POSITION STATEMENT ON THE USE OF BORTEZOMIB IN MULTIPLE MYELOMA

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Summary

Bortezomib (Velcade™) is a boron containing molecule which reversibly inhibits the proteasome, an intracellular organelle which is central to the breakdown of ubiquinated proteins and consequently for normal cellular homeostasis. Phase II clinical trials demonstrate it is effective for the treatment of relapsed refractory myeloma, and a phase III trial comparing bortezomib to dexamethasone showed superiority in progression free and overall survival. It is administered intravenously in the outpatient setting on days 1, 4, 8 and 11 of a 21 day cycle and regular monitoring for side effects is essential. It is currently approved for the treatment of multiple myeloma patients who have received at least 1 prior therapy and who have already undergone or are unsuitable for transplantation. Given the strength of this data the UK myeloma forum and British Committee for Standards in Haematology believe that bortezomib should be available for prescription by UK haematologists according to its licensed indication in patients with relapsed myeloma.

Background

Myeloma is a malignant disorder of plasma cells which is characterized by an excess of abnormal plasma cells within the bone marrow, lytic bone lesions and paraproteins in the serum and urine. It is frequently associated with painful bone lesions, fractures, myelosuppression and renal failure. It is a relatively common disease with an increasing incidence with age, the majority of cases occurring over the age of sixty. It is currently incurable but with modern treatments the median survival is approximately 4 years. Given this outcome myeloma should be considered a relapsing, recurring disease, with each recurrence requiring treatment. Early trials comparing simple alkylating agent treatments showed that melphalan and cyclophosphamide improved survival equally but despite this oral melphalan plus prednisolone developed into the standard approach. The value of combination chemotherapy was tested and in the UK the MRC Myeloma V trial, compared melphalan with ABCM (MacLennan *et al* 1992). ABCM was significantly better in this study however, overviews of a number of published trials comparing oral melphalan to combination chemotherapy did not show a significant advantage for combinations (MTCG 1998). Consistently high response rates were reported with the VAD regimen and dexamethasone was recognized as a key component in this regimen (Samson *et al* 1989). Dose escalation of melphalan was investigated and the development of autologous stem cell rescue allowed doses of melphalan of 200mg/m^2 to be given safely, which was associated with increased numbers of complete responses and bone healing. High dose therapy was compared to standard treatments and was shown to be superior, making it the current standard approach for patients who can tolerate it (Attal *et al* 1996, Child *et al* 2003).

The development of high dose treatment and its widespread application has lead to a change in approach to the management of myeloma. Using standard dose treatments the aim was the achievement of a disease phase called “plateau” where there is an absence of overt clinical symptoms and paraprotein levels are stable. With high dose treatment the approach is to maximise responses. Consequently when introducing new agents into the management of myeloma, it has become important to define the appropriate clinical settings and the therapeutic strategies with which to use them. These clinical settings include therapy for induction, maintenance, relapse, and for

refractory disease. It is also important to recognise that myeloma is a relapsing recurring disorder, which will usually require multiple lines of treatment, and it is therefore important to understand the best order in which to use new agents.

Mechanism of action

Bortezomib (Velcade™) is a boron containing molecule which is a reversible inhibitor of the proteosome. The proteasome is a large multi subunit protein, present in all eukaryotic cells which functions to degrade proteins targeted to it by ubiquitination. Ubiquitinated proteins enter at one end of the proteasome and are degraded to their individual peptides which are shed from the far end of its barrel like structure. It consequently has a critical role in maintaining intracellular homeostasis allowing complex intracellular signalling events to take place which are essential for the control of cell cycle progression, transcription and apoptosis, as well as mediating inter-cell signalling events such as those leading to chemotaxis, angiogenesis and adhesion (Adams *et al* 1999, Adams, 2004). Proteasome inhibition with bortezomib can induce apoptosis in myeloma cell lines particularly those resistant to conventional chemotherapy (Hideshima *et al* 2001, Mitsiades *et al* 2003), suggesting that it works by a distinct mechanism not affected by the drug resistance mechanisms leading to alkylator and steroid resistance. 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. Other molecules stabilized by proteasome inhibition include p53, p21 and p27. One mechanism of apoptosis induction is via the simultaneous accumulation of contradictory cell cycle regulatory signals. Recent reports also suggest that bortezomib may dysregulate intracellular calcium metabolism resulting in caspase activation and cell death (Landowski *et al* 2005). Bortezomib 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 IL6, IGF1, VEGF and TNFα (Hideshima et al, 2001)

Pharmacology

The standard regimen for bortezomib is 4 doses, given on days 1, 4, 8, and 11 of a 21-day treatment cycle. In initial dose finding studies using this schedule DLT occurred at 1.56 mg/m2/dose and the MTD was defined as 1.3 mg/m2/dose (Orlowski *et al* 2002). In a 35-day treatment cycle with 4 once weekly doses of bortezomib the MTD was 1.6 mg/m2/dose (Papandreou *et al* 2004), suggesting that slightly higher doses may be used in a weekly schedule. Following injection maximum proteosome inhibition is observed within the first hour (80% inhibition), followed by partial recovery of proteasome activity over the next 6 to 24 hours to within 50% of the pre-treatment activity. Using the standard schedule, 10%-30% proteasome inhibition is observed at the next scheduled dosing. This approach of using intermittent injections with a 1 week treatment holiday allows cells to recover proteasome activity and prevents excessive side effects. It is therefore important for the clinical use of bortezomib that its dose interval should not be brought closer together than 72 hours and the week off treatment is observed. Bortezomib does not cross the blood brain barrier. It is metabolised by the cytochrome P450 enzyme system in the liver, which, de-boronates the molecule and removes it from the body, and only a small proportion is removed by the kidneys.

Clinical trials

The safety and efficacy of bortezomib in myeloma patients has been investigated in two phase II studies of patients at relapse after at least 2 previous lines of treatment. The first, 'SUMMIT' enrolled 202 patients and the overall response rate (CR, PR, and MR) was 35%, with 10% CR or near CR (Richardson *et al*, 2003). Responses were usually seen within the first 2-3 cycles of treatment and the response rate increased to 50% with the addition of dexamethasone (20mg on days 1,2, days 4,5 days 8,9 and days 11,12). In a sub-analysis it was noted that response was independent of the number of previous lines of treatment, and type of previous treatment, confirming in-vitro data that bortezomib works via a different mechanism and overcomes resistance to other treatments. A second study, 'CREST' enrolled 54 patients and evaluated two dose levels (1.3mg/m2 and 1.0mg/m2) using the standard 21-day schedule. Response rates (CR and PR) were similar between the two doses (30% vs 38% respectively) with manageable toxicities (Jagannath *et al* 2004).

This encouraging phase II data lead to the phase III study 'APEX' being set up. This study in 669 patients compared single agent bortezomib with standard dose dexamethasone in patients at first or subsequent relapse. The study was a cross-over design therefore at relapse all patients were eligible for bortezomib treatment. The study was closed early because of superior responses and disease free survival in the bortezomib treated cases. The response rate (CR+PR) was 38% in the bortezomib arm compared to 18% in the dexamethasone arm. At the time of analysis 29% of patients receiving bortezomib had progressed compared to 52% of patients receiving dexamethasone, resulting in a median time to progression of 6.2 months versus 3.5 months respectively. This translated into a 22% difference in overall survival at 12 months (Richardson *et al* 2004). Based on this phase III data it can be concluded that bortezomib is a better treatment than dexamethasone at relapse.

In a series of observational studies carried out on patients entered into these three studies it was shown that patients who respond to therapy had improved levels of haemoglobin, decreased transfusion requirements and an improved quality of life based on data collected using a patient-directed questionnaire. There was a marked improvement in disease free and overall survival for the patients who responded compared to those who did not. The median disease free progression for patients who responded in the SUMMIT was 12 months which is highly significant at second relapse for a disease with a median survival of 3-5 years from presentation.

Licenced indication

Bortezomib is currently approved for the treatment of progressive multiple myeloma in patients who have received at least 1 prior therapy and who have already undergone or are unsuitable for transplantation. The Scottish Medicines Consortium have accepted it for use within NHS Scotland for the treatment of patients who have received at least two prior therapies and submission to NICE is pending.

Combinations including bortezomib

Bortezomib combinations are being developed based on synergy seen in-vitro (Ma *et al*, 2003, Mitsiades *et al* 2003). There is evidence for an additive effect with dexamethasone, and this is supported by clinical data. In-vitro, at non therapeutic doses, it has been possible to sensitise cell lines to the cytotoxic effects of melphalan,

doxorubicin and mitroxantrone (Mitsiades *et al*, 2003). Ongoing clinical trials are using bortezomib in combination with other agents, including melphalan, thalidomide, doxorubicin and cyclophosphamide (Zanagri *et al*, 2003, Berenson *et al*, 2004, Mateos *et al* 2004, Orlowski *et al* 2005). Clinically, these regimes have not been fully evaluated but seem to be effective and do not unacceptably increase toxicity, although neurotoxicity has to be carefully monitored. Developing relapse/refractory regimens which work by mechanisms different to those utilised by induction regimens is an exciting potential approach.

Use as induction therapy

A number of studies have demonstrated that bortezomib is effective as induction therapy although the response rate when used as a single agent is lower than traditional regimens (Harousseau *et al* 2004, Richardson *et al* 2004, Jagannath *et al* 2004). Response rates are much improved when used in combination with dexamethasone (Harousseau *et al* 2004, Jagannath *et al* 2004). In younger patients where an autologous transplant is planned as part of the induction regimen, studies have demonstrated that both bortezomib with dexamethasone and the combination of bortezomib, hydroxydaunorubicin (Adriamycin) and dexamethasone (PAD) are effective and do not seem to impair the capacity to harvest stem cells (Harousseau *et al* 2004, Richardson *et al* 2004, Jagannath *et al* 2004, Cavenagh *et al* 2004). Neuropathic side effects do still occur and therefore patients need to be closely monitored.

Side effects

Proteosome inhibition results in a different range of side effects compared to that seen with classical chemotherapy. Practitioners need to be aware of this spectrum of side effects in order to ensure its safe use. While the range of side effects of bortezomib is wide, the majority are readily manageable, however because it is delivered in the outpatient setting, it is important to put in place a means of assessing and managing these effects. The spectrum of side effects is organ specific as outlined below.

Haemopoietic system

Neutropenia and thrombocytopenia can occur after exposure to bortezomib, but they constitute less of a problem than after cytotoxic chemotherapy. Fortunately, as a

single agent bortezomib does not damage the haemopoietic stem cell and initial results suggest that prior exposure does not impair the ability to carry out progenitor cell harvesting. However, despite this it remains important to treat pyrexia as an emergency as would be done with any chemotherapy which can cause neutropenia. Anaemia can occur and erythropoietins can prevent and reverse this. Thrombocytopenia is seen especially in patients with low starting platelet counts, but the mechanism by which this occurs differs from that with cytotoxics. Bortezomib appears to block megakaryocyte budding leading to low circulating levels of platelets but the effect is reversible with platelet counts coming up in the treatment break. It can be anticipated that there will be an approximately 40% reduction from the initial platelet count and that the nadir will be maximum at day 13-14. Cumulative suppression may occur with successive courses especially if the platelet count fails to return to basline at the beginning of subsequent courses. Platelet transfusion can be helpful and should be used according to standard guidelines. (BCSH guidelines 2003).

Immune system

Immune suppression may occur but is not severe. Cases of Herpes Zoster have been reported, and should be treated with acyclovir, however prophylaxis with this agent is not routinely recommended. Prophylaxis with co-trimoxazole is not essential but may be considered as a sensible precaution. There are no data on the use of irradiated blood products and they are not considered necessary unless there are other indications present for the use of irradiated blood or blood products.

Nervous system

Effects on the nervous system are common and require close monitoring. Central effects such as tiredness and fatigue may occur, and can be difficult to manage, but may respond to dose reduction. Peripheral neuropathy is the most severe side effect. This is mainly sensory but motor neuropathy can also occur. Dose reduction or withdrawal according to the nomogram below may be required to control neuropathic problems. Usually symptoms will resolve if the bortezomib is dose reduced or stopped at an early stage, occasionally however, there is persistent damage. Painful progressive peripheral neuropathy is an absolute indication to discontinue treatment. It is not possible to predict who will develop neuropathy but patients with previous peripheral neuropathy are at greater risk although this is not an absolute

contraindication to the initiation of treatment. Patients previously exposed to vincristine, thalidomide or who have diabetes are at greater risk and management of myeloma now needs to take into account the long term risks and management of peripheral neuropathy. There are no clear data to guide prophylactic strategies for peripheral neuropathy ; anecdotally folate and vitamin B12 levels may be low in myeloma patients and should be checked and replacement given as necessary. Vitamin supplements can be used including folic acid, vitamin B complex, pyridoxine, together with L-carnitine, α-lipoic acid and L-glutamine, but there is no evidence base to support this approach. Treatment of established painful peripheral neuropathy follows a standard approach including pharmacological intervention with amitriptyline or gabapentin and if severe, referral to a pain clinic is an appropriate strategy.

As a consequence of damage to the autonomic nervous system, postural hypotension may also occur. This can be effectively managed by ensuring adequate hydration and the use of fluid transfusions at the time of the bortezomib infusion (500ml over 1-2 hours). Dose reductions may also be effective if this does not work.

Gastrointestinal system

Gastrointestinal side effects are common and variable. Bortezomib may cause nausea and is mildly emetogenic; metoclopramide and ondansetron are effective in preventing this. Diarrhoea and constipation may also occur and this needs to be effectively managed using standard approaches. Bortezomib is metabolised by the liver with only a small proportion being extracted via the kidney. There are no data on the use of bortezomib in patients with impaired liver function, although its use in this setting may be appropriate, it will require careful monitoring.

Renal system

A small proportion of bortezomib is excreted by the kidneys and consequently care should be exercised with its use in patients with impaired renal function. There is limited experience in the use of bortezomib in patients with renal failure and creatinine clearances of less than 30ml/minute. However in cases where it has been used it has been safe and renal function has improved in a proportion of cases. Even at moderate levels of creatinine clearance, care needs to be exerted. At lower levels

or in patients on dialysis, experience with the use of bortezomib is limited however it seems to be feasible starting at a dose of 1.0mg/m^2 at the standard daily intervals (days 1,4,8,and 11). Obviously patients treated in this way need to be closely monitored. Tumour lysis can occur and should be watched for; consequently allopurinol should be used during initial cycles as well as maintaining hydration.

Cardiovascular system

Cardiac arrhythmias have been described but are rare. Other cardiac complications are similarly rare. Venous thrombotic events are not reported to be increased compared to other therapeutic approaches.

Miscellaneous

A number of miscellaneous side effects have been described including mild skin rashes and fever. Diabetes may be exacerbated by the use of bortezomib.

Suggested dose reduction schedule

Before each dose patients should be evaluated for possible toxicities and the dose of bortezomib reduced or withheld if necessary. Bortezomib-related neuropathic pain or peripheral sensory neuropathy must be closely monitored as either dose reduction or withdrawal may be required. The following table contains the recommended dose modifications. If the toxicity does not resolve after dosing has been withheld for 2 weeks, then the patient should be discontinued from treatment.

Recommended Dose Modifications for Bortezomib-Related Neuropathic Pain and/or Peripheral Sensory Neuropathy	
Severity of Peripheral Neuropathy Signs and Symptoms	**Modification of Dose and Regimen**
Grade 1 (paraesthesia 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 bortezomib to 1.0 mg/m2

Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold bortezomib therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of bortezomib at 0.7 mg/m2 and change treatment schedule to once per week.
Grade 4 (Permanent sensory loss that interferes with function)	Discontinue bortezomib

If the neutrophil count falls below $0.5x10^9$/l the drug should be withheld until the neutropenia has resolved and then the dose reduced to 1.0mg/m^2 or 0.7mg/m^2. If the neutropenia is felt to be due to marrow infiltration rather than poor marrow reserve then continuing with the same bortezomib dose and using G-CSF may be a useful therapeutic option. Dose reduction or temporary withdrawal of bortezomib may also be required for thrombocytopenia, although if this is felt to be due to marrow infiltration by myeloma then support with platelet transfusions while continuing with twice weekly dosing is appropriate.

Bortezomib should be withheld at the onset of any grade 3 or grade 4 non-haematologic toxicity for up to 2 weeks until the toxicity returns to at least grade 2. Dose reduction to either 1.0 mg/m^2 or 0.7 mg/m2 should then be considered. If grade 3 or 4 toxicity persists then bortezomib treatment should be withdrawn.

Clinical organisation and delivery of care

Currently patients on bortezomib are seen frequently in the outpatient setting. This lends itself to the use of a clinical nurse specialist who can assess side effects, particularly neurotoxicity and arrange for appropriate management. In future as experience with its use grows delivering it in the home setting may be appropriate but will require close monitoring by either medical or nurse practitioners experienced with its use. While it does not cause irreversible myelosuppression, regular blood tests are required to assess the need for red cell and platelet transfusion especially for those patients with initial low blood counts. Regular biochemical assessment is also

important although bortezomib is not nephrotoxic, and in many cases renal function will improve.

Practical and financial considerations

In the SUMMIT trial the median number of cycles delivered has been 4.71. The use of bortezomib in this trial was based on the introduction of dexamethasone after 2 cycles if progression had occurred or after 4 cycles if no response to single agent bortezomib was seen. However, as it has been established that responses with the combination of bortezomib and dexamethasone are approximately 20% greater than with single agent bortezomib, we would recommend that this combination should be used for all patients, unless there is a specific clinical reason to avoid dexamethasone. Data from studies to date would suggest that the majority of responses are detectable within 2-3 cycles (Jagganath *et al* 2004, Richardson *et al* 2003, 2004), and therefore patients should be closely monitored during the early treatment phase with a view to stopping treatment after 3-4 cycles if no response is seen. A few responses have been seen after this number of cycles but the basis of such late responses is difficult to rationalise and currently continuing treatment would be difficult to justify. In future it seems likely that bortezomib will be used more widely in combination with drugs including cytotoxics, thalidomide and other new agents.

A practical understanding of the clinical use of bortezomib has significant implications for financial planning. Not all patients with myeloma will be suitable for bortezomib. It is likely to be used more widely in younger patients. A reasonable estimation of the number of patients eligible for treatment with bortezomib in the second relapse setting is approximately 33%. Based on an annual incidence rate of 3,000 cases, we estimate from standard survival curves, that 1,500 will be alive and eligible for some form of treatment at second relapse. Thus approximately 500 cases annually in the UK will be potential recipients of bortezomib. Bortezomib induces responses in up to 50% of cases and of patients who are going to respond the majority can be identified in the early treatment cycles, so it is reasonable to suggest that non-responders after 3-4 cycles could be discontinued from treatment. Consequently the financial impact of bortezomib to the health service will be less then superficial estimates based on myeloma incidence data alone would suggest.

If it is estimated that approximately 8.5 patients per million population may be suitable for treatment at an average cost of £14,000 per patient the budget impact would be in the region of £120,000 per million of the population. This estimate ignores any savings, which would result from stopping non-responding patients early. A recent economic evaluation of the impact of bortezomib suggested that the quality of life utility score is 0.65 (where 1 is perfect health and 0 is death). This translates into a cost per life year saved of £21,728 (£17,000-£33,000) and a cost per quality adjusted life year (QALY) of £33,472 (£26,000-£51,000), which is in line with other novel cancer therapies (Bagust *et al*, 2004).

Conclusions

Bortezomib is a proteasome inhibitor which is effective in the treatment of myeloma patients. It works via a novel mechanism and has been shown to give responses in heavily pre-treated patients. In a phase III randomised trial of relapsed patients it has been shown to be better than standard dexamethasone alone. There is, therefore, good clinical evidence for the use of bortezomib, the activity of which is increased in combination with dexamethsone, as a treatment for second relapse in myeloma. It also has a clearly identifiable role for the treatment of patients at first relapse who have been exposed to a range of therapies including thalidomide as either induction therapy or as maintenance treatment. These patients are highly likely to be resistant to a range of treatment options, and bortezomib has been shown to be active in this setting and preliminary data based on small numbers of patients suggest that the response rate is greater in first compared to subsequent relapses. Currently the best order in which to use bortezomib in the context of other novel agents including thalidomide is unknown. However, from a clinical perspective, the availability of multiple effective non-cross reactive chemotherapy regimens is highly beneficial for patients. The aims of therapy in relapsed myeloma are to maximise quality and duration of survival, further means to achieve disease control form a key component in achieving these objectives. The availability of a range of effective regimens, from which the most appropriate therapy can be chosen for the treatment of presentation and relapse, represents a big step forward for myeloma patients. The inevitable consequence of this advance however is a requirement for increased funding as the traditional approaches although cheap are ineffective and associated with poor outcomes.

- Bortezomib is licensed for use at first relapse. Clinical evidence would suggest benefits when combined with dexamethsone as a treatment for second relapse, as well as for the treatment of patients at first relapse who have been exposed to a range of therapies including thalidomide as either induction therapy or as maintenance treatment.
- It is given at a dose of 1.3 mg/m^2 on days 1, 4, 8 & 11 as an i.v. push.
- Strict attention should be given to the spacing of the drugs. It should not be given at more frequent intervals than 72hours.
- Side effects include constipation, diarrhoea and nausea, all of which need to be managed appropriately.
- It can cause peripheral neuropathy and if painful peripheral neuropathy occurs the drug should be stopped immediately.
- Prophylaxis for neuropathy may be useful but evidence supporting its use is limited.
- Myelosuppression and thrombocytopenia are transient and reversible.
- Combinations are possible but appropriate doses are not currently well defined.

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