Acta Oncologica, 2005; 44: 440–448

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REVIEW ARTICLE

Bortezomib: A valuable new antineoplastic strategy in multiple myeloma

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Abstract
Although the treatment of multiple myeloma has improved over the past decade, the disease remains incurable. Bortezomib, a first-in-class selective proteasome inhibitor, was approved in the United States in 2003 and the European Union in 2004 for the treatment of relapsed and refractory multiple myeloma in patients who have received at least 2 prior therapies and demonstrated disease progression on the last therapy. *In vitro*, bortezomib induces apoptosis of multiple myeloma cells and inhibits cell adhesion within the bone marrow microenvironment. Preclinical and clinical data have shown that bortezomib enhances sensitivity and reverses resistance to standard therapeutic agents used in multiple myeloma. The efficacy and safety of bortezomib was established in patients with relapsed and/or refractory disease. In a large phase III trial in patients with relapsed multiple myeloma, median time to progression and overall survival were significantly improved with bortezomib compared with high-dose dexamethasone. Importantly, the preliminary results of several phase I and II studies are also showing high antimyeloma activity of bortezomib alone or in combination with dexamethasone or cytotoxic agents such as doxorubicin, mephalan, or thalidomide in patients with newly diagnosed multiple myeloma. Ideally, the introduction of bortezomib will result in a significant improvement in the future management of multiple myeloma.

Despite increasing knowledge and understanding of the disease mechanisms of multiple myeloma (MM), the results of its therapy are disappointing. Multiple myeloma, a B-cell malignancy characterized by aberrant monoclonal expansion of plasma cells, will become a resistant disease even in patients showing initial responses to chemotherapy. In fact, high-dose therapy with autologous peripheral blood stem cell (PBSC) rescue, which has emerged as part of the front-line therapy for younger patients, only produces complete response (CR) in about one-third of patients, with a median event-free survival of 3 years and overall survival of about 5 years [1]. Salvage regimens for disease relapse are limited and seldom result in durable responses, further underscoring the urgent need for novel therapeutic approaches. An important emerging strategy for the treatment of MM is the targeted inhibition of the proteasome by bortezomib (VELCADE®, formerly PS-341). Bortezomib was approved based on a noteworthy clinical development for the treatment of MM patients who had received at least two prior therapies and demonstrated disease progression on the last therapy in 2003 by the USA Food and Drug Administration (FDA) and in 2004 by the European Agency for the Evaluation of Medicinal Products (EMEA). This review article focuses on the effects of bortezomib in myeloma cells and on its clinical safety and efficacy profiles shown in recent reports and ongoing clinical trials in MM.

Biology of the proteasome

The proteasome is responsible for degrading proteins that regulate essential cellular functions, such as cell-cycle control, cellular adhesion, proliferation, survival, and apoptosis [2,3]. The primary function of the proteasome, a multisubunit protein complex found in the cytoplasm and nucleus of all eukaryotic cells, is to degrade intracellular proteins that have been tagged with a polyubiquitin chain [4,5]. Structurally, the proteasome is a cylindrical complex composed of a 20S catalytic core capped at one or both ends by 19S regulatory subunits (Figure 1).

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(Received 21 March 2005; accepted 10 May 2005)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860510030002

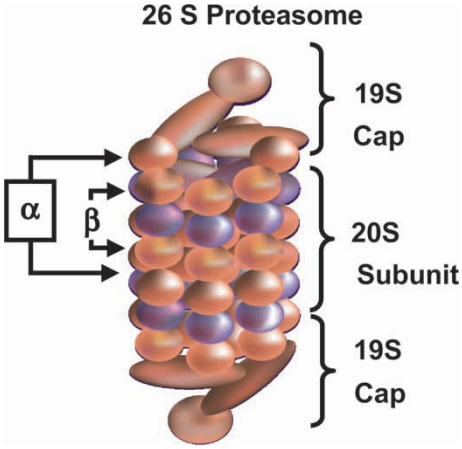

Figure 1. Scheme of the 26S proteasome composed of the 20S catalytic core and a 19S regulatory subunit at each end. Copyright Millennium Pharmaceuticals, Inc., Cambridge, Massachusetts.

The 20S core consists of 4 stacked rings: 2 outer α-rings that interact with the 19S subunit to control protein entry into the catalytic core, and 2 inner β-rings that contain the enzyme sites for degrading the protein. As a result, the protein substrate is progressively degraded, resulting in the release of oligopeptides consisting of 3 to 22 amino acids in length [6].

Proteasome inhibition By Bortezomib

Peptide boronic acids are established inhibitors of serine proteases, such as chymotrypsin [7]. Because threonine proteases resemble serine proteases at the active site residue, it was postulated that peptide boronic acids might bind to the chymotrypsin-like site of the proteasome and inhibit its catalytic activity. This hypothesis was confirmed by the synthesis of tripeptide boronic acids [8]. Subsequently, dipeptidyl boronic acids were developed, which offered several advantages: simplified synthesis, smaller molecular weight, and most importantly, high selectivity for the proteasome over common serine proteases [8]. A series of 13 peptide boronic acids was tested for anticancer activity against the National Cancer Institute (NCI) panel of 60 cancer cell lines [9]. One of these compounds, bortezomib (previously known as PS-341; Figure 2) potently inhibited the activity of the purified proteasome, with a Ki of 0.6 nM, and exhibited substantial cytotoxicity against a broad range of cancer cell lines. Notably, bortezomib showed a unique "fingerprint" of cytotoxicity in these cell lines compared with the NCI's historical file of 60 000 compounds, showing little correlation to any standard or investigational agent [9]. On the basis of its profile, bortezomib was selected for further preclinical and clinical evaluation.

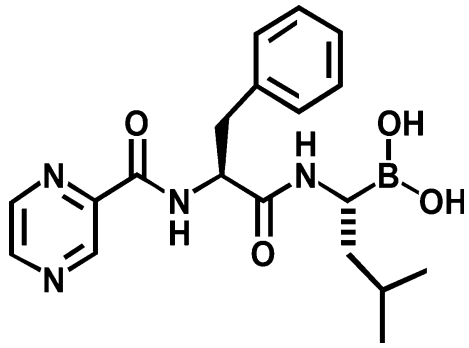

Figure 2. Structure of bortezomib.

The pharmacokinetic plasma profile of bortezomib was first studied in cynomolgus monkeys and was subsequently demonstrated to be similar in humans [10]. The drug is well characterized by a 2-compartment/biphasic pharmacokinetic model with a rapid initial plasma disposition phase ($t_{1/2\alpha} < 10$ min), followed by a long terminal disposition phase ($t_{1/2\beta} > 10$ h), a large volume of distribution, and rapid distribution into the tissues. Bortezomib is metabolized by oxidative deboronation and several cytochrome P450 liver microenzymes into inactive metabolites that are further processed and eliminated, both by renal and billiary excretion [11,12]. In multiple-dose studies in cynomolgus monkeys, stabilization of the plasma pharmacokinetics of the drug occurred within the first cycle of dosing and appeared to be reproducible over several cycles thereafter. Furthermore, there was no evidence of drug accumulation in the plasma after the second dose [10]. Pharmacodynamic studies suggest that proteasome inhibition by bortezomib occurs in a time- and dose-dependent fashion. Proteasome activity was found to be fully reversible, without a change in sensitivity to proteasome inhibition, as long as proteasome levels were allowed to return to baseline between doses [13,14]. In 2 clinical studies, bortezomib did not appear to alter pharmacokinetic profiles when given with either irinotecan or gemcitabine. Furthermore, bortezomib pharmacokinetic and pharmacodynamic profiles were not modified by co-administration with either of these therapies [10,15].

The effects of bortezomib are evident in both hematological malignancies and solid tumors. Because the proteasome degrades numerous protein substrates and affects multiple cellular pathways, it is likely that the effects of this agent are mediated through several proteasomal targets, which may vary, depending on the type of malignancy and even from patient to patient. In the following sections, the effects of bortezomib in myeloma cells and its safety and efficacy in clinical trials involving myeloma patients will be discussed.

Preclinical evaluation of Bortezomib in myeloma

Biology of proteasome inhibition in myeloma

Bortezomib activity leads to inhibition of nuclear factor (NF)-κB, which is of particular interest, because increased NF-κB activity and downstream effects are observed in a number of hematological malignancies, such as MM [16,17]. NF-κB transcriptional activity has been implicated in promoting growth and survival of MM cells within the bone marrow microenvironment and in conferring resistance to chemotherapy [18,19]. In unstimulated cells, the regulatory protein I-κB binds to and thereby inhibits NF-κB activation and translocation to the nucleus. The NF-κB pathway is activated when cells are exposed to certain cytokines, such as tumor necrosis factor (TNF)-α, or stressed by exposure to chemotherapy or radiation [17]. This process involves phosphorylation of I-κB, which targets I-κB for polyubiquitination and proteasomal degradation. Nuclear NF-κB upregulates transcription of antiapoptotic proteins, thus promoting survival, and can thereby confer resistance to chemotherapy and radiation. Of note, NF-κB increases TNF-α expression in myeloma cells, and in turn TNF-α activates NF-κB in bone marrow stromal cells to produce interleukin (IL)-6, a major growth and survival factor for myeloma cells [19]. In general, bortezomib inhibits increased expression of cytokines (e.g. IL-6), growth factors (e.g. insulin-like growth factor [IGF]-1), cell adhesion molecules (e.g. intracellular adhesion molecule [ICAM] and vascular cellular adhesion molecule [VCAM]), and angiogenic factors (e.g. vascular endothelial growth factor [VEGF]) in MM. [17,18,20,21].

In vitro studies

Bortezomib has been shown to inhibit the growth of MM cell lines, including those resistant to dexamethasone (MM.1R cells), doxorubicin (Dox40 cells), mitoxantrone (MR20 cells), or melphalan (LR5 cells) [16]. Complete growth inhibition was observed with 100 nM bortezomib in chemoresistant lines and at 10 nM in dexamethasone-resistant cells. It also produced concentration-dependent inhibition of proliferation of myeloma cells purified from bone marrow samples obtained from 4 patients [16]. Bortezomib completely inhibited growth at concentrations of 100 nM or lower in 3 of these cell samples and produced 80% growth inhibition at 1 μM in the remaining sample.

Bortezomib also enhanced the sensitivity of myeloma cells to chemotherapy. Incubation of MM.1S cells with 2 nM bortezomib shifted the LD50 of doxorubicin from 150 nM to 26 nM ($p < 0.001$) [22]. The combination of bortezomib and doxorubicin was more potent than either agent alone, regardless of the treatment sequence. However, the most pronounced synergy was observed when the MM.1S cells were pretreated with doxorubicin for 24 hours and then treated with bortezomib for an additional 24 hours [22]. Bortezomib was also shown to enhance sensitivity to doxorubicin in other myeloma cell lines (RPMI-8226/S, ARP-1, S6B45, NCI-H929, and INA6) and to enhance sensitivity to doxorubicin, melphalan, and mitoxantrone in cells resistant to these drugs [20,22]. Whereas high concentrations of melphalan did not inhibit growth of LR5 or LR7 cells, these cell lines became highly sensitive to melphalan after exposure to bortezomib [20]. Similar results were obtained with doxorubicin in U266/dox 4 and RPMI 8226/dox 4 cells and with mitoxantrone in MR20 cells. Synergistic effects between bortezomib and doxorubicin were also seen in primary myeloma cells isolated from a patient who had relapsed after conventional and high-dose chemotherapy, as well as after regimens that included interferon alfa, thalidomide, and bortezomib (Figure 3) [22].

These *in vitro* data suggest that bortezomib acts on various cell systems as it inhibits growth and induces apoptosis of myeloma cells, prevents myeloma cell interactions with the bone marrow microenvironment, and reverses chemoresistance to drugs commonly used to treat MM, including doxorubicin and melphalan.

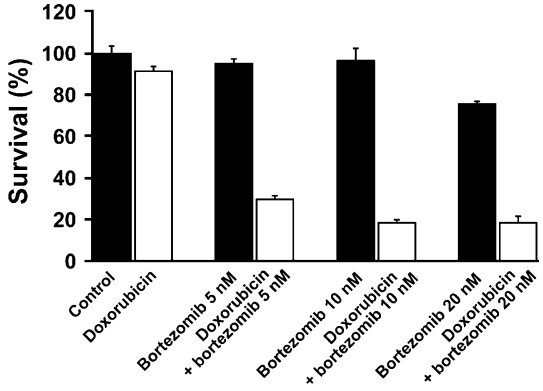

Figure 3. Synergistic growth inhibition with bortezomib and doxorubicin. Multiple myeloma cells were isolated from a patient who had relapsed following conventional and high-dose chemotherapy, interferon alfa, thalidomide-based therapy, liposomal doxorubicin, and bortezomib alone or with dexamethasone. These cells had low sensitivity *in vitro* to bortezomib and doxorubicin alone, but significant cytotoxicity was observed when cells were incubated with doxorubicin at 100 ng/mL for 24 hours and then bortezomib at 5–20 nM for an additional 24 hours. From Mitsiades et al. [22], with permission.

Murine xenograft model

The effect of bortezomib *in vivo* was explored in a murine xenograft model, in which immunodeficient (beige-nude-xid) mice were inoculated with myeloma RPMI-8226 cells [23]. When tumors became measurable, the mice started treatment with bortezomib at doses of 0.05, 0.1, 0.5, or 1 mg/kg given intravenously by tail vein twice a week for 4 weeks and then once weekly thereafter. Another group of animals received vehicle (0.9% saline). At 0.5 or 1 mg/kg, bortezomib significantly inhibited tumor growth compared with the control group ($p = 0.02$ and 0.01, respectively). At 1 mg/kg, tumor growth was completely suppressed in half of the animals for an average of 9 days, whereas at 0.5 mg/kg, tumor growth was delayed (median time for tumor to reach 2 cm in size: 30 vs. 14 days, $p < 0.001$). Moreover, median survival was prolonged from 14 to 30 days at 0.5 mg/kg and to 34 days at 1 mg/kg (both $p < 0.0001$). Tumor sections harvested from mice treated with bortezomib 0.5 and 1 mg/kg showed significantly more apoptosis ($p < 0.001$) and less angiogenesis ($p = 0.0001$) than those from vehicle-treated animals. Similar antiangiogenic effects due to proteasome inhibition were observed in a squamous cell carcinoma xenograft model, as bortezomib markedly inhibited microvessel density in these tumors [24].

These preclinical *in vivo* data supported the *in vitro* findings and demonstrated that bortezomib is highly effective in models of MM and other malignancies, therefore warranting clinical development.

Clinical trials in multiple myeloma

Bortezomib alone in refractory/relapsed disease

In a phase I trial, 43 heavily pretreated patients with advanced solid tumors received bortezomib at doses ranging from 0.13 to 1.56 mg/m^2, as a rapid intravenous bolus twice weekly for 2 consecutive weeks followed by a 1-week recovery period [14]. In this phase I trial, dose-limiting toxicity occurred at the highest dose level of 1.56 mg/m^2 and consisted of grade 3 diarrhea and grade 4 sensory neuropathy.

The feasibility of using bortezomib in relapsed and refractory hematologic malignancies was evaluated in a phase I study of 27 heavily pretreated patients, including 12 patients with MM [13]. Patients received bortezomib at doses of 0.4 to 1.38 mg/m^2 twice weekly for 4 weeks, followed by a 2-week rest. Over this dose range, the 20S proteasomal activity in blood was inhibited by 36% to 74%, with maximal inhibition observed within 1 hour of administration [13]. The maximum tolerated dose in this study was 1.04 mg/m^2. Dose-limiting toxicities included thrombocytopenia, hyponatremia, hypokalemia, fatigue, and malaise. Nine of 9 evaluable patients with refractory plasma cell dyscrasia achieved a decrease in either marrow plasmacytosis, paraprotein level, or both, including one patient who reached a durable CR [13].

The schedule and dose selected for phase II studies were based on the solid-tumor and hematologic malignancies phase I trial results: 1.0 to 1.3 mg/m^2 twice weekly for 2 weeks followed by a 10-day recovery period (days 1, 4, 8, and 11 of a 3-week cycle).

When evaluating the clinical efficacy of a novel therapeutic regimen in MM, it should be noted that different response criteria have been used. To provide consistency among different trials, the European Group for Blood and Marrow Transplantation (EBMT) developed new response criteria for MM [25]. Briefly, these criteria include: 1) the definition of complete remission by negative immunofixation, 2) confirmation of any degree of response 6 weeks apart, and 3) definition of relapse from CR and progression from any other degree of response. The EBMT criteria are more stringent than those previously used, thus resulting in lower response rates.

The safety and activity of bortezomib in MM were evaluated in 2 phase II multicenter studies in the United States [26,29] (Table I). Responses, which are discussed below, were assessed using the EBMT criteria. An additional response category, near CR (nCR), was added to define patients who met all the criteria for CR but still had a positive immunofixation test result. The first open-label phase II study (SUMMIT) enrolled 202 patients with relapsed and refractory myeloma in the United States [26]. Bortezomib was administered at a dose of 1.3 mg/m^2 on days 1, 4, 8, and 11 of a 3-week cycle for up to 8 cycles. Of 193 patients with measurable disease, 178 patients (92%) had received at least 3 prior therapies commonly used for MM [26]. In this regard, most patients (64%) had undergone previous stem-cell transplantation. According to the stringent EBMT criteria, bortezomib produced a response rate of 35%, which included CR or nCR in 19 patients (10%), partial response (PR) in 34 patients (18%), and minimal response (MR) in 14 (7%) [26]. Patients who achieved CR or PR after 2 cycles of treatment had significantly longer survival than those who did not ($p = 0.007$) [26]. The median time to response was 38 days, and the median duration of response was 12.7 months. Bortezomib appeared to produce meaningful survival benefits, since the median survival of all 202 patients enrolled in the SUMMIT trial was more than 17 months [27].

Table I. Bortezomib in relapsed/refractory myeloma.

Study	Regimen	No. patients	Response rate (PR+CR)
Richardson et al. (SUMMIT) [26]	Bortezomib	202	27%
Jagannath et al. (CREST) [29]	Bortezomib (1.0 vs. 1.3 mg/m^2)	54	30% vs. 38%
Richardson et al. (APEX) [31]	Bortezomib	333	38%
Berenson et al. [32]	Bort/Mel	24	33%
Zangari et al. [33]	Bort/Thal	79	40%
Hollmig et al. [34]	Bort/Doxo/Thal/Dex	14	50%
Chanan-Khan et al. [35]	Bort/peg Dox/Thal	13	38%

Bort = bortezomib, Mel = melphalan, Thal = thalidomide, Doxo = doxorubicin, Dex = dexamethasone, peg Dox = pegylated doxorubicin.

Patients with documented disease responses also experienced improvement in hemoglobin and platelet count, background immunoglobulins, and performance status [28]. Baseline prognostic factors predicting a higher likelihood of response included patient age <65 years and $\leq 50\%$ plasma cell infiltration in the bone marrow prior to treatment. Toxicities were manageable, and grade 3 adverse events included thrombocytopenia in 28%, fatigue or peripheral neuropathy, both observed in 12%, and neutropenia in 11% of patients. Grade 4 adverse events were observed in 14% of patients. Concerning peripheral neuropathy, most of the patients who experienced a worsening of their symptoms on study had peripheral neuropathy to some extent at baseline, and only 1 of 33 patients who had no baseline neuropathy developed grade 3 neuropathy. Overall, 18% of patients discontinued bortezomib due to adverse events.

In the second pivotal phase II study (CREST), bortezomib was administered to 54 patients with either relapsed or refractory myeloma after front-line therapy [29]. Two different doses of bortezomib—1.0 mg/m^2 (n = 28) or 1.3 mg/m^2 (n = 26)—were evaluated using the same 3-week schedule as in the SUMMIT study for up to 8 cycles. The overall response rate (CR+PR) was 30% and 38% at the 1.0 mg/m^2 and 1.3 mg/m^2 dose levels, respectively. Considering complete, partial, and minimal responses, the overall response rate was 33% and 50% at the 1.0 mg/m^2 and 1.3 mg/m^2 dose level, respectively. These data suggest that when there is a need for dose reduction from 1.3 to 1.0 mg/m^2 in patients with drug-related adverse events, significant clinical benefit can still be achieved with bortezomib therapy given at the lower dose. The safety profile in CREST was similar to that of SUMMIT, thrombocytopenia being the most common adverse event, with grade 3 occurring in 29% of patients. In patients developing thrombocytopenia, the platelet counts predictably decrease during each treatment cycle, with a recovery toward baseline during the rest period within each cycle. Peripheral neuropathy and gastrointestinal toxicity (nausea, vomiting, and diarrhea) were more common at the higher dose level.

All patients in SUMMIT and CREST whom the investigators believed might benefit from extended treatment were offered continuation of or re-treatment with bortezomib alone or in combination with dexamethasone in an extension trial [30]. The safety profile and type and frequency of new or worsening treatment-emergent adverse events for the patients receiving extended therapy or re-treatment with bortezomib for up to a median of $\sim$11 months were generally similar to those observed within the first 8 cycles.

A large phase III study (APEX) comparing bortezomib with high-dose dexamethasone in patients with relapsed or refractory myeloma after front-line therapy was conducted in 12 countries, including 9 European countries, the United States, Canada, and Israel. The results of the final analysis of this study were presented at the last American Society of Hematology (ASH) Meeting in December, 2004 [31]. A total of 669 patients who had relapsed following previous treatment with 1 to 3 prior therapies were randomly assigned to receive either bortezomib 1.3 mg/m^2 by intravenous bolus administration on days 1, 4, 8, and 11 every 3 weeks for 8 cycles followed by 1.3 mg/m^2 on days 1, 8, 15, and 22 every 5 weeks for 3 cycles or oral dexamethasone 40 mg on days 1–4, 9–12, and 17–20 every 5 weeks for 4 cycles followed by 40 mg on days 1–4 every 28 days for 5 cycles. In a preplanned interim analysis, responses were assessed using EBMT criteria. Statistically significant benefit in median time to progression (TTP) as well as in overall and 1-year survival were observed among patients receiving bortezomib compared with patients given dexamethasone. No major safety differences were observed between the two treatment groups.

Combination therapy in refractory/relapsed disease

Several studies have evaluated the use of bortezomib in combination therapy [32–35] (Table I). In SUMMIT and CREST, patients with progressive disease after 2 cycles or stable disease after the first 4 cycles were given dexamethasone 20 mg daily for 2 days with each bortezomib dose [36]. Thirteen of 74 patients (18%) in the SUMMIT trial and 9 of 27 patients (33%) in the CREST study had an upgraded response compared with that achieved with bortezomib alone.

A phase I/II trial evaluated the safety and activity of bortezomib 1.0 mg/m^2 on days 1, 4, 8, and 11 every 3 weeks in combination with thalidomide added to the second cycle at increasing dose levels of 50, 100, 150, and 200 mg (in absence of grade >2 neurotoxicity) and the addition of dexamethasone as early as cycle 4 in the absence of a PR, in patients who had relapsed from prior autologous transplantation [37]. By the end of the third cycle, more than 40% of patients had achieved at least a PR, and preexisting thalidomide-related neuropathy had not been aggravated. After 8 cycles, nCR ($>90\%$ M-protein decrease) and CR were reported in 22% of patients, and the response was independent of both cytogenetic abnormalities and dosing of bortezomib and thalidomide. Importantly, no cumulative grade >2 neurotoxicity was observed after 4 cycles, and the combination was well tolerated in this high-risk population.

The feasibility of administering bortezomib in combination with either pegylated liposomal doxorubicin or melphalan has been evaluated in phase I trials. Bortezomib at escalating doses of 0.9 to 1.50 mg/m^2 was administered with pegylated liposomal doxorubicin at a fixed dose of 30 mg/m^2 on day 4 to patients with advanced hematologic malignancies [38]. Among the 22 evaluable myeloma patients in the series, an overall response rate of 73% was achieved (5 CR+3 nCR+8 PR), of note the 38% CR+nCR rate in patients with disease previously unresponsive to anthracyclines. Frequent dose reductions were necessary when bortezomib was started at dose levels of 1.40 mg/m^2 or higher. Accordingly, the combination of bortezomib 1.30 mg/m^2 plus pegylated liposomal doxorubicin 30 mg/m^2 was recommended for further studies.

Combination therapy with bortezomib and melphalan was explored in patients with relapsed or refractory disease using a 4-week treatment cycle [32]. In this study, a fixed dose of bortezomib 0.7 or 1.0 mg/m^2 was given on days 1, 4, 8, and 11, with melphalan escalated over 5 dose levels, starting at 0.025 mg/kg and ending at 0.25 mg/kg on days 1–4 every 28 days. At the first 3 dose levels, patients received all 8 planned treatment cycles, and at the fourth and fifth dose levels, they received 7 and 5 cycles, respectively. Toxicities with this combination regimen were manageable, with grade 3 toxicities mostly related to myelosuppression in patients with cytopenias at baseline. The regimen has resulted in promising activity, as responses (CR+PR+MR) were observed in over 60% of assessable patients. The evaluation of bortezomib at 1.0 mg/m^2 with escalating doses of melphalan is ongoing.

Newly diagnosed disease

Because bortezomib has demonstrated durable responses in previously treated patients with advanced disease, a number of studies are evaluating this agent as part of first-line therapy in patients with newly diagnosed MM. In this regard, the preliminary results from 6 phase I/II trials were presented at the 2004 ASH Meeting (Table II) [39–44]. Richardson et al. [39] reported a 41% PR with 5% CR rate after at least 2 cycles of single-agent bortezomib. Jagannath et al. [40] also reported 83% major responses, with 13% CR and 17% nCR, starting therapy with bortezomib and adding dexamethasone in patients with less than PR after 2 cycles or less than CR after the first 4 cycles, at a dose of 40 mg on the day of and day after each bortezomib dose. With the same combination, bortezomib and dexamethasone, the Intergroupe Français du Myelome (IFM) obtained an 83% response rate (66% PR and 17% CR) [41]. A 3-drug combination with bortezomib, doxorubicin, and dexamethasone (PAD) achieved a 95% response rate (PR+CR) [42], while the response rate reported after adding thalidomide to the bortezomib and dexamethasone combination has been 84% [43]. Finally, in a small phase I/II trial, the PR and CR obtained with the combination of melphalan, prednisone, and bortezomib in untreated myeloma patients older than 65 years of age was 60% (with 16% nCR) and 12%, respectively [44 and personal communication]. The positive results of these trials have stimulated the development of large phase III trials.

In addition, regarding the use of bortezomib in the front-line regimens, it is important to note that PBSC collection and engraftment in patients who are candidates for high-dose therapy intensification are not impaired by the use of this drug.

Safety

Bortezomib was generally well tolerated when used alone or in combination with dexamethasone in the SUMMIT and CREST trials. The most common toxicity was gastrointestinal, with nausea, vomiting,

Table II. Front-line phase II trials with bortezomib.

Study	Regimen	No. patients	Response rate, %		
			CR	PR	MR
Richardson et al. [39]	Bortezomib	28	5	36	23
Jagannath et al. [40]	Bort + Dex	23	13	70*	13
Harousseau et al. [41]	Bort/Dex	18	17	66	0
Cavenagh et al. [42]	Bort/Doxo/Dex	21	–	95	0
Alexanian et al. [43]	Bort/Thal/Dex	25	–	84	0
Mateos et al.† [44]	Bort/Mel/Pred	25	12	60‡	12

*17% nCR.
†Phase I; updated Feb, 2005.
‡16% nCR.
Bort = bortezomib, Dex = dexamethasone, Doxo = doxorubicin, Thal = thalidomide, Mel = melphalan, Pred = prednisone.

and diarrhea reported in 62% of all patients, which was usually mild to moderate and manageable with routine support. The most frequently reported grade 3 and 4 adverse events were thrombocytopenia (27% grade 3, and 3% grade 4), neutropenia (12% grade 3, and 2% grade 4), peripheral neuropathy (11% grade 3), and fatigue (11% grade 3) [26,29]. The incidence of thrombocytopenia was analyzed in all patients receiving bortezomib at 1.3 mg/m^2 in SUMMIT and CREST, and the incidence of grade 3 and 4 thrombocytopenia was inversely related to the platelet count at baseline [45]. The incidence of grade 3 thrombocytopenia was less than 10% if the baseline platelet 0count was above 70 000/μL. The overall platelet count predictably decreased an average 60% from baseline to the recorded nadir on treatment.

Peripheral sensory neuropathy is considered the most clinically relevant toxicity. Overall, 35% of patients in the SUMMIT and CREST studies developed new or worsening symptoms of peripheral neuropathy [46], and 80% of the patients in these trials had signs or symptoms of peripheral neuropathy at entry into the study. In SUMMIT, patients with neuropathy at enrollment were more likely to develop grade 3 toxicity than those without symptoms at baseline (16% vs. 3%). Peripheral neuropathy led to dose reductions and discontinuation of therapy in 12% and 5% of patients, respectively. Complete resolution or improvement of symptoms was observed in the majority of patients during follow-up. Bortezomib dose-related peripheral neuropathy is generally grade 1 or 2 and has the potential for partial or complete reversibility in the majority of patients. Further studies are needed in order to determine the most appropriate interventions that will allow continuation of therapy [26]. Postural hypotension is seen in about 10% of patients and is clearly dose-related.

Importantly, toxicities reported for patients in the SUMMIT and CREST trials who received extended therapy were manageable, with no signs of cumulative toxicity related to extended bortezomib therapy for a median duration of 14 cycles (i.e. almost 1 year). The majority of patients completed the study at the same dose of bortezomib that they had initially received, suggesting that extended treatment is manageable and tolerable [30]. Some uncommon toxicities have been reported, such as tumor lysis syndrome [47,48], which is exceedingly rare in myeloma patients treated with other agents, and a case of recurrent bortezomib-induced hepatitis [49].

Characteristics of response to Bortezomib

It is of interest that bortezomib acts very quickly, as response is usually achieved within the first two cycles. In this regard, and as already mentioned, clinicians should be aware of possible tumor lysis syndrome, particularly in patients with high tumor mass. On the other hand, we have seen impressive responses of extramedullary plasmacytomas to bortezomib, in contrast with the lack of efficacy of thalidomide on soft-tissue plasmacytomas [50], supporting different mechanisms of action of these two drugs. In this regard, in the SUMMIT trial a number of patients resistant to thalidomide responded to bortezomib.

Future prospects for the use of Bortezomib

After a notably rapid clinical development, bortezomib is now established as a safe and highly effective drug to be added to the current treatment strategies for MM. The reported efficacy and safety from the SUMMIT, CREST, and APEX trials, as well as data from a number of more recently activated clinical studies, are proof of the viability of the proteasome as a molecular target in MM therapy. Bortezomib, alone or in combination with dexamethasone, is a valuable treatment for patients with newly diagnosed or pretreated MM. Ongoing studies are evaluating

the combination of this agent with other antimyeloma drugs, including melphalan, prednisone, doxorubicin, liposomal doxorubicin, thalidomide, and dexamethasone as initial induction therapy. The possible role of bortezomib as maintenance therapy is also under investigation. It is hoped that results from these studies will allow further optimization of bortezomib-based therapy and improve the care for myeloma patients at all stages of the disease.

Acknowledgement

This work has been supported in part by Spanish grant 2003-REDG-136-O.

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