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Clinical challenges associated with bortezomib therapy in multiple myeloma and Waldenströms Macroglobulinemia

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Abstract

Rapid development of the small molecule proteasome inhibitor bortezomib has yielded important clinical benefit for patients with multiple myeloma. Early phase clinical trials suggest the agent has similar efficacy in Waldenströms Macroglobulinemia. Optimization of bortezomib-based therapy, though, requires an understanding of the various challenges associated with use of the drug. This review highlights the rationale for bortezomib therapy in patients with multiple myeloma and Waldenströms Macroglobulinemia, mechanisms of bortezomib resistance, important therapy-related side effects, and new directions for the use of proteasome inhibitors in these disorders.

Keywords

Drug resistance; myeloma; pharmacotherapeutics; clinical result

Introduction

The dipeptidyl boronic acid small molecule bortezomib has activity against a variety of malignancies that derives from its ability to potently inhibit the proteasome, a 26S nuclear/cytosolic complex that in concert with the ubiquitin pathway regulates protein degradation and thus influences various important cellular processes such as cell cycle progression. Selective, reversible inhibition of the proteasome by bortezomib leads to accumulation of undegraded proteins and interferes with various processes associated with tumor growth, including angiogenesis, migration, proliferation and anti-apoptotic signaling [1]. The impact of bortezomib-based therapy in the treatment of cancer has been most striking in multiple myeloma (MM), where rapid translation from preclinical investigation to phase I/II and subsequently to international randomized trials [2,3] led to FDA approval of bortezomib first in relapsed/refractory MM and later in newly diagnosed, previous untreated MM. It is likely bortezomib will also assume an increasingly important role in the management of other plasma cell disorders based on its successful use in light chain deposition disease [4,5], Castleman's disease [6], AL amyloidosis [7] and Waldenströms Macroglobulinemia (WM) [8–10].

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As the clinical application of bortezomib in the management of plasma cell disorders has broadened, important challenges associated with its use have been identified and evaluated. This review focuses on several of these key issues as they relate specifically to MM and WM, including mechanisms of bortezomib resistance, peripheral neuropathy and thrombocytopenia as consequences of bortezomib therapy, and bortezomib-based induction prior to stem cell transplantation. Consideration is then given to the role of bortezomib maintenance and the development of novel, second-generation proteasome inhibitors, both areas of ongoing clinical inquiry that will likely build on advances already made in the field.

Clinical rationale for use of bortezomib in multiple myeloma and Waldenströms Macroglobulinemia

Multiple myeloma

The clinical activity of bortezomib in MM was confirmed by a series of trials culminating in a phase III study involving individuals with relapsed and/or refractory MM who received either bortezomib or high-dose dexamethasone [2]. Bortezomib monotherapy was superior to high dose dexamethasone in terms of partial response (PR) rate or better (38% vs. 18%), complete response (CR) rate (6% vs. 1%), median time to progression (TTP) (6.22 months vs. 3.49 months) and one-year overall survival (OS) rate (80% vs. 66%). With extended follow-up, a significant benefit in response rate and OS persisted despite a high rate of crossover from the dexamethasone to bortezomib arms of the study [11]. More recently, the benefit of bortezomib therapy to individuals ineligible for transplant was demonstrated by a phase III trial in which patients with newly diagnosed disease received bortezomib plus melphalan-prednisone (VMP) or melphalan-prednisone (MP) [3]. In this study, VMP was superior to MP in terms of PR rate or better (71% vs. 35%), CR rate (30% vs. 4%), median TTP (24 months vs. 16.6 months) and overall survival. These studies have underscored the activity of bortezomib as a single agent, the synergy of bortezomib with other drug classes frequently employed in MM (e.g. alkylators, corticosteroids), and the overall efficacy of bortezomib-based therapy in either newly diagnosed or relapsed/refractory MM.

Waldenströms Macroglobulinemia

Therapeutic options for WM include alkylating agents, nucleoside analogues and rituximab as a single agent or in combination with other compounds. However, these approaches result in low CR rates and short treatment-free survival intervals in most instances. Furthermore, no specific agent or regimen has proven to be superior to others and, moreover, no treatment has been specifically approved for WM. As such, new approaches to the treatment of WM are needed. In an effort to achieve this, investigators have pursued targeted therapies such as bortezomib to exploit the biological characteristics of WM.

Based on its activity in MM, single agent bortezomib was evaluated using the standard FDA-approved schedule in several phase II trials involving patients with WM [8–10]. In the NCI-Canada study, Chen *et al.* observed a 78% overall response (OR) rate, with a major response occurring in 44% of patients. These results were confirmed in a multi-center study conducted by the Waldenström Macro-globulinemia Clinical Trials Group (WMCTG) involving individuals with relapsed WM [10]. Responses occurred at a median of 1.4 months and the median TTP for all responding patients in this study was 7.9 months. Interestingly, a discordance between serum IgM levels and bone marrow responses has been observed in a subset of WM patients treated with bortezomib, suggesting that bortezomib in these individuals may inhibit IgM secretion independent of direct tumor cell killing [10].

Clinical challenges associated with bortezomib therapy

Bortezomib resistance

Insight regarding bortezomib resistance has come primarily from the myeloma literature. It is clear that although bortezomib has potent anti-MM activity, not all MM patients respond to bortezomib and most of those who respond ultimately relapse. It is also clear that as the use of bortezomib in MM and other malignancies expands, an understanding of mechanisms that drive bortezomib-resistance will augment efforts to improve the outcomes of individuals with MM.

Multiple clinical trials have documented the ability of bortezomib to overcome the poor prognosis conferred by diverse clinical, biochemical and cytogenetic factors associated with poor outcome in the context of conventional anti-MM therapies [12–15]. This suggests that sensitivity (*versus* resistance) to bortezomib is determined by different molecular mechanisms than those that determine responsiveness to conventional MM treatment, and has led to extensive research efforts to identify these. To date, however, no marker(s) has been identified and validated in a manner that would allow clinical use and distinguish patients likely to respond to bortezomib treatment from those who would not. For example, gene expression profiling studies of MM cells from patients participating in two phase II trials of bortezomib in MM, specifically the SUMMIT and APEX clinical trials, identified groups of genes in bortezomib-treated patients that correlate with response and survival [16]. While these molecular classifiers provided intriguing biological insights on molecular features of bortezomib-responsive *versus* resistant patients, differences between the patient populations in the SUMMIT and APEX trials suggested considerable heterogeneity and precluded general application of these markers.

Similarly, data from acute lymphoblastic leukemia (ALL) cell line models have suggested that mutations of proteasome subunits (e.g. the Ala49Thr mutation in the highly conserved bortezomib-binding pocket of proteasome $\beta 5$ subunit (PSMB5) protein) [17] may be associated with bortezomib resistance. However, studies of this particular mutation have not confirmed that it plays a role in MM [18,19]. Furthermore, at the level of preclinical laboratory investigation, there has been limited, if any, experience with robust models involving bortezomib-resistant MM cells, which has in turn hampered efforts to identify clinically relevant molecular markers of bortezomib-resistance.

On the other hand, an extensive body of preclinical research in recent years has provided valuable insight into molecular pathways that can modulate the activity of proteasome inhibitors. Importantly, these studies have also provided the basis for bortezomib-based combination therapies that enhance the anti-MM effect of bortezomib. Several of these combinations have now been evaluated in clinical trials and have led to an increased frequency, depth and durability of response to bortezomib-based therapy. Of note, some of these bortezomib-based combination regimens have now been approved by the FDA for the treatment of MM.

Indeed, one of the most intriguing features of bortezomib is its potent chemo-sensitizing effect. Preclinical studies by our center [20] as well as others [21] showed that bortezomib is not only active against MM cells resistant to conventional chemotherapy but can also sensitize chemo-resistant MM cells to the same agents to which they have developed resistance. Of particular interest is the fact that in preclinical studies bortezomib exhibited synergy with DNA-damaging agents, even against MM cells resistant to both bortezomib and conventional chemotherapy.

Several features of bortezomib can account for its potential chemosensitizing effect. First, bortezomib inhibits NF- κ B activity, which has been shown in several models, including MM, to be involved in resistance to conventional chemotherapy. Second, gene expression and proteomic studies have confirmed that bortezomib suppresses the expression of diverse molecules involved in the repair of DNA damage caused by standard cytotoxics, which suggests that bortezomib impairs the ability of MM cells to repair damage caused by conventional chemotherapy [21]. In addition, bortezomib suppresses the expression of several molecules with known anti-apoptotic functions, including caspase inhibitors [22].

These preclinical observations have provided the framework for clinical trials combining bortezomib with conventional chemotherapy. Following informative phase I/II studies [23], the combination of bortezomib with liposomal doxorubicin was tested in a randomized phase III clinical trial where the comparator arm received bortezomib alone. This trial confirmed that the combination of liposomal doxorubicin with bortezomib had longer progression free survival (PFS) and OS than the bortezomib only arm [24]. This superior outcome was consistent across subgroups, irrespective of the number of prior lines of therapy or previous anthracycline exposure. The results of that trial provided the basis for the recent FDA approval of this combination for treatment of bortezomib-naïve MM patients.

Several other studies have also confirmed the clinical relevance of the anthracycline-sensitizing properties of bortezomib, as in the so-called PAD regimen consisting of bortezomib, doxorubicin and dexamethasone [25]. The chemo-sensitizing impact of bortezomib is also evident in the phase III trial comparing VMP to MP referenced previously, wherein the TTP and OS advantage of VMP over MP was noted even in patients with adverse prognostic features such as advanced international staging system (ISS) stage or chromosomal abnormalities such including deletion of chromosome 13 [3]. These randomized clinical trials have thus provided validation for a preclinically-identified concept of bortezomib-mediated chemosensitization. Importantly, these studies also showed that the chemosensitizing property of bortezomib applies both to alkylators and anthracyclines.

Another important therapeutic strategy involves coupling of bortezomib with immunomodulatory drugs (IMiDs), including lenalidomide or thalidomide. The premise for the combination of bortezomib with lenalidomide (Rev-Vel) or with lenalidomide-dexamethasone (RVD) was provided by preclinical studies showing enhanced anti-MM activity of bortezomib when combined with low doses of immunomodulatory thalidomide derivatives, such as lenalidomide or pomalidomide. These preclinical studies were based on the hypothesis that bortezomib-induced apoptosis of MM cells is mediated by a dual caspase activation cascade involving caspase 8 and caspase 9, while the direct anti-MM activity of IMiDs such as lenalidomide or pomalidomide is mediated predominantly by activation of caspase 8. Therefore, it was believed that combining modest to low doses of these two drug classes could allow dual activation of caspase 8 and 9 to occur [26], while exposing the patient fewer of the side effects associated with maximal doses of either drug given alone.

Several clinical trials have demonstrated the feasibility of this particular combination. A phase I study of the Rev-Vel combination in heavily pre-treated patients established that lenalidomide at 15 mg daily and bortezomib at 1.0 mg/m² on standard dosing interval provided optimal balance between efficacy and adverse events [27]. In 36 evaluable patients, the ORR was 58% after a median of six cycles with a very favorable side effect profile and remarkable durability of response. The addition of dexamethasone in nine patients progressing on the Rev-Vel couplet was shown to be both feasible and active, with stabilization of disease in 83% of patients and response (MR or better) in 28%. A phase II

study of RVD in relapsed/refractory MM [28] and a phase I/II study in the upfront setting [29] have also shown promising results. Specifically, RVD produced a 73% response rate (CR/nCR +PR +MR) in relapsed/refractory MM, with 55% CR/nCR +PR and, importantly, a favorable safety profile. Only one patient experienced grade 3 peripheral neuropathy, two patients deep venous thrombosis, while dexamethasone was dose-reduced in 14 patients leading to protocol amendment stipulating a lower dose of dexamethasone (20 mg) [28]. In the setting of newly diagnosed disease, RVD produced an OR rate of 100%, with 26% CR, 18% nCR (CR/nCR of 44%), and 55% PR, with 30% VGPR and VGPR or better at 74% [29].

Peripheral neuropathy

As reflected by clinical trials involving bortezomib in both MM and WM, peripheral neuropathy (PN) frequently occurs as a consequence of the diseases themselves and of bortezomib-based therapy. Important insight on this issue emerged from the phase II SUMMIT and CREST trials, in which study participants completed the Functional Assessment of Cancer Therapy Scale/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) questionnaire and were evaluated by a neurologist for neuropathic symptoms at specific points throughout the study period [30,31]. Motor and sensory nerve conduction studies were also performed in a subset of patients enrolled in these trials.

Pooled analysis of these trials showed that baseline PN was present in 81% of patients based on the FACT/GOG-Ntx questionnaire and 83% based on neurologist exams [32]. Bortezomib-induced PN occurred in 35% of patients, including 21% of patients who received the 1.0 mg/m² dose and 37% of those who received the 1.3 mg/m² dose. The prevalence of treatment-emergent PN among study participants reached a plateau at a cumulative dose level of 30 mg/m² (~cycle 5). While the prevalence of bortezomib-related PN was similar among patients with and without baseline PN, individuals with PN tended to experience more severe treatment-related PN. Grade 3/4 symptoms requiring treatment discontinuation occurred in 39% of individuals who experienced treatment-emergent PN. Neuropathic symptoms improved or resolved to baseline levels in approximately 70% of patients who experienced treatment-emergent PN in these studies.

Similar rates of treatment-emergent PN have been observed in studies of patients with WM who receive bortezomib. In the multicenter phase II trial conducted by the WMCTG, PN was the most common grade 3/4 treatment-related toxicity, occurring as a grade 3 event (there were no grade 4 events) in 22.2% of study participants [10]. Of six patients with ≥grade 3 PN, five experienced improvement or resolution of symptoms after a median of six months. Meanwhile, in the NCI-Canada study, baseline PN was present in nine (33%) patients and new or worsening PN occurred in 20 (74%) during therapy [9]. Grade 3 symptoms developed in five of the 20 patients who experienced treatment-related PN in this study. Symptoms improved or resolved in the majority of patients (75%) who developed bortezomib-induced PN, including all patients with grade 3 symptoms.

Symptoms associated with bortezomib-induced PN generally include neuropathic pain involving the finger tips and toes, sensory and proprioceptive loss, weakness of distal musculature in the upper and lower extremities, and suppression of deep tendon reflexes [33–35]. Patients are assessed for neuropathic symptoms prior to treatment initiation with a bortezomib-based regimen and monitored for development or progression of such symptoms as therapy progresses. The degree of PN can be formally assessed using one of several grading systems, among them the Eastern Cooperative Oncology Group criteria [36], the World Health Organization criteria [37], National Cancer Institute-Common Toxicity Criteria (NCI-CTC) [38], and the FACT/GOG-Ntx [39]. While unnecessary under most circumstances, electrophysiological testing through nerve conduction studies (NCS) and

electromyography (EMG) can be considered in instances where the diagnosis of PN before or during bortezomib therapy is equivocal and requires clarification.

A variety of measures have been adopted by clinicians to prevent bortezomib-induced PN on the one hand and manage the condition when it occurs. Nutritional supplements such as α -lipoic acid [41], glutamine [41,42], and L-carnitine [43] exhibit neuroprotective properties that provide rationale for their use in patients with MM who receive neuropathic drugs such as bortezomib, although prospective studies are needed to validate their efficacy in this setting. Vitamin B6 (pyridoxine) supplementation may also benefit patients receiving potentially neurotoxic therapy [44]. However, a high serum level of vitamin B6 is itself neurotoxic and so must be avoided. A proactive program of bortezomib dose reductions such as that adhered to in the APEX trial is recommended for individuals who receive bortezomib-based therapy (Table I) [2]. Despite preemptive strategies aimed at limiting the frequency and severity of bortezomib-induced PN, many patients with this condition ultimately require pharmacologic interventions for symptom control. Effective options in this respect include the anticonvulsants gabapentin and pregabalin; tricyclic antidepressants amitriptyline and desipramine; serotonin-norepinephrine reuptake inhibitors such as duloxetine; and opioids such as oxycodone, morphine sulfate and hydrocodone [45]. These are important measures to consider given the fact that many patients who receive bortezomib as part of induction therapy will receive it at a subsequent point in their course as part of salvage therapy.

Thrombocytopenia

Thrombocytopenia frequently occurs in association with bortezomib therapy for plasma cell dyscrasias such as MM and WM. The mechanism through which bortezomib exerts its effect on the platelet count is unknown but does not appear related to a direct cytotoxic effect on megakaryocytes or alteration in thrombopoietin levels [46]. Thrombocytopenia was the most common grade 3 treatment-related toxicity in the SUMMIT (28%) and CREST (24%) trials, as well as in the phase II NCI-Canada trial for patients with WM [9,31]. In the SUMMIT and CREST studies, the platelet count during a standard 21-day cycle typically followed a biphasic pattern, with a decline of, on average, 60% during the two-week period of bortezomib administration followed by recovery during the rest period [46]. Grade 3 or 4 thrombocytopenia occurred in 30% of participants in these studies overall, a rate similar to that seen in the phase III APEX trial (30% grade 3/4 thrombocytopenia) [2]. However, it was uncommon (13%) in patients with a baseline platelet count $>200 \times 10^9/L$ and there was an inverse correlation between baseline platelet count and the incidence of grade 3/4 thrombocytopenia. Bleeding episodes associated with bortezomib-induced thrombocytopenia were rare in these studies but did occur in two patients, one in an individual with grade 3 thrombocytopenia who developed gastrointestinal bleeding and the other in a patient who experienced epistaxis along with gingival and hemorrhoidal bleeding in the setting of grade 4 thrombocytopenia.

Patients are monitored during bortezomib therapy for a predictable decline in platelet count and receive platelet transfusions according to standard parameters. For reasons outlined above, this is particularly important in patients with significant thrombocytopenia at the time of treatment initiation. Furthermore, co-administration of bortezomib with other compounds that cause myelosuppression –including alkylating agents, anthracyclines and lenalidomide – necessitates additional caution with respect to thrombocytopenia. Interestingly, transfusion requirements in patients with relapsed and refractory myeloma who received treatment in the SUMMIT and CREST trials actually decreased as therapy progressed, with the greatest need for platelet transfusions occurring during cycles 1 and 2, and decidedly less need during later cycles [46].

Bortezomib induction in preparation for autologous stem cell transplantation in multiple myeloma

High dose therapy followed by autologous stem cell transplantation (ASCT) is a standard of care for younger MM patients considered eligible for the procedure. Historically, conventional therapy followed by HDT-ASCT has produced higher complete response (CR) rates than conventional therapy alone [47–49]. In turn, the achievement of a CR in response to therapy has translated into improved patient outcomes in patients receiving either conventional therapy or HDT-ASCT [50–53]. A meta-analysis of nine randomized controlled studies comparing conventional therapy to HDT-ASCT demonstrated superior PFS, though not OS, in patients treated with HDT-ASCT [54].

While pre-transplant induction therapy has historically consisted of dexamethasone alone or vincristine, adriamycin, plus dexamethasone (VAD), novel agents such as thalidomide, lenalidomide and bortezomib are now utilized in this setting. Clinical trials incorporating bortezomib-based induction prior to HDT-ASCT have yielded promising results. In the IFM 2005/01 trial, for example, 482 transplant-eligible patients ≤ 65 years of age stratified according to cytogenetic abnormalities and β_2 microglobulin levels were randomized to VAD or bortezomib plus dexamethasone (VD) induction, followed by a second randomization to dexamethasone/etoposide/cisplatin (DCEP) consolidation or no consolidation, followed by high dose melphalan and ASCT [55]. VD induction was superior to VAD across all response criteria and in all prognostic subgroups, with higher rates of PR or better, very good partial response (VGPR) or better, near CR (nCr) [56] plus CR, and CR. Importantly, the benefit of VD pre-transplant translated into improved post-transplant outcomes, with superior response rates and a significant two-year survival benefit observed in the VD arm. The CR +nCR rate in the VD group was 39%, and the VGPR or better rate, 68%. DCEP consolidation did not produce clinical benefit in either treatment group.

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 or bortezomib plus TD (VTD) [57]. After three induction cycles, individuals in both groups underwent stem cell mobilization and collection followed by HDT-ASCT. Those in the VTD arm then received two cycles of VTD consolidation whereas those in the TD group received two cycles of TD consolidation. VTD led to superior rates of PR or better, VGPR or better, and CR +nCR rates than TD, as well as a significant two-year PFS benefit (90% vs. 80%).

Bortezomib has also been effectively incorporated within the Total Therapy 3 regimen, a program in which patients receive induction and consolidation chemotherapy with two cycles of VTD-PACE (bortezomib, thalidomide, dexamethasone with 4-day infusions of cisplatin, doxorubicin, cyclophosphamide and etoposide) along with maintenance VTD (year one post consolidation) and TD [58]. At two years, the nCR rate was 83%, EFS 84% and OS 86%.

High response rates associated with bortezomib induction therapy in trials involving transplant-eligible patients with newly diagnosed MM, the apparent synergy between bortezomib induction and high dose therapy, and the efficacy of the bortezomib in high risk patients who undergo HDT-ASCT provide sound evidence to support its use in this setting. Updated results of ongoing clinical trials utilizing bortezomib induction are anticipated with interest, and at present bortezomib-based induction therapy prior to HDT-ASCT is considered a standard of care.

Future directions

Maintenance bortezomib following autologous SCT

The practice of maintenance thalidomide therapy in the aftermath of autologous SCT in MM is supported by the results of several clinical trials [59–61]. This approach is based on the premise that MM is an incurable condition in which a population of tumor cells persists even after intensive therapy, and that further suppression of the malignant clone during the maintenance interval can delay disease progression and extend survival. Whether bortezomib can be utilized safely and effectively is uncertain. An ongoing phase III trial led by the Hemato-Oncologie voor Volwassenen Nederland/German Multicenter Myeloma Group (HOVEN/GMMG) study groups will provide insight on this issue [62]. The trial involves transplant-eligible individuals with newly diagnosed MM who are randomized to receive either vincristine-doxorubicin-dexamethasone (VAD) or bortezomib-doxorubicin-dexamethasone (PAD) induction followed by high-dose melphalan and autologous SCT. Patients in the VAD induction group then receive thalidomide 50 mg/day maintenance for two years, while those in the PAD induction group receive bortezomib 1.3 mg/m² every two weeks for two years. Based on a planned interim analysis presented at the 2008 American Society of Hematology meeting, PAD induction was superior to VAD with respect to the rate of PR or better (5% vs. 1%), VGPR or better (42% vs. 15%) and CR/nCR (5% vs. 1%). Importantly, PAD *versus* VAD induction led to an improvement in the post-transplant rate of PR or better (93 vs. 80%), VGPR or better (80 vs. 50%), and CR/nCR (23% vs. 9%).

Novel proteasome inhibitors in multiple myeloma and Waldenströms Macroglobulinemia

Two novel proteasome inhibitors are currently undergoing evaluation in MM and WM, NPI-0052 and PR-171 (carfilzomib). In MM, NPI-0052 has generated significant interest based on its ability *in vitro* to inhibit growth of MM cells resistant to not only conventional agents but also to bortezomib [63]. The compound is now being evaluated in a phase I dose escalation study involving patients with relapsed/refractory MM, including individuals who have previously received bortezomib and/or lenalidomide [64]. PR-171, meanwhile, has demonstrated significant cytotoxicity against MM cells *in vitro* [65]. Like NPI-0052, it is being evaluated in clinical trials, with an ongoing phase II study involving patients with relapsed myeloma [66] and another involving individuals with relapsed and refractory disease [67].

In preclinical studies of NPI-0052 in WM, the compound inhibited proliferation and induced apoptosis in WM cell lines and patient samples [68]. Moreover, the combination of NPI-0052 and bortezomib induces synergistic cytotoxicity in WM cells, leading to inhibition of nuclear translocation of p65NF- κ B and synergistic induction of apoptosis. The combination blocks the canonical and non-canonical NF κ B pathways and acts synergistically through their differential effect on Akt activity and on chymotrypsin-like, caspase-like and trypsin-like activities of the proteasome. Moreover, NPI-0052 and bortezomib inhibited migration and adhesion *in vitro* and homing of WM cells *in vivo*. These studies have not only underscored the potential clinical efficacy of NPI-0052 in WM, but have also furthered the understanding of the proteasome's role in WM.

Two phase I dose-escalation studies will be initiated in order to determine the safety, tolerability and clinical response associated with PR-171 in WM and other hematologic malignancies. Patients with multiple myeloma, non-Hodgkin lymphoma, Hodgkin disease, or Waldenström Macroglobulinemia who have received two or more prior treatments are eligible for these trials. Two different dose-intensive schedules will be employed in these phase I studies. PR-171 was well-tolerated, and several subjects have achieved long-lasting SD, reduction in paraprotein levels, or symptomatic improvement.

Summary

The development of bortezomib through laboratory-based research and translation of preclinical findings into clinical application in MM and WM has produced important clinical benefit for patients with these diseases. Moreover, the incorporation of bortezomib within regimens that target multiple pathways in these diseases provides reason to believe that improvements in patient outcomes can be advanced still further. It is important, however, to anticipate clinical issues that may arise with bortezomib use in MM and WM so as to optimize both response to therapy and quality of life of individuals with these diseases.

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Table I

Dose modification guideline for bortezomib-related neuropathic pain and/or peripheral sensory or motor neuropathy.

Severity of peripheral neuropathy signs and symptoms	Modification of bortezomib dose and regimen
Grade 1 (paresthesias, weakness and/or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce to 1.0 mg/m ²
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold treatment until toxicity resolves, then reinitiate at a dose of 0.7 mg/m ² once weekly
Grade 4 (sensory neuropathy that is disabling or motor neuropathy that is life-threatening or leads to paralysis)	Discontinue

Grading for this currently recommended dose modification guideline is based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0. In APEX, the dose modification guideline used was the same, but based on NCI CTC version 2.0 grading; in addition, patients experiencing grade 3 peripheral neuropathy with pain were to discontinue bortezomib.