104/10
November 15, 2005

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Published for the American Cancer Society by John Wiley & Sons, Inc.

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**BACKGROUND.** Bortezomib, a first-in-class proteasome inhibitor, is active with manageable toxicities in relapsed and/or refractory myeloma.

**METHODS.** Bortezomib 1.0 or 1.3 mg/m$^2$ was administered Days 1, 4, 8, and 11 every 21 days for up to 8 cycles to patients with relapsed and/or refractory myeloma participating in two Phase II trials. Dexamethasone could be added because of progressive disease after 2 cycles or stable disease after 4 cycles. Continuation of or retreatment with bortezomib was offered to patients who, in the investigator's opinion, would benefit from extended treatment.

**RESULTS.** Sixty-three patients with relapsed/refractory myeloma treated in this extension trial received a median of 7 additional cycles of therapy, for a total of 14 cycles (range, 7–32) over a median duration of therapy of 45.1 weeks in the parent and extension studies. Seventy-eight percent of patients completed this study at the same or higher bortezomib dose than they started on during this study, and the treatment schedule of twice-weekly administration remained unchanged in 89%. Overall, 75% of patients received dexamethasone in combination with bortezomib for a median of 5 cycles starting either in the parent or extension study. The safety profile was similar between the extension and parent trials, with no evidence of new cumulative toxicity. The most commonly reported Grade 3/4 toxicities were thrombocytopenia (29%), with a consistent pattern of recovery during the rest period of each cycle, diarrhea (11%), anemia (11%), and neutropenia (10%). Neuropathy was reported less frequently.

**CONCLUSIONS.** Retreatment with or continuation of bortezomib ± dexamethasone beyond 6 months was safe, and toxicities were manageable, in patients with relapsed and/or refractory myeloma. ***Cancer* 2005;104:2141–8.**


**KEYWORDS: bortezomib, CREST, extension, myelomas, proteasome, SUMMIT.**

Dr. Berenson has received research grant support, Speaker's Bureau honoraria and consultancy fees from Millennium Pharmaceuticals, Inc. Dr. Jagannath has received research grant support and Speaker's Bureau honoraria from Millennium Pharmaceuticals, Inc. Dr. Barlogie has received Speaker's Bureau honoraria and consultancy fees from Millennium Pharmaceuticals, Inc. Dr. Richardson has received research grant support, Speaker's Bureau honoraria and is on the advisory board of Millennium Pharmaceuticals, Inc. Dr. Alsina has received research grant support and Speaker's Bureau honoraria from Millennium Pharmaceuticals, Inc. Dr. Rajkumar has received research grant support from Millennium Pharmaceuticals, Inc. Dr. Singhal has received Speaker's Bureau honoraria and consultancy fees from Millennium Pharmaceuticals, Inc. Dr. Limentani has received research grant support from Millennium Pharmaceuticals, Inc. Dr. Esseltine is a full-time employee of and owns stocks in Millennium Pharmaceuticals, Inc. Dr. Trehu is a full-time employee of and own stocks in Millennium Pharmaceuticals, Inc. Dr. Schenkein is a full-time employee of and own stocks in Millennium Pharmaceuticals, Inc. Dr. Anderson has received research grant support, Speaker's Bureau honoraria and consultancy fees from Millennium Pharmaceuticals, Inc.

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Received August 24, 2004; revision received March 30, 2005; accepted May 26, 2005.


DOI 10.1002/cncr.21427
Published online 4 October 2005 in Wiley InterScience (www.interscience.wiley.com).

Bortezomib (VELCADE®, Millennium Pharmaceuticals, Inc., and Johnson & Johnson Pharmaceutical Research & Development, L.L.C.) is a first-in-class proteasome inhibitor that has recently received full approval from the United States for the treatment of multiple myeloma patients who have received at least one prior therapy based on the randomized phase III APEX trial demonstrating survival benefit. This expands upon the initial accelerated approval for the treatment of relapsed and refractory multiple myeloma based on 2 phase II clinical trials. In the first trial, Study of Uncontrolled Multiple Myeloma Managed with Proteasome Inhibition Therapy (SUMMIT), 202 patients who had previously received a median of 6 prior lines of therapy were allowed therapy for up to 8 cycles with bortezomib 1.3 mg/m$^2$ given twice weekly for 2 weeks every 3 weeks.[1] In Clinical Response and Efficacy Study of Bortezomib in the Treatment of Relapsing Multiple Myeloma (CREST), a supportive Phase II study, the activity and safety of bortezomib 1.0 and 1.3 mg/m$^2$ were investigated in patients with relapsed or refractory myeloma who had received 1 prior line of therapy.[2] By using the same treatment schedule as in SUMMIT, patients received up to 8 cycles. In both trials, patients could receive oral dexamethasone 20 mg on the day of and the day after bortezomib in combination with bortezomib if a suboptimal response (progressive disease [PD] after 2 cycles or stable disease [SD] after 4 cycles) was achieved[1,2] according to criteria of the European Group for Blood and Marrow Transplantation.[3]

An extension trial was designed to provide additional cycles of bortezomib to patients whom the investigators believed would continue to benefit from further treatment. The objective of this article is to describe the safety profile of bortezomib for patients with relapsed and/or refractory myeloma who received bortezomib retreatment or continued therapy beyond 8 cycles.

## MATERIALS AND METHODS

A total of 63 patients with relapsed and/or refractory multiple myeloma initially treated in SUMMIT and CREST were enrolled in this Phase II, open-label extension study. Because the purpose of the trial was to evaluate the safety of bortezomib therapy beyond 8 cycles, no formal efficacy data were collected. Institutional review board approval was obtained from each treatment site, and the study was conducted in accordance with the International Conference for Harmonization good clinical practice guidelines.

### Patients

Adult patients with multiple myeloma were eligible for SUMMIT if they relapsed after a response to first-line chemotherapy and were refractory to their most recent chemotherapy, or they were eligible for CREST if they received previous front-line therapy and had documentation of relapse.[1,2] Patients were eligible for the extension trial if they demonstrated response or any other tangible clinical benefit in the SUMMIT or CREST trials or relapsed after completing therapy and, in the opinion of the investigator, might continue to benefit from additional therapy or retreatment with bortezomib therapy.

The patients enrolled in the extension study were a selected group. Determinants of a patient's participation in this study included the investigator's assessment, the approval of the institutional review board, and the patient's consent. The parent protocol also required a posttreatment end-of-therapy visit so that the earliest that most patients could be screened for this protocol was within 6–8 weeks of the last dose on the parent protocol.

### Treatment

Upon entry into the extension study, patients were to receive bortezomib on the same dose and schedule on which they completed the parent protocol, without a prespecified maximum of treatment duration. Dose escalation at study entry or during the extension trial was allowed up to 1.3 mg/m$^2$ per dose. Patients who received at least 6 cycles of therapy in the extension study were allowed to switch to a less intensive schedule: either twice weekly for 2 weeks with a 17-day rest or once weekly for 4 weeks with a 13–20-day rest. Toxicity management permitted stepwise dose reductions (1.3–1.0 and then to 0.7 mg/m$^2$, or 1.0–0.7 mg/m$^2$ and then to 0.5 mg/m$^2$), with an option to change the schedule from twice-weekly to weekly administration.

Patients on dexamethasone could enter the extension trial if they were receiving it in the parent protocol. In addition, patients receiving single-agent bortezomib who progressed at any time during the extension study were allowed to add dexamethasone at the same dose and schedule as in the parent study (20 mg on the day of and the day after bortezomib administration). No other investigational drug other than bortezomib or any chemotherapeutic agent was allowed. Local radiation therapy and the administration of supportive therapy (e.g., antiemetics, transfusion support, growth factors, bisphosphonates) were permitted.

TABLE 1
**Baseline Demographic and Disease Characteristics of the Extension Study Patients Compared with all Patients on Entry to the Parent Trials (SUMMIT/CREST)**

| Characteristic | All SUMMIT/CREST | Extension[a] |
|---|---|---|
| *N* | 256 | 63 |
| Male, *n* (%) | 144 (56) | 33 (52) |
| White, *n* (%) | 209 (82) | 53 (84) |
| Median age, yrs (range) | 60.0 (30–84) | 60.0 (42–84) |
| Age ≥ 65, *n* (%) | 95 (37) | 22 (35) |
| KPS ≤ 70, *n/N* (%) | 47/250 (19) | 9/62 (15) |
| IgG myeloma, *n* (%) | 154 (60) | 33 (52) |
| $\beta_2$-microglobulin ≥ 4 mg/L, *n/N* (%) | 106/234 (45) | 24/58 (38) |
| Abnormal cytogenetics, *n/N* (%) | 78/218 (36) | 15/55 (27) |
| Chromosome 13 deletion, *n/N* (%) | 31/218 (14) | 7/55 (13) |
| Median albumin, g/L | 36.0 (1.3 mg/m$^2$, *n* = 228)<br>38.0 (1.0 mg/m$^2$, *n* = 28) | 37.0 |
| Mean C-reactive protein, mg/L | 13.1 (n = 233) | 8.8 (*n* = 57) |
| Median hemoglobin <10 g/dL (range)<br>*n/N* (%) | 105 (54.0–146.0)<br>98/256 (38) | 104.0 (79.0–145.0)<br>23/63 (37) |
| Median platelets < 75 × 10$^9$/L (range)<br>*n/N* (%) | 168 (11.0, 479.0)<br>47/253 (19) | 181 (31.0, 412.0)<br>9/63 (14) |
| Median no. of prior regimens (range) | 6 (2–15) (SUMMIT)<br>3 (1–7) (CREST) | 5 (1–15) |

KPS: Karnofsky performance status.
[a] Extension study patients (*N* = 63) at baseline of enrollment in the SUMMIT/CREST parent trials.

### Safety Assessments

The safety population included all patients who received at least 1 dose of bortezomib on the extension study. Safety evaluations included vital signs, physical examination, Karnofsky performance status (KPS), routine hematologic and clinical chemistry parameters, and C-reactive protein. Complete blood counts were obtained at baseline and on Days 1, 4, 8, and 11 of each cycle. New or worsening adverse events in this extension study were assessed according to the National Cancer Institute Common Toxicity Criteria (NCI CTC) version 2.0 and reported up to 30 days after the last dose of bortezomib.

### Statistics

Descriptive statistics were calculated using SAS statistical software (version 8.2; SAS Institute, Cary, NC). For categorical variables, the number and percentage were calculated, and for continuous variables, the mean, median, standard deviation, and minimum and maximum values were determined.

## RESULTS

### Patient Demographics and Disposition

A total of 63 (25%) patients from 256 originally enrolled in the SUMMIT and CREST parent trials received further treatment in the extension trial (Table 1), with 46 patients enrolling from SUMMIT and 17 from CREST. As expected, patients enrolling in the extension study were predominantly responders: 43 of 63 (68%) achieved SD or better as their best response during the parent study, whereas 20 of 63 (32%) entered with relapse, PD, or unknown status (Table 2). Efficacy data were not collected in the extension trial. The demographic and disease characteristics of these 63 patients at the time of initial enrollment in

TABLE 2
**Responses of Patients on the Parent Protocol Who Entered the Extension Trial (*N* = 63) and Details of Dexamethasone Addition**

| Parent protocol response[a] | No. of patients | Dexamethasone first added on parent protocol, *n* | Dexamethasone first added on extension trial, *n* |
|---|---|---|---|
| Complete response | 5 | 1 | 2 |
| Partial response | 23 | 8 | 7 |
| Minimal response | 6 | 5 | 0 |
| Stable disease | 9 | 6 | 3 |
| Progressive disease | 6 | 6 | 0 |
| Relapse from complete response off Rx | 1 | 0 | 0 |
| Partial response to progressive disease | 9 | 3 | 6 |
| N/A | 4 | 0 | 0 |

[a] European Group for Blood and Marrow Transplantation criteria were used, and response was assessed by an independent review committee. The best response on the parent protocol is provided.

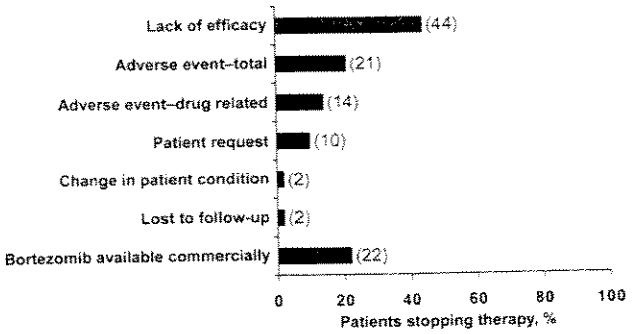


**FIGURE 1.** Reasons for stopping therapy ($N = 63$).

the parent trials were similar to those of the overall patient population in the parent trials, with the exception of a slightly lower incidence of abnormal cytogenetics, a lower mean concentration of C-reactive protein, and a lower frequency of increased $\beta_2$-microglobulin (Table 1).

The time between bortezomib treatment in the parent protocol and the extension study ranged from 1.7 to 59.7 weeks, with a mean of 14.3 weeks and a median of 8.7 weeks. A gap of less than 6 weeks was reported for 38% (24 of 63) of the patients, whereas a gap of ≥ 12 weeks was reported for 33% (21 of 63) of the patients. Unless patients entered the trial for retreatment after relapse, reasons for delays in starting continued therapy included convenience, patient-preference, or delays in obtaining institutional review board approval of the protocol. During the extension trial, 2 patients reported long interruptions beginning at Cycle 9. The first patient received alternative antineoplastic therapy and, after a delay of almost 1 year, was retreated with bortezomib. The second patient received 2 cycles separated by 91 days and, 77 days later, began a third cycle, before resuming a more regular schedule; in this case, the delays occurred because of patient convenience and not toxicity. The reasons for discontinuing therapy are listed in Figure 1.

### Drug Exposure

Exposure to bortezomib and dexamethasone in the parent trial, the extension trial, and overall are presented in Table 3. In the parent trial, the median dose intensity was 1.4 mg/m$^2$ each week, and the maximum dose intensity expected with 8 cycles per protocol was 1.73 mg/m$^2$ each week, corresponding to 1.3 mg/m$^2$ on Days 1, 4, 8, and 11 of the 21-day schedule. In the extension trial, the median dose intensity was 1.4 mg/m$^2$ per week. Fifty-nine percent (37 of 63) of patients received a complete cycle (≥ 3 of 4 doses) for at least 6 cycles of therapy in the extension trial with or without dexamethasone. More than 90% (57 of 63) of patients in the extension trial received at least 2 or more complete cycles in the parent trial, with 73% (46 of 63) receiving at least 4 cycles (Fig. 2).

The majority of patients received dexamethasone (Table 2, Fig. 3). Overall, 75% (47 of 63) of patients received dexamethasone in combination with bortezomib for a median of 5 cycles.

The majority of patients (49 of 63 or 78%) completed the extension study receiving the same or a higher dose than at the start of the extension study. Seven patients (11%) received a dose escalation (Fig. 4). Although schedule modification was allowed, the majority of patients (56 patients or 89%) finished the extension study on the standard twice-weekly regimen (3-week cycles). Only 7 (11%) patients underwent a schedule modification to weekly administration: 3 started the extension trial on the weekly schedule most likely because of prior toxicity, and 4 patients were changed to this schedule for convenience after 9 ($n = 2$) or 10 ($n = 2$) cycles, respectively.

### Safety

Three deaths occurred during the extension trial or within 30 days of the last dose; all were attributed to progressive multiple myeloma and were not considered drug related. Thirty (48%) of the 63 patients on the extension study had at least 1 serious adverse event compared with 21 (33%) of the 63 during the parent trials. The most common serious adverse events observed were pneumonia in 9, renal failure in 5, pyrexia in 4, PD in 4, dehydration in 3, and vomiting in 2 patients.

The most common adverse events reported during prolonged therapy affecting ≥ 20% of patients on the extension trial were diarrhea, fatigue, thrombocytopenia, nausea, and constipation (Fig. 5). The type and frequency of new or worsening treatment-emergent toxicities were generally similar among the overall population of the parent trials, the extension-trial patients while they participated in the parent trials, and the safety population in the extension trial, with the exception of events described in Tables 4 and 5. There was no evidence of any new cumulative toxicity.

Adverse events reported less frequently in the extension study compared with the parent study included peripheral neuropathy, pyrexia, and vomiting, among others, as shown in Table 4. Adverse events reported more frequently in the extension study included edema of the lower limb, hypoproteinemia, and increased creatinine. Although the incidences of these events were higher, most were mild or moderate in intensity, and none was reported as a serious adverse event.

TABLE 3
Exposure to Bortezomib and Dexamethasone During the Parent Trial, the Extension Trial, and the Overall Total

| Parameter | Parent trial $N = 63$ | Extension trial $N = 63$ | Total $N = 63$ |
|---|---|---|---|
| Median total bortezomib dose, mg/m$^2$ (range) | 32.6 (3.9–42.2) | 27.3 (2.0–117.5) | 60.5 (30.7–158.6) |
| Median total bortezomib dose, mg (range) | 61.9 (7.8–86.3) | 49.7 (4.8–182.0) | 106.0 (46.4–263.8) |
| Duration of bortezomib, median wk (range) | 22.6 (1.1–33.7) | 24.4 (1.1–77.3) | 45.1 (23.3–99.9) |
| Median total bortezomib doses (range) | 31.0 (3–32) | 28.0 (3–94) | 56.0 (28–126) |
| Median number of cycles completed (range) | 8.0 (1–8) | 7.0 (1–24) | 14.0 (7–32) |
| Dexamethasone treatment, *n* | 28 | 46 | 47 |
| Median total dose, mg (range) | 480.0 (40–960) | 590.0 (100–2760) | 880.0 (40–2920) |
| Duration of dexamethasone, median wk (range) | 7.7 (0.3–17.7) | 13.6 (1.3–77.3) | 18.6 (0.3–84.3) |
| Median number of cycles dexamethasone completed (range) | 3 (0.3–17.7) | 3 (0–18) | 5 (0–22) |

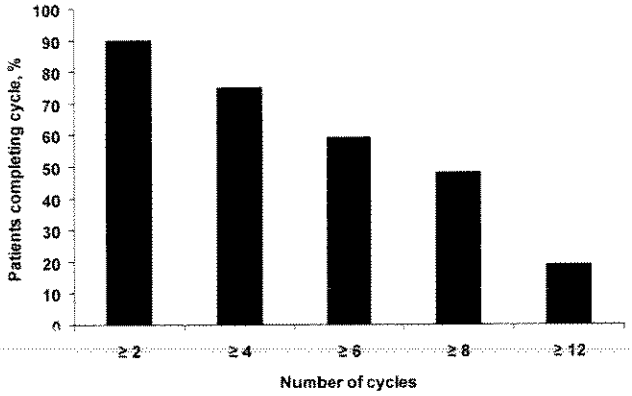


**FIGURE 2.** Bortezomib cycles completed per patient on the extension study.

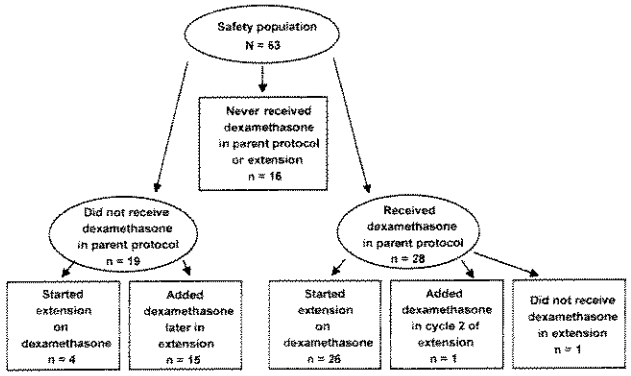


**FIGURE 3.** Timing of addition of dexamethasone for patients in the extension study.

Some adverse events were reported for the first time during the extension trial (Table 5). These events included hyperuricemia, deep venous thrombosis, mental status changes, complete atrioventricular block, seizures, and upper limb edema. Thrombocytopenia was reported in 44% of patients on the extension trial, an incidence similar to the incidence and severity during the parent trials overall (41%) and for the 63 patients while they participated in the parent trial (40%). The cyclic pattern of platelet nadir and recovery during the 10-day rest period was similar in the extension study compared with the parent trials, with no sign of cumulative toxicity (Fig. 6). A progressive increase in mean platelet count was noted throughout all cycles of the extension study.

During the parent protocol, the incidence of peripheral neuropathy, as measured by the number of events per 100 patient doses, steadily increased through the first 5 cycles, peaking at 5.3% at Cycle 5, and thereafter steadily decreased. Consistently, reports of new or worsening peripheral neuropathy in the extension trial (14%) were less than one half of that seen in the extension study population compared with when they participated in the parent trial (30%) and in the parent-trial population overall (29%). Twenty-two (35%) of the 63 patients on the extension study had a prior history of peripheral neuropathy (16 patients with Grade 1 or 2 and 6 with Grade 3). Of these 22 patients, 6 reported peripheral neuropathy in the extension study.

During the parent protocol, 4 of 63 patients had reported central nervous (CNS) events (confusion and memory impairment), which resolved in 3 of the 4 patients before they entered the extension study and did not recur thereafter. During the extension study, CNS events, including seizures, mental status changes, confusion, and memory impairment, were reported in 7 patients. For 6 of these 7 patients, the reports were made in the context of disease progression and confounding medical illnesses, such as renal failure, hyponatremia, high fever, intracerebral hemorrhage, stroke, and oxycodone overdose. Five of these 7 patients were also receiving high-dose dexamethasone when the CNS events occurred.

Edema of any type, including lower limb edema, was reported as a treatment-emergent adverse event

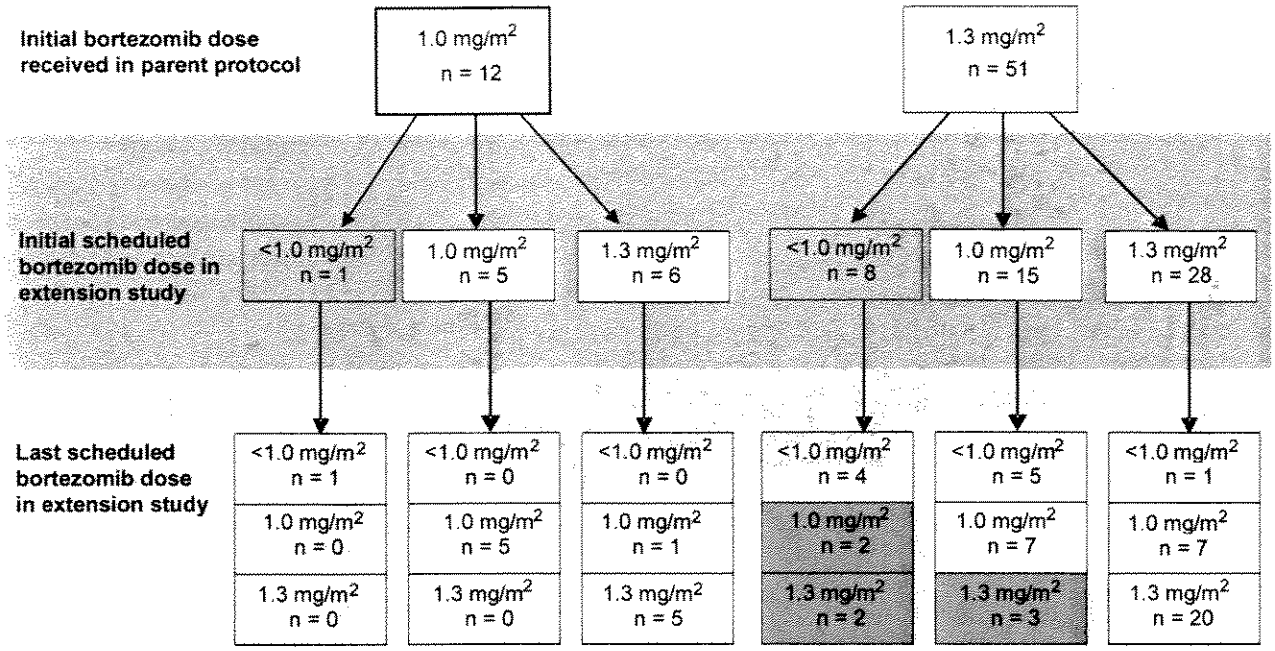


**FIGURE 4.** Changes in bortezomib dose from parent protocol to start of the extension study to last dose on extension study.

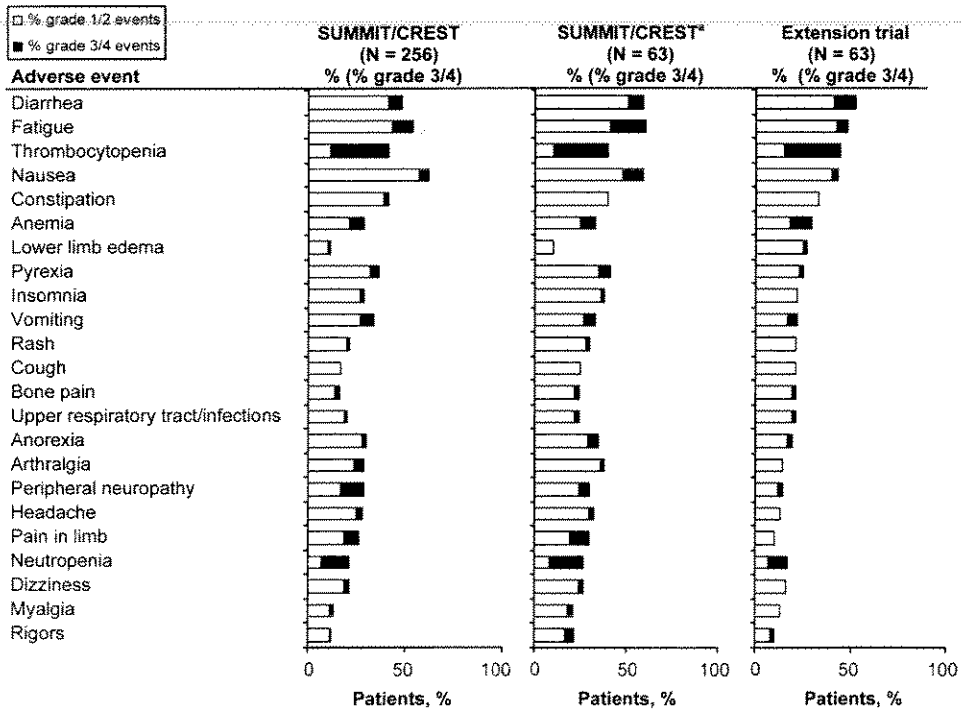


**FIGURE 5.** Treatment-emergent adverse events reported in ≥ 20% of patients in the parent protocol or the extension trial. Percentage of patients with Grade 1 or 2 adverse events or Grade 3 or 4 adverse events. [a]Extension study patients ($N = 63$) while on the SUMMIT/CREST parent trials.

in 41% of these patients during the extension study compared with 29% during the parent protocol. Most were mild or moderate in intensity, and none was reported as a serious adverse event.

No apparent overall increase in the incidence of treatment-emergent cardiac rate or rhythm abnormalities was observed in patients with prolonged bortezomib exposure on the extension study. The incidence of treatment-emergent hypotension of any type reported during the extension study was similar to

TABLE 4
Adverse Events Reported with a Change in Frequency Compared with the Parent Study

| Adverse event | SUMMIT/CREST $N = 256$ (% grade 3/4) | SUMMIT/CREST[a] $N = 63$ (% grade 3/4) | Extension trial ($N = 63$) (% grade 3/4) |
|---|---|---|---|
| Neutropenia[b] | 21 (14) | 27 (19) | 17 (10) |
| Eye irritation[b] | 6 (0) | 14 (0) | 3 (0) |
| Nausea[b] | 62 (5) | 59 (11) | 43 (3) |
| Vomiting[b] | 34 (7) | 33 (6) | 22 (5) |
| Fatigue[b] | 54 (11) | 60 (19) | 48 (6) |
| Peripheral edema[b] | 12 (0) | 13 (0) | 3 (0) |
| Peripheral neuropathy[b] | 29 (12) | 30 (6) | 14 (2) |
| Pyrexia[b] | 36 (4) | 41 (6) | 25 (2) |
| Rigors[b] | 12 (1) | 22 (5) | 10 (2) |
| Anorexia[b] | 30 (2) | 35 (6) | 19 (2) |
| Arthralgia[b] | 29 (5) | 38 (2) | 14 (0) |
| Pain in limb[b] | 26 (7) | 30 (11) | 10 (0) |
| Dizziness[b] | 21 (2) | 27 (3) | 16 (0) |
| Headache[b] | 28 (3) | 32 (2) | 13 (0) |
| Insomnia[b] | 29 (2) | 38 (2) | 22 (0) |
| Erythema[b] | 7 (0) | 14 (0) | 3 (0) |
| Edema lower limb[c] | 11 (1) | 10 (0) | 27 (2) |
| Hypoproteinemia[c] | 2 (0) | 0 (0) | 10 (0) |
| Increased creatinine[c] | 5 (1) | 3 (0) | 13 (2) |
| Hyperglycemia[c] | 7 (2) | 5 (0) | 19 (0) |
| Chest wall pain[c] | 1 (1) | 0 (0) | 10 (0) |
| Productive cough[c] | 6 (0) | 2 (0) | 13 (0) |

[a] Extension study patients ($N = 63$) while on the SUMMIT/CREST parent trials.
[b] Adverse event reported less frequently than in the parent study.
[c] Adverse event reported more frequently than in the parent study.

TABLE 5
Clinically Relevant Adverse Events Reported for the First Time During the Extension Study

| Adverse event | Extension trial $N = 63$ no. (no. grade 3/4) |
|---|---|
| Hyperuricemia | 5 (4) |
| Deep venous thrombosis | 5 (4) |
| Mental status changes | 3 (2) |
| Seizures | 2 (1) |
| Upper limb edema | 3 (0) |
| Eye pain | 2 (0) |
| Complete atrioventricular block | 1 (1) |
| Cardiomegaly | 1 (0) |
| Myocardial infarction[a] | 1 (1) |
| Supraventricular tachycardia[a] | 1 (0) |
| Arrhythmia due to dehydration | 1 (0) |
| Pulmonary edema[a] | 1 (1) |

[a] Occurred in the same patient.

that reported for these patients during their parent-protocol experience.

Of the 13 patients who discontinued treatment, 4 (31%) discontinued because of disease progression, 3 (23%) because of neuropathy/paresthesia, and 1 (8%) patient each because of syncope, acute renal failure, diarrhea, cerebrovascular accident, elevated liver function tests, and weight loss. Two of these patients discontinued after the events recurred after bortezomib rechallenge (neuropathy in 1 patient and elevated liver enzymes in the other).

No clinically meaningful changes or trends in median blood pressure values were noted across time during the extension study. Assessment of KPS across the study was stable during therapy, with a mean decrease of 1.5% from baseline to the last assessment for the 33 patients for whom data were available.

## DISCUSSION

The SUMMIT and CREST trials demonstrated significant activity of bortezomib with manageable toxicity in relapsed/refractory multiple myeloma.[1,2,4] With continued therapy or retreatment during the extension trial, there was no evidence of new cumulative toxicities, and the adverse event profile was similar to that of the first 8 cycles of treatment, with few exceptions. Treatment beyond 2 years was not observed, because the trial was stopped when bortezomib became commercially available, and follow-up data were not collected. The mean duration of approximately 11 months of bortezomib treatment in the parent and the extension studies suggests that bortezomib may have a role in long-term and maintenance therapy regimens.

As in the parent trials, on the extension trial, thrombocytopenia was the most common Grade 3 or greater observed toxicity and appeared transient, with recovery of platelet counts toward baseline during the rest phase of each cycle. The same platelet decrease and recovery pattern was observed previously in the SUMMIT trial.[1] The ability of the platelet counts to rapidly recover from bortezomib-induced thrombocytopenia suggests that the capacity for platelet regeneration remains intact. Therefore, the mechanism by which bortezomib causes thrombocytopenia is likely to differ from that of certain common chemotherapeutic drugs that cause cytotoxicity and death to megakaryocytes. This observation is consistent with preclinical data from a murine model in which bortezomib did not negatively affect the bone marrow.[5]

In the extension trial, the reported onset of new or worsening peripheral neuropathy was less than one half that of the overall parent population or of the extension trial patients when they were in the parent trials. The decreasing incidence of neuropathy in the extension trial appeared to be a continuation of the trend observed during the parent study,

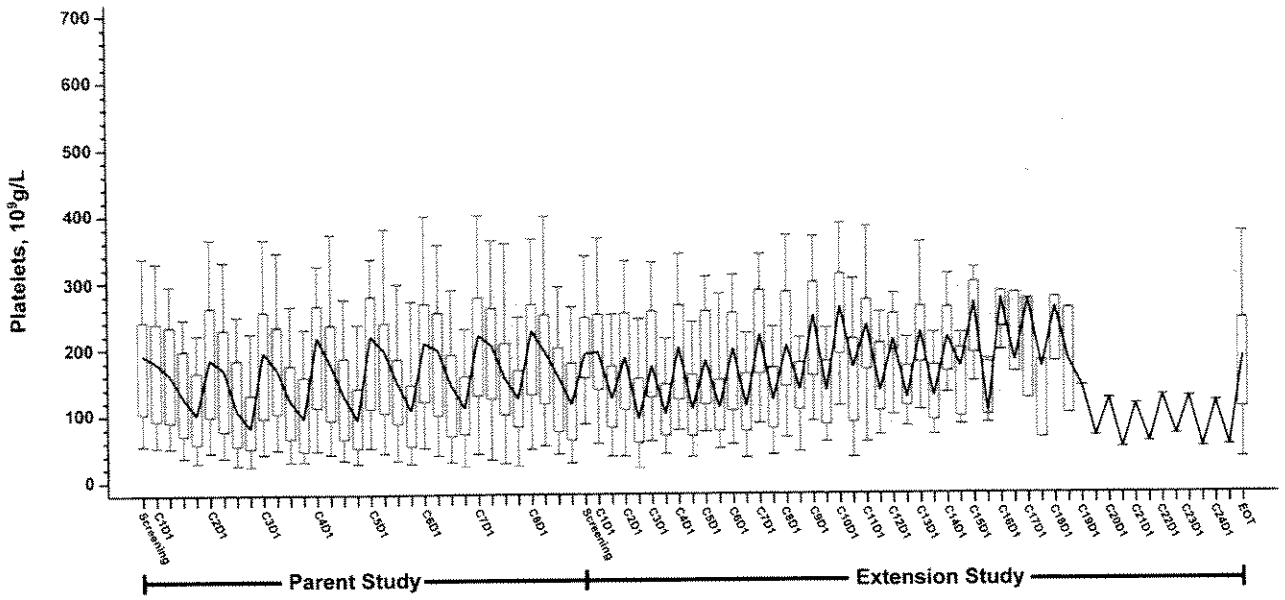


**FIGURE 6.** Mean platelet counts during treatment with bortezomib. Box plots represent the 25th through the 75th percentiles. The error bars represent the 5th and 95th percentiles. C: cycle.

in which the incidence of new or worsening neuropathy peaked at Cycle 5 and steadily decreased over time. This observation suggests that some patients are not likely to develop neuropathy, despite prolonged therapy.

More instances of lower limb edema and hyperglycemia were observed during the extension trial. Possibly relevant to these reports are the increased reporting of hypoproteinemia, the frequent use of high-dose dexamethasone, and other confounding medical illnesses. Events not previously reported in this subset of patients included mental status changes, seizures, and some cardiac events, but underlying or predisposing illnesses were present in these patients, with no indication that these represented cumulative toxicity.

The majority of patients completed the study on the same or on a higher dose of bortezomib than that on which they started this extension study, and most remained on the biweekly schedule, suggesting that long-term treatment, even with the dose-intensive schedule, is manageable and tolerable. A less dose-intensive, more convenient schedule may be preferable for use in a maintenance regimen.

The current study demonstrated that prolonged therapy or retreatment with bortezomib is possible and tolerable. Further investigations will help to determine the optimal duration of bortezomib therapy and to assess an efficacy advantage to therapy beyond 8 cycles.

## REFERENCES

1. Richardson PG, Barlogie B, Berenson J, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. *N Engl J Med.* 2003;348:2609–2617.
2. Jagannath S, Barlogie B, Berenson J, et al. A phase 2 study of two doses of bortezomib in relapsed or refractory myeloma. *Br J Haematol.* 2004;127:165–172.
3. Blade J, Samson D, Reece D, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. *Br J Haematol.* 1998;102:1115–1123.
4. Richardson PG, Sonneveld P, Schusler MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med.* 2005;352:2487–2498.
5. Fitzgerald M, Fraser C, Webb I, Schenkein D, Esseltine D, Weich N. Normal hematopoietic stem cell function in mice following treatment with bortezomib. *Biol Blood Marrow Transplant.* 2003;9:193.