numerous genes associated with proliferation, survival, signaling, and the UPP correlate with time to disease progression.[50] Although these prognostic factors may enable clinicians to predict which patients will have a better response to bortezomib, their use is currently limited to patients with refractory or relapsed multiple myeloma. Future studies are warranted to address the clinical applicability of these prognostic factors to other types of malignancies.

Future Directions

Long-Term Therapy With Bortezomib

Studies of bortezomib have usually investigated eight or fewer cycles. Berenson and colleagues[52] evaluated the long-term use of bortezomib, with or without dexamethasone, in 59 patients with refractory or relapsed multiple myeloma initially treated with eight cycles of bortezomib, with or without dexamethasone. Bortezomib alone (median duration: 12 cycles; range: 7–24 cycles) or in combination (median duration: 5 cycles, range: 0–17 cycles) appeared to be well tolerated.[52] Interestingly, the incidence of peripheral neuropathy, gastrointestinal complaints (eg, nausea, vomiting, constipation), fatigue, rash, and neutropenia decreased

in patients receiving more than eight cycles of bortezomib; however, the incidence of lower-extremity edema increased compared with patients who received eight or fewer cycles of bortezomib.[38,52] Possible explanations for these differences in adverse events include improved management of adverse events, smaller sample size, number of patients receiving dexamethasone, and bias in reporting only responding patients. Although bortezomib has been administered for as long as 32 cycles in some patients, the optimal duration of therapy with this agent has not been defined.[52]

The phase III, international, multicenter Assessment of Proteasome Inhibition for Extending Remissions (APEX) trial is also evaluating long-term bortezomib therapy in patients with earlier-stage relapsed or refractory multiple myeloma (patients having received one to three prior therapies).[53] Patients receive induction therapy with either (1) bortezomib 1.3 mg/m² twice weekly for 2 weeks, with cycles repeated every 3 weeks for 8 cycles, followed by weekly bortezomib for 4 weeks, with cycles repeated every 5 weeks for 3 cycles; or (2) oral dexamethasone 40 mg/d on days 1 through 4, 9 through 12, and 17 through 20 repeated every 5 weeks for 4 cycles, followed by 40 mg/d on days 1 through 4 every 28 days for 3 cycles. Depending on the response, patients in either treatment arm may continue therapy for up to 10 months.[54]

A planned interim analysis demonstrated a 58% improvement in median time to disease progression (bortezomib, 5.7 mo vs dexamethasone, 3.6 mo; $P < .0001$). Patients treated with bortezomib had a higher incidence of grade 3 or 4 hematologic, gastrointestinal, and nervous system adverse events, whereas patients treated with dexamethasone had a higher incidence of grade 3 or 4 psychiatric, metabolic, and infectious adverse events.[53] Based on time to disease progression and an early survival advantage for bortezomib, the data monitoring committee recommended that the study be closed early and bortezomib offered to all patients treated on the dexamethasone arm.

Quality of Life and Cost-Effectiveness of Bortezomib

Bortezomib has primarily been evaluated in patients with advanced or refractory cancers. In these patients, the goals of therapy are usually cost-effective prolongation of survival and improvement of quality of life. In the SUMMIT trial, quality of life was assessed using validated quality-of-life questionnaires (eg, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30).[55] Responding patients experienced a decrease in disease symptoms, pain, fatigue, and an overall improvement in their quality of life compared with baseline.[55] These improvements may have been associated with an increase in normal immunoglobulin levels, improved hemoglobin levels and platelet counts, better renal function, and decreased requirement for red blood cell transfusions, all of which were observed in responding patients. However, quality-of-life data by its nature is subjective and was collected in an unblinded manner. Furthermore, no internal control group existed, and bortezomib's effect on quality of life in nonresponding patients was not reported. Despite these limitations, results of the SUMMIT trial showed bortezomib to be cost-effective compared with best-supportive care or thalidomide, with a marginal cost-per-life-year gain of \$49,807 and \$21,758, respectively.[56]

Conclusions

Proteasome inhibition is a new and promising treatment option for certain patients with cancer. The proteasome inhibitor bortezomib is the first agent in this novel class of antineoplastics to be studied in clinical trials and receive FDA approval. Preclinical study results suggest that bortezomib has a unique mechanism of action and may display selective targeting of malignant cells over normal cells. Furthermore, these study results suggest that bortezomib may overcome resistance of cancer cells to standard chemotherapy agents and radiation therapy in patients with relapsed or refractory disease. Results

of studies evaluating bortezomib in patients with renal cell carcinoma are mixed.[44] Additionally, the use of bortezomib in combination with chemotherapy may allow for the use of lower doses of cytotoxic chemotherapy agents, which may minimize toxicity and decrease the likelihood of developing drug resistance.[57,58]

Bortezomib has been investigated primarily as a salvage therapy. However, current and future trials are now and will be investigating bortezomib as first-line therapy.[59,60] Finally, a fuller understanding about the regulation of the cell cycle and interactions among various proteins may lead to the use of bortezomib in combination with other targeted, nonstandard chemotherapy agents.[61]

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