Bortezomib: Safety and Efficacy in the Treatment of Multiple Myeloma

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Abstract: Multiple Myeloma is the second leading hematologic cancer in the United States with approximately 20,000 new cases diagnosed each year. Although myeloma remains incurable, significant progress has been made in developing new therapeutics resulting in improved overall survival. In the last ten years, the average survival of patients with advanced myeloma has almost doubled. Much of this success can be attributed to the development and clinical use of the first-in-class proteasome inhibitor bortezomib. The proteasome is a multicatalytic protease complex essential for protein metabolism and regulation of cellular homeostasis. Through inhibition of proteasome function, bortezomib has demonstrated significant anti-myeloma responses in both pre-clinical models and in human studies. Bortezomib is now approved for use in patients with newly diagnosed and refractory myeloma, and in combination with other chemotherapeutic agents. This review will discuss the pre-clinical studies evaluating the mechanism of action of proteasome inhibition, outline the clinical development of bortezomib as treatment for patients with newly diagnosed and relapsed multiple myeloma and describe the safety of bortezomib in human studies. Several second generation proteasome inhibitors are now showing promise in early phase clinical trials, foreshadowing a new era of targeted therapy for multiple myeloma.

Keywords: bortezomib, proteasome, apoptosis, lenalidomide
Introduction
The proteasome complex
Normal cellular homeostasis requires an active process for protein degradation. Over eighty percent of cellular proteins are degraded by a special organelle known as the proteasome. The 26S proteasome complex is made up of several proteins organized in a conical structure of 4 rings containing three active sites; known as the chymotrypsin-like (CT-L), caspase-like (C-L) and trypsin-like (T-L) catalytic sites (Fig. 1). Proteins are designated for proteasome degradation by attachment of ubiquitin moieties to lysine residues. These ubiquitin structures are recognized by proteasome complexes and they facilitate degradation. Proteasome inhibitors, like bortezomib, specifically block the chymotryptic enzymatic site and thus prevent protein turnover. The build-up of cellular proteins or perhaps “debris” causes many changes within the cell that eventually results in apoptosis. In vitro studies has shown more apoptosis or an enhanced sensitivity to proteasome inhibition in cancer cells versus normal cells. However, the actual mechanism of this enhanced activity and the mechanism of apoptosis remains unknown.

Preclinical studies
Many investigators have shown that proteasome inhibition affects the transcription factor nuclear factor-κB (NFκB). NFκB stimulates the production of growth stimulatory cytokines, induces cell cycle proteins, and enhances anti-apoptotic regulators. An overactive NFκB contributes to the pathogenesis of many cancers, including myeloma. The activity of NFκB is closely regulated by the inhibitory protein-κB (IκB). IκB binds to NFκB, trapping NFκB in the cytosol and preventing NFκB induced DNA transcription. Under normal homeostasis and during cellular stress, IκB is degraded by the proteasome, thus promoting NFκB activity. Proteasome inhibition (PI) results in the opposite effect; intracellular IκB levels rise and NFκB activity is diminished.

Several in vitro studies in myeloma cell lines have failed to demonstrate NFκB stabilization following exposure to PI, and thus additional mechanisms must be involved. Published studies have described activation and inactivation of many cellular processes and over or under expression of several important regulatory proteins following PI. For example, myeloma cell lines exposed to bortezomib produce lower levels of stimulatory cytokines including TNF-a and IL-6, and demonstrate diminished levels of important cell adhesion molecules making MM cells more prone to apoptosis. Gene expression and proteomic studies have confirmed that bortezomib suppresses molecules involved in DNA repair, thus limiting the ability of MM cells to repair damage caused by conventional chemotherapy. PI also effects the cycle cell through stabilization of the tumor suppressor protein p53 and the checkpoint proteins p21 and p27. Additional proteins directly responsible for apoptosis may also be affected by PI. Data suggest that Bax and Bak are upregulated following exposure to bortezomib, and anti-apoptotic proteins, including Bcl-2 and caspase inhibitors, are suppressed.
Another emerging mechanism for PI-induced apoptosis is through a direct effect on the unfolded protein response (UPR). Myeloma cells are professional “factories” for protein (i.e. immunoglobulin) production which requires a highly developed endoplasmic reticulum (ER). Proper protein translation and folding occurs in the ER and this is closely regulated by the UPR. The UPR can transmit information to the nucleus about the protein folding status (i.e. health) of the ER and can induce either apoptosis or enhanced protein production. Misfolded or unfolded proteins are recognized by the ER quality control systems and are actively sent out of the ER to the proteasome for degradation. Data suggest that bortezomib can promote a pro-apoptotic response via the UPR by blocking degradation of misfolded proteins and allowing proteins to accumulate in the ER.12–14

Bortezomib has been tested in a wide range of human MM cell lines, primary human MM cells and murine xenograft models showing potent dose-dependent anti-tumor responses. Similar models have shown synergy with radiation, a variety of chemotherapeutic agents, immune modulatory drugs (Imids), histone deacetylase inhibitors and other proteasome inhibitors.15,16 The marked activity of bortezomib in preclinical studies provided strong support for initiating clinical studies in patients with myeloma.9

Clinical Studies
Early phase studies leading to FDA approval
Several Phase I clinical trails evaluated bortezomib in patients with advanced hematologic and solid tumor malignancies. These studies demonstrated potent inhibition of the proteasome (50%–75%), and the best clinical responses, including one complete remission, in patients with plasma cell disorders. The studies recommended a Phase II Bortezomib dose of 1.3 mg/m² administered twice weekly for 2 of every 3 weeks.17–19 Two pivotal Phase II trials (SUMMIT and CREST trials) subsequently demonstrated efficacy for bortezomib in relapse and refractory myeloma. The SUMMIT trial enrolled 192 evaluable patients, 91% of which had received 3 or more prior myeloma therapies, and showed an overall response rate of 35% with 10% achieving complete or near complete remission.20,21 The CREST trial, involving 54 patients with relapse myeloma (median 3 prior regimens), randomized patients to bortezomib 1 mg/m² versus 1.3 mg/m² at standard intervals. The results showed improved overall response rate (38% versus 30%; CR+PR) in patients receiving bortezomib at 1.3 mg/m², but fewer adverse events in the 1 mg/m² dose group.22 Both studies reported a median duration of response of approximately 12 months in heavily pretreated patients. Consequently, the FDA granted accelerated approval for bortezomib as treatment for relapsed MM in 2003. Of note, both studies reported improved response rates (10% higher) with the addition of dexamethasone to those not responding after 2 cycles of bortezomib alone. A large Phase III trial (APEX) involving 669 patients with relapse and refractory myeloma subsequently confirmed the results of the Phase II trials, demonstrating an ORR of 38% with bortezomib versus 18% with dexamethasone alone. Complete remissions (CR) were noted in 9% of bortezomib treated subjects, an impressive finding since CRs had not been previously achievable in the relapse and refractory setting. Time to progression and overall survival also favored the bortezomib arm. This trial led to full FDA approval in relapse myeloma in 2005.23,24

Bortezomib combinations
Following the SUMMIT and APEX trials, numerous studies have evaluated bortezomib in combination with a variety of biologic and chemotherapeutic agents, both as salvage therapy and in the front-line setting. Many of these combinations were based on pre-clinical models showing synergy and enhanced activation of pathways for cell death. Due to the limits of this review, only the highlights of the most influential clinical trials will be described.

Bortezomib with alkylators
Since the early 1960’s, melphalan and prednisone (MP) has been the mainstay of treatment for elderly patients with myeloma. In addition, preclinical studies showed synergy for bortezomib with alkylators consequently, there was great interest in combining these agents. Mateos et al, were the first to report a front-line Phase I/II trial using bortezomib, melphalan and prednisone (VMP). In older, transplant-ineligible patients, VMP produced an overall response rate of 89%, including 32% CRs.25 The median time to progression was 27.2 months and 85% of these elderly
patients were alive at 3 years. These positive results promoted a large, multi-national, randomized Phase III (VISTA) trial comparing VMP × 9 cycles to standard MP × 9 cycles in elderly patients with newly diagnosed MM. The randomized study confirmed the positive results seen in Phase II. VMP provided much more anti-myeloma activity (ORR 71% vs. 35%; CR 30% vs. 4%), and time to progression strongly favored VMP (24 months versus 16.6 months; \( P < 0.001 \)).

A more recent update has confirmed an overall survival advantage in those receiving VMP versus MP (35% reduced risk of death; HR, 0.653; \( P < 0.001 \)). This trial led to FDA approval for bortezomib as front-line therapy in the US and approval by the EMEA in Europe. VMP is now considered a standard regimen for non-transplant candidates with newly diagnosed multiple myeloma.

More recently, Mateos et al, compared front-line VMP to bortezomib, thalidomide and prednisone (VTP) in elderly patients with MM. Patients received 9 cycles of VMP or VTP and then a second randomization compared maintenance with VT versus VP. The results, presented at the American Society of Hematology meetings in December 2009, showed similar overall and complete response rates for VMP vs. VTP (ORR 80% vs. 81%, CR 32% vs. 31%). After the first six weeks of therapy, both groups subsequently received bortezomib weekly rather than twice weekly. The reduced frequency of bortezomib appeared to improve tolerability with less neuropathy and without compromising efficacy. The VTP arm was associated with increased cardiac events. Both regimens of maintenance (VT and VP) were well tolerated and responses improved following maintenance therapy (higher ORR, VGPR and CR rates). The authors concluded that both VMP and VTP were very active in this elderly population and that further studies evaluating maintenance therapy with bortezomib are warranted.

Since significant synergy had been demonstrated with bortezomib and melphalan (i.e. an alkylator), studies evaluating the combination of cyclophosphamide, bortezomib and dexamethasone (CyBorD) were initiated. An advantage for cytotoxin is the lack of stem cell toxicity, thus allowing use as front-line therapy in young transplant eligible subjects. In a Mayo Clinic study, bortezomib 1.3 mg/m² given intravenously on days 1, 4, 8 and 11, was combined with cyclophosphamide 300 mg/m² orally on days 1, 8, 15 and 22 and dexamethasone 40 mg orally on days 1–4, 9–12 and 17–20 on a 28-day cycle. The study reported an impressive ORR of 88%, with 61% achieving VGPR and 39% CR/nCR following 4 cycles of therapy. All patients undergoing stem cell harvest had a successful collection and all patients receiving transplantation engrafted as expected. Toxicity was significant, promoting Reeder and colleagues to modified the regimen (Mod-CyBorD) by changing the bortezomib to 1.5 mg/m² given weekly (D1, 8, 15, 22), and decreasing the dexamethasone to once weekly after the first two cycles. The results demonstrated similar efficacy (ORR 93%, CR/nCR 43%) but marked improved tolerability. The incidence of grade ≥3 thrombocytopenia, neutropenia and peripheral neuropathy decreased from 21% to 0%, 12% to 7% and 6% to 0%, respectively. The authors suggested that mod-CyBorD is now their preferred induction regimen for younger transplant eligible patients.

**Bortezomib with anthracyclines**

Trials investigating the combination of bortezomib and doxorubicin were initiated based on preclinical data suggesting that doxorubicin resistance was, in part, due to activation of NFκB. Early Phase I/II trials were promising, propelling Orlowski and colleagues to perform a large randomized, multi-center Phase III trial comparing bortezomib alone versus bortezomib plus pegylated liposomal doxorubicin (30 mg/m² given on Day 4) in patients with relapse and refractory MM. The study enrolled 646 patients and showed improved time to progression (9.3 versus 6.6 months, \( P \leq 0.01 \)), improved duration of response (10.2 versus 7 months, \( P \leq 0.01 \)) and an overall survival advantage at 15 months (76% versus 65%, \( P = 0.03 \)) for combination therapy. Based on this trial, the FDA approved the combination of bortezomib and pegylated liposomal doxorubicin as first salvage in bortezomib naïve patients in 2007. Since then, many front-line studies investigating combinations of bortezomib, doxorubicin and dexamethasone have been reported. In general, ORRs of >90% and CRs of >20% have been noted. These combinations have been used with success in both transplant eligible and in-eligible patients. One interesting finding from Olowskis’s randomized trial was that single nucleotide polymorphisms in the multidrug resistance protein 1 and in P-glycoprotein 1 genes
were predictive of treatment outcomes in patients with advanced multiple myeloma. The authors propose that this genetic data could be used in future studies to help identify patients most likely to benefit from bortezomib and anthracycline-based therapy.41

Bortezomib and imids
The immune modulatory drugs (Imids; thalidomide an lenalidomide) have played a significant role in the treatment of MM over the past decade. Consequently, there has been great interest for combining, arguably, the two most potent classes of anti-myeloma drugs, imids and proteasome inhibitors. Alexanian and colleagues at MD Anderson Cancer Center were the first to report a front-line Phase II study combining bortezomib, thalidomide and dexamethasone (VTD). A total of 38 patients received up to 3 cycles of therapy (bortezomib 1.3 mg/m² × 4, Thalidomide 100–200 mg daily, dexamethasone 20 mg/m² day 1–4, 9–12, 17–20; every 28 days). Rapid responses were achieved with an ORR of 87% and 6 patients achieving CR (16%).42 Several groups have reported equally impressive results with VTD both in elderly patients and in transplant eligible patients.43,44

In vitro, lenalidomide is much more potent than thalidomide and shows improved synergy with bortezomib. Consequently, the combination was expected to show greater clinical activity. Richardson et al performed a Phase I combining lenalidomide and bortezomib with subsequent addition of dexamethasone (RVD) in patients with relapse and refractory MM. In 38 heavily pretreated patients, (median 5 prior therapies), the ORR was 39%.45 Richardson also performed a front-line Phase I/II RVD clinical trial involving 66 patients. Treatment consisted of eight 3-week cycles of bortezomib 1.0–1.3 mg/m² (days 1, 4, 8, 11), lenalidomide 15–25 mg (days 1–14), and dexamethasone 40 or 20 mg (days 1, 2, 4, 5, 8, 9, 11, 12). Despite that only 20 patients were treated at MTD, RVD was quite active with an ORR of 100%, including VGPR in 67% and CR/nCR in 37% of patients. Many patients (73%) required at least one dose-reduction due to toxicity (doses reduced due to dexamethasone > bortezomib > lenalidomide).46 Of note, patients responded to therapy regardless of adverse prognostic features. Overall, RVD is considered one of the most effective regimens for frontline therapy in young transplant candidates and is frequently used in those with abnormal karyotype or adverse prognostic features.

Several 4-drug combination studies have now been reported including; RVD plus liposomal doxorubicin, RVD plus cyclophosphamide and VTD plus cyclophosphamide.47–49 The overall response rates have been impressive (>90%) with excellent VGPR and CR rates. It is unclear if these 4-drug combinations provide an advantage over 2 or 3 drug combinations.50 A multicenter, randomized Phase II trial comparing RVD, VCD and RVCD (EVOLUTION Trial) is currently underway with promising initial results in all arms.51 A large multi-national phase III trial is underway in France and the US comparing RVD (8 cycles) versus RVD (5 cycles) with autologous stem cell transplantation. This will be one of the first trials to compare transplant versus non-transplant therapy in the novel drug era.

Bortezomib with novel agents
There are numerous novel agents under investigation for the treatment of relapse myeloma. Many of these have been rationally combined with bortezomib due to overlapping or synergistic activities. Histone deacetylase inhibitors, which block the autophagy pathway and decrease a cells’ ability to degrade mis-folded proteins demonstrate significant in vitro synergy with bortezomib. In a Phase I study using vorinostat with standard bortezomib (4 doses every 3 weeks), the MTD for vorinostat was 400 mg daily for 8 days. Twenty-three heavily pretreated patients (median 7 prior treatments) received treatment and 41% achieved partial remission.52 Several other HDAC inhibitor trials are underway, testing many different schedules and combinations of agents.53,54 Perifosine is an inhibitor of akt, a pro-survival protein kinase which partially acts by promoting NFκB. In a Phase II trial, perifosine plus bortezomib resulted in an ORR of approximately 41%; 32% in truly bortezomib refractory.55 A Phase III trial comparing bortezomib and dexamethasone with or without perifosine is now underway. Several monoclonal antibodies, one targeting the myeloma cell surface protein CS-1 and another targeting IL-6, are now being evaluated in Phase II clinical trials. Initial results are promising with little additional toxicity noted from antibody-based therapy.56–59
Bortezomib with autologous transplantation

Clinical trials incorporating bortezomib-based induction prior to autoSCT have yielded promising results. In the IFM 2005/01 trial, 482 transplant-eligible patients <65 years of age were randomized to receive vincristine, adriamycin and dexamethasone (VAD) or bortezomib plus dexamethasone (VD) as induction, followed by a high dose melphalan-based autoSCT. VD induction was superior to VAD across all response criteria, with higher rates of PR, very good partial response (VGPR), and CR/near CR (nCr). In addition, pre-transplant VD versus VAD resulted in superior response rates post-transplant and a significantly higher two-year overall survival. In another phase III trial by the Italian Myeloma Network GIMEMA, 480 transplant-eligible MM patients <65 years of age were randomized to three cycles of TD versus VTD. After three induction cycles, individuals in both groups underwent stem cell mobilization followed by autoSCT. Overall, VTD led to superior rates of PR, VGPR, and CR/nCR rates, as well as a significant two-year PFS benefit (90% vs. 80%). These studies suggest a role for bortezomib as induction therapy pre-transplant, and a continued role for autoSCT, with improved CR rates following transplant, in the novel drug era. At UCSF, transplant eligible patients are encouraged to undergo autoSCT following induction therapy to enhance the remission.

Many centers are now investigating the use of bortezomib with high-dose melphalan as preparative therapy for ASCT. A large French study has confirmed the safety of adding bortezomib (1 mg/m² on Day −6, −3, +1, +4) to high-dose melphalan (200 mg/m² on Day −2). In a matched control analysis, patients receiving melphalan + bortezomib were more likely to achieve CR versus those receiving high-dose melphalan alone (36% versus 11%). These results need to be confirmed in a large Phase III trial. However, emerging data suggest that the sequence of administration may be important. Researchers from Emory University have reported that bortezomib given on the day following high-dose melphalan is associated with more apoptotic marrow plasma cells than if bortezomib is given before melphalan. Alternative dosing schedules of both bortezomib and melphalan are also being tested and the optimal regimen remains unclear. At the ASH meeting last year, a group from the Netherlands reported a trend towards less disease progression post-autologous transplant for patients receiving bortezomib maintenance therapy versus observation (12% vs. 6%; P = 0.08). Currently, there are no published randomized trials investigating bortezomib as part of preparative therapy or for maintenance therapy with autologous transplantation. Additional studies are warranted before these practices can be recommended.

Overall, most combinations utilizing bortezomib as frontline therapy have demonstrated ORR of approximately 85%–95% with VGPR and CR seen in approximately 40%–70% and 25%–35%, respectively. These remissions have occurred independent of age and regardless of poor risk features. This was unexpected, but the data suggest that patients with well-classified adverse prognostic features including abnormal karyotype (del 13, t(4,14), t(14,16), complex cytogenetics), high β2 m, and high LDH have generally responded equally as well as patients without these features. One caveat may be the presence of gain of chromosome 1q21 by interphase fish. Chang and colleagues demonstrated shorter progression free and overall survival in cases with 1q21 gain. Overall, most experts recommend including bortezomib as part of front-line treatment of all patients with adverse prognostic features.

Safety

We now have over 10 years of clinical experience with bortezomib, and consequently the safety profile has been well defined. In general, this first-in-class proteasome inhibitor has been well tolerated but some patients will require dose adjustment, delay or discontinuation due to toxicity. The most common side effects have been infusional symptoms, asthenia, gastrointestinal symptoms, neuropathy and bone marrow suppression. Of these, neuropathy is the most concerning and most likely to impact quality of life. Severe toxicity including death has been reported in <3% of patients. Most adverse effects are reversible and can be alleviated with dose reductions and/or temporary delays in therapy. The following sections will describe in detail the safety information for bortezomib in patients with myeloma.

Infusion reactions and general toxicity

Infusional side effects including fever, chills and mild hypotension occur in <10% of patients. These
symptoms may be exacerbated by dehydration thus prompting the recommendation to give intravenous saline hydration just prior to bortezomib. Pyrexia can be controlled with acetaminophen administration and these symptoms are rarely dose limiting. Tumor lysis syndrome has been described (<2%) and patients with more severe symptoms following initiation of therapy should be evaluated for TLS. Allopurinol should be considered when initiating therapy in patients with advanced disease. Two of the most common symptoms associated with bortezomib are fatigue and asthenia. These symptoms occur in approximately 15%–30% of patients and are dose limiting in a minority of cases.20,27,66

Gastrointestinal toxicity
Gastrointestinal adverse events have been very common with bortezomib including nausea, vomiting, diarrhea, abdominal pain and constipation. The APEX trial reported an incidence of nausea and diarrhea of 57%, constipation 42% and vomiting 35%. In the VISTA trial, nausea and diarrhea was present in 48% and 46% of patients, but severe, grade ≥3, symptoms were seen in only 4% and 8% respectively.66 Most centers give a serotonin 5-HT3 antagonist as anti-nausea prophylaxis and loperamide may be used as needed for diarrhea. There have been rare cases of paralytic ileus, thus anti-diarrheals should be used with caution. Severe peripheral neuropathy is associated with an increased risk for ileus.

Cardiopulmonary toxicity
Most studies have described a low incidence of cardiac or pulmonary toxicity. Patients with new or worsening pulmonary or upper respiratory symptoms must be evaluated for an acute infection. The APEX trial reported pneumonia in 7% of bortezomib treated patients and other studies have described symptoms of cough and dyspnea.20,27,66 Bacterial and viral infections have been the most common causes for these symptoms however, idiopathic pulmonary infiltrates, pneumonitis, pulmonary hypertension, and congestive heart failure with decreased cardiac ejection fraction have all been described (<5% incidence). The randomized pegylated liposomal doxorubicin plus bortezomib trial reported an incidence of cardiomyopathy of 3% in the combination arm versus 2% with bortezomib alone.35 Although infrequent, cardiopulmonary symptoms can occasionally be severe, requiring prompt evaluation and possible discontinuation of bortezomib therapy.

Skin toxicity
Skin reactions have been mild and have ranged between 5% and 24%.20,67 A maculopapular rash is most common but nodular lesions, generalized erythema and edematous plaques have all been described. In general, the pathology has shown vasculitic reactions although hypersensitivity reactions and sweets syndrome have also been reported.68,69 The rash may recur with re-treatment and corticosteroids have been used with success for preventing these recurrences. Rarely, discontinuation of therapy is required either due to severe hypersensitivity reaction or worsening/recurrent rash.

Infectious complications
The large APEX trial demonstrated a risk of herpes zoster reactivation of 13% although the incidence can be decreased (3%) with the use of prophylactic acyclovir.70,71 Viral and bacterial infections occur in 10%–15%, and most commonly cause pneumonia, bronchitis and nasopharyngitis. Other than herpes zoster, the infection risk does not appear increased in MM patients receiving bortezomib versus other anti-myeloma therapies. Despite that moderate to severe lymphopenia is common with bortezomib, other immunocompromised infections are rare.

Marrow toxicity
Bone marrow suppression is a common side effect of bortezomib and one of the main causes of dose reductions and delays in therapy. In the large APEX trial, hematologic toxicity included grade ≥3 neutropenia in 14%, grade ≥3 thrombocytopenia in 30% and Gr ≥ 3 anemia in 10%.66 Similar patterns of marrow suppression have been seen in most bortezomib clinical trials. The neutropenia and thrombocytopenia follow a cyclical pattern with nadir counts occurring around day 11–14 of a typical 21-day cycle (Day 1, 4, 8, 11 dosing). The counts uniformly recover by the start of the next cycle and cumulative marrow suppression has not been problematic. Presumably, the thrombocytopenia is due to inhibition of platelet release rather
than direct megakaryocyte cytotoxicity. The degree of thrombocytopenia following bortezomib therapy can often be correlated to pre-treatment platelet levels and disease burden in the marrow. The use of concomitant marrow-toxic agents like lenalidomide, melphalan or cyclophosphamide frequently causes more neutropenia and thrombocytopenia.\(^{27}\) When making dose adjustments due to cytopenias one must consider the disease status of the patient and the goals of therapy. For example, one may accept a much lower platelet count before dose reduction in those patients with higher disease burden whereas a low platelet count in a patient in remission may deserve a dose reduction. A general schema for dose reduction and delays based on pre-treatment platelet counts and nadir counts has been proposed (Fig. 2).

### Neurologic toxicity

Common neurologic side effects have included peripheral neuropathy, headache, insomnia and dizziness. In general, these symptoms have been mild to moderate and improve with bortezomib withdrawal or dose reduction. There have been rare reports of autonomic neuropathy (AN) causing moderate to severe hypotension and alteration in gastrointestinal motility, and of reversible posterior leukoencephalopathy syndrome (RPLS) which is associated with blindness, confusion, seizures and other neurological symptoms. If RPLS is suspected, imaging of the brain should be performed and bortezomib should be discontinued. AN is a clinical diagnosis and often requires dose reduction and/or discontinuation of therapy.

Bortezomib induced peripheral neuropathy (BIPN) is the most significant neurologic toxicity. Patients should be monitored closely for BIPN as severe neuropathic symptoms can limit future therapeutic options and may significantly affect quality of life. The mechanism of BIPN remains unclear. Some potential causes of BIPN include direct cytotoxicity to schwann cells and primary nerve cells, dysregulation of NF-κB thus decreasing transcription of the trophic nerve growth factor, direct damage to mitochondria and endoplasmic reticulum in dorsal root ganglia neurons, and induction of a pro-inflammatory effect with possible autoimmunity.\(^{72}\) Pathologic evaluation of bortezomib treated animals shows apoptosis in the dorsal root ganglion neurons, axonopathy of small nerve fibers and mild myelin sheath degeneration of

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**Figure 2.** Dose modifications guidelines for hematologic toxicity.\(^{*}\)

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<table>
<thead>
<tr>
<th>A. Dose Modifications for Bortezomib Monotherapy</th>
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<tbody>
<tr>
<td>Hematologic Toxicity During a Cycle</td>
</tr>
<tr>
<td>1. Neutrophils &gt;1 × 10^9/L, Platelets &gt;50 × 10^9/L</td>
</tr>
<tr>
<td>2. Neutrophils ≥0.5 × 10^9/L, but &lt;1 × 10^9/L, or Platelets ≥25 × 10^9/L, but &lt;50 × 10^9/L</td>
</tr>
<tr>
<td>3. Neutrophils &lt;0.5 × 10^9/L, Platelets &gt;25 × 10^9/L</td>
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*Once toxicity has resolved reinitiate bortezomib at a 25% reduced dose (1.3 mg/m^2/dose reduced to 1 mg/m^2/dose; 1 mg/m^2/dose reduced to 0.7 mg/m^2/dose).

<table>
<thead>
<tr>
<th>A. Dose Modifications for Bortezomib, Melphalan and Prednisone Therapy</th>
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<tbody>
<tr>
<td>Hematologic Toxicity During a Cycle</td>
</tr>
<tr>
<td>Prolonged Grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle</td>
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<tr>
<td>If platelet count ≤30 × 10^9/L or ANC ≤0.75 × 10^9/L on a bortezomib dosing day (other than day 1)</td>
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<tr>
<td>If several bortezomib doses in consecutive cycles are withheld due to toxicity</td>
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*Bortezomib prescribing information
large nerve fibers.73,74 A more complete physiologic and pathologic understanding of BIPN is needed so that better therapeutics can be developed.

The clinical characteristics of BIPN are well described. The symptoms are more sensory (tingling, burning, numb) than motor, occur more distal than proximal and involve the feet and toes more than the hands and fingers. Symptoms often begin within the first 1–2 cycles, progress until cycle 5–6 (ie, cumulative bortezomib dose of 30 mg/m²) and thereafter remain stable. Patients who are neuropathy-free by cycle 5–6 tend to avoid neuropathy altogether. Pain is less common but, can be debilitating and difficult to treat. Diminished or absent deep tendon reflexes are common and nerve conduction studies show low amplitude action potentials. The severity of BIPN has been dependent on a number of factors including bortezomib dose and schedule, concomitant medical illness and prior exposure to other neuropathic agents.75 Patients receiving bortezomib therapy need to be followed closely for BIPN so that appropriate dose adjustments can be made (Fig. 3).

Pooled data from 256 patients treated on the Phase II CREST and SUMMIT trials demonstrated that BIPN was one of the most common adverse events occurring in 35% of enrolled patients. The majority of patient experienced grade 1 to 2 events (22%) whereas grade 3 and 4 events were less frequent (13% and 0.4%).20-22 In the APEX trial, the incidence of BIPN was 44% versus only 9% in the dexamethasone treatment arm.66 In the VISTA trial, BIPN was reported more frequently in the VMP vs. MP arm; 44% overall with 14% grade 1, 17% grade 2, 13% grade ≥3.27 Surprisingly, the concomitant use of other agents, including thalidomide and lenalidomide, does not appear to affect BIPN. Trials using a reduced bortezomib dose or schedule (i.e. CREST and mod-CyBorD) have been shown to decrease the incidence and severity of BIPN and may be appropriate in older MM patients or those at high-risk for BIPN.31,76 Once severe BIPN occurs, bortezomib therapy must be discontinued. A recent update from the VISTA trial has shown that 79% of the BIPN events in the VMP arm improved within 1.9 months and that 60% of events resolved completely after a median of 5.7 months.28 Similar data was reported from the APEX trial. Forty-four of 87 patients (51%) experiencing grade ≥2 BIPN, showed improved neuropathy with a median time to improvement of approximately 3.5 months. Forty patients had resolution of BIPN, or a return to baseline, and 4 had improvement without complete resolution.66 Since not all patients with moderate to severe BIPN improve over time, our best strategy is with close monitoring, early detection

<table>
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<tr>
<th>Severity of PN signs/symptoms</th>
<th>Modification of dose and regimen</th>
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<tr>
<td>GRADE *1 (Paresthesia, weakness and/or loss of reflex) without pain or loss of function</td>
<td>• No action</td>
</tr>
<tr>
<td>GRADE 1 with pain or GRADE 2 (interfering with function but not activities of daily living)</td>
<td>• Reduce BORTEZ to 1.0 mg/m² or at a 25% reduced dose</td>
</tr>
</tbody>
</table>
| GRADE 2 with pain or GRADE 3 (interfering activities of daily living) | • Withhold BORTEZ until toxicity resolves  
• Consider alternative therapies (or)  
• May reinitiate at reduced dose (0.7 mg/m² once weekly) |
| GRADE 4 (Sensory neuropathy that is disabling, or motor neuropathy that is life-threatening or leads to paralysis) | • Discontinue BORTEZ |

BORTEZ = bortezomib

Figure 3. Dose modification for peripheral neuropathy (PN).
of BIPN and early intervention with appropriate dose adjustments.

Conclusions
The proteasome is certainly a potent target for anticancer therapy. Bortezomib, the first-in-class proteasome inhibitor, has demonstrated impressive anti-tumor responses in both preclinical models and clinical trials. Bortezomib is now one of the most common agents used as initial and salvage therapy for patients with myeloma. Overall response rates of >90% can now be routinely achieved in patients with newly diagnosed myeloma and survival has been extended. Further clinical studies are underway attempting to identify the optimal combinations of agents and duration of treatment. Additional studies are combining bortezomib with melphalan-based preparative therapy for autologous transplantation, and testing the role of bortezomib as maintenance therapy. A new generation of targeted therapies including akt inhibitors, histone deacetylase inhibitors, heat shock protein inhibitors, monoclonal antibodies and others are currently being evaluated. Some inhibitors including oral agents are currently being extended. Further clinical studies are underway attempting to identify the optimal combinations of agents and duration of treatment. Additional studies are combining bortezomib with melphalan-based preparative therapy for autologous transplantation, and testing the role of bortezomib as maintenance therapy. A new generation of targeted therapies including akt inhibitors, histone deacetylase inhibitors, heat shock protein inhibitors, monoclonal antibodies and others are currently being evaluated. Some inhibitors including oral agents are currently being extended. Further clinical studies are underway attempting to identify the optimal combinations of agents and duration of treatment. Additional studies are combining bortezomib with melphalan-based preparative therapy for autologous transplantation, and testing the role of bortezomib as maintenance therapy. A new generation of targeted therapies including akt inhibitors, histone deacetylase inhibitors, heat shock protein inhibitors, monoclonal antibodies and others are currently being evaluated. Some inhibitors including oral agents are currently being extended. Further clinical studies are underway attempting to identify the optimal combinations of agents and duration of treatment. Additional studies are combining bortezomib with melphalan-based preparative therapy for autologous transplantation, and testing the role of bortezomib as maintenance therapy. A new generation of targeted therapies including akt inhibitors, histone deacetylase inhibitors, heat shock protein inhibitors, monoclonal antibodies and others are currently being evaluated. Some inhibitors including oral agents are currently being extended. Further clinical studies are underway attempting to identify the optimal combinations of agents and duration of treatment. Additional studies are combining bortezomib with melphalan-based preparative therapy for autologous transplantation, and testing the role of bortezomib as maintenance therapy.

Disclosures
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