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Bortezomib in multiple myeloma: treatment approach and outcomes ☆

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Abstract

Because multiple myeloma (MM) remains incurable, new therapeutic approaches are needed. Proteasome inhibition represents a new therapeutic strategy with the potential to inhibit multiple pathogenic pathways in MM. In phase I trials, the novel proteasome inhibitor bortezomib demonstrated encouraging activity in patients with advanced MM. In the SUMMIT phase II trial, 202 heavily pre-treated patients with relapsed and refractory MM received bortezomib 1.3 mg/m^2 twice weekly for 2 weeks, followed by a 1-week rest. The overall response rate, defined as complete + partial + minimal responses (CR + PR + MR), was 35%, with CR or near-CR in 10% of patients. Median duration of response was 12 months and median duration of survival 16 months for all patients. Adverse effects included manageable gastrointestinal symptoms, thrombocytopaenia, and peripheral neuropathy. Thrombocytopaenia and neuropathy were generally reversible and occurred mainly in patients who already had these toxicities at time of enrollment. In the CREST phase II trial, 54 patients with relapsed or refractory MM after first-line therapy were randomised to receive bortezomib 1.0 mg or 1.3 mg/m^2, twice weekly for 2 weeks, followed by a 1-week rest. Overall response rates were 33% at the 1.0 mg dose and 50% at the 1.3 mg dose. Toxicities were similar to those seen in SUMMIT, with nausea, diarrhoea and peripheral neuropathy occurring more frequently at the higher dose level. In conclusion, the results of the SUMMIT and CREST trials show that bortezomib is highly active in patients with relapsed and refractory MM. A large phase III trial comparing bortezomib with dexamethasone in relapsed MM patients was recently stopped after a pre-specified interim analysis showed a statistically significant improvement in time to disease progression for patients receiving bortezomib. Studies testing bortezomib as front-line therapy are ongoing.

Keywords: Proteasome; Bortezomib; Multiple myeloma; NF-κB; Dipeptides; Boronic acids

1. Introduction

Multiple myeloma (MM) is the second most common haematological malignancy, with an estimated annual incidence of approximately 75,000 cases worldwide [1]. Although most patients respond initially to treatment with chemotherapy and radiation, the majority eventually relapse with chemo-resistant disease. Mechanisms of resistance in MM involve both the myeloma cells themselves and the protective interaction between myeloma cells and the bone marrow microenvironment [2]. Because MM remains incurable, new therapeutic approaches are needed.

The transcription factor nuclear factor-κB (NF-κB) appears to play a central role in the pathogenesis of myeloma. Tumor cells and bone marrow stromal cells (BMSC) from patients with MM show enhanced NF-κB activity compared with normal bone marrow, and chemo-resistant MM cell lines show enhanced NF-κB activity compared with sensitive lines [3,4]. Proteasome-mediated activation of NF-κB results in the expression of multiple cytokine and cell adhesion molecules promoting myeloma cell growth and survival [5].

Inhibition of the proteasome thus represents a new therapeutic strategy for MM, with the potential to inhibit multiple pathogenic pathways. In preclinical experiments, the novel dipeptide boronic acid proteasome

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inhibitor bortezomib is not only cytotoxic against MM cells, but also downregulates protective interactions between MM cells and BMSC's [6]. In addition, bortezomib has been shown to markedly increase the sensitivity of chemo-resistant MM cell lines to chemotherapeutic agents such as melphalan and doxorubicin [3].

In a phase I trial in patients with refractory haematologic malignancies, 27 patients were treated with doses of bortezomib ranging from 0.40–1.38 mg/m^2 by intravenous (IV) bolus twice weekly for 4 weeks, followed by a 2-week rest. The study included 11 patients with MM and one patient with Waldenström's macroglobulinaemia. Of the 12 patients with plasma cell dyscrasias, 9 completed at least one full cycle of therapy and were assessable for response. A complete response by Southwest Oncology Group (SWOG) criteria was documented in one patient with IgG-κ myeloma treated at the 1.04 mg/m^2 dose level. The other eight patients with myeloma experienced either a minor response or stable disease [7].

Based on the strong preclinical rationale together with these encouraging phase I clinical results, bortezomib moved rapidly into phase II and III clinical testing in patients with refractory and relapsed MM.

2. Bortezomib in patients with relapsed and refractory myeloma: The SUMMIT trial

The SUMMIT trial was an open-label, multicenter, phase II trial conducted in 202 patients [8]. Adult patients with MM in relapse after at least two prior lines of treatment, and refractory to their last line of treatment, were eligible. Other eligibility criteria included a Karnofsky performance status (PS) of $\geqslant 60$, creatinine clearance $\geqslant 10$ mL/min, haemoglobin $\geqslant 8$ g/dL, platelet count $\geqslant 30{,}000/\text{mm}^3$, and absolute neutrophil count $\geqslant 500/\text{mm}^3$. Patients were treated with bortezomib 1.3 mg/m^2 by IV bolus twice weekly for 2 weeks, followed by 1 week rest, in 21-day cycles. Patients with progressive disease after two cycles or stable disease after four cycles were eligible to add treatment with dexamethasone 20 mg p.o. on the day of and day after each dose of bortezomib. Patients were permitted to receive up to eight cycles of bortezomib; patients with clinical benefit could receive additional treatment in a separate extension study. The primary study endpoint was overall response rate, defined as complete + partial + minimal responses (CR + PR + MR) [8]. Responses were assessed by an independent review committee according to the criteria of the European Group for Blood and Marrow Transplantation (the Blade criteria) [9]. Secondary endpoints were time to progression, survival, safety, rate of response to bortezomib in combination with dexamethasone, and quality of life. A complete response was defined as normal serum calcium, stable skeletal disease, absence of soft-tissue plasmacytomas, <5% plasma cells in the marrow in two specimens obtained 6 weeks apart, and a negative immunofixation test for myeloma protein in serum and urine. A near-complete response was defined by the absence of myeloma protein on electrophoresis, independent of the immunofixation-test result [8].

Most patients (84%) had IgG or IgA myeloma. At baseline, 20% of patients had a Karnofsky PS of $\leqslant 70$ and 80% had symptoms of peripheral neuropathy. Median time since diagnosis was 4 years, median serum β_2-microglobulin concentration was 3.5 mg/L, and 35% of 172 patients tested had cytogenetic abnormalities, including 15% with chromosome 13 deletion [8].

Fig. 1 shows the prior therapy received by patients enrolled in the study. The median number of prior lines of therapy was 6 [8,10]. Sixty-four percent had received at least one autologous transplantation. Almost all patients had received corticosteroids, over 90% had been treated with alkylating agents, and over 80% had

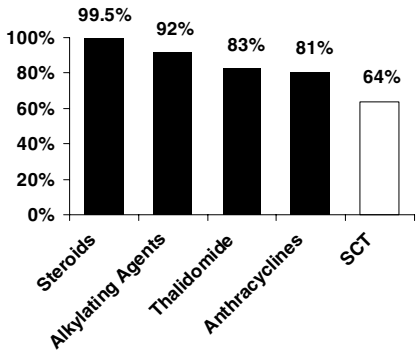

Fig. 1. Previous myeloma therapy received by patients in the SUMMIT trial [8,10]. Median number of lines of prior therapy was six (range 2–15). Ninety-two percent of patients received at least three drug therapies (excluding SCT) and 91% of patients were refractory to last therapy.

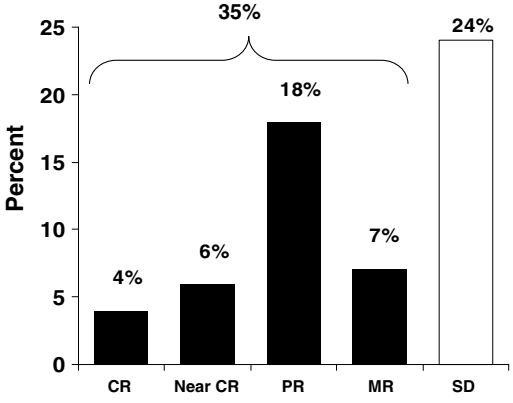

Fig. 2. The SUMMIT trial: response rates. Of 193 evaluable patients, there was a 35% overall response rate (CR + PR + MR); 27% experienced CR + PR; and 24% had stable disease (SD). Overall, 59% had SD or better. Findings were assessed by Independent Review Committee [8].

received thalidomide. Altogether, 92% of patients had been treated with three or more of the major classes of agents for myeloma. Ninety-one percent of patients were refractory to their last prior line of therapy [8].

Fig. 2 shows the patient responses [8]. Overall, of 193 patients with measurable disease, 35% had a CR, PR, or MR. Four percent of patients had a CR with negative immunofixation, and 6% of patients had a near-CR with M-protein undetectable by electrophoresis, but with immunofixation remaining positive. In 12 of the 19 patients with a CR or near-CR, the response to bortezomib was their first CR. The overall rate of CR + PR was 27%. Twenty-four percent of patients had stable disease; such patients also experienced a meaningful therapeutic outcome, since 91% of patients were progressive at the time of study entry [8].

The response rate to bortezomib was independent of sex, myeloma type, level of serum β_2-microglobulin, and type and number of previous therapies. Older age ($\geqslant 65$ years) showed a loose association with lower probability of response; the presence of >50% plasma cells in the bone marrow at baseline was associated with a statistically significant lower response rate (20% vs. 35% in those with $\leqslant 50\%$ plasma cells; $P = 0.03$). Presence or absence of chromosome 13 deletion was not predictive for response [8].

The median duration of response to bortezomib among patients with a CR, PR, or MR ($n = 67$) was 12 months (Fig. 3a). The median time to progression for all 202 patients was 7 months. The median overall survival for all 202 patients was 16 months (Fig. 3b) [8,11].

Among patients with a CR or PR, 89% had an increase in haemoglobin of at least 1 g/dL, and 72% had an increase of at least 2 g/dL. As shown in Fig. 4, none of the responding patients required a transfusion after cycle 4 [8,12]. Analysis of quality of life (QOL) scores among 143 patients showed improvements in global QOL scores and a decrease in the scores for severity of disease symptoms, pain, and fatigue [8].

Seventy-eight patients who had either stable or progressive disease while being treated with bortezomib alone subsequently received dexamethasone in combination with bortezomib. Among 74/78 patients evaluable for response, 18% had an MR or PR. Six of these 13 patients had previously been refractory to corticosteroid therapy [8].

The side effects associated with bortezomib treatment are shown in Fig. 5 [8]. The most common adverse events were gastrointestinal symptoms including nausea and vomiting, diarrhoea, and constipation; fatigue; thrombocytopaenia; and sensory neuropathy. The gas-

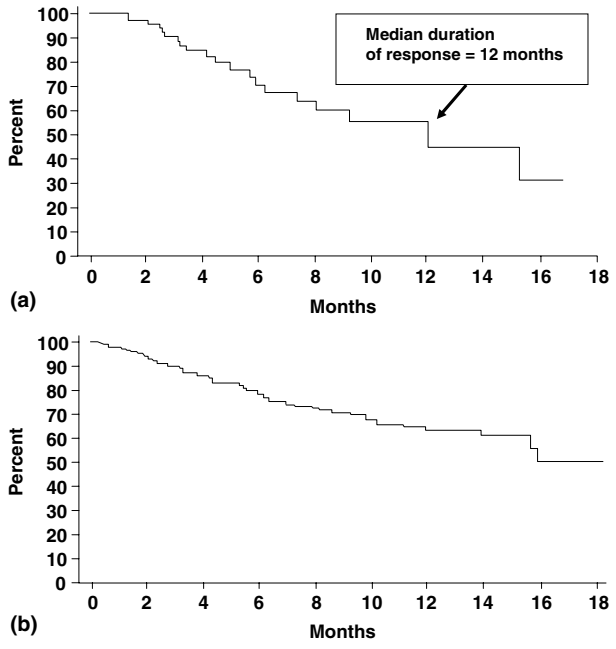

Fig. 3. (a) The SUMMIT trial: duration of response (CR + PR + MR) of patients receiving bortezomib alone over time [8]; $N = 67$. (b) Overall survival in the SUMMIT trial, shown over time [8,11]. As of October 2002, the median overall survival was 16 months; with longer-term follow-up, median survival has since been measured at 17.8 months.

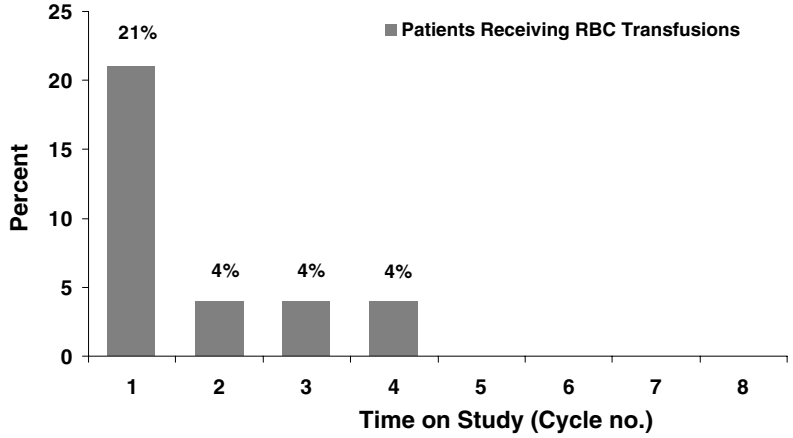

Fig. 4. The SUMMIT trial: red blood cell (RBC) transfusion requirements over time [8,12]. Fifty-three patients experienced a CR + PR.

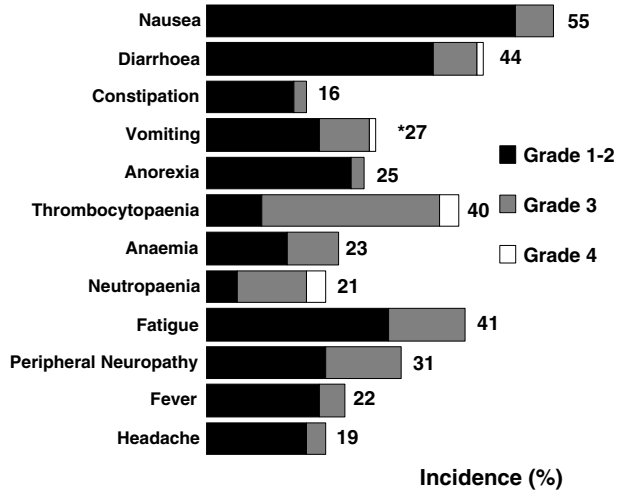

Fig. 5. The SUMMIT trial: most common adverse experiences [8]. *One patient reported grade 4 vomiting (<1%).

trointestinal symptoms were mostly mild to moderate in severity and were manageable with routine support. The most common grade 3 adverse events were thrombocytopaenia (28%), fatigue (12%), and neuropathy (12%) [8]. Thrombocytopaenia developed primarily in patients with a low baseline platelet count, was transient, and was not associated with serious bleeding complications [8]. New or worsening peripheral sensory neuropathy developed in 34% of patients, with a severity of grade 3 in 12%, and no case of grade 4 neuropathy. Improvement or complete resolution of neuropathy was observed in the majority of patients during the follow-up period. Grade 3 neuropathy developed during treatment in only one patient who did not have neuropathy at baseline [8].

3. Bortezomib in patients with relapsed and refractory myeloma: the CREST trial

A second phase II trial comparing two dose levels of bortezomib was conducted in patients with somewhat earlier stage MM. In the CREST trial, 54 patients who had relapsed after or were refractory to front-line therapy were randomised to receive bortezomib 1.0 or 1.3 mg/m^2 twice weekly for 2 weeks, followed by a 1-week rest, in 21-day cycles. As in the SUMMIT trial, patients were permitted to receive up to eight cycles of treatment. Similarly, the addition of dexamethasone was permitted for patients with progressive disease after two cycles or stable disease after four cycles. The primary study endpoint was overall response rate, defined as CR + PR + MR [13]. Responses were once again assessed by an independent review committee according to strict Blade criteria [9].

The response rates in the CREST trial are shown in Fig. 6 [13]. For patients treated with 1.0 mg/m^2, the overall response rate was 33%, including 11% CR or near-CR, 19% PR, and 4% MR. For patients treated at the 1.3 mg/m^2 dose, the overall response rate was 50%, including 4% CR, 35% PR, and 12% MR. Thus, the response rate appeared to be higher in patients treated at the higher dose level [13].

Adverse effects observed in the study consisted mainly of gastrointestinal symptoms, including nausea and diarrhoea, and peripheral neuropathy. Fig. 7 shows the comparative incidence of the side effects with the most divergent incidence rates at the two dose levels in the

	1.0 mg/m^2 (*n*=27)	1.3 mg/m^2 (*n*=26)	All patients (*n*=53)
ORR* (CR+PR+MR)	33%†	50%	41%
CR	4%	4%	4%
Near CR	7%	–	4%
PR	19%	35%	26%
MR	4%	12%	8%
SD	26%	19%	23%

* Overall response rate (ORR). One patient with non-secretory myeloma inevaluable.
† Three (11%) and three (12%) patients were not IRC evaluable in 1.0 and 1.3 mg/m^2 dose groups, respectively.

Fig. 6. Response rates to bortezomib alone in the CREST trial [13].

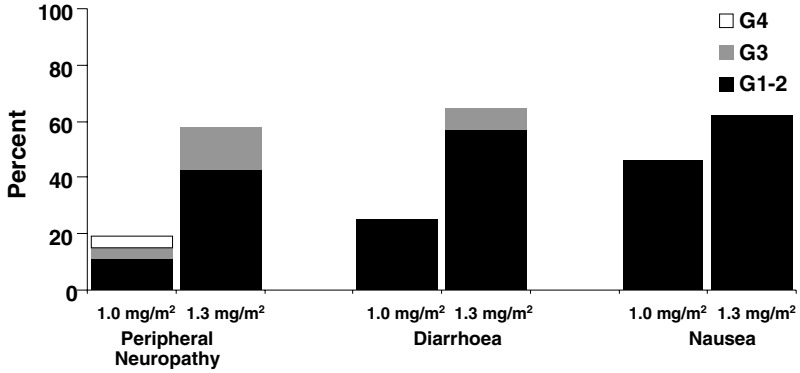

Fig. 7. The CREST trial: most divergent adverse effects. Results show 1.0 and 1.3 mg/m^2 doses by grade [13]. The incidence of other adverse effects was similar between doses.

CREST trial [13]. The incidence of diarrhoea and peripheral neuropathy was appreciably higher at the 1.3 mg/m^2 dose, compared with the 1.0 mg/m^2 dose [13].

Overall, the CREST trial confirmed the intrinsic activity of bortezomib at both dose levels. The higher response rate observed with the 1.3 mg/m^2 dose suggests a possible dose–response effect for efficacy. Similarly, the incidence of several major adverse effects was higher at the 1.3 mg/m^2 dose. Given the relatively small sample size, a dose–response relationship cannot be confirmed based on the results of the CREST trial alone. However, at present it appears appropriate to begin treatment with bortezomib at a dose of 1.3 mg/m^2 with a dose reduction to 1.0 mg/m^2 if indicated [13].

4. Conclusions and future directions

The results of the SUMMIT and CREST trials show that bortezomib is highly active in patients with relapsed and refractory MM. In the SUMMIT trial, a high response rate was seen in a cohort of heavily pre-treated patients, most of whom had received virtually all available anti-myeloma therapy. Treatment with bortezomib was generally well tolerated, with major toxicities including manageable gastrointestinal side effects and reversible thrombocytopaenia and peripheral neuropathy. Both thrombocytopaenia and neuropathy occurred mainly in patients in whom these toxicities had already been present prior to initiating bortezomib treatment.

Based on the results of the SUMMIT and CREST trials, it appears reasonable to begin treatment with a dose of 1.3 mg/m^2 and to lower the dose to 1.0 mg/m^2 if necessary for the management of side effects. The response rate demonstrated in the CREST study indicates that 1.0 mg/m^2 is an active dose. It is not recommended to reduce the dose of bortezomib below 0.7 mg/m^2.

A large international, randomised phase III trial comparing bortezomib with high-dose dexamethasone in patients with relapsed MM (the APEX trial) completed accrual of more than 600 patients in 2003. The trial was stopped after a pre-specified interim analysis showed a statistically significant improvement in time to disease progression for patients receiving bortezomib. Additional studies testing bortezomib as front-line therapy, either as a single agent or in combination therapy, are ongoing. Encouraging activity using bortezomib in combination with thalidomide [14], melphalan [15], and liposomal doxorubicin [16] has already been seen in patients with relapsed and refractory disease.

Conflict of interest statement

Prof. Harousseau is a member of an advisory board for Millennium Pharmaceuticals and Ortho Biotech. He has also received research funding for participation in the APEX clinical trial.

Role of the funding source

Prof. Harousseau is a member of an advisory board for Millennium Pharmaceuticals and Ortho Biotech. He has also received research funding for participation in the APEX clinical trial.

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