Clinical impact review

Bortezomib: the evidence of its clinical impact in multiple myeloma

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Abstract

Introduction: Multiple myeloma is a relatively common and incurable form of hematologic malignancy for which there is currently no single standard therapy. Bortezomib inhibits the 20S proteasome involved in the degradation of intracellular proteins, induces apoptosis, reverses drug resistance in multiple myeloma cells, and influences their microenvironment by blocking cytokine circuits, cell adhesion and angiogenesis *in vivo*.

Aims: The objective of this review is to evaluate the evidence for the use of bortezomib in the treatment of multiple myeloma.

Evidence review: In patients with relapsed multiple myeloma bortezomib significantly prolongs overall survival and time to progression, and improves response rates, duration of response, and quality of life compared with oral high-dose dexamethasone. Although the incidence of grade 4 adverse events was similar, grade 3 events and herpes zoster infections occur more frequently in patients treated with bortezomib than with high-dose dexamethasone. Evidence from a pharmacoeconomic study indicates that the benefits of bortezomib compared to thalidomide plus best standard care may be achieved at a reasonable cost.

Clinical value: Bortezomib is a valuable treatment option in the management of relapsed multiple myeloma that improves survival and delays disease progression compared with oral high-dose dexamethasone treatment, albeit with an increased incidence of some adverse events such as grade 3 thrombocytopenia and neutropenia.

Key words: bortezomib, evidence, multiple myeloma, outcomes, treatment

Core evidence clinical impact summary for bortezomib in relapsed refractory multiple myeloma

Outcome measure	Evidence	Implications
Patient-oriented evidence		
Prolongation of OS	Substantial	Median OS is significantly longer with bortezomib than with standard high-dose dexamethasone therapy, maintained during extended follow-up
Improvement of 1-year survival rate	Substantial	Significantly more patients survive for 1 year with bortezomib than with standard high-dose dexamethasone therapy
Prolongation of TTP	Substantial	Median TTP is significantly longer with bortezomib than with standard high-dose dexamethasone therapy
Adverse events	Moderate	A significantly higher proportion of patients treated with bortezomib than with standard high-dose dexamethasone therapy report grade 3 adverse events, mainly thrombocytopenia or neutropenia. However, the rates of grade 4 adverse events and serious adverse events appear to be similar with bortezomib and high-dose dexamethasone
Reduction of skeletal events	No evidence	Further studies required
Infections	Limited	The rate of grade ≥3 infection did not differ significantly between bortezomib and high-dose dexamethasone. However, a significantly higher proportion of patients treated with bortezomib than with standard high-dose dexamethasone therapy experience herpes zoster infections
Improvement of quality of life	Moderate	Patient-reported outcomes improve with bortezomib
Disease-oriented evidence		
Improvement of response rate (complete plus partial response)	Substantial	A significantly higher proportion of patients treated with bortezomib than with standard high-dose dexamethasone therapy respond to treatment
Duration of response	Substantial	Bortezomib therapy produces durable responses
Economic evidence		
Cost effectiveness	Limited	Further studies required

OS, overall survival; TTP, time to progression.

Scope, aims, and objectives

Multiple myeloma is an incurable form of hematologic cancer. Bortezomib (LDP-341, MG-341, MLN-341, PS-341, Velcade®) inhibits the 20S proteasome involved in the degradation of intracellular proteins, including those affecting cell cycle regulation in mammalian cells. The objective of this review is to evaluate the evidence for the use of bortezomib in the treatment of relapsed or refractory multiple myeloma.

Methods

The English language medical literature was reviewed for appropriate articles relating to bortezomib for the treatment of multiple myeloma. The following databases were searched on September 2, 2005 using the search terms "Bortezomib OR LDP-341 OR MG-341 OR MLN-341 OR PS-341 OR Velcade AND multiple myeloma". The cut-off date was from the beginning of the database to the date of the search unless otherwise stated.

- PubMed, http://www.ncbi.nlm.nih.gov/entrez, 1966 to date
- EMBASE, http://www.datastarweb.com, 1974 to date
- Centre for Reviews and Dissemination (CRD) databases [Database of Abstracts of Reviews of Effects (DARE); Health Technology Assessment (HTA); National Health Service (NHS) Economic Evaluations Database (NHSEED)], http://www.york.ac.uk/inst/crd/crddatabases.htm
- Cochrane Database of Systematic Reviews (CDSR), http://www.cochrane.org
- Clinical Evidence (BMJ), http://www.clinicalevidence.com
- BIOSIS, http://www.datastarweb.com
- National Guideline Clearinghouse, http://www.guideline.gov
- National Institute for Health and Clinical Excellence, http://www.nice.org.uk
- Clinical trial registers, http://www.clinicaltrials.gov, http://www.clinicalstudyresults.org
- American Society of Clinical Oncology, http://www.asco.org/asco/publications

Following hand-searching, no systematic reviews were identified for the use of bortezomib in multiple myeloma, two papers and two abstracts were of level 2 evidence, and there were four papers and one abstract of level ≥3 evidence (including economic evidence) (Table 1).

A further search of the English language literature on PubMed using the search terms "bortezomib in multiple myeloma," "clinical trial," "meta analysis," "randomized controlled trial," and "humans" was conducted with the date limits September 1, 2005 to May 24, 2006.

Table 1 | Evidence base included in the review

Category	Number of records	
	Full papers	Abstracts
Initial search	209	31
records excluded	202	25
records included	7	6
Additional studies identified	2	0
Search update, new records	11	28
records excluded	2	16
records included	9	12
Level 1 clinical evidence	1	1
Level 2 clinical evidence	5	4[a]
Level ≥3 clinical evidence	11[a]	12[a]
trials other than RCT	11	12
case reports	0	0
Economic evidence	1	1

For definition of levels of evidence, see Editorial Information on inside back cover.
[a]Five of these records are extensions of original trials and/or pooled analyses.
RCT, randomized controlled trial.

The limits were imposed to provide specificity to the search. Eleven records were found, of which two were excluded because they were nonsystematic reviews (n=1) or a case study (n=1). A further PubMed search between May 25 and June 26, 2006 identified two additional relevant studies. Finally, a search of the 2005 Annual Meeting of the American Society of Hematology (http://www.hematology.org) revealed 28 further abstracts. Hand-searching resulted in 12 being included; the remaining subanalyses (n=1), interim analysis of phase I/II trials (n=4), use in previously untreated patients (n=6), observational usage studies (n=1), case series (n=1), off-label regimen (n=1), and duplicates (n=2) were excluded.

Disease overview

Multiple myeloma is a malignant proliferation of plasma cells which is characterized by the presence of paraproteins in the serum, bone marrow infiltration, bone destruction, and renal impairment (ACS 2005a; NCI 2005). With conventional treatments, multiple myeloma remains an incurable disease, and patients have a median survival of 3–4 years with a 5-year relative survival rate of approximately 32% (UK Myeloma Forum Guidelines Working Group 2001; Barlogie et al. 2004; ACS 2005a).

Epidemiology

Multiple myeloma accounts for about 10% of all hematologic malignancies (ACS 2005b). In the USA and the UK, respectively, about 15 000 and 2500–3000 new cases of multiple myeloma are reported annually (Joshua & Gibson 2002; Kyle et al. 2003;

Morgan & Davies 2005). Potential risk factors for multiple myeloma that have been studied include: declining immune function, genetic factors, certain occupations, exposure to radiation, and exposure to certain chemicals (MMRF 2005a; NCI 2005). However, no strong associations between potential risk factors and multiple myeloma have been noted and, in most cases, individuals who develop multiple myeloma have no clear risk factors (MMRF 2005a; NCI 2005). Multiple myeloma is predominantly a disease of the elderly, with most cases diagnosed in patients over 65 years of age and the level of risk seems to be highest among groups of African ethnic origin (NCI 2005). A history of monoclonal gammopathy of undetermined significance, in which abnormal plasma cells make a low level of monoclonal immunoglobulin [myeloma (M)] proteins, has also been associated with increased risk of multiple myeloma (NCI 2005). However, most people with these known risk factors do not get multiple myeloma (NCI 2005). Unfortunately, the economic burden imposed by multiple myeloma has not been well quantified (Mehta et al. 2004).

Clinical features

The clinical course of patients with multiple myeloma varies markedly (Harousseau et al. 2004). Bone marrow infiltration due to overgrowth of plasma cells leads to anemia, thrombocytopenia, and leukopenia. Active bone resorption, due to increased osteoclast activity, also leads to bone pain, vertebral collapse, fractures, hypercalcemia, and renal impairment (ACS 2005a; NCI 2005). In addition, reductions in the normal levels of immunoglobulins contribute to the tendency for patients with multiple myeloma to have recurrent infections (MMRF 2005a; NCI 2005).

Diagnosis

The diagnosis of multiple myeloma is often made incidentally during routine blood tests for other conditions such as anemia. Laboratory tests performed on blood and/or urine to help confirm a diagnosis of myeloma include: complete blood count; chemistry profile; serum beta 2-microglobulin (beta 2-M); C-reactive protein; quantitative immunoglobulins; serum and urine protein electrophoresis; and 24-hour urine protein. The quantification of serum-free immunoglobulin light chain levels (FLC assay) and kappa/lamda ratio can be used as an alternative to quantifying urinary light chains. The serum tests are particularly useful for diagnosis and monitoring free light chain only myeloma and patients in whom the serum and urine is negative on immunofixation (nonsecretory myeloma). In addition, X-ray imaging, magnetic resonance imaging (MRI), and computerized tomography (CT) scans may be used to assess changes in bone structure as well as number and size of bone lesions; bone marrow aspiration/biopsy is used to assess the number of plasma cells in bone marrow (ACS 2005a; MMRF 2005b; NCI 2005; UK Nordic Guidelines Working Group 2005).

Disease staging

The Durie–Salmon staging system (Durie & Salmon 1975) is the most commonly utilized staging system for patients with multiple myeloma (Table 2) (MMRF 2005b).

Table 2 | The Durie-Salmon and ISS Myeloma staging systems (Greipp et al. 2003; MMRF 2005b)

Stage	Durie–Salmon criteria	ISS criteria
I	All of the following: • Hemoglobin >10 g/dL • Serum calcium normal or ≤12 mg/dL • Bone X-ray, normal bone structure (scale 0) or solitary bone plasmacytoma only • Low M-component production rate — IgG <5 g/dL; IgA <3 g/dL • Bence Jones protein <4 g/24 h	Beta 2-M <3.5 and albumin ≥3.5 mg/L (median survival 62 months)
II	Neither stage I nor stage III	Neither stage I nor stage III[a] (median survival 45 months)
III	One or more of the following: • Hemoglobin <8.5 g/dL • Serum calcium >12 mg/dL • Advanced lytic bone lesions (scale 3) • High M-component production rate — IgG >7 g/dL; IgA >5 g/dL — Bence Jones protein >12 g/24 h	Beta 2-M >5.5 mg/L (median survival 29 months)

Durie–Salmon subclassifications (either A or B):
A: Relatively normal renal function (serum creatinine <2.0 mg/dL)
B: Abnormal renal function (serum creatinine ≥2.0 mg/dL)
[a]In the ISS stage II there are two subcategories:
Serum beta 2-M <3.5 mg/L, but serum albumin <3.5 g/dL, or
Serum beta 2-M 3.5–5.5 mg/L irrespective of the serum albumin level
Beta 2-M, beta 2-microglobulin; h, hour; Ig, immunoglobulin; ISS, International Staging System; M, myeloma.

In this system, the clinical stage of disease (stage I, II, or III) is based on four measurements: levels of M protein, number of bone lesions, hemoglobin values, and serum calcium levels. The stages are also classified further (as A or B) according to renal function. However, increasingly, physicians are relying less on the Durie–Salmon staging system and more on biologically relevant markers as prognostic indicators when making treatment choices. A new International Staging System (ISS) for myeloma has recently been proposed, based on measurement of serum levels of beta 2-M and albumin (Table 2), that separates patients into three prognostic groups irrespective of type of therapy (Greipp et al. 2003), and which appears to provide better discrimination between staging groups. Incorporation of cytogenetic data into the ISS may further improve staging (UK Nordic Guidelines Working Group 2005).

Evaluation of response

In 1998, the European Group for Blood and Marrow Transplant (EBMT) proposed strict criteria for the assessment of complete response (CR) in patients with multiple myeloma undergoing stem cell transplantation (SCT) (Bladé et al. 1998). These criteria include the complete absence of M protein by immunofixation techniques as well as by serum and urine protein electrophoresis (SPEP and UPEP). In addition, partial response (PR) was defined as a reduction of M protein in serum of at

least 50% and a reduction in urine of at least 90%. A minimal response (MR) was defined as a reduction of M protein in serum of 25–49% and a reduction in urine of 50–89%. Progressive disease (PD) was defined by any of the following: an increase of M protein in serum or urine of >25%, an increase in bone marrow plasma cells of >25%, new or increased bone lesions or plasmacytomas, or new hypercalcemia. Furthermore, CR, PR, and MR have to be confirmed by repeated measurements of M protein in serum and urine after 6 weeks, and PD has to be confirmed by repeated measurements of M protein in serum and urine after 1–3 weeks. Near-complete response (nCR), a subcategory of PR, was defined as a CR with a positive immunofixation test (lower limit of detection, 0.15–0.25 mg/mL). Unfortunately, not all studies in patients with multiple myeloma have used the EBMT criteria and therefore, because they have used less-stringent criteria, it is not possible to directly compare response rates between treatments.

In clinical trials in patients with multiple myeloma it has been regarded as important to distinguish between agents that produce good but transient responses and those for which overall responses may be less but which may be maintained for longer (Morgan & Davies 2005). In view of the incurable nature of multiple myeloma, overall survival (OS) has traditionally been considered to be the major endpoint for a single line of treatment. However, patients with myeloma typically receive multiple courses of treatment during the course of the disease, the sequencing of which may or may not be important. In view of this there is a need to distinguish between survival and progression, and also to recognize that OS may be affected by subsequent treatment regimens (Morgan & Davies 2005).

Goals of therapy

Treatment regimens for multiple myeloma are designed to meet a variety of different therapeutic goals, which can include: eradication of all evidence of disease; control of disease activity to prevent damage to other organs; preservation of normal performance and quality of life for as long as possible with minimal intervention; provision of lasting relief of pain and other disease symptoms; and long-term management of myeloma that is in remission, when applicable (MMRF 2005a).

Current therapy options for multiple myeloma

There is currently no single standard therapy for active multiple myeloma although, since the introduction of high-dose melphalan treatment (McElwain & Powles 1983), the superiority of high-dose therapy (HDT) with SCT over conventional chemotherapy in selected patients with newly diagnosed disease has been established in two large-scale, randomized controlled trials (Attal et al. 1996; Child et al. 2003). However, HDT is not suitable for all patients. Recently, greater understanding of the pathogenesis of multiple myeloma has led to the introduction of novel therapies such as thalidomide, lenalidomide, and bortezomib (Singhal et al. 1999; Richardson et al. 2002; Cavenagh & Oakervee 2003; Richardson et al. 2003; Richardson et al. 2005a).

Conventional chemotherapy

The benefit of single-agent cyclophosphamide was shown to be equivalent to the alkylating agent melphalan in an early Medical Research Council (MRC) trial (MRC 1980) and, in the 1980s, a number of trials investigated the use of combination chemotherapy compared to single-agent melphalan. In particular, the ABCM regimen (doxorubicin, carmustine, cyclophosphamide, and melphalan) was compared to melphalan alone in the MRC Myeloma V trial which showed significant benefits in favor of the combination in terms of achievement of plateau disease and in OS (MacLennan et al. 1992). In contrast, in a collaborative worldwide overview of randomized trials of combination chemotherapy versus melphalan plus prednisone (MP), no evidence of any significant difference in mortality between combination chemotherapy and MP was noted (MTCG 1998). However, unlike the ABCM regimen, relatively few of the combination regimens included the use of an anthracycline such as doxorubicin.

High-dose chemotherapy, corticosteroids, and stem cell transplants

The escalation of melphalan dosage to 140 mg/m^2 was found to improve response rates, with CR reported in approximately 30% of patients, and it also produced evidence of bone healing (McElwain & Powles 1983). Subsequently, the development of autologous SCT has allowed escalation of melphalan dosage to 200 mg/m^2 and has led to further improvements in CR rates compared with standard doses of oral melphalan (Barlogie et al. 1999; Davies et al. 2001). High response rates (84%) have also been reported with high-dose dexamethasone, in combination with vincristine and doxorubicin (VAD), as first-line therapy for multiple myeloma (Samson et al. 1989). The major advantage of this regimen is its lack of adverse effects on the hematopoietic stem cell compartment (Samson et al. 1989), which makes it useful for harvesting stem cells prior to autologous transplantation. However, it has been estimated that approximately 85% of the therapeutic effect of VAD can be attributed to the dexamethasone component (Alexanian et al. 1992; Sonneveld et al. 2001). The HDT strategy that has been developed consists of initial treatment with VAD to induce disease response, at which point hematopoietic stem cells are harvested. These cells are then used to support high-dose melphalan treatment in order to consolidate the responses obtained. Analyses of the effect of response after high-dose treatment have suggested that patients achieving a CR had better progression-free survival (PFS) and OS than those who did not (Barlogie et al. 1999; Lahuerta et al. 2000; Davies et al. 2001). It has also been shown that two successive SCTs significantly improves OS compared with single SCT following HDT (Attal et al. 2003).

Thalidomide

Early studies on the use of thalidomide as a single agent in patients with relapsed refractory multiple myeloma produced a promising 30% response rate (Singhal et al. 1999). As thalidomide is not a cytotoxic agent these results provided a rationale for

adding it to standard treatment regimens for patients deemed unsuitable for SCT. For example, preliminary studies have suggested that a CR rate of 22%, comparable to that achieved with HDT, can be achieved by adding thalidomide to MP chemotherapy (Palumbo et al. 2003). This regimen also produces higher response rates and 3-year survival rates than MP alone (Palumbo et al. 2006). Low-dose thalidomide plus dexamethasone is better than conventional chemotherapy as a first salvage regimen in patients with relapsed or refractory multiple myeloma (Palumbo et al. 2004). The dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide (DT-PACE) regimen has also been developed for use in refractory patients who are candidates for HDT (Lee et al. 2003). In addition, the integration of thalidomide into combination chemotherapy regimens for the treatment of previously untreated multiple myeloma is currently under investigation.

Radiation therapy

Hemibody radiation therapy for multiple myeloma has been used as a consolidation following induction combination chemotherapy or as salvage therapy for chemotherapy-resistant myeloma (Thomas et al. 1984; Mackenzie et al. 1992). Total body irradiation can also be used as a component of ablative therapy before SCT.

Unmet needs in the treatment of multiple myeloma

Ultimately, there is a need to be able to characterize multiple myeloma as a treatable condition in the future rather than as an incurable condition, through improvements in OS, delaying disease progression, and improving CR rates. In view of this, the development of treatments with mechanisms of action distinct from cytotoxic chemotherapy would be advantageous and improvements in the efficacy of first-line treatments are highly desirable. There is also a paucity of data on the economic burden imposed by multiple myeloma and on the cost effectiveness and cost utility of treatments.

Clinical evidence for the role of bortezomib in the treatment of multiple myeloma

The 20S proteasome plays a crucial role in the maintenance of intracellular homeostasis in eukaryotic cells (Adams 2004). Bortezomib (LDP-341, MG-341, MLN-341, PS-341, Velcade) is a dipeptide boronic acid that reversibly inhibits the chymotrypsin-like proteolytic activity site of the 20S proteasome (Adams 2002), which induces apoptosis, reverses drug resistance in multiple myeloma cells, and which influences their microenvironment by blocking cytokine circuits, cell adhesion, and angiogenesis *in vivo* (Hideshima et al. 2001; LeBlanc et al. 2002; Hideshima et al. 2003).

Bortezomib received full approval in 2005 from the US Food and Drug Administration (FDA) for the treatment of multiple myeloma patients who have received at least one prior therapy (Kane et al. 2006) on the basis of the results of safety and efficacy data from the Assessment of Proteasome inhibition for EXtending remissions (APEX) trial. This large international trial included 669 patients with relapsed multiple myeloma who received either intravenous bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11 of cycles one through eight (21-day cycles) and on days 1, 8, 15, and 22 of cycles nine to eleven (35-day cycles), for a maximum treatment period of 273 days; or oral high-dose dexamethasone (40 mg) on days 1 to 4, 9 to 12, and 17 to 20 of cycles one through four (35-day cycles) and on days 1 to 4 of cycles five through nine (28-day cycles), for a maximum treatment period of 280 days (Richardson et al. 2005a).

The first approval of bortezomib in patients with relapsed or refractory multiple myeloma was secured in 2003 on the basis of two generally well-conducted phase II clinical trials. A small-scale, open-label, randomized Clinical Response and Efficacy Study of bortezomib in the Treatment of refractory myeloma (CREST) was performed in 54 patients who received intravenous bortezomib 1.0 or 1.3 mg/m^2 on days 1, 4, 8, and 11 in a 21-day cycle for up to eight cycles with response rates of 30 and 38%, respectively, to bortezomib alone (Jagannath et al. 2004). In addition, a multicenter, nonrandomized, open-label, phase II Study of Uncontrolled Myeloma Managed with proteasome Inhibition Therapy (SUMMIT) was conducted in which 27% of 202 heavily pretreated patients who received intravenous bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11 in a 21-day cycle for up to eight cycles had CR or PR to bortezomib alone (Richardson et al. 2003).

Extensions and subanalyses of APEX, CREST, and SUMMIT have been reported (Berenson et al. 2005; Lonial et al. 2005; Richardson et al. 2005a; Dubois et al. 2006; Richardson et al. 2006). In addition, there are numerous reports of the use of bortezomib in previously untreated patients and in combination regimens. Since these are in abstract form, they are referenced but full appraisal is not possible.

Patient-oriented evidence

There is good evidence of significant efficacy for bortezomib in the prolongation of OS, improvements in 1-year survival rate, and prolongation of time to progression (TTP) (Table 3) in patients with relapsed or refractory multiple myeloma.

Overall survival

In the APEX trial, OS was significantly longer among patients who received bortezomib, both for those who had received one previous treatment (hazard ratio 0.42; P=0.01) and for those who had received more than one previous treatment (hazard ratio 0.63; P=0.02) (Richardson et al. 2005a). The survival advantage for patients receiving treatment with bortezomib was retained even though 147 patients (44%) in the dexamethasone group, who had disease progression, were crossed over to receive bortezomib in a companion study. As a result of early closure of the dexamethasone group, the median follow-up of surviving patients in both groups was limited to 8.3 months and the median survival time could not be calculated (Richardson et al. 2005a) (Table 3). A subsequent report updated the survival analysis based on median follow-up of 22 months (Richardson et al. 2005c). Median OS was 29.8 months in the bortezomib group compared with 23.7 months

Table 3 | Summary of outcome evidence for bortezomib in APEX, CREST, and SUMMIT: overall survival, 1-year survival rate, and median time to progression/progression-free survival in patients with multiple myeloma

Level of evidence	Design	Treatment and dose	Outcomes			Reference
			OS	1-year survival rate	TTP/PFS	
2	Open, RCT, n=669 pts with relapsed multiple myeloma	BOR 1.3 mg/m^2 (i.v.)	OS was significantly longer with BOR than DEX, in pts with one or >1 previous treatment (HR 0.42 and 0.63, respectively)	BOR 80% (P=0.003)	Median TTP 6.22 months (189 d) (P<0.0001)	Richardson et al. 2005a (APEX)
		High-dose DEX 40 mg (oral)		DEX 66%	Median TTP 3.49 months (106 d)	
2	Open, RCT, n=669 pts with relapsed multiple myeloma	BOR 1.3 mg/m^2 (i.v.)	Median OS 29.8 months	BOR 80% (P=0.0002)	Median TTP 6.2 months	Richardson et al. 2005c (APEX update)
		High-dose DEX 40 mg (oral)	Median OS 23.7 months	DEX 67%	Median TTP 3.5 months	
2	Open, RCT, n=54 pts with relapsed refractory multiple myeloma	BOR 1.3 mg/m^2 (i.v.)	Median OS not reached	–	Median TTP 11.0 months (333 d)	Jagannath et al. 2004 (CREST)
		BOR 1.0 mg/m^2 (i.v.) (alone or in combination with oral DEX 20 mg)	Median OS 26.7 months (813 d)		Median TTP 7.0 months (212 d)	
3	Open, n=202 pts with relapsed refractory multiple myeloma	BOR 1.3 mg/m^2 (i.v.) (alone or in combination with oral DEX 20 mg)	Median OS 17.2 months	–	Median TTP 7 months with BOR 1.3 mg/m^2 vs 3 months during the last treatment prior to enrollment (P=0.01)	Richardson et al. 2003, 2004, 2006 (SUMMIT)

BOR, bortezomib; d, day; DEX, dexamethasone; HR, hazard ratio; i.v., intravenous; M, melphalan; OS, overall survival; PFS, progression-free survival; pts, patients; RCT, randomized controlled trial; TTP, time to progression.

with dexamethasone (P=0.02), despite more than 62% of dexamethasone patients crossing over to bortezomib. Median survival appeared to be longer for patients receiving bortezomib earlier rather than later.

The two open-label, phase II clinical trials [Richardson et al. 2003 (SUMMIT); Jagannath et al. 2004 (CREST)], and an observational analysis of compassionate use of bortezomib (Wu et al. 2005), have also provided some evidence on OS in patients with relapsed or refractory multiple myeloma although OS was not a primary study endpoint and/or follow-up was of insufficient duration. In the CREST trial, median survival was not reached for all patients randomized to both bortezomib dose groups (1.3 mg/m^2 vs 1.0 mg/m^2), during a median duration of follow-up of 26 months. However, the study was only powered to assess the response rate to bortezomib and thus the patient population (n=54) was too small to allow an adequate assessment of survival (Jagannath et al. 2004). In contrast, in the nonrandomized SUMMIT trial, updated median survival among all 202 patients with relapsed or refractory multiple myeloma was 17.2 months (Richardson et al. 2004), and 17 months in 193 evaluable patients after extended follow-up (Richardson et al. 2006a). A subanalysis of the SUMMIT trial found that lower OS was associated with factors indicative of greater tumor burden (e.g. bone marrow plasma cell infiltration >50%, hypoalbuminemia, thrombocytopenia) (Richardson et al. 2005b).

1-year survival rate

The APEX trial also provides good supporting evidence that bortezomib produces a superior level of survival after 1 year than conventional therapy (oral high-dose dexamethasone) in patients with relapsed multiple myeloma. The between-treatment difference was highly statistically significant (Table 3) and reflected a 41% reduction in the risk of death in the bortezomib group during the first year after enrollment (Richardson et al. 2005a). The updated follow-up to APEX showed 1-year survival rates were of 80 and 67%, respectively (P=0.0002), for bortezomib and dexamethasone (Richardson et al. 2005c). A systematic review (in abstract form) reported 1-year survival rates of 81% for bortezomib compared with 67% for thalidomide (P<0.001; n=6 studies) (Prince et al. 2005).

A small-scale, open-label, nonrandomized study of bortezomib alone or in combination with dexamethasone in patients with previously untreated multiple myeloma has also estimated that the 1-year survival rate would have been 87% of patients. However, the calculation was

Table 4 | Summary of outcome evidence for bortezomib: adverse events in patients with multiple myeloma

Level of evidence	AE incidence	Comparators	Study population	Reference
2	Grade 3 AEs (61%) (P<0.01 vs DEX) Grade 4 AEs (14%) Serious AEs (44%) Grade 3/4 thrombocytopenia (30%) All (including grade 3) peripheral neuropathy (36%)	BOR 1.3 mg/m^2 (i.v.)	n=669 pts with relapsed multiple myeloma	Richardson et al. 2005a (APEX)
	Grade 3 AEs (44%) Grade 4 AEs (16%) Serious AEs (43%) Grade 3/4 thrombocytopenia (6%) All and grade 3 peripheral neuropathy (9%)	High-dose DEX 40 mg (oral)		
2	Combined grade 4 AEs (9%) Grade 3/4 thrombocytopenia (26%). All peripheral neuropathy (41%) Grade 3 peripheral neuropathy (9%)	BOR 1.3 mg/m^2 (i.v.) vs BOR 1.0 mg/m^2 (i.v.) (alone or in combination with oral DEX 20 mg)	n=54 pts with relapsed refractory multiple myeloma	Jagannath et al. 2004 (CREST)
3	Grade 4 AEs (14%) Grade 3/4 thrombocytopenia (31%) All peripheral neuropathy (34%) Grade 3 peripheral neuropathy (12%)	BOR 1.3 mg/m^2 (i.v.) (alone or in combination with oral DEX 20 mg)	n=202 pts with relapsed refractory multiple myeloma	Richardson et al. 2003 (SUMMIT)
3	Grade 3/4 thrombocytopenia (29%) Grade 3/4 diarrhea (11%) Grade 3/4 anemia (11%) Grade 3/4 neutropenia (10%)	BOR 1 or 1.3 mg/m^2 (i.v.) (alone or in combination with oral DEX 20 mg)	n=63 pts with relapsed refractory multiple myeloma	Berenson et al. 2005[a]
3	Grade 3/4 neutropenia (40%) Grade 3/4 thrombocytopenia (40%) Grade 3/4 anemia (28%)	BOR 0.7–1 mg/m^2 (in combination with M 0.025–0.25 mg/kg)	n=35 pts with relapsed refractory multiple myeloma	Berenson et al. 2006
3	Grade 3 thrombocytopenia (50% of cycles) Peripheral neuropathy (10% of cycles)	BOR 1.3 mg/m^2 (i.v.) (alone or in combination with oral or i.v. DEX 20 mg)	n=7 pts with relapsed refractory multiple myeloma	Lee et al. 2005a
3	Grade 3/4 thrombocytopenia (19%) Grade 3 leucopenia (5%) Grade 3 peripheral neuropathy (5%) Grade 3 vasculitis (5%)	BOR 1.3 mg/m^2 (i.v.)	n=21 pts with relapsed refractory multiple myeloma	Musto et al. 2006
4	All peripheral neuropathy (47%) Grade 3 peripheral neuropathy (20%) All thrombocytopenia (25%) Grade 3 thrombocytopenia (17%)	BOR 1.3 mg/m^2 (i.v.) [plus high-dose M and autologous stem cell support (n=29) or allogeneic SCT (n=8)]	n=50 pts with relapsed or refractory multiple myeloma	Wu et al. 2005

[a]Extension of CREST and SUMMIT.
AE, adverse event; BOR, bortezomib; DEX, dexamethasone; i.v., intravenous; M, melphalan; pts, patients; SCT, stem cell transplant.

based on a relatively short duration of follow-up (median 5.5 months) in a small number of patients (n=32) (Jagannath et al. 2005a).

Prolongation of TTP

There is evidence that bortezomib produces a highly statistically significant prolongation of TTP (median 6.22 months) compared to conventional therapy (median 3.49 months) in patients with relapsed multiple myeloma in the APEX trial (Richardson et al. 2005a) (Table 3). These results are consistent with those of the previous SUMMIT trial, which indicated that bortezomib alone or in combination with dexamethasone produced a significantly longer median TTP than the patients' last treatment prior to enrollment (Table 3) (Richardson et al. 2003). Of particular note in the APEX trial was the observation that median TTP was even longer (7.0 months) in bortezomib-treated patients who had received only one previous treatment (Richardson et al. 2005a). In the APEX trial, disease progression led to early discontinuation in 98 patients who received bortezomib (29%) and in 174 (52%) who received dexamethasone (P<0.001) (Richardson et al. 2005a).

Adverse events

The APEX trial provides supporting evidence for the tolerability profile of bortezomib in patients with relapsed multiple myeloma (Table 4) (Richardson et al. 2005a) which is consistent with the results of the CREST and SUMMIT trials (Richardson et al. 2003; Jagannath et al. 2004).

Gastrointestinal events, thrombocytopenia, and peripheral neuropathy occurred more frequently in the bortezomib group than in the dexamethasone group and grade 3 adverse events were significantly more frequent in the bortezomib group than in the dexamethasone group ($P<0.01$). Improvement or resolution of grade 2 or higher peripheral neuropathy was noted in 44 of 87 patients (51%) in whom it developed during bortezomib treatment (median time to resolution 107 days). In an updated analysis of APEX, 120 of 331 patients developed peripheral neuropathy, including 91 with grade ≥2 (San Miguel et al. 2005). Of these, 30 had grade ≥3, and 68 required dose modification including 31 who discontinued treatment. However, neuropathy improved in 26 of 37 patients requiring dose modification (all with complete resolution of symptoms in a median of 78 days), in 19 of the 31 patients discontinuing bortezomib (resolution in 17) within 121 days, and in 12 of 23 within a median of 106 days without dose modification. Similarly, Richardson et al. (2006b) reported improvement or resolution of symptoms in 25 of the 35 patients with grade ≥3 neuropathy or who discontinued bortezomib treatment in the SUMMIT and CREST trials.

Thrombocytopenia was essentially transient and reversible in nature. The most common grade 3/4 adverse events (reported in >10% of patients in either group) were thrombocytopenia, anemia, and neutropenia in the bortezomib group in contrast with anemia in the dexamethasone group. However, the bortezomib group and the dexamethasone group had similar rates of grade 4 and serious adverse events. A total of 121 of 333 patients in the bortezomib group (37%) and 96 of 336 in the dexamethasone group (29%) had adverse events necessitating early discontinuation of treatment. A dose-escalation study reported a maximum tolerated dose of bortezomib 1 mg/m^2 (in combination with melphalan 0.1 mg/kg), with grade 4 neutropenia as the dose-limiting toxicity in two of six in the high-dose cohort (Berenson et al. 2006). An extension to the CREST and SUMMIT trials found that continued treatment with bortezomib for a median of 45 weeks did not result in cumulative toxicity (Richardson et al. 2005b).

The thrombocytopenia seen with bortezomib appears to be reversible, with platelet counts recovering between treatment cycles and the pretreatment count increasing during subsequent cycles (Lonial et al. 2005). It appears to be the result of a reversible effect on megakaryocytic function rather than direct cytotoxicity.

Skeletal events

Osteolytic lesions weaken the bones of patients with multiple myeloma, causing pain and increasing the risk of fractures (MMRF 2005a). The median time to a first skeletal event in patients with relapsed multiple myeloma treated with either bortezomib or dexamethasone could not be calculated in the APEX trial in which all patients also received treatment with bisphosphonates for bone disease (Richardson et al. 2005a). Data on skeletal events have not been reported in other published bortezomib studies in patients with multiple myeloma. Thus, it is currently not possible to evaluate whether bortezomib has any effect on the incidence of fractures in patients with multiple myeloma. However, a retrospective analysis of SUMMIT and APEX trial data has indicated that bortezomib treatment produced rapid elevation of alkaline phosphatase in responding patients (CR+PR) in the absence of other liver function abnormalities, which suggested that it may promote osteoblastic activity (Zangari et al. 2005).

Infections

The overall rate of grade ≥3 infections was not significantly different between the bortezomib and dexamethasone arms of the APEX trial (13 and 16%, respectively). However, the incidence of herpes zoster infection was significantly more frequent during treatment with bortezomib (13%) than with dexamethasone (5%; $P<0.001$). These infections were manageable with appropriate antiviral therapy (Richardson et al. 2005a) and in the SUMMIT study, grade 4 neutropenia, related febrile neutropenia, and sepsis were rare (Richardson et al. 2003).

Quality of life

APEX provides some evidence that bortezomib is associated with better health-related quality of life (HRQOL) than high-dose dexamethasone in the treatment of patients with relapsed multiple myeloma (Lee et al. 2005b). Two HRQOL instruments were used in APEX [European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 and Functional Assessment of Cancer Therapy Gynecologic Oncology Group—Neurotoxicity (FACT/GOG-NTX)]. Over 42 weeks a significant difference in favor of bortezomib was found for the primary endpoint of Global Health, as well as the secondary endpoints of Physical, Role, Cognitive, and Emotional Functioning, and the symptom scales of Nausea, Dyspnea, Sleep, Diarrhea, and Financial Impact. There were no HRQOL domains in which high-dose dexamethasone was shown to be superior (Lee et al. 2005b).

Further supporting evidence has also come from an analysis of quality of life among 143 patients in the SUMMIT trial, in which improvements in the mean global quality of life score and disease symptoms, including pain and fatigue, suggested that bortezomib improved patients' wellbeing. Patients with a CR or PR also had a general improvement in global and physical domain scores on the QLQ-C30, as well as a decrease in the severity of symptoms of disease, pain, and fatigue (Richardson et al. 2003). This has been further corroborated in another subanalysis of the SUMMIT trial (Dubois et al. 2006). Patient-reported outcomes (PROs), as assessed by the QLQ-C30, the myeloma-specific QLQ-MY24, the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue scale, and the FACT/GOG-NTX scale, showed an improvement between best endpoint and baseline. PRO scores correlated with response, with significant differences between the improvements seen in responding patients compared with deteriorations in PRO scores in nonresponders. Fatigue significantly improved with bortezomib, whereas neuropathy scores were largely unchanged. Improvements in role, social, and future perspective

Table 5 | Summary of outcome evidence for bortezomib in APEX, CREST, and SUMMIT: CR and PR rate, and duration of response (CR+PR+MR) in patients with multiple myeloma

Level of evidence	Design	Treatment and dose	Outcomes		Reference
			Response rate	Response duration	
2	Open, RCT, n=669 pts with relapsed multiple myeloma	BOR 1.3 mg/m^2 (i.v.)	CR+PR rate 38% (P<0.001) CR rate 6% (P<0.001) nCR rate 7% (P<0.001)	Median duration of response 8 months	Richardson et al. 2005a (APEX)
		High-dose DEX 40 mg (oral)	CR+PR rate 18% CR rate <1% nCR rate 1%	Median duration of response 5.6 months	
2	Open, RCT, n=669 pts with relapsed multiple myeloma	BOR 1.3 mg/m^2 (i.v.)	CR+PR rate 43% CR rate 9% nCR rate 7%	Median duration of response 7.8 months	Richardson et al. 2005c (APEX update)
		High-dose DEX 40 mg (oral)	CR+PR rate 18% CR rate <1% nCR rate 1%	Median duration of response 5.6 months	
2	Open, RCT, n=54 pts with relapsed refractory multiple myeloma	BOR 1.3 mg/m^2 (i.v.)	CR+PR rate 50% CR rate 4%	Median duration of response 13.7 months	Jagannath et al. 2004 (CREST)
		BOR 1.0 mg/m^2 (i.v.) (alone or in combination with oral DEX 20 mg)	CR+PR rate 37% CR+nCR rate 19%	Median duration of response 9.5 months	
3	Open, n=202 pts with relapsed refractory multiple myeloma	BOR 1.3 mg/m^2 (i.v.) (alone or in combination with oral DEX 20 mg)	CR+PR rate 27% CR+nCR rate 10%	Median duration of response 12–12.7 months	Richardson et al. 2003, 2006 (SUMMIT)

BOR, bortezomib; CR, complete response; DEX, dexamethasone; i.v., intravenous; MR, minimal response; nCR, near-complete response; PR, partial response; pts, patients; RCT, randomized controlled trial.

domains were consistently seen in more than 35% of patients using different definitions of improvement (>5, >3 points, effect size >0.2, effect size >0.5, >10% change from baseline). Global quality of life improved in more than 35% of patients for all improvement definitions apart from effect size >0.5.

Disease-oriented evidence

Response rates and duration of response

Complete responses are rare in patients with relapsed/refractory multiple myeloma. There is good evidence supporting the efficacy for bortezomib in terms of response rates (CR+PR) (Table 5) and also for duration of response (Table 5), as defined by stringent EBMT criteria, in patients with relapsed or refractory multiple myeloma. In particular, CR+PR rates of up to 50% with single-agent bortezomib are noteworthy in this population. Recently, a response rate of 61% (14 of 23 patients) has been reported for bortezomib, but patient numbers are small (Bruno et al. 2006). The median duration of response to bortezomib in extended follow-up in the SUMMIT trial was 12.7 months (Richardson et al. 2006a). A systematic review (in abstract form) reported overall response rate, using EBMT criteria, of 36% for bortezomib compared with 22% for thalidomide (P<0.001; n=4 studies) (Prince et al. 2005).

More complete suppression of M protein levels may be correlated with more complete reduction of the myeloma cell mass and with longer survival (Bross et al. 2004). In the APEX extended follow-up, patients with greater M protein reduction tended to have longer duration of response (Richardson et al. 2005c). In the SUMMIT trial, it was found that achievement of CR or PR to bortezomib alone was associated with significantly longer survival than that in all other patients (P=0.007) (Richardson et al. 2003), and with longer median TTP (13.9 vs 7 months in overall patient population) (Richardson et al. 2006a).

Interestingly, first response to bortezomib was seen in 54% of patients after cycle 2, including 29% on or after cycle 4 and 7% on or after cycle 6; approximately 20% of patients responding to bortezomib achieved maximal M protein suppression on or after cycle 8 (Richardson et al. 2005c).

A subanalysis of the SUMMIT trial revealed that better response to bortezomib was associated with younger age (response rate 32% in patients aged <65 years vs 19% in those over 65; P<0.05), and with plasma cell infiltration in bone marrow of ≤50% (35% response rate vs 20% with >50% infiltration; P<0.05) (Richardson et al. 2005b).

Evidence is emerging for the use of bortezomib in patients with relapsed or refractory myeloma in combination with melphalan

(Popat et al. 2005); melphalan, prednisone, and thalidomide (V-MPT) (Palumbo et al. 2005); melphalan, dexamethasone, and thalidomide (VMDT) (Terpos et al. 2005); dexamethasone, thalidomide, and zoledronic acid (VTD-Z) (Teoh et al. 2005); pegylated liposomal doxobubicin and dexamethasone (VDD) (Jakubowiak et al. 2005); pegylated liposomal doxobubicin and melphalan (Chari et al. 2005); dexamethasone and cyclophosphamide (Kropff et al. 2005); or prednisone and cyclophosphamide (Reece et al. 2005). These ongoing studies, most of which are still recruiting and have small numbers of patients, report promising results with response rates of over 50%.

Economic evidence

It is likely that, during the treatment of multiple myeloma, every patient will receive all the available treatments and therefore the cost of each treatment will have to be met. Thus a key question for hematologists is what combination should they receive the treatments in and in what sequence to give the patient the best chance of survival. Some limited information on the cost effectiveness of bortezomib in patients with relapsed refractory multiple myeloma has been derived from the results of the single-arm, phase II SUMMIT study (Richardson et al. 2003). The objective of this retrospective analysis, which was conducted from the viewpoint of third party (e.g. health plan) or government healthcare payers in the USA, was to assess the cost effectiveness of bortezomib relative to current therapeutic options [thalidomide and best standard care (BSC) and thalidomide] (Mehta et al. 2004). The results of the analysis suggest that the clinical benefits of bortezomib, in terms of response, delay in disease progression, and improved OS, could be derived at a reasonable cost [incremental cost-effectiveness ratio (ICER) $US45 356 per life-year gained], relative to thalidomide and BSC, in patients with relapsed refractory multiple myeloma. In addition, sensitivity analyses, which varied the prices of bortezomib and thalidomide, the proportion of patients sing bisphosphonates, frequencies of chronic events, frequency of skeletal events, and median survival by ±25%, indicated that these results were robust and reproducible (Mehta et al. 2004).

The demographic, clinical, and limited medical resource-utilization data for the bortezomib group were derived from the results of the SUMMIT study, but were derived from expert opinion and published sources for the comparator thalidomide plus BSC group. The ideal data source would have been a sufficiently powered, head-to-head, randomized controlled trial. This expert panel approach has been used in health services research but it has been criticized for comparing data from different sources and on the basis of potential loss of objectivity, although it may have added an element of external validity to the clinical trial data in the cost-effectiveness analysis. The decision analysis model used in this study did not attempt to incorporate the indirect costs of multiple myeloma treatment, which have not been well quantified. However, it did include the relevant direct costs associated with treatment of multiple myeloma, which was a valid approach to economic analysis from a payer's viewpoint.

In addition, an assessment of the cost effectiveness of bortezomib from a UK NHS perspective, which also utilized medical resource-utilization data from SUMMIT, has been published, although only in abstract form. This analysis reported that the cost effectiveness of bortezomib (ICER £17 161–33 539 per life-year gained), based on a mean additional survival benefit of 8–12 months, with good quality of life, compared favorably to other currently used salvage therapies (Bagust et al. 2004). A further analysis from a UK perspective estimated a cost per patient of £16 772, and cost per 100 000 population of £33 545, based on APEX trial data, UK prices, and UK incidence rates (Anon. 2006). The authors also estimate a cost per life-year gained of £117 404 with bortezomib.

However, additional economic studies of bortezomib compared to thalidomide and BSC that include quality of life measures are required, and data on the cost utility of the treatment of multiple myeloma with bortezomib are not yet available.

Resource utilization

Medical resource utilization in the treatment of multiple myeloma falls into three broad components: pharmacotherapy used to delay disease progression; disease management (i.e. concomitant medications, consultations, and diagnostic tests); and management and avoidance of adverse events (Mehta et al. 2004). In the American cost-effectiveness analysis of bortezomib based on the SUMMIT study, published sources of cost data were used to retrospectively assign unit costs to medical resource utilization components (Mehta et al. 2004). The costs of concomitant treatment with bisphosphonates and analgesics were included in the model, along with blood testing, bone marrow biopsy, and skeletal surveys. In addition, the management of both chronic adverse events (anemia requiring red blood cell transfusion or erythropoietin or thrombocytopenia that required platelet transfusions) was included along with acute adverse events (grade 3/4 infections, skeletal complications, hypercalcemia, central nervous system disturbances, fatigue, peripheral neuropathy, deep vein thrombosis, and gastrointestinal disorders). However, it was unclear if it included the costs of antiviral therapy for management of shingles. Patients treated with bortezomib were assumed to have received between three and eight cycles of therapy while those in the comparator group were assumed to have received thalidomide for as long as they continued to respond (mean duration 6 months for responders and 2 months for nonresponders). In this model, from the viewpoint of US healthcare payers, the total medical resource utilization costs (including therapy, disease management, and adverse events) for a bortezomib-treated patient with relapsed refractory multiple myeloma were $US65 222, compared with $US14 423 for a patient receiving BSC, based on median OS of 16 and 2.5 months, respectively (Mehta et al. 2004). However, since 17% of the patients in the study had not had thalidomide, a stratified model was developed to analyze the potential benefit of thalidomide in these patients. In the stratified model, the total medical resource utilization costs for patients with prior thalidomide use were $US69 200 and $US14 423 based on median OS of 15.7 and 2.5 months for bortezomib and BSC, respectively. On the other hand, the costs for patients without prior thalidomide use were $US68 816 and $US 37 265 based on median OS of 26 and

8.6 months for bortezomib and thalidomide, respectively. Thus, the use of thalidomide or BSC was less expensive overall than bortezomib but this may, at least in part, be due to the shorter duration of patients' survival compared to bortezomib. However, healthcare payers that provide coverage for patients with multiple myeloma will have to reach their own decisions regarding balancing the resource impact versus the clinical outcomes achieved with bortezomib.

Patient group/population

The evidence to support the use of bortezomib in its licensed indication as a single agent for the treatment of progressive multiple myeloma patients who have had at least one prior therapy, and who have already undergone or are unsuitable for bone marrow transplantation, was provided primarily by the international, randomized, phase III APEX trial that compared bortezomib favorably with oral high-dose dexamethasone (Richardson et al. 2005a). The patient populations included in these studies had measurable PD after one-to-three previous treatments, Karnofsky performance status scores ≥60, platelet count ≥50 000/mm^3, and an absolute neutrophil count ≥750/mm^3 (Richardson et al. 2005a). The response to bortezomib was not influenced by standard prognostic factors in patients with relapsed refractory multiple myeloma (Richardson et al. 2005b). These included gender, type of myeloma, serum level of beta 2-M, type, and number of previous therapies. Age ≥65 years was however loosely associated with lower response in SUMMIT (Richardson et al. 2003; Richardson et al. 2005a). Furthermore, there is good evidence, from both the SUMMIT and APEX trials, that responses to bortezomib were unaffected by chromosome 13 deletion, which predicts a poor outcome with conventional therapy (Richardson et al. 2003; Jagannath et al. 2005b). This observation has been corroborated elsewhere (Drach et al. 2005). Additionally, there is good evidence from a limited number of patients in the SUMMIT study that bortezomib is feasible in patients with impaired renal function (Jagannath et al. 2005c), and may be given to patients with renal failure receiving hemodialysis (Chanan-Khan et al. 2005).

There is a growing body of evidence on the use of bortezomib in combination regimens, giving promising results in patients with relapsed or refractory myeloma.

Dosage, administration, and formulations

Bortezomib (LDP-341, MG-341, MLN-341, PS-341, Velcade) is a modified dipeptide boronic acid. It is available for intravenous injection as a sterile lyophilized powder in single-dose vials containing 3.5 mg bortezomib and 35 mg mannitol, USP. The lyophilized powder drug product is reconstituted with 0.9% NaCl to a final concentration of 1 mg/mL before injection.

Bortezomib is indicated for the treatment of multiple myeloma patients who have received at least one prior therapy. The recommended dose of bortezomib is 1.3 mg/m^2 per dose administered as a 3–5 second bolus intravenous injection twice weekly for 2 weeks (days 1, 4, 8, and 11) followed by a 10-day rest period (days 12–21) for a maximum recommended number of eight cycles. At least 72 hours should elapse between consecutive doses of bortezomib (Anon. 2005). Bortezomib therapy should be withheld at the onset of any grade 3 nonhematologic or grade 4 hematologic toxicities, excluding neuropathy. Once the symptoms of the toxicity have resolved, bortezomib therapy may be reinitiated at a 25% reduced dose (i.e. 1.3 mg/m^2 per dose reduced to 1.0 mg/m^2 per dose; or 1.0 mg/m^2 per dose reduced to 0.7 mg/m^2 per dose) (Anon. 2005). No dose modification is required if grade 1 peripheral sensory neuropathy (paresthesias and/or loss of reflexes) occurs but, if it occurs with pain or at the grade 2 (interfering with function but not activities of daily living), the dose of bortezomib should be reduced to 1.0 mg/m^2. If grade 2 neuropathy occurs with pain, or at the grade 3 (interfering with activities of daily living), bortezomib should be discontinued until the toxicity is resolved and then reinitiated at 0.7 mg/m^2 once weekly. Bortezomib therapy should be discontinued in patients with grade 4 (disabling) neuropathic pain/peripheral sensory neuropathy, and patients with preexisting severe neuropathy should be treated with bortezomib only after careful risk–benefit assessment (Anon. 2005).

Clinical value

Bortezomib produces significant prolongation of OS and TTP compared with standard oral high-dose dexamethasone treatment in patients with relapsed multiple myeloma following 1–3 prior therapies, albeit with an increased incidence of grade 3 adverse events and herpes zoster infections. There is some evidence that improved clinical outcomes with bortezomib compared to high-dose dexamethasone are also accompanied by significantly improved HRQOL.

The APEX trial provides good level 2 evidence, but the fact that it was stopped early as a result of significantly improved survival and TTP in the bortezomib patients initially limited the availability of longer-term survival benefit. However, an extended follow-up to APEX confirms that the survival benefit is maintained, despite over 62% of the patients from the high-dose dexamethasone arm crossing over to bortezomib (Richardson et al. 2005c). After a median follow-up of 22 months, median OS was 29.8 months in the bortezomib group compared with 23.7 months for dexamethasone. Despite these encouraging results, the trial has been criticized in the UK where the relevance of dexamethasone as a comparator may not mirror clinical practice, unlike the rest of Europe and North America (Anon. 2006).

Clearly, the higher acquisition cost of bortezomib compared with thalidomide and BSC is an issue but there is some evidence that the clinical benefits of bortezomib, in terms of response, delay in disease progression, and improved OS, can be derived at a reasonable cost in patients with relapsed refractory multiple myeloma. While there may be higher unit cost, the length of therapy also needs to be considered; bortezomib was given for a median of six cycles in APEX, while the thalidomide or dexamethasone regimen was typically administered until progression, thus incurring the cost over a longer period (up to 1 year).

Bortezomib is the first and only single agent that has demonstrated a survival advantage for patients with relapsed or refractory multiple myeloma, and the current evidence supports its use as a valuable treatment option for this patient population.

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