

A phase 2 study of two doses of bortezomib in relapsed or refractory myeloma

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Summary

In a phase 2 open-label study of the novel proteasome inhibitor bortezomib, 54 patients with multiple myeloma who had relapsed after or were refractory to frontline therapy were randomized to receive intravenous 1.0 or 1.3 mg/m² bortezomib twice weekly for 2 weeks, every 3 weeks for a maximum of eight cycles. Dexamethasone was permitted in patients with progressive or stable disease after two or four cycles respectively. Responses were determined using modified European Group for Blood and Marrow Transplantation criteria. The complete response (CR) + partial response (PR) rate for bortezomib alone was 30% [90% confidence interval (CI), 15.7–47.1] and 38% (90% CI, 22.6–56.4) in the 1.0 mg/m² (8 of 27 patients) and 1.3 mg/m² (10 of 26 patients) groups respectively. The CR + PR rate for patients who received bortezomib alone or in combination with dexamethasone was 37% and 50% for the 1.0 and 1.3 mg/m² cohorts respectively. The most common grade 3 adverse events were thrombocytopenia (24%), neutropenia (17%), lymphopenia (11%) and peripheral neuropathy (9%). Grade 4 events were observed in 9% (five of 54 patients). Bortezomib alone or in combination with dexamethasone demonstrated therapeutic activity in patients with multiple myeloma who relapsed after frontline therapy.

Keywords: bortezomib, myeloma, relapsed, refractory, dexamethasone.

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Multiple myeloma is an incurable haematological malignancy of B-cell origin. The median duration of survival among patients with multiple myeloma is 3 years with standard therapy, and approximately 25% of patients survive 5 years or longer; fewer than 5% are alive at 10 years (Alexanian & Dimopoulos, 1994; Rajkumar *et al*, 2002). Although patients generally respond to front-line chemotherapy, most either relapse or become refractory to these therapies.

Proteasome inhibition is an attractive approach to cancer therapy because it can potentially target multiple signalling pathways that are critical for tumour cell growth and survival, including cell cycle regulation (King *et al*, 1996), apoptosis (Orlowski, 1999), cell adhesion (Read *et al*, 1995), transcription

(Desterro *et al*, 2000) and angiogenesis (Dulic *et al*, 1994). Bortezomib reversibly inhibits proteasome function by targeting the chymotryptic-like site ($K_i = 0.6$ nmol/l) of the proteasome, with little affinity for other proteases, such as chymotrypsin ($K_i = 320$ nmol/l) and thrombin ($K_i = 13\,000$ nmol/l) (Adams *et al*, 1998).

Preclinical studies suggested that bortezomib could be effective in patients with multiple myeloma (Hideshima *et al*, 2001; LeBlanc *et al*, 2002). Application of bortezomib to either myeloma cell lines or cells freshly isolated from myeloma patients directly inhibited proliferation and induced apoptosis, regardless of p21, p27 or p53 expression (Hideshima *et al*, 2001). In xenograft mouse models, bortezomib significantly

inhibited myeloma tumour growth, including complete tumour regression, and prolonged overall survival compared with controls (LeBlanc *et al*, 2002). Taken together, these results provide strong evidence supporting the use of bortezomib as a therapy for multiple myeloma.

In a phase 1 analysis of patients with refractory haematological malignancies, activity was reported in nine of nine fully assessable patients with heavily pretreated plasma cell dyscrasias (Orlowski *et al*, 2002). Based on an evaluation of two phase 1 studies (Aghajanian *et al*, 2002; Orlowski *et al*, 2002), the dose and schedule selected for bortezomib administration for the phase 2 SUMMIT trial was 1.3 mg/m² given twice weekly for 2 weeks every 21 d (Richardson *et al*, 2003).

In the exploratory phase 2 study reported here (CREST), the safety and efficacy of two doses of bortezomib (1.0 and 1.3 mg/m²) were evaluated in patients with relapsed or refractory multiple myeloma who had received only front-line therapy. In order to be sure that the activity of the two dose levels was studied in similar patient populations, a centre-specific randomization was used, based on disease stage and previous chemotherapy. As preclinical studies reported additive activity with bortezomib in combination with dexamethasone (Hideshima *et al*, 2001), patients with a suboptimal response to bortezomib alone were allowed to receive dexamethasone.

Methods

Patients

Patients were at least 18 years of age and had either relapsed following or were refractory to front-line chemotherapy, which was defined as their first regimen for the treatment of myeloma (e.g. high-dose therapy with stem cell support). Other requirements were measurable disease, a Karnofsky performance status $\geq 60\%$, a life expectancy > 3 months, aspartate aminotransferase or alanine aminotransferase $\leq 3 \times$ upper limit of normal, total bilirubin $\leq 2 \times$ upper limit of normal, creatinine clearance ≥ 30 ml/min (exceptions were allowed for creatinine clearance ≥ 10 and < 30 ml/min), platelet count $\geq 30 \times 10^9$ /l, haemoglobin ≥ 8 g/dl and absolute neutrophil count $\geq 0.5 \times 10^9$ /l. Patients agreed to use contraception, and women were required to have a confirmed negative pregnancy test result before enrolment. All patients provided signed informed consent before study entry. The study was performed in accordance with the Declaration of Helsinki, with prior approval of the institutional review board at each of the participating centres.

Study design and treatment

Patients were randomized to receive bortezomib (VELCADE® for Injection, Millennium Pharmaceuticals, Inc., Cambridge, MA, USA) 1.0 or 1.3 mg/m² as a 3–5-s intravenous bolus twice weekly for 2 weeks (days 1, 4, 8 and 11) of a 21-d cycle for up to eight cycles. Patients with progressive disease after two cycles or stable disease after the first four cycles were eligible to

receive 20 mg oral dexamethasone on the day of and the day following each bortezomib dose. The overall dexamethasone dose of 160 mg over a 3-week cycle was similar to the amount received with standard monthly high-dose treatment, such as 40 mg/d for 4 d every 4 weeks. Treatment was withheld from patients with drug-related $\geq$ grade 3 non-haematological or grade 4 haematological toxicity and then resumed at a 25% dose reduction upon resolution of the toxicity to grade 1 or better. Reduction to 0.7 mg/m² was allowed, but lower doses were not permitted. Continuation of therapy in a separate extension study was available if, in the investigator's opinion, the patient might benefit or continue to benefit from treatment or re-treatment.

Investigators and representatives from Millennium Pharmaceuticals, Inc. designed the study. Medical and statistical representatives from Millennium collected and analysed data in conjunction with the investigators. All investigators had access to the primary data and authored this report. All participating institutions received clinical grant support for the conduct of the study.

Assessment of efficacy

The primary end-point was overall response rate (ORR) [the sum of complete response (CR), partial response (PR) and minimal response (MR)] to bortezomib alone. Time to progression on bortezomib alone or in combination with dexamethasone, survival, safety and response rate to bortezomib in combination with dexamethasone were also assessed. Evaluation of response was performed between days 11–18 of cycles 2, 4 and 6, and following cycle 8. Responses were assessed using the European Group for Blood and Marrow Transplantation (EBMT) response criteria (Bladé *et al*, 1998) by an independent review committee (IRC) consisting of three independent myeloma experts not otherwise involved in the trial. As per the EBMT criteria, CR required a negative immunofixation test result for myeloma protein in serum and urine, disappearance of soft-tissue plasmacytomas, normal serum calcium, stable skeletal disease and $< 5\%$ plasma cells in the marrow with confirmation of response by all of these criteria 6 weeks later. An additional category of near CR was defined as the absence of M protein by electrophoresis but with positive immunofixation, plus stable bone disease and normal serum calcium. Patients with insufficient data to assess efficacy were considered treatment failures (not evaluable) by the IRC and considered non-responders in the analyses.

Time-to-event analyses were performed using the Kaplan–Meier method, and results are reported as of 11 May 2004. The time to first response was from the date of the first administration of bortezomib to the first evidence of a confirmed response. The duration of response was the time from achievement of response to progression. The time to disease progression for patients receiving bortezomib alone or in combination with dexamethasone was the interval from the initial administration of bortezomib to disease progression.

(without censoring for the addition of either dexamethasone or additional bortezomib in the extension study). For the bortezomib-alone analysis, patients who received dexamethasone in combination with bortezomib or alternate therapy, and patients who died without a reported date of progression, were censored at the last evaluation before starting additional therapy or before death. Patients who were characterized as refractory to dexamethasone were those who had received dexamethasone alone or in combination as prior therapy and had disease progression within 30 days of receiving steroid-containing therapy.

Assessment of safety and other secondary end points

Adverse events were assessed at each visit and graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0, from the first dose until 20 d after the last dose of bortezomib. Patients completed the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-NTX) questionnaire to evaluate peripheral neurological symptoms at the screening visit and on day 1 of cycles 3, 5 and 7 and at the end of study. A neurologist performed a complete neurological evaluation during the initial screening, during treatment if needed and at the end of the study. Electromyography and testing for amyloidosis were not required.

Randomization procedures and statistical analysis

Patients who met all eligibility criteria at cycle 1, day 1, were eligible for randomization, at which point the next available randomization envelope was selected, based on the patient's Durie-Salmon disease stage (I/II or III) and front-line chemotherapeutic regimen (conventional standard-dose therapy or high-dose therapy/stem cell transplantation). The goal of the randomization schema was to achieve balance of treatment group assignment (bortezomib 1.0 or 1.3 mg/m²) within each stratum by utilizing a centre-specific strategy that would prevent early closure or delayed enrolment of any stratum.

The study was prospectively designed to determine whether the rate of response to bortezomib alone was at least 20% ($\alpha = 0.05$), with at least 80% power to conclude a response rate of 40% or more. This study was planned to enrol 64 patients (32 patients in each dose group); no formal statistical comparisons of bortezomib between the two dose groups were planned or conducted in this exploratory study. All descriptive statistical analyses were performed using SAS statistical software (version 8.2).

Results

Patient characteristics

Fifty-four patients were accrued onto this multi-institutional study between May 2001 and January 2002 from 10 centres,

with 53 patients evaluable for response by the IRC (one patient with non-secretory myeloma was excluded as preplanned). The median age was 63 years (range, 30–84 years) (Table I). Twenty-eight patients received 1.0 mg/m² and 26 patients received 1.3 mg/m². The two dose groups were balanced with respect to most demographics and baseline characteristics, with some exceptions. There were more women and more patients identified with IgG myeloma in the higher dose group. A higher proportion of patients in the 1.0 mg/m² group had a platelet count $<75 \times 10^9/l$ at baseline, whereas a higher percentage in the 1.3 mg/m² group had abnormal cytogenetics in a bone marrow sample. The median duration of time from the diagnosis of multiple myeloma to the first dose of bortezomib was 2.0 years for both dose groups, and 56 and 62% of patients in the 1.0 and 1.3 mg/m² dose groups, respectively, were Durie-Salmon stage III disease at diagnosis. Table II details prior therapy in the two groups and shows that the majority of patients had previously received corticosteroids.

At baseline, the majority of patients in each dose group (21 of 25 and 15 of 23 patients in the 1.0 and 1.3 mg/m² dose groups, respectively) reported symptoms of peripheral neuropathy, as assessed by the FACT/GOG-NTX questionnaire. Neurological examination detected sensory and/or motor symptoms in 34 of 51 patients (67%) and functional impairment in 16 of 51 patients (31%) prior to bortezomib therapy.

Dose intensity and duration of treatment and follow-up

Twenty-four patients (86%) in the 1.0 mg/m² dose group and 19 patients (73%) in the 1.3 mg/m² dose group completed four or more cycles of treatment, and 61% of the 1.0 mg/m² patients and 27% of the 1.3 mg/m² patients completed all eight

Table I. Demographics and baseline characteristics (all treated patients, $n = 54$).

Characteristic	Bortezomib dose group	
	1.0 mg/m ² ($n = 28$)	1.3 mg/m ² ($n = 26$)
Age [years, Mean (range)]	64 (39–82)	60 (30–84)
Males [n (%)]	14 (50)	9 (35)
Type of myeloma [n (%)]		
IgG/IgA/other*	15 (54)/8 (29)/ 5 (18)	17 (65)/6 (23)/ 3 (12)
Karnofsky performance status ≤ 70 [n (%)]	3 (11)	4 (15)
β_2 -microglobulin ≥ 4 mg/l [n/N (%)]	14/24 (58)	11/23 (48)
Platelet count $<75 \times 10^9/l$ [n/N (%)]	5/26 (19)	0/25 (0)
Abnormal cytogenetics [n/N (%)]	7/24 (29)	11/23 (48)

*Includes L-chain myeloma and one patient with non-secretory myeloma.

Table II. Prior therapy for all treated patients ($n = 54$).

Prior therapy	Bortezomib dose group	
	1.0 mg/m ² ($n = 28$)	1.3 mg/m ² ($n = 26$)
Steroids, e.g. dexamethasone, VAD [n (%)]	27 (96)	26 (100)
Alkylating agents, e.g. MP, VBMCP [n (%)]	21 (75)	18 (69)
Anthracyclines, e.g. VAD, mitoxantrone [n (%)]	12 (43)	17 (65)
Thalidomide therapy [n (%)]	9 (32)	7 (27)
Stem cell transplantation or other high-dose therapy [n (%)]	15 (54)	11 (42)
Radiation therapy [n (%)]	10 (36)	8 (31)
Number of prior regimens of treatment* [Median (range)]	3 (1–7)	3 (1–7)

*A regimen was defined as a single drug or combination therapy. Front-line therapy could be composed of more than one regimen. The intent of this protocol was to enroll patients for second-line therapy. VAD, vincristine, adriamycin, dexamethasone; MP, melphalan, prednisone; VBMCP, vincristine, carmustine, melphalan, cyclophosphamide, prednisone.

cycles of therapy. The mean duration of treatment was 142.6 d in the 1.0 mg/m² group (range, 1–228 d) and 115.9 d (range, 12–172 d) in the 1.3 mg/m² group. Dexamethasone was added to the bortezomib treatment regimen for 16 patients (57%) in the 1.0 mg/m² dose group and 12 patients (46%) in the 1.3 mg/m² dose group. One patient began dexamethasone therapy in cycle 2, seven in cycle 3, one in cycle 4, 10 in cycle 5 and the remaining nine in later cycles. The median duration of follow-up was 796 d (26.2 months) for the group receiving

1.0 mg/m² and 794 d (26.1 months) for the group receiving 1.3 mg/m².

Dose reduction was necessary in a higher proportion of patients in the 1.3 mg/m² dose group because of an adverse event (nine of 26 patients, 35%), compared with the lower-dose group (three of 28 patients, 11%). The maximum percentage of patients who required a dose reduction for any cycle on study was 11%, occurring in both cycles 7 and 8 in the lower-dose group, and 19% at cycle 3 for the higher-dose group. Seventeen of 54 patients (31%) continued onto the extension study. Early discontinuation occurred in 12 of 54 patients (22%) because of adverse events, in 11 (20%) because of lack of efficacy and in two patients (4%) by their request.

Response to bortezomib treatment

Response rates to bortezomib monotherapy and the combination of bortezomib and dexamethasone are listed in Table III. Of the 27 patients in the 1.0 mg/m² dose group with measurable disease and the 26 from the 1.3 mg/m² dose group, the ORR (CR + PR + MR) to bortezomib alone was 33% (nine of 27 patients) in the 1.0 mg/m² dose group and 50% in the 1.3 mg/m² dose group (13 of 26 patients). One patient in each dose group experienced CR using the EBMT criteria (immunofixation negative), and in addition, two patients from the 1.0 mg/m² dose group achieved near CR. An additional seven patients (26%) in the 1.0 mg/m² cohort and five patients (19%) in the 1.3 mg/m² cohort had evidence of stable disease in response to bortezomib alone.

The ORR for patients who received bortezomib alone or in combination with dexamethasone was 44% in the 1.0 mg/m² dose group and 62% in the 1.3 mg/m² dose group. In the 1.0 mg/m² dose group, there were two patients with CR and three with near CR. In the 1.3 mg/m² dose group, one patient

Table III. Summary of responses to bortezomib (IRC-evaluated population, $n = 53$).

	Bortezomib dose group			
	1.0 mg/m ² ($n = 27$)*		1.3 mg/m ² ($n = 26$)	
	Bortezomib alone (%) (90% CI)	Bortezomib ± Dex. (%) (90% CI)	Bortezomib alone % (90% CI)	Bortezomib ± Dex. % (90% CI)
Confirmed response combined				
Overall response (CR + PR + MR)	33 (18.6–50.9)	44 (28.0–61.8)	50 (32.7–67.3)	62 (43.6–77.4)
CR + PR	30 (15.7–47.1)	37 (21.7–54.7)	38 (22.6–56.4)	50 (32.7–67.3)
Confirmed response by category				
CR + near CR	11 (3.1–26.3)	19 (7.6–35.1)	4 (0.2–17.0)	4 (0.2–17.0)
PR	19 (7.6–35.1)	19 (7.6–35.1)	35 (19.4–52.6)	46 (29.2–63.8)
MR	4 (0.2–16.4)	7 (1.3–21.5)	12 (3.2–27.2)	12 (3.2–27.2)
NC†	26	19	19	12
PD/NE (non-responders)†	41	37	31	27

*One patient with non-secretory myeloma was not evaluable.

†Confidence intervals not calculated.

Dex., dexamethasone; CI, confidence interval; CR, complete response; MR, minimal response; NC, no change; NE, not evaluable; PD, progressive disease; PR, partial response.

achieved CR. Of nine patients who were previously determined to have steroid-refractory disease (progression within 30 d of steroid-containing therapy), two (22%) achieved improved response after the addition of dexamethasone.

Time to response

The median time to first response (CR, PR or MR) for treatment with bortezomib alone was similar in both treatment groups: 1.3 months (39 d) in the 1.0 mg/m² dose group and 1.5 months (45 d) in the 1.3 mg/m² dose group. The first measurement of response as specified by the protocol was after two cycles.

Duration of response and time to progression

The median duration of response (CR, PR and MR) for treatment with bortezomib alone or in combination with dexamethasone was 9.5 months (288 d) and 13.7 months (417 d) in the 1.0 mg/m² (*n* = 12) and 1.3 mg/m² groups (*n* = 16) respectively. The median time to progression for patients who received bortezomib alone or in combination with dexamethasone was 7.0 months (212 d) and 11.0 months (333 d) in the 1.0 mg/m² and 1.3 mg/m² groups respectively (Fig. 1).

Overall survival

The median survival for all patients in both dose groups combined has not been reached. Median duration of follow-up was approximately 26 months (796 d for the 1.0 mg/m² dose group, and 794 d for the 1.3 mg/m² dose group). The median survival for the patients in the 1.0 mg/m² group was 26.7 months (813 d) but has not been reached in the 1.3 mg/m² group.

Adverse events

Overall, the most commonly reported adverse events of any grade in this study were fatigue (70%), nausea (54%),

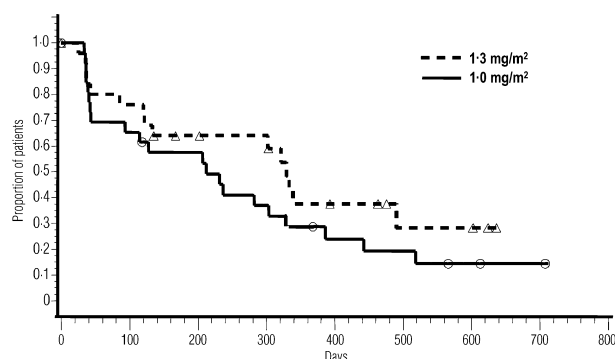


Fig 1. Kaplan-Meier curve for time to progression for 28 patients in the 1.0 mg/m² and 26 patients in the 1.3 mg/m² bortezomib cohorts. Censoring for the addition of dexamethasone or additional bortezomib was not performed. Results are reported as of 11 May 2004.

diarrhoea (44%), pyrexia (41%), constipation (37%), peripheral neuropathy (41%), arthralgia (35%), insomnia (35%), headache (31%), limb pain (31%), thrombocytopenia (30%) and upper respiratory tract infection (30%). The most common grade 3 and 4 adverse events in each dose group are shown in Table IV. Grade 4 events were observed in five subjects. Three patients had grade 4 events unrelated to bortezomib therapy (incidental finding of aortic aneurysm, hypercalcaemia with progressive disease and perforation of the large intestine). Two grade 4 adverse events were considered probably (peripheral neuropathy) or possibly (thrombocytopenia) related to the study drug. The patient with grade 4 peripheral neuropathy had symptoms at baseline consistent with grade 3 neuropathy and developed grade 4 neuropathy on the 1 mg/m² dose. For the patient with grade 4 thrombocytopenia, this event was recorded at cycle 1 day 5, after two doses of bortezomib.

Figure 2 displays the events that occurred at a $\geq 20\%$ greater rate in the 1.3 mg/m² dose group compared with patients treated at the 1.0 mg/m² dose. Comparing these adverse events by grade suggests that the divergence between the two dose groups occurs primarily in the grade 1 and grade 2 events. In contrast, arthralgia and peripheral oedema occurred with a $\geq 20\%$ higher incidence in the 1.0 mg/m² dose group *versus* the 1.3 mg/m² group.

Figure 3 displays the mean platelet count over the time course of bortezomib administration by dose group (1.0 and 1.3 mg/m²) and illustrates the dose-related decrease in platelet counts with recovery observed during the rest period within each cycle.

Peripheral neuropathy was reported in at least one patient in every cycle. In the group receiving 1.3 mg/m², its incidence peaked at cycle 6. Symptoms of peripheral neuropathy were recorded on the baseline FACT/GOG-NTX questionnaire in 71% of patients (20 of 28) who later developed worsening of peripheral neuropathy or any potential symptoms of peripheral neuropathy, and the remaining 28% (8 of 28) reported

Table IV. Treatment-emergent grade 3 and 4 adverse events reported by $\geq 10\%$ of patients.

Adverse event	Bortezomib dose group			
	1.0 mg/m ² (<i>n</i> = 28)		1.3 mg/m ² (<i>n</i> = 26)	
	Grade 3 [<i>n</i> (%)]	Grade 4 [<i>n</i> (%)]	Grade 3 [<i>n</i> (%)]	Grade 4 [<i>n</i> (%)]
Peripheral neuropathy	1 (4)	1 (4)	4 (15)	0 (0)
Pain in limb	3 (11)	0 (0)	2 (8)	0 (0)
Thrombocytopenia	8 (29)	0 (0)	5 (19)	1 (4)
Weakness	1 (4)	0 (0)	3 (12)	0 (0)
Neutropenia	3 (11)	0 (0)	6 (23)	0 (0)
Lymphopenia	3 (11)	0 (0)	3 (12)	0 (0)
Pneumonia NOS	0 (0)	0 (0)	4 (15)	0 (0)
Hyponatraemia	3 (11)	0 (0)	2 (8)	0 (0)

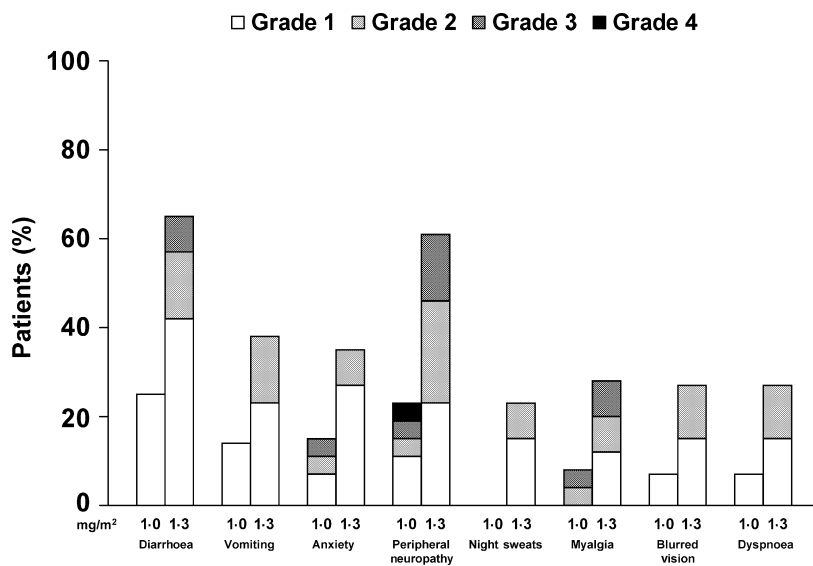


Fig 2. Incidence of overall adverse events that occurred at a $\geq 20\%$ greater rate in the 1.3 mg/m² dose group relative to the 1.0 dose group by CTC grade.

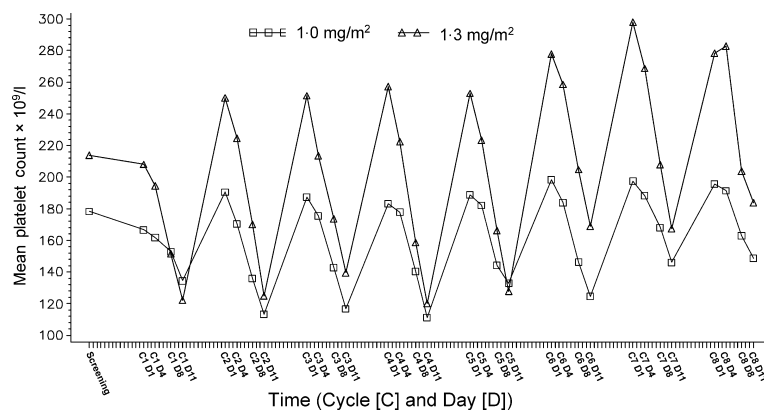


Fig 3. Mean platelet count by dose of bortezomib over the time course of treatment for all patients (1.0 mg/m²: $n = 28$; 1.3 mg/m²: $n = 26$).

new-onset symptoms. Among the patients without treatment-emergent peripheral neuropathy, 80% had baseline symptoms. The dose of bortezomib was reduced at least once in six patients, held at least once in two patients, and permanently discontinued in five patients because of peripheral neuropathy. At the end of the study, symptoms of peripheral neuropathy had resolved in three patients and were ongoing in 19 patients.

A rash was reported in an approximately equal proportion of patients in each dose group: 21% of patients in the 1.0 mg/m² and 19% of patients in the 1.3 mg/m² dose group. No apparent trend was observed with regard to the cycle at which a rash appeared, and no rash was graded >2 .

Twelve patients discontinued because of adverse events, of which eight were considered possibly or probably attributed to bortezomib. Five patients discontinued because of peripheral neuropathy, and one patient each discontinued because of limb pain, cardiac arrhythmia and myelosuppression (anaemia and thrombocytopenia).

One patient from the 1.3 mg/m² dose group died of pneumonia within 20 d after the last administration of bortezomib. No deaths were reported for the 1.0 mg/m² dose

group during the study. An additional seven patients died in the poststudy period: six patients from progressive myeloma and one patient from multi-organ failure at 84 d after the last dose.

Discussion

Bortezomib is the first of a novel class of anti-cancer agents that functions by inhibiting proteasome activity. Based in part on data from the SUMMIT and CREST studies, single-agent bortezomib was approved at 1.3 mg/m² twice weekly every 3 weeks for the treatment of patients with relapsed and refractory myeloma. This study (CREST) is the first prospective multicentre study to report the activity of bortezomib at 1.0 mg/m² in a patient group. Although the study was not designed to be comparative with 1.3 mg/m², the patient groups were comparable by individual centre randomization. An ORR (CR + PR + MR) of 33% was observed for patients treated with bortezomib monotherapy in the 1.0 mg/m² dose group and an ORR of 50% was observed in the 1.3 mg/m² dose group. This trial provides valuable information to the treating

physician who needs to reduce the bortezomib dose for toxicity, because it demonstrated meaningful benefit at the 1.0 mg/m² dose.

The results of this phase 2 study in patients with relapsed or refractory multiple myeloma after front-line therapy suggest that bortezomib in combination with dexamethasone is active at both doses evaluated. Dexamethasone was added to the regimens of patients who were not adequately responding to bortezomib therapy alone. With the addition of dexamethasone, the ORR was 44% in the 1.0 mg/m² dose group and 62% in the 1.3 mg/m² dose group.

The results from this trial compare favourably with those published by Richardson *et al* (2003), who treated a more advanced relapsed and refractory myeloma population. The patients in their study were at a median of 4 years since diagnosis and had had a median of 6 prior lines of therapy. In the trial reported here, the median duration of disease since diagnosis was 2 years for both groups, and the patients were treated after front-line therapy (a median of three regimens). At 1.3 mg/m², Richardson *et al* (2003) demonstrated an ORR of 35%; the higher response rate at 1.3 mg/m² in this current study suggests that enhanced efficacy may be observed in an earlier patient population.

In the current study, toxicities were manageable and consistent with those observed in phase 1 and other phase 2 clinical trials (Orlowski *et al*, 2002; Richardson *et al*, 2003). Overall, the most commonly reported adverse events in this study were fatigue, nausea, diarrhoea, pyrexia, constipation, peripheral neuropathy, arthralgia, insomnia, headache, limb pain, thrombocytopenia and upper respiratory tract infection. Adverse events that were reported more frequently in the 1.3 mg/m² compared with the 1.0 mg/m² dose group with a $\geq 20\%$ difference in incidence rates included diarrhoea, peripheral neuropathy, vomiting, anxiety, myalgia, night sweats, dyspepsia and blurred vision, indicating a possible dose effect. Fatigue, constipation and thrombocytopenia occurred at a similar rate in both dose groups. Interestingly, arthralgia and peripheral oedema were more common in the lower-dose group.

As has been observed in previous phase 1 trials (Aghajanian *et al*, 2002; Orlowski *et al*, 2002), the occurrence of thrombocytopenia with bortezomib is transient, with recovery within the rest period suggesting a possible different pathogenesis than that seen with conventional chemotherapeutic agents. In addition, a trend towards overall improvement of the baseline was also noted and possibly relates to improvement in the haematopoietic reserve in responding patients. Grade 4 events were uncommon and observed in five patients; of these, only two were attributed to the study drug. No study drug-related deaths were reported.

Treatment-emergent neuropathy of any grade was reported in 41% of patients, a rate similar to that observed in the more advanced population reported by Richardson *et al* (2003). Although the patients in the current trial were earlier in their course of disease, a high proportion entered the study with baseline findings of neuropathy by their own report and by the

neurologist's assessment. It is noteworthy that one patient with significant neuropathy at baseline developed grade 4 neuropathy while on the lower dose. A phase 3 trial is being conducted in which the management of peripheral neuropathies and effectiveness of dose reduction will be evaluated in an exploratory analysis.

The intent of this protocol was to treat patients after front-line therapy. Although patients in first relapse are treated with chemotherapeutic regimens, such as VAD (vincristine, adriamycin, dexamethasone) (Rajkumar *et al*, 2002), thalidomide has recently emerged as a potential single-agent salvage therapy in myeloma patients who have relapsed or become refractory to standard therapies (Rajkumar *et al*, 2002; Strasser & Ludwig, 2002). Singhal *et al* (1999) demonstrated an ORR (defined as a decrease in M protein levels by 25% or more) of 32%, and 2% of patients in that study achieved CR (100% decrease in M protein levels by standard electrophoresis).

The findings in this study demonstrate that bortezomib has substantial therapeutic activity in patients with relapsed or refractory multiple myeloma after front-line therapy at two different dose levels. Some additional response effect occurred after the addition of dexamethasone in patients that had a less than optimal response to bortezomib alone and is suggestive of possible synergy. The efficacy results described herein are also favourable relative to other standard cytotoxic therapies used for salvage therapy after front-line treatment.

The observation of activity at lower doses supports the feasibility of a dose reduction strategy to manage certain toxicities, such as those observed less frequently in the 1.0 mg/m² dose group, and will potentially enhance the safety profile of bortezomib. By assuring activity at lower doses, this observation also facilitates the clinical testing of the preclinical synergy noted with the combination of bortezomib and other active agents in this disease, and also in other cancers. Ongoing and future clinical studies include examining bortezomib as a single agent or in combination therapy as initial therapy in multiple myeloma and in non-Hodgkin's lymphoma, other haematological diseases and solid tumours.

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