# Bortezomib (Velcade™) in the treatment of multiple myeloma

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**Abstract:** The introduction of bortezomib, a novel first-in-class proteasome inhibitor, has been a major break through in the treatment of multiple myeloma. It is currently approved for the treatment of myeloma in the relapsed setting post transplant or as a second line treatment in patients unsuitable for transplantation. In pre-clinical studies bortezomib showed a number of different anti-myeloma effects including disruption of the cell cycle and induction of apoptosis, alteration of the bone marrow microenvironment and inhibition of nuclear factor kappa B (NFκB). Due to its novel mechanism of action, bortezomib has been shown to induce responses in previously refractory patients (including those with poor risk cytogenetics), and results in an increased progression free and overall survival in relapsed patients when compared with dexamethasone treatment alone. It is well tolerated and can be administered in the outpatient setting with manageable toxicities. Peripheral neuropathy is the most common dose limiting toxicity and thrombocytopenia can generally be managed with platelet transfusions without reducing or omitting doses. Bortezomib shows a synergistic effect in combination with dexamethasone and also sensitises myeloma cells to the effects of other chemotherapeutic agents with major response rates of over 50% being shown in the relapsed setting. Initial data from ongoing trials in front line therapy are encouraging with response rates of 80%–90% when bortezomib is given in combination with other agents and importantly, the ability to mobilize peripheral blood stem cells is not impaired.

**Keywords:** myeloma, bortezomib, proteasome inhibition, treatment

## Introduction

Much has been learnt about multiple myeloma pathobiology over the last decade. We have elucidated many of the important growth and survival pathways and understand in some detail the relationship between the plasma cell and the bone marrow microenvironment. The current emphasis of research is to translate these findings into the clinic and to develop novel targeted treatment approaches to improve patient outcome. Inhibition of the proteasome represents a completely new approach to the treatment of myeloma with studies demonstrating that this strategy is effective at killing myeloma cells that are otherwise resistant to conventional lines of therapy. Bortezomib is the first proteasome inhibitor to be approved for the treatment of myeloma and represents a step forward in the management of these patients. Phase III data from the landmark APEX trial demonstrate a significant survival advantage in patients with relapsed multiple myeloma treated with bortezomib compared with those treated with dexamethasone alone (Richardson et al 2005a). Since its approval by the US Food and Drug Administration (FDA) in 2003 there has been rapid clinical development and it is now approved in over 50 countries worldwide. This review aims to discuss the data supporting the use of bortezomib in the treatment of myeloma, as well as highlighting some of the more practical issues surrounding its use in the clinical setting.

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# What is bortezomib and how does it work?

Bortezomib, formerly known as PS-341, is a boron containing molecule that specifically and reversibly inhibits the threonine residue of the 26S proteasome, an enzyme complex that plays a key role in the cell by regulating protein degradation in a controlled fashion. Proteins that are no longer required, including those involved in cell cycle control, apoptosis and cell signaling, are tagged with ubiquitin which directs them to the proteasome which subsequently degrades them. This process maintains the balance of inhibitory and stimulatory proteins involved in cell cycle, thus inhibition of the proteasome results in a loss of the tight control of the process with a build up of cell cycle and regulatory proteins leading to cell death (Adams et al 1999; Adams 2004). Recent reports also suggest that bortezomib may disregulate intracellular calcium metabolism resulting in caspase activation and apoptosis (Landowski et al 2005).

Bortezomib has potential as a chemotherapeutic agent in many different tumor types as proteasomes are present in all eukaryotic cells; however it also has a number of myeloma specific effects. One central mechanism by which bortezomib functions in myeloma is via the inhibition of the breakdown of inhibitory kappa B (IκB) and consequently stabilization of the nuclear factor kappa B (NFκB) complex. This prevents NFκB translocation to the nucleus with consequent inactivation of multiple downstream pathways known to be important in myeloma cell signaling (Karin et al 2002). It also decreases the adhesion of the myeloma plasma cell to stromal cells which increases sensitivity to apoptosis, as well as interrupting pro-survival paracrine and autocrine cytokine loops in the bone marrow microenvironment mediated by interleukin-6 (IL-6), insulin-like growth factor 1 (IGF-1), vascular endothelial growth factor (VEGF) and tumor necrosis factor-α (TNF-α) (Hideshima et al 2001, 2003). Other effects in myeloma include inhibition of angiogenesis, inhibition of DNA repair and impairment of osteoclast activity (Rajkumar et al 2005). Tumor cells appear to be more sensitive to the effects of proteasome inhibition than normal cells due to a loss of checkpoint mechanisms occurring during tumorgenesis; this means that normal cells can usually recover as the inhibition is transient and reversible.

# Phase II and III clinical trials

Encouraging data from preclinical work (Hideshima et al 2001; LeBlanc et al 2002) and later Phase I studies in 2002 (Aghajanian et al 2002; Orlowski et al 2002) led to the initiation of two phase II studies, Study of Uncontrolled Myeloma Management with proteasome Inhibition Therapy (SUMMIT) and Clinical Response and Efficacy Study of bortezomib in the Treatment of refractory myeloma (CREST) in multiple myeloma. In the SUMMIT trial, 202 patients with relapsed and refractory myeloma were treated with single agent bortezomib for up to 8 cycles with an overall response rate of 35% using the European Group for Blood and Marrow Transplantation (EBMT) criteria (Blade et al 1998). The response rate was increased to 50% with the addition of dexamethasone on the day of and the day after each injection of bortezomib (Richardson et al 2003). Responses were independent of the type or number of previous treatments, β2-microglobulin and chromosome 13 deletion status – factors which have previously influenced response to other types of chemotherapy (Richardson, Barlogie, et al 2005).

In the CREST study, 54 patients with relapsed myeloma following one line of therapy were randomized to receive bortezomib at either $1.0\,mg/m^2$ or $1.3\,mg/m^2$. Overall response rates were 33% and 50% respectively (Jagannath et al 2004). Again when dexamethasone was added, response rates were higher at 44% and 62% respectively. The incidence of adverse events was 20% lower in the group receiving $1.0\,mg/m^2$ suggesting that patients with unacceptable toxicities receiving $1.3\,mg/m^2$ may be able to tolerate a reduced dose of bortezomib and still achieve good response rates.

The Assessment of Proteasome inhibition for EXtending remissions (APEX) trial was a randomized phase III trial set up to compare bortezomib with high dose dexamethasone in 669 patients with multiple myeloma who had relapsed after one or more therapies. The results showed a significant survival benefit in the bortezomib group and the trial was terminated early with the dexamethasone patients crossing over to the bortezomib arm (Richardson et al 2005a). Overall response rates were 38% in the bortezomib arm versus 18% with dexamethasone alone (p<0.001). The results were updated at American Society of Hematology (ASH) in December 2005 based on a median follow up of 15.8 months with a response rate of 43% to single agent bortezomib and 9% of patients achieving a complete response. Response rates were higher in those who had only received one prior line of therapy. At one year, overall survival was 80% in those who had received bortezomib compared with 67% in the dexamethasone arm, with a six month survival advantage for patients treated with bortezomib (Richardson et al 2005b). It can be concluded from this phase III data that

bortezomib is superior to high dose dexamethasone as second line treatment for relapsed myeloma.

Based on the results of these three trials in May 2003, the FDA approved bortezomib for use in patients with relapsed and refractory myeloma who had received 2 or more prior therapies, and in April 2005 the European Commission approved its use as a second-line treatment in patients with multiple myeloma who have already undergone or are unsuitable for bone marrow transplantation.

## Clinical use

Bortezomib is usually given on an outpatient basis as a short intravenous infusion on days 1, 4, 8, 11 of a 3 weekly cycle. The 72 hour gap between infusions is important to allow recovery of the proteasome inhibition in the normal cell. The 10 day treatment-free period allows cell recovery and prevents excessive side effects. A total of up to 8 cycles may be given depending on response and toxicities.

On the basis of laboratory data showing an additive anti-proliferative effect (Hideshima et al 2001), bortezomib was combined with dexamethasone at a dose of 20 mg on the day of and day after each injection. Although the initial phase II trials were designed so that dexamethasone was added in when there was failure to respond to 2 cycles of single agent therapy, it can be argued given the synergistic effect of the combination of bortezomib and dexamethasone, that dexamethasone should be given to all patients who are able to tolerate it from the start of treatment. In the SUMMIT trial, 18% of patients who had a suboptimal response to single agent bortezomib showed an improved response when dexamethasone was added (Richardson et al 2003).

Data from SUMMIT and APEX suggest that in most patients response to treatment is quick with the median time to a first response 1.3 months (Richardson et al 2003, 2005a). This suggests that if patients are not responding to treatment after 4 courses of therapy (2 as single agent and 2 with the addition of dexamethasone) then therapy should be changed.

## Side effects and toxicities

Based on data from the SUMMIT trial, the most common side effects are fatigue and weakness, gastrointestinal disturbances (including nausea and vomiting, diarrhea, constipation), thrombocytopenia and peripheral neuropathy (Richardson et al 2003). It is recommended that bortezomib should be withheld at the onset of grade 3 non-hematological or grade 4 hematological toxicity, until the toxicity resolves and then treatment restarted at a lower dose. Although gastrointestinal disturbances and fatigue are the most common side effects, peripheral neuropathy and thrombocytopenia are the most problematic and clinically significant and are therefore discussed in further detail below.

## Peripheral neuropathy

Bortezomib causes a predominantly sensory peripheral neuropathy in approximately 30%–40% of patients characterized by a burning sensation, paresthesias, numbness and/or neuropathic pain (Richardson et al 2004; San Miguel et al 2005). Although this is reversible in the majority of cases, care should be taken to avoid causing permanent disabling neuropathy in patients and at the onset of any grade 3 toxicity, bortezomib should be withheld until symptoms have resolved and then reinstated with a 25% dose reduction. In most instances the neuropathy improves or resolves once treatment is completed over a median of 3 months (San Miguel et al 2005). Based on experience from the phase II single agent trials a number of recommendations for dose modification in patients experiencing peripheral neuropathy as graded by the National Cancer Institute common terminology criteria for adverse events have been made. These are summarized in Table 1 (NCI 2003).

Patients with pre-existing neuropathy may experience worsening symptoms during treatment with bortezomib and should therefore be monitored closely; however pre-existing neuropathy, for example from previous thalidomide, should not in itself preclude the use of bortezomib. Supportive measures include the use of agents such as gabapentin and amitryptiline, opiates, and referral to a specialist pain service. It is important to ensure vitamin B and folate levels are normal and not exacerbating the neuropathy. The actual mechanism of nerve damage is not known and has been difficult to establish as many patients in the trials had pre-existing neuropathy. Hypotheses range from damage to the peripheral nerve blood supply because of its anti-angiogenic effect, a possibility of an increased inhibitory effect on the proteasome within nerve endings and a dose related disruption of normal homeostasis of cytosolic proteins involved in axonal transport (EMEA 2004).

Postural hypotension can also be problematic and is presumably related to an autonomic neuropathy. Patients complaining of dizziness should have regular lying and standing blood pressures taken and an increase in hydration may be beneficial, for example 500 mls of normal saline

**Table 1** Recommended dose modification for bortezomib-related neuropathy and/or neuropathic pain (NCI 2003)

| Severity | Signs and symptoms of peripheral neuropathy | Dose modification |
|---|---|---|
| Grade 1 | Asymptomatic; loss of deep tendon reflexes or parathesia (including tingling) but not interfering with function | No action |
| Grade 2 or Grade 1 with pain | Sensory alteration or parathesia (including tingling) interfering with function but not with ADL | Reduce bortezomib to 1.0 mg/m2 (25% dose reduction) |
| Grade 3 or Grade 2 with pain | Sensory alteration or parathesia interfering with ADL | Withhold bortezomib until toxicity resolves then restart at 0.7 mg/m2 (50% dose reduction) |
| Grade 4 | Permanent sensory loss interfering with function (disabling) | Discontinue bortezomib |

**Abbreviations:** ADL, activities of daily living.

with each bortezomib injection. Mineralcorticoids may be useful and patients should be advised about rising slowly from sitting or lying and not driving.

## Thrombocytopenia

Thrombocytopenia is the most common hematological toxicity occurring in approximately 30% of patients while neutropenia and anemia have not been found to be problematic (Lonial et al 2005). The development of thrombocytopenia is dependent upon the baseline platelet count, which in turn is related to the degree of bone marrow plasma cell infiltration, and bone marrow toxicity/reserve caused by previous lines of therapy.

Patients experience reductions in their platelet count of around 60% and therefore do not usually develop grade 4 thrombocytopenia unless the baseline count is below 70. The thrombocytopenia is transient and reversible showing a cyclical pattern with platelets dipping at day 11 but returning to baseline by day 1 of the next cycle. This is different to the pattern of thrombocytopenia seen with other cytotoxic agents where platelet counts drop after 1–2 weeks and can take up to 4 weeks to recover or may not recover at all. This is due to a difference in the mechanism of thrombocytopenia in proteasome inhibition, which is related to a transient effect on megakaryocyte function and platelet budding as opposed to damage to marrow stem cells (Lonial et al 2005).

In the SUMMIT, trial only 2 patients had bleeding episodes associated with thrombocytopenia, neither of which were serious, and less than 15% of patients required platelet transfusions (Richardson et al 2003). The SMPC guidelines suggest that bortezomib should be withheld at the onset of grade 4 hematological toxicity (hemoglobin <6.5 g/dL, white blood cell <1.0 x $10^9$/L with neutrophils <0.5 x $10^9$/L, platelets <25 x $10^9$/L) and reinitiated once symptoms have resolved. In practice patients experiencing hematological toxicity can be managed safely with blood and platelet support and granulocyte colony stimulating factor (GCSF) and dose interruptions should not be necessary provided patients are closely monitored. Full blood counts should be checked prior to each injection of bortezomib and again in the rest week if baseline platelet counts are low. Platelet transfusion is recommended to keep the platelet count above 30. If the thrombocytopenia is due to marrow infiltration then patients responding to treatment will generally experience a progressive increase in their blood counts following the second cycle of therapy.

## Use of prophylaxis

Although the incidence of varicella zoster infection is high in multiply relapsed and refractory patients, the APEX trial demonstrated an incidence of 13% in the bortezomib-treated arm compared with 5% in the dexamethasone-treated arm (p<0.001) (Richardson et al 2005a). Prophylactic acyclovir should therefore be given to high-risk patients treated with bortezomib.

## Use in renal failure and liver disease

A retrospective analysis of patients enrolled to the SUMMIT and CREST trials examined the use of bortezomib in patients with relapsed and refractory myeloma with renal impairment (creatinine clearance less than 30 ml/min). This showed that response rates and toxicities were similar to that obtained for the whole trial population however the incidence of serious adverse events was higher in patients with lower creatinine clearance. In patients with creatinine clearance (CrCl) >80 ml/min, 41% experienced serious adverse events, compared with 51% of patients with CrCl 51–80 ml/min and 60% of patients with CrCl <50 ml/min (Jagannath, Barlogie, et al 2005). The data suggests that patients with renal impairment can be safely and effectively treated with bortezomib, however they should be closely monitored for

toxicities and managed accordingly. Up to 30% of patients with myeloma have renal failure, the most common cause of which is interstitial nephritis, and renal function may improve following chemotherapy administration. It is therefore important not to exclude this group of patients when considering bortezomib treatment, particularly as many other conventional chemotherapies are often directly nephrotoxic and are either not suitable for patients with impaired renal function or require dose modification in this setting. There is limited data on the use of bortezomib in patients with renal failure requiring dialysis, although a number of anecdotal reports and a recent small study (Chanan-Khan et al 2005) have suggested that it can be delivered safely.

There is less data available on the use of bortezomib in patients with impaired liver function although its use is not recommended in patients with liver enzymes 2.5–3 times the upper limits of normal as its metabolism may be impaired. There has been one case of bortezomib-induced severe hepatitis recently reported in the literature (Rosinol et al 2005).

## Combinations of bortezomib with other chemotherapeutic agents

Early laboratory data showed that the combination of bortezomib with dexamethasone resulted in an increase myeloma cell kill in comparison to bortezomib alone (Hideshima et al 2001). Data from the CREST trial confirmed this synergistic effect in patients with an improved response rate of 62% in patients treated with bortezomib 1.3 mg/m$^2$ with dexamethasone 20 mg on the day of and day after injection versus 50% with bortezomib alone (Jagnannath et al 2004). Further preclinical work has demonstrated that bortezomib sensitizes myeloma cells to the effects of other cytotoxic agents (Ma et al 2003; Mitsiades et al 2003) and there are now numerous phase I and II studies looking at bortezomib in combination with different agents for both relapsed disease and as front line treatment to establish whether response rates and survival times can be improved further with manageable toxicities. The results of these studies are summarized in Tables 2 and 3.

In the relapsed setting, the data is very encouraging with bortezomib combination regimes repeatedly showing major response rates of greater than 50% (although not all are graded by EBMT criteria) without an increase in toxicity (Table 2). Importantly these trials show that it is possible to combine the agent with drugs known to cause peripheral

neuropathy (eg, thalidomide) or thrombocytopenia (eg, melphalan) without an increase in these side effects, although careful monitoring and a dose reduction may be required. Phase I data combining bortezomib with lenalidomide (Revlimid™), an immunomodulatory agent, is particularly interesting especially as many of the patients treated in this study demonstrated responses despite being resistant previously to one or other of the agents (Richardson, Schlossman, et al 2005).

To date the gold standard treatment for younger fitter patients with myeloma is vincristine, adriamycin, and dexamethasone (VAD), or cyclophosphamide, vincristine, adriamycin, and methyl prednisolone (C-VAMP) induction chemotherapy followed by high dose melphalan with peripheral blood stem cell return. The major response rate (complete response [CR] + partial response [PR]) for this approach is 60% with up to 50% of patients achieving a complete response after completion of the whole therapy and 15% after completion of the induction phase (Alvares et al 2005). Recent reports have suggested that thalidomide and dexamethasone is superior to VAD as induction therapy prior to transplantation, with response rates of 76% and 52% respectively (p<0.001) (Cavo et al 2005). The early reports of bortezomib in front line therapy indicate a response rate of 80%–90% which compares very favorably to other standard pre-transplant induction regimens. For example, in the study by Wang et al (2005) response rates were 30% higher than those observed previously among similar patients treated with thalidomide and dexamethasone (p<0.01). Importantly the data using bortezomib with dexamethasone or bortezomib with doxorubicin and dexamethasone (PAD) demonstrates that stem cell mobilization is not impaired and that there is no increased toxicity during the transplant procedure (Harousseau et al 2004; Jagannath, Durie, et al 2005; Oakervee et al 2005; Wang et al 2005). Phase III trials are underway to compare this to standard induction approaches, for example the Stichting Hemato-Oncologie voor Volwassenen Nederland (HOVON) group are assessing PAD prior to stem cell transplant followed by maintenance therapy with bortezomib compared with VAD prior to transplant with thalidomide maintenance.

New regimens for non-transplant candidates also look promising especially in the elderly where the Spanish group have shown that it is possible to combine bortezomib with melphalan and prednisolone (MP) (Mateos et al 2005). The MP regimen, although the current gold standard, is known only to induce responses in 60% of patients with less than

**Table 2** Combinations of bortezomib with other chemotherapeutic agents in relapsed and refractory disease

| Study drugs | Reference | | No of assessable patients | Median no of prior regimes | Median no of cycles | Major response rate (CR+PR) | Response rates | Follow up | Toxicities |
|---|---|---|---|---|---|---|---|---|---|
| **Bortezomib Cyclophosphamide Dexamethasone** | Kropff et al 2005 | Phase II | 50 | 2 | 6 | **76%** | CR 10% PR 66% MR 12% | Median EFS 10 months | Neuropathy Infections, herpes zoster Thrombocytopenia Cardiovascular events |
| **Bortezomib Cyclophosphamide Prednisolone** | Reece et al 2005 | Phase I/II | 15 | All had at least 1 prior autograft | 2 patients completed 8 cycles | 31% | CR 6% PR 25% MR 25% | Not yet complete | Infections Hypophosphatemia Cytopenia |
| **Bortezomib Thalidomide +/- Dexamethasone** | Zangari et al 2005 | Phase I/II | 85 | 66% received 2 prior autografts | 2–12 cycles given | 71% | ≥n-CR 16% PR 55% MR 15% | Median OS/EFS 9/22 months | Myelosuppression Neuropathy |
| **Bortezomib +/- Methylprednisolone (weekly dosing)** | Suvannasankha and Smith 2005 | Phase II | 28 | 70% prior autograft | 5 | 59% | CR 3% n-CR 3% PR 53% | Not yet complete | Neuropathy Gastrointestinal Congestive heart failure |
| **Bortezomib Low dose Melphalan +/- Dexamethasone** | Popat et al 2005 | Phase I/II | 16 | 3 | 4 | **50% ORR (75% with dex)** | Median time to any response 1 cycle | Not yet complete | Neuropathy Myocardial infraction Thrombocytopenia Neutropenia |
| **Bortezomib Melphalan** | Berenson et al 2006 | Phase I/II | 34 | 3 | 15 patients completed 8 cycles | 47% | CR 6% n-CR 9% PR 32% MR 21% | Median free PFS 8 months | Myelosuppression Neuropathy Gastrointestinal |
| **Bortezomib Melphalan Prednisolone Thalidomide** | Palumbo et al 2005 | Phase II | 20 | 55% received 2 prior therapies | 3 | 50% | CR 10% n-CR 5% PR 35% MR 13% | Not yet complete | Thrombocytopenia Febrile neutropenia Herpes zoster Neuropathy |
| **Bortezomib Lenalidomide +/-Dexamethasone** | Richardson, Schlossman, et al 2005 | Phase I | 17 | 7 | 4 | 59% | CR 6% n-CR 6% PR 47% MR 17% | Not yet complete | Thrombocytopenia Hyponatraemia Hypotension Fatigue Neutropenia |
| **Bortezomib Pegylated liposomal doxorubicin (advanced hematological malignancies)** | Orlowski et al 2005 | Phase I | 22 patients with myeloma | 5 (all patients) | 4 | 73% | CR 23%, n-CR 14% PR 36% MR or stable disease 23% | Not yet complete | Myelosuppression Fatigue Pneumonia Neuropathy Diarrhea |

**Abbreviations:** CR, complete response; EFS, event free survival; MR, minor response; n-CR, near complete response; ORR, overall response rate (CR+PR+MR); OS, overall survival; PR, partial response; TTP, time to progression.

**Table 3** Combinations of bortezomib with other chemotherapeutic agents as first line therapy

| Study drugs | Reference | No of patients | Median assessable cycles | Major no of rate (CP+PR) | Response rates response | Follow up | Toxicities |
|---|---|---|---|---|---|---|---|
| **Bortezomib +/- Dexamethasone** | Jagannath, Durie, et al 2005 | 40 | Up to 6 cycles given | 85% | 28 patients had dex added and 64% showed improved response | 12 patients underwent SCT | Neuropathy Fatigue Constipation Neutropenia |
| **Bortezomib Dexamethasone** | Harousseau et al 2004 | 18 | 16 patients received 4 cycles | 83% | CR 17% VGPR 11% PR 55% | Stem cells collected in all cases | Neuropathy |
| **Bortezomib Doxorubicin Dexamethasone** | Oakervee et al 2005 | 21 | 19 patients received 4 cycles | 95% | CR 24% n-CR 5% VGPR 33% PR 33% | 18 patients underwent SCT with 44% CR and 95% ORR at 3 months | Neuropathy Postural hypotension Shingles Gastrointestinal |
| **Bortezomib Melphalan Prednisolone** | Mateos et al 2005 | 53 | 3 | 84% | CR 28% n-CR 11% PR 45% MR 2% | 90% alive at 7 months | Gastrointestinal Myelosuppression Infection Neuropathy |
| **Bortezomib Thalidomide Dexamethasone** | Alexanian et al 2004 | 25 | Up to 2 cycles given | 84% | 76% had >75% reduction in paraprotein +/- >95% reduction in BJP | Median time to remission 0.6 months (compared with 1.1 months with Thal/Dex) 12 patients underwent SCT | Infection Postural hypotension DVT Cytopenia |
| **Bortezomib Thalidomide Dexamethasone** | Wang et al 2005 | 36 | No more than 2 cycles needed for response | 92% | CR 19% PR 73% | 22 patients underwent SCT 89% in remission (31% CR) at 4 months | Neuropathy DVT Infections |

**Abbreviations:** CR, complete response; DVT, deep vein thrombosis; MR, minor response; n-CR, near complete response; ORR, overall response rate (CR+PR+MR); PR, partial response; SCT, stem cell transplant; VGPR, very good partial remission.

10% complete response and often takes up to nine months to induce a stable disease phase (Facon et al 2006). The early data in combination with bortezomib demonstrates a response rate of 85% with manageable toxicities, although a dose reduction was required in some cases due to prolonged cytopenias (Berenson et al 2006). The randomized phase III VISTA trial is currently underway to compare bortezomib and MP to standard MP in newly diagnosed myeloma patients not suitable for transplant.

Clinical trials are also underway looking at the use of bortezomib in other hematological malignances including lymphoma, acute leukemia and solid tumors including non small cell lung cancer, prostate, ovarian, and breast (Ludwig et al 2005). So far results look promising particularly in mantle cell lymphoma where a major response rate of 41% in previously heavily treated patients was seen (Goy et al 2005).

## Summary

The introduction of bortezomib in the treatment of myeloma has been a major breakthrough, first in the relapsed setting and increasingly as a front line approach prior to stem cell transplantation as well as in combination with MP in patients unsuitable for transplantation. It is able to induce responses in previously refractory patients and results in an increased progression free and overall survival in relapsed patients when compared with dexamethasone treatment alone. Following its approval by the US and European regulatory authorities for the treatment of myeloma nearly 3 years ago, there have been a large number of studies confirming these initial results. It has become evident that proteasome inhibition, due to its novel mechanism of action, is often effective in cases previously refractory to other more conventional treatments as well as in patients with high risk disease as defined by cytogenetics, and that there is a synergistic effect when bortezomib is added to other chemotherapeutic agents. Experience shows that bortezomib can be administered safely and effectively in the outpatient setting provided clinicians use it at an appropriate stage in an individual's management, have an understanding of its different mechanism of action and can manage toxicities appropriately. Neuropathy is the most common dose limiting toxicity and thrombocytopenia can generally be managed with platelet transfusions without reducing or omitting doses. Bortezomib is currently approved for use in the relapsed setting post transplant or as a second line treatment in patients unsuitable for transplantation, although as more data becomes available it will inevitably be used routinely as induction therapy in combination with other agents in newly diagnosed patients. With the advent of bortezomib and other new small molecules, the future for myeloma patients looks promising as other ways of targeting myeloma cells and the bone marrow microenvironment are exploited.

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