Clinical Medicine Reviews in Oncology

Libertas Academica
FREEDOM TO RESEARCH

CMR
Clinical Medicine Reviews

REVIEW

Bortezomib: Safety and Efficacy in the Treatment of Multiple Myeloma

Tom Martin and Jeffrey Wolf

Adult Myeloma Program and Stem Cell Transplantation, University of California, San Francisco, CA 94143, USA.
Corresponding author email: tmartin@medicine.ucsf.edu

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 proteinase 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

Clinical Medicine Reviews in Oncology 2010:2 293–304

doi: 10.4137/CMRO.S1631

This article is available from http://www.la-press.com.

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).[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.[2,3] 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.[4,5]

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.[6,7] 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.[8] 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.[3] PI also effects the cycle cell through stabilization of the tumor suppressor protein p53 and the checkpoint proteins p21 and p27.[9] 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.[10,11]

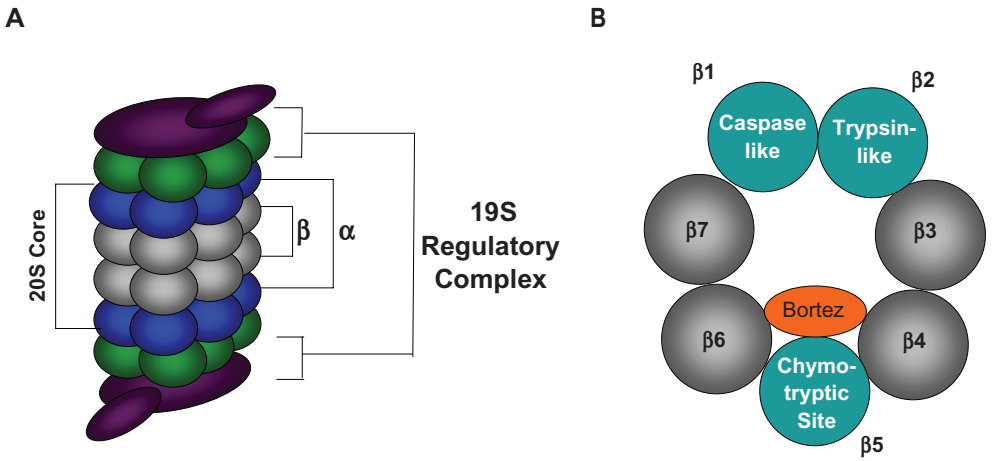

Figure 1. The human proteasome: **A**) Cylindrical view: 26S complex **B**) Axial view: inner beta rings with bortezomib (Bortez) blocking the chymotryptic enzymatic site.

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/m^2 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/m^2 versus 1.3 mg/m^2 at standard intervals. The results showed improved overall response rate (38% versus 30%; CR+PR) in patients receiving bortezomib at 1.3 mg/m^2, but fewer adverse events in the 1 mg/m^2 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.[26] 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; $P < 0.001$).[27] A more recent update has confirmed an overall survival advantage in those receiving VMP versus MP (35% reduced risk of death; HR, 0.653; $P < 0.001$).[28] 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.[29]

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 cytoxan 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/m^2 given intravenously on days 1, 4, 8 and 11, was combined with cyclophosphamide 300 mg/m^2 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.[30] Toxicity was significant, promoting Reeder and colleagues to modified the regimen (Mod-CyBorD) by changing the bortezomib to 1.5 mg/m^2 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.[31] 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.[32] Early Phase I/II trials were promising,[33,34] 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/m^2 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.[35,36] 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.[37–39] These combinations have been used with success in both transplant eligible and in-eligible patients.[40] One interesting finding from Olowski'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/m^2 × 4, Thalidomide 100–200 mg daily, dexamethasone 20 mg/m^2 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/m^2 (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).[60] 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%).[44] 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/m^2 on Day −6, −3, +1, +4) to high-dose melphalan (200 mg/m^2 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%).[61] 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 then if bortezomib is given before melphalan.[62] 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%; $P = 0.08$).[63] 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.[64] 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.[65] 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 in approximately 10%.[23,27,66] 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/recurring 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 antimyeloma 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

A. Dose Modifications for Bortezomib Monotherapy

Hematologic Toxicity During a Cycle	Dose modification or delay
1. Neutrophils >1 × 10^9L, Platelets >50 × 10^9L	No dose reduction
2. Neutrophils ≥0.5 × 10^9L, but <1 × 10^9L, or Platelets ≥25 × 10^9L, but <50 × 10^9L	Consider holding dose depending on clinical scenario
3. Neutrophils <0.5 × 10^9L, Platelets >25 × 10^9L	Bortezomib therapy should be withheld*

***Once toxicity has resolved reinitiate bortezomibat a 25% reduced dose (1.3 mg/m2/dose reduced to 1 mg/m2/dose; 1 mg/m2/dose reduced to 0.7 mg/m2/dose).**

A. Dose Modifications for Bortezomib, Melphalan and Prednisone Therapy

Hematologic Toxicity During a Cycle	Dose modification or delay
Prolonged Grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle	Consider reduction of the melphalan dose by 25% in the next cycle
If platelet count ≤30 × 10^9/L or ANC ≤0.75 × 10^9/L on a bortezomibdosing day (other than day 1)	Bortezomib dose should be withheld
If several bortezomib doses in consecutive cycles are withheld due to toxicity	Reduced bortezomib dosing by 1 dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2)

^Bortezomib prescribing information

Figure 2. Dose modifications guidelines for hematologic toxicity.^

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/m^2) 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

Severity of PN signs/symptoms	Modification of dose and regimen
GRADE *1 (Paresthesia, weakness and/or loss of reflex) without pain or loss of function	• No action
GRADE 1 with pain or GRADE 2 (interfering with function but not activities of daily living)	• Reduce BORTEZ to 1.0 mg/m^2 or at a 25% reduced dose
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/m^2 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 anti-cancer 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 now undergoing preclinical an early clinical studies in combination with bortezomib. Although bortezomib has been well tolerated, common toxicities including gastrointestinal symptoms and peripheral neuropathy need to be monitored closely. Early intervention for those experiencing toxicity and further strategies for improving safety while maintaining efficacy are warranted. Second generation proteasome inhibitors including oral agents are currently under investigation.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

References

1. Wakata A, Lee HM, Rommel P, Toutchkine A, Schmidt M, Lawrence DS. Simultaneous fluorescent monitoring of proteasomal subunit catalysis. *Journal of the American Chemical Society*. 2010 Feb 10;132(5):1578–82.
2. Orlowski RZ, Eswara JR, Lafond-Walker A, Grever MR, Orlowski M, Dang CV. Tumor growth inhibition induced in a murine model of human burkitt's lymphoma by a proteasome inhibitor. *Cancer Research*. 1998 Oct 1; 58(19):4342–8.
3. Ma MH, Yang HH, Parker K, et al. The proteasome inhibitor PS-341 markedly enhances sensitivity of multiple myeloma tumor cells to chemotherapeutic agents. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*. 2003 Mar;9(3):1136–44.
4. Cilloni D, Martinelli G, Messa F, Baccarani M, Saglio G. Nuclear factor κB as a target for new drug development in myeloid malignancies. *Haematologica*. 2007 Sep;92(9):1224–9.
5. Mitsiades N, Mitsiades CS, Poulaki V, et al. Molecular sequelae of proteasome inhibition in human multiple myeloma cells. *Proceedings of the National Academy of Sciences of the United States of America*. 2002 Oct 29;99(22):14374–9.
6. Hideshima T, Chauhan D, Richardson P, et al. NF-κB as a therapeutic target in multiple myeloma. *The Journal of Biological Chemistry*. 2002 May 10;277(19):16639–47.
7. Meister S, Schubert U, Neubert K, et al. Extensive immunoglobulin production sensitizes myeloma cells for proteasome inhibition. *Cancer Research*. 2007 Feb 15;67(4):1783–92.
8. Hideshima T, Mitsiades C, Akiyama M, et al. Molecular mechanisms mediating antimyeloma activity of proteasome inhibitor PS-341. *Blood*. 2003 Feb 15;101(4):1530–4.
9. Kisselev AF, Goldberg AL. Proteasome inhibitors: From research tools to drug candidates. *Chemistry and Biology*. 2001 Aug;8(8):739–58.
10. Mitsiades N, Mitsiades CS, Richardson PG, et al. Molecular sequelae of histone deacetylase inhibition in human malignant B cells. *Blood*. 2003 May 15;101(10):4055–62.
11. Adams J. The proteasome: structure, function and role in the cell. *Cancer Treat Rev*. 2003 May;29, Suppl 1:3–9.
12. Obeng EA, Carlson LM, Gutman DM, Harrington WJ Jr, Lee KP, Boise LH. Proteasome inhibitors induce a terminal unfolded protein response in multiple myeloma cells. *Blood*. 2006 Jun 15;107(12):4907–16.
13. Dong H, Chen L, Chen X, et al. Dysregulation of unfolded protein response partially underlies proapoptotic activity of bortezomib in multiple myeloma cells. *Leukemia and Lymphoma*. 2009 Jun;50(6):974–84.
14. Lee AH, Iwakoshi NN, Anderson KC, Glimcher LH. Proteasome inhibitors disrupt the unfolded protein response in myeloma cells. *Proceedings of the National Academy of Sciences of the United States of America*. 2003 Aug 19;100(17):9946–51.
15. Altun M, Galardy PJ, Shringarpure R, et al. Effects of PS-341 on the activity and composition of proteasomes in multiple myeloma cells. *Cancer Research*. 2005 Sep 1;65(17):7896–901.
16. LeBlanc R, Catley LP, Hideshima T, et al. Proteasome inhibitor PS-341 inhibits human myeloma cell growth in vivo and prolongs survival in a murine model. *Cancer Research*. 2002 Sep 1;62(17):4996–5000.
17. Orlowski RZ, Stinchcombe TE, Mitchell BS, et al. Phase I trial of the proteasome inhibitor PS-341 in patients with refractory hematologic malignancies. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2002 Nov 15;20(22):4420–7.
18. Dy GK, Thomas JP, Wilding G, et al. A phase I and pharmacologic trial of two schedules of the proteasome inhibitor, PS-341 (bortezomib, velcade), in patients with advanced cancer. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*. 2005 May 1;11(9):3410–6.
19. Aghajanian C, Soignet S, Dizon DS, et al. A phase I trial of the novel proteasome inhibitor PS341 in advanced solid tumor malignancies. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*. 2002 Aug;8(8):2505–11.
20. Richardson PG, Barlogie B, Berenson J, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. *The New England Journal of Medicine*. 2003 Jun 26;348(26):2609–17.
21. Richardson PG, Barlogie B, Berenson J, et al. Extended follow-up of a phase II trial in relapsed, refractory multiple myeloma: Final time-to-event results from the SUMMIT trial. *Cancer*. 2006 Mar 15;106(6):1316–9.
22. Jagannath S, Barlogie B, Berenson J, et al. A phase 2 study of two doses of bortezomib in relapsed or refractory myeloma. *British Journal of Haematology*. 2004 Oct;127(2):165–72.
23. Richardson PG, Sonneveld P, Schuster M, et al. Extended follow-up of a phase 3 trial in relapsed multiple myeloma: Final time-to-event results of the APEX trial. *Blood*. 2007 Nov 15;110(10):3557–60.

24. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *The New England Journal of Medicine*. 2005 Jun 16;352(24):2487–98.
25. Mateos MV, Hernandez JM, Hernandez MT, et al. Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: Results of a multicenter phase 1/2 study. *Blood*. 2006 Oct 1;108(7): 2165–72.
26. Mateos MV, Hernandez JM, Hernandez MT, et al. Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: Updated time-to-events results and prognostic factors for time to progression. *Haematologica*. 2008 Apr;93(4):560–5.
27. San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *The New England Journal of Medicine*. 2008 Aug 28;359(9):906–17.
28. Mateos MV, Richardson PG, Schlag R, et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: Updated follow-up and impact of subsequent therapy in the phase III VISTA trial. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2010 May 1; 28(13):2259–66.
29. Mateos MV, Oriol A, Martinez J, et al. A prospective, multicenter, randomized, trial of Bortezomib/Melphalan/Prednisone (VMP) versus Bortezomib/Thalidomide/Prednisone (VTP) as induction therapy followed by maintenance treatment with Bortezomib/Thalidomide (VT) versus Bortezomib/Prednisone (VP) in elderly untreated patients with multiple myeloma older than 65 years. *Blood*. 2009 Nov;114:3a.
30. Reeder CB, Reece DE, Kukreti V, et al. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: High response rates in a phase II clinical trial. *Leukemia: Official Journal of the Leukemia Society of America, Leukemia Research Fund, U.K*. 2009 Jul;23(7):1337–41.
31. Reeder CB, Reece DE, Kukreti V, et al. Once- versus twice-weekly bortezomib induction therapy with CyBorD in newly diagnosed multiple myeloma. *Blood*. 2010 Apr 22;115(16):3416–7.
32. Baumann P, Mandl-Weber S, Oduncu F, Schmidmaier R. Alkylating agents induce activation of NFκB in multiple myeloma cells. *Leukemia Research*. 2008 Jul;32(7):1144–7.
33. Orlowski RZ, Voorhees PM, Garcia RA, et al. Phase 1 trial of the proteasome inhibitor bortezomib and pegylated liposomal doxorubicin in patients with advanced hematologic malignancies. *Blood*. 2005 Apr 15;105(8):3058–65.
34. Biehn SE, Moore DT, Voorhees PM, et al. Extended follow-up of outcome measures in multiple myeloma patients treated on a phase I study with bortezomib and pegylated liposomal doxorubicin. *Annals of Hematology*. 2007 Mar;86(3):211–6.
35. Orlowski RZ, Nagler A, Sonneveld P, et al. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: Combination therapy improves time to progression. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2007 Sep 1; 25(25):3892–901.
36. Shah JJ, Orlowski RZ, Thomas SK. Role of combination bortezomib and pegylated liposomal doxorubicin in the management of relapsed and/or refractory multiple myeloma. *Therapeutics and Clinical Risk Management*. 2009 Feb;5(1):151–9.
37. Oakervee HE, Popat R, Curry N, et al. PAD combination therapy (PS-341/bortezomib, doxorubicin and dexamethasone) for previously untreated patients with multiple myeloma. *British Journal of Haematology*. 2005 Jun; 129(6):755–62.
38. Jakubowiak AJ, Kendall T, Al-Zoubi A, et al. Phase II trial of combination therapy with bortezomib, pegylated liposomal doxorubicin, and dexamethasone in patients with newly diagnosed myeloma. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2009 Oct 20;27(30):5015–22.
39. Popat R, Oakervee HE, Hallam S, et al. Bortezomib, doxorubicin and dexamethasone (PAD) front-line treatment of multiple myeloma: Updated results after long-term follow-up. *British Journal of Haematology*. 2008 May;141(4):512–6.
40. Gozzetti A, Fabbri A, Oliva S, et al. Weekly bortezomib, pegylated liposomal doxorubicin, and dexamethasone is a safe and effective therapy for elderly patients with relapsed/refractory multiple myeloma. *Clinical Lymphoma, Myeloma and Leukemia*. 2010 Feb;10(1):68–72.
41. Buda G, Ricci D, Huang CC, et al. Polymorphisms in the multiple drug resistance protein 1 and in P-glycoprotein 1 are associated with time to event outcomes in patients with advanced multiple myeloma treated with bortezomib and pegylated liposomal doxorubicin. *Annals Hematology*. 2010 Jun 8;EPub.
42. Wang M, Giralt S, Delasalle K, Handy B, Alexanian R. Bortezomib in combination with thalidomide-dexamethasone for previously untreated multiple myeloma. *Hematology (Amsterdam, Netherlands)*. 2007 Jun;12(3):235–9.
43. Eom HS, Kim YK, Chung JS, et al. Bortezomib, thalidomide, dexamethasone induction therapy followed by melphalan, prednisolone, thalidomide consolidation therapy as a first line of treatment for patients with multiple myeloma who are non-transplant candidates: Results of the korean multiple myeloma working party (KMMWP). *Annals of Hematology*. 2010 May; 89(5):489–97.
44. Cavo M, Tacchetti P, Patriarca F, Petrucci MT, et al. A phase III study of double autotransplantation incorporating bortezomib-thalidomide-dexamethasone (VTD) or thalidomide-dexamethasone (TD) for multiple myeloma: Superior clinical outcomes with VTD compared to TD. *Blood*. 2009 Nov;114:351a.
45. Richardson PG, Weller E, Jagannath S, et al. Multicenter, phase I, dose-escalation trial of lenalidomide plus bortezomib for relapsed and relapsed/refractory multiple myeloma. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2009 Dec 1;27(34): 5713–9.
46. Richardson PG, Weller E, Lonial S, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. *Blood*. 2010 Apr 12;EPub.
47. Kim YK, Sohn SK, Lee JH, et al, and Korean Multiple Myeloma Working Party (KMMWP). Clinical efficacy of a bortezomib, cyclophosphamide, thalidomide, and dexamethasone (vel-CTD) regimen in patients with relapsed or refractory multiple myeloma: A phase II study. *Annals of Hematology*. 2010 May;89(5):475–82.
48. Kumar SK, Flinn I, Noga SJ, et al. Bortezomib, dexamethasone, cyclophosphamide and lenalidomide combination for newly diagnosed multiple myeloma: Phase 1 results from the multicenter EVOLUTION study. *Leukemia: Official Journal of the Leukemia Society of America, Leukemia Research Fund, U.K*. 2010 May 27.
49. Jakubowiak AJ, Reece DE, Hofmeister CC, et al. Lenalidomide, bortezomib, pegylated liposomal doxorubicin, and dexamethasone in newly diagnosed multiple myeloma: Updated results of phase I/II MMRC trial. *Blood*. 2009; Nov;114:132a.
50. Kumar S, Flinn IW, Noga SJ, et al. Safety and efficacy of novel combination therapy with bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in newly diagnosed multiple myeloma: Initial results from the phase I/II multi-center EVOLUTION study. *Blood*. 2008 Nov;112:93a.
51. Kumar S, Flinn IW, Hari PN, et al. Novel three– and Four–Drug combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide, for newly diagnosed multiple myeloma: Encouraging results from the multi-center, randomized, phase 2 EVOLUTION study. *Blood*. 2009 Nov;114:127a.
52. Badros A, Burger AM, Philip S, et al. Phase I study of vorinostat in combination with bortezomib for relapsed and refractory multiple myeloma. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*. 2009 Aug 15;15(16):5250–7.
53. Jagannath S, Dimopoulos MA, Lonial S. Combined proteasome and histone deacetylase inhibition: A promising synergy for patients with rel apsed/refractory multiple myeloma. *Leukemia Research*. 2010 May 14.
54. Hayden PJ, Mitsiades CS, Anderson KC, Richardson PG. Novel therapies in myeloma. *Current Opinion in Hematology*. 2007 Nov;14(6):609–15.
55. Richardson Paul, Wolf JL, Jakubowiak AJ, et al. Perifosine in combination with bortezomib and dexamethasone extends progression-free survival and overall survival in Relapsed/Refractory multiple myeloma patients previously treated with bortezomib: Updated phase I/II trial results. *Blood*. 2009 Nov;114:1869a.

56. Voorhees PM, Chen Q, Kuhn DJ, et al. Inhibition of interleukin-6 signaling with CNTO 328 enhances the activity of bortezomib in preclinical models of multiple myeloma. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*. 2007 Nov 1;13(21):6469–78.
57. van Rhee F, Szmania SM, Dillon M, et al. Combinatorial efficacy of anti-CS1 monoclonal antibody elotuzumab (HuLuc63) and bortezomib against multiple myeloma. *Molecular Cancer Therapeutics*. 2009 Sep; 8(9):2616–24.
58. Jakubowiak AJ, Bensinger W, Siegel D, et al. Phase 1/2 study of elotuzumab in combination with bortezomib in patients with multiple myeloma with one to three prior therapies: Interim results. *Blood*. 2009 Nov;114:3876a.
59. Rossi JF, Manges R, Sutherland H, et al. Preliminary results of CNTO 328, an anti-interleukin-6 monoclonal antibody, in combination with bortezomib in the treatment of relapsed or refractory multiple myeloma. *Blood*. 2008;112:867a.
60. Harousseau JL, Avet-Loiseau H, Attal M, et al. High complete and very good partial response rates with Bortezomib—Dexamethasone as induction prior to ASCT in newly diagnosed patients with high-risk myeloma: Results of the IFM2005–01 phase 3 trial. *Blood*. 2009 Nov;114:353a.
61. Roussel M, Moreau P, Huynh A, et al. Bortezomib and high-dose melphalan as conditioning regimen before autologous stem cell transplantation in patients with de novo multiple myeloma: A phase 2 study of the intergroupe francophone du myelome (IFM). *Blood*. 2010 Jan 7;115(1):32–7.
62. Lonial S, Kaufman J, Torre C, et al. A randomized phase I trial of melphalan + bortezomib as conditioning for autologous transplant for myeloma: The effect of sequence of administration. *Blood*. 2008 Nov;112:3332a.
63. Mellqvist UH, Westin J, Gimsing P, et al. Improved response rate with bortezomib consolidation after high dose melphalan: First results of a nordic myeloma study group randomized phase III trial. *Blood*. 2009 Nov; 114:530a.
64. Curran MP, McKeage K. Bortezomib: A review of its use in patients with multiple myeloma. *Drugs*. 2009;69(7):859–88.
65. Chang H, Trieu Y, Qi X, Jiang NN, Xu W, Reece D. Impact of cytogenetics in patients with relapsed or refractory multiple myeloma treated with bortezomib: Adverse effect of 1q21 gains. *Leukemia Research*. 2010 May; EPub.
66. APEX (assessment of proteasome inhibition for extending remissions) trial: Phase III randomized, multicenter, placebo-controlled trial to evaluate the efficacy and safety of bortezomib versus dexamethasone in patients with recurrent or treatment-resistant multiple myeloma. 2003. *Clinical Advances in Hematology and Oncology: H&O*. Mar;1(3):190.
67. Scheinfeld N. A review of deferasirox, bortezomib, dasatinib, and cyclosporine eye drops: Possible uses and known side effects in cutaneous medicine. *Journal of Drugs in Dermatology: JDD*. 2007 Mar;6(3):352–5.
68. Ozkurt ZN, Sucak GT, Aki SZ, Yagci M, Erdem O. Bortezomib-induced perivascular dermatitis in a patient with multiple myeloma. *Cutaneous and Ocular Toxicology*. 2009;28(3):141–3.
69. Sanchez-Politta S, Favet L, Kerl K, Dietrich PY, Piguet V. Bortezomib-induced skin eruption. *Dermatology (Basel, Switzerland)*. 2008;216(2): 156–8.
70. Basler M, Lauer C, Beck U, Groettrup M. The proteasome inhibitor bortezomib enhances the susceptibility to viral infection. *Journal of Immunology (Baltimore, Md.: 1950)*. 2009 Nov 15;183(10):6145–50.
71. Chanan-Khan A, Sonneveld P, Schuster MW, et al. Analysis of herpes zoster events among bortezomib-treated patients in the phase III APEX study. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2008 Oct 10;26(29):4784–90.
72. Mohty B, El-Cheikh J, Yakoub-Agha I, Moreau P, Harousseau JL, Mohty M. Peripheral neuropathy and new treatments for multiple myeloma: Background and practical recommendations. *Haematologica*. 2010 Feb; 95(2):311–9.
73. Cavaletti G, Gilardini A, Canta A, et al. Bortezomib-induced peripheral neurotoxicity: A neurophysiological and pathological study in the rat. *Experimental Neurology*. 2007 Mar;204(1):317–25.
74. Meregalli C, Canta A, Carozzi VA, et al. Bortezomib-induced painful neuropathy in rats: A behavioral, neurophysiological and pathological study in rats. *European Journal of Pain (London, England)*. 2010 Apr;14(4):343–50.
75. El-Cheikh J, Stoppa AM, Bouabdallah R, et al. Features and risk factors of peripheral neuropathy during treatment with bortezomib for advanced multiple myeloma. *Clinical Lymphoma and Myeloma*. 2008 Jun;8(3):146–52.
76. Jagannath S, Durie BG, Wolf JL, et al. Extended follow-up of a phase 2 trial of bortezomib alone and in combination with dexamethasone for the frontline treatment of multiple myeloma. *British Journal of Haematology*. 2009 Sep;146(6):619–26.