# Bortezomib in Recurrent and/or Refractory Multiple Myeloma

## *Initial Clinical Experience in Patients with Impaired Renal Function*

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**BACKGROUND.** Bortezomib is a potent, reversible proteasome inhibitor that has been approved for the treatment of recurrent and/or refractory multiple myeloma, but its activity in patients with renal impairment has not been studied to date.

**METHODS.** Response rates, safety, and 20S proteasome activity were assessed in relation to baseline creatinine clearance (CrCl) among patients with recurrent and/or refractory myeloma ($n$ = 256 patients) who were treated with bortezomib in 2 Phase II trials. Bortezomib was administered by intravenous bolus on Days 1, 4, 8, and 11 of a 21-day cycle at 2 doses, 1.0 mg/m$^2$ ($n$ = 28 patients) and 1.3 mg/m$^2$ ($n$ = 228 patients).

**RESULTS.** Of 10 patients with CrCl $\leq$ 30 mL/minute, 7 patients completed the protocol-specified 8 cycles of treatment; 4 patients received the 1.3 mg/m$^2$ bortezomib dose, and 3 patients received the 1.0 mg/m$^2$ bortezomib dose. Using the European Group for Blood and Marrow Transplantation criteria, responses were assigned by an independent committee to 3 of the 10 patients (2 partial responses and 1 minimal response), a response rate similar to that of the overall treated population. Patients with CrCl $>$ 80 mL/minute ($n$ = 105 patients), 51–80 mL/minute ($n$ = 99 patients), and $\leq$ 50 mL/minute ($n$ = 52 patients) had similar rates of discontinuation and similar adverse event profiles. Renal function did not appear to affect the 1-hour postdose proteasome inhibition or its recovery.

**CONCLUSIONS.** Clinical experience in a limited number of patients with impaired renal function suggests that bortezomib provides clinical benefit with manageable toxicities in this high-risk population. ***Cancer*** **2005;103:1195–200.**
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**KEYWORDS: bortezomib, myeloma, proteasome, renal failure.**

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Received August 11, 2004; revision received November 19, 2004; accepted November 19, 2004.

© 2005 American Cancer Society
DOI 10.1002/cncr.20888
Published online 2 February 2005 in Wiley InterScience (www.interscience.wiley.com).

At the time of presentation, up to 50% of patients with myeloma have decreased creatinine clearance, and between 20% and 30% of patients have concomitant renal failure.[1–3] The most common cause of renal failure is interstitial nephritis due to the development of light-chain tubular casts, so-called *myeloma kidney*. Renal failure is generally a complication of high tumor burden and is a risk factor for a lower response to treatment and a poor prognosis.[1,3,4] However, after chemotherapy, it has been reported that renal function recovers in approximately 25% of patients.[1] Effective treatment delivered at full dose in this high-risk group represents an ideal therapeutic goal.

Bortezomib (VELCADE®; Millennium Pharmaceuticals, Cambridge, MA) is a first-in-class selective and reversible proteasome inhibitor that has been approved for the treatment of myeloma in patients who have received at least two prior treatments and who progressed on their last therapy. Durable responses and meaningful survival have been observed in patients with recurrent and/or refractory myeloma who were treated with bortezomib for up to 8 cycles in 2 Phase II trials. In the first of 2 trials, Study of Uncontrolled Multiple Myeloma Managed with Proteasome Inhibition Therapy (SUMMIT), the overall response rate according to the criteria of the European Group for Blood and Marrow Transplantation (EBMT)[5] was 35% (complete responses [CRs], plus partial responses [PRs], plus minimal responses [MRs]) after bortezomib at a dose of 1.3 mg/m$^2$, and the median overall survival was 518 days ($\approx$ 17 months) among all 202 patients.[6,7] In the second Phase II trial, Clinical Response and Efficacy Study of Bortezomib in the Treatment of Relapsing Multiple Myeloma (CREST), bortezomib either at 1.0 mg/m$^2$ or at 1.3 mg/m$^2$ was administered, and the overall response rates were 33% and 50%, respectively.[8] Recently, a Phase III, randomized, clinical trial comparing bortezomib with high-dose dexamethasone as therapy for recurrent multiple myeloma demonstrated a significant advantage in the time to disease progression and survival on the bortezomib arm in a preplanned interim analysis.[9]

After intravenous bolus administration, bortezomib rapidly distributes from the plasma into the systemic and extrasystemic cellular compartment. Bortezomib is inactivated through oxidative deboronation, a process that occurs throughout the body by both cytochrome P450-mediated and nonenzymatic mechanisms.[10] In animal studies with $^{14}$C-labeled bortezomib, 25% of radioactivity was recovered in the urine, but little or no active drug was present, suggesting that renal impairment may not limit the use of bortezomib significantly.

The objectives of this retrospective analysis were to examine the response rate and safety of bortezomib in recurrent and/or refractory myeloma in patients with renal impairment who were enrolled in the SUMMIT and CREST trials. Proteasome activity relative to renal function also was assessed.

## MATERIALS AND METHODS

### Patients

Patients with multiple myeloma who received at least two prior therapies and who had progressive disease were enrolled into the SUMMIT trial, the methodology of which has been published previously.[6] Patients with a creatinine clearance of $>$ 30 mL/minute were permitted to enroll into the study according to the protocol, but patients with a creatinine clearance $>$ 10 mL/minute but $\leq$ 30 mL/minute were permitted to enroll with approval from the investigator and sponsor. Creatinine clearance was calculated based on the Cockroft–Gault formula using serum creatinine values, age, and gender and was not based on 24-hour urine collection. Other inclusion criteria included a Karnofsky performance score (KPS) $\geq$ 60%, hepatic aminotransferases within 3 times the upper limit of normal (ULN), serum total bilirubin concentration $\leq 2 \times$ ULN, hemoglobin level $\geq$ 8 g/dL, absolute neutrophil count $\geq 500/\mu$L, and platelet count $\geq 30 \times 10^9$/L. No patient who was receiving dialysis was permitted to participate. Patients with myeloma who had a recurrence after first-line treatment were enrolled in the CREST trial,[8] and the remaining inclusion criteria were identical to those for the SUMMIT trial. All patients who participated in these trials provided written informed consent.

### Treatment

Bortezomib was administered in SUMMIT and CREST as described above. In the event of Grade $\geq$ 3 nonhematologic events or Grade 4 hematologic adverse events, bortezomib was withheld until the effects were Grade 1 or better, at which time doses were reduced (from 1.3 mg/m$^2$ to 1.0 mg/m$^2$ or from 1.0 mg/m$^2$ to 0.7 mg/m$^2$). Patients who had progressive disease after $\geq$ 2 cycles or who had stable disease after $\geq$ 4 cycles were eligible to receive oral dexamethasone 20 mg on the day of and on the day after bortezomib administration. Patients in either trial who received benefit or had the potential for benefit after eight cycles of treatment were eligible to enroll in an extension study in which they could continue to receive bortezomib using the same dose and schedule that they had received last in the parent trial.

### Response and Safety

Response was based on the criteria of the EBMT[5] and was confirmed by an independent review committee. A CR was defined as no quantifiable M-protein on serum and urine protein electrophoresis, a negative immunofixation on 2 measurements confirmed 6 weeks apart, < 5% plasma cells in the bone marrow on 1 measurement, an absence of soft-tissue plasmacytomas, stable skeletal disease, and normal serum calcium concentration. A PR was defined as a decrease ≥ 50% in M-protein and a decrease ≥ 90% in urinary light chains or < 200 mg/24 hours, confirmed at 6 weeks. An MR was defined as a decrease ≥ 25% in M-protein and a 50–89% decrease in urinary light chains but ≥ 200 mg/24 hours and was confirmed on repeat measurements in 6 weeks. Safety and tolerability were assessed at each visit and were graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0).

### Proteasome Inhibition Assay

Blood samples were collected before and 1 hour after bortezomib administration to measure 20S proteasome activity on Days 1 and 11 of Cycles 1 and 7. In brief, samples were collected in sodium heparin-containing tubes, frozen at − 80 °C, then thawed prior to the assay. After lysis of the blood cells with 5 mM ethylenediamine tetraacetic acid, pH 8.0, 20S proteasome activity was measured spectrofluorometrically, as described previously.[11]

## RESULTS

Among the 256 patients in the pooled population from both studies, baseline calculated creatinine clearance was > 80 mL/minute in 105 patients, 51–80 mL/minute in 99 patients, 30–50 mL/minute in 42 patients, and < 30 mL/minute in 10 patients. The baseline characteristics of patients with creatinine clearance < 30 mL/minute ($n$ = 10 patients) are compared with the overall population ($n$ = 256 patients) in Table 1. The median age of these patients was similar to that of the overall population, but there was a greater tendency for them to have a baseline KPS ≤ 70% and $\beta_2$-microglobulin ≥ 4 mg/L. Their median platelet counts tended to be lower, and their routine bone marrow cytogenetics tended to be abnormal. Among these 10 patients with creatinine clearance < 30 mL/minute, 6 patients had a history of renal failure, and 3 patients had a history of hypertension. Diabetes mellitus was reported in one patient. These patients had received a median of three prior lines of therapy. Mild to moderate neuropathy was present at baseline in five patients.

**TABLE 1**
**Baseline Demographics and Disease Characteristics**

| Demographic | Overall population ($n$ = 256) | Patients with creatinine clearance < 30 mL/min ($n$ = 10) |
|---|---|---|
| Age (yrs) | | |
| Median | 61 | 69 |
| Range | 30–84 | 51–75 |
| KPS ≤ 70% (%) | 19 | 40 |
| Type of myeloma (% IgG/IgA/LC) | 60/24/14 | 70/0/30 |
| $\beta_2$-microglobulin ≥ 4 mg/L (%) | 45 | 90 |
| Median hemoglobin (g/dL) | 10.5 | 9.7 |
| Median platelet count (× $10^9$/L) | 168.0 | 114.5 |
| Serum creatinine ($\mu$mol/L) | | |
| Median | 88.4 | 247.5 |
| Range | 44.2–389 | 124–389 |
| Range of creatinine clearance (mL/min)[a] | 13.8–220.9 | 13.8–29.6 |
| No. at bortezomib starting dose (1.3 mg/m$^2$/1.0 mg/m$^2$) | 228/28 | 6/4 |
| Percent with abnormal cytogenetics ($n$) | 36 (78/218) | 50 (4/8) |

KPS: Karnofsky performance status; IgG: immunoglobulin G; IgA: immunoglobulin A; LC: light chain.
[a]Creatinine clearance = 140-age in yrsSerum creatinine (mg/dL) × lean body mass (kg)72.
For women, multiply the result by 0.85.

Seven of the 10 patients with creatinine clearance < 30 mL/minute completed the protocol-specified maximum of 8 cycles of bortezomib, including 4 patients at the 1.3 mg/m$^2$ bortezomib dose and 3 patients at the 1.0 mg/m$^2$ bortezomib dose. Two patients continued therapy beyond 8 cycles in the extension study—1 patient received bortezomib 1.0 mg/m$^2$ for an additional 4 cycles, and the other patient received bortezomib 1.3 mg/m$^2$ for an additional 2 cycles and a single dose in the third cycle. Three patients discontinued early: the reasons for discontinuation were failure to thrive unrelated to bortezomib in 1 patient age 74 years at Cycle 5 (1.0 mg/m$^2$), peripheral neuropathy in 1 patient with light-chain disease in Cycle 1 after 3 doses (1.3 mg/m$^2$), and severe pelvic pain in 1 patient at Cycle 2 (1.3 mg/m$^2$) who had immunoglobulin G myeloma that progressed soon after discontinuation. Six patients received added dexamethasone because of a less than optimal response to bortezomib alone.

The overall response rate (CRs, plus PRs, plus MRs) according to the EBMT criteria in the entire population ($n$ = 256 patients) was 45% (45 of 101 patients) among patients with a baseline creatinine clearance > 80 mL/minute, 33% (31 of 93 patients) among patients with a baseline creatinine clearance 51–80 mL/minute, and 25% (13 of 52 patients) among patients with a baseline creatinine clearance ≤ 50 mL/minute.

Among the 10 patients who had severe renal im-

**TABLE 2**
**Baseline Characteristics of Patients with Creatinine Clearance < 30 mL/Minute and Best Response to Treatment**

| Patient no. | Age (yrs) | Myeloma type | Serum-M protein (g/L)[a] | $\beta_2$-microglobulin (mg/L) | Hb (g/dL) | Platelet count ($\times 10^9$/L) | Serum creatinine ($\mu$mol/L) | Creatinine clearance (mL/min) | Bortezomb starting dose (mg/m$^2$) | Best response |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 70 | IgG | 27.8 | 6.6 | 12.4 | 117 | 159 | 26.9 | 1.3 | PR |
| 2 | 56 | IgG | 29.0 | 4.2 | 9.7 | 132 | 362 | 26.8 | 1.3 | PR |
| 3 | 65 | IgG | 44.0 | 1.5 | 8.3 | 68 | 239 | 22.1 | 1.0 | MR |
| 4 | 74 | IgG | 63.0 | 15.0 | 8.7 | 45 | 389 | 17.5 | 1.0 | SD |
| 5 | 69 | LC$\kappa$ | 3.362 | 83.0 | 11.1 | 205 | 256 | 26.7 | 1.0 | PD |
| 6 | 53 | IgG | 3.7[b] | 108.0 | 10.4 | 67 | 283 | 22.9 | 1.0 | PD |
| 7 | 69 | LC$\kappa$ | 2.986 | 5.4 | 10.7 | 112 | 124 | 28.3 | 1.3 | PD |
| 8 | 68 | IgG | 1.9 | 9.3 | 8.9 | 158 | 141 | 28.6 | 1.3 | PD |
| 9 | 51 | LC$\kappa$ | 6.890 | 11.9 | 9.6 | 25 | 354 | 13.8 | 1.3 | NE |
| 10 | 75 | IgG | 17.5 | 7.4 | 9.3 | 177 | 159 | 29.6 | 1.3 | NE |

Hb: hemoglobin; IgG: immunoglobulin G; LC: light chain; PR: partial response; MR: minimal response; SD: stable disease; PD: progressive disease; NE: not evaluable.
[a] Twenty-four hour urinary paraprotein levels (g) are shown in parentheses for patients with light chain disease.
[b] Serum IgG concentration (g/L).

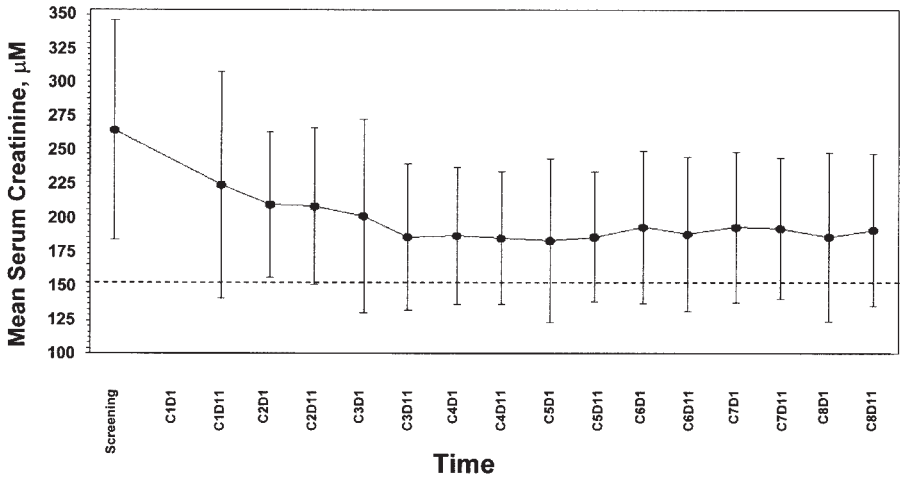


**FIGURE 1.** Mean serum creatinine over time with treatment in patients with creatinine clearance (CrCL) < 30 mL/minute ($n$ = 10 patients). Bars indicate standard deviation. The dashed line indicates the upper level of normal at 150 $\mu$mol/L. C: cycle; D: day.

pairment (creatinine clearance ≤ 30 mL/minute), 2 PRs and 1 MR were confirmed by the independent review committee. Stable disease was reported in one patient, and progressive disease was reported in four patients. Responders did not have any characteristics that would have distinguished them readily from nonresponders (Table 2). The independent review committee could not determine the response in two patients because of a lack of confirmatory data. The mean serum creatinine did not worsen; initially, it decreased somewhat early in the course of therapy and then remained stable outside the normal range (Fig. 1).

There was no clear relation between the discontinuation rate and renal function. Discontinuations were reported in 28% of 105 patients with creatinine clearance > 80 mL/minute, in 22% of 99 patients with creatinine clearance 51–80 mL/minute, and in 38% of 52 patients with creatinine clearance ≤ 50 mL/minute. Serious adverse events were reported in 41%, 51%, and 60% of patients in the same groups, respectively.

Adverse events Grade ≥ 3 that occurred in ≥ 10% of patients with creatinine clearance > 80 mL/minute, 51–80 mL/minute, or ≤ 50 mL/minute were thrombocytopenia (30%, 27%, and 33%, respectively), fatigue (12%, 10%, and 10%, respectively), diarrhea (7%, 6%, and 10%, respectively), anemia (10%, 6%, and 10%, respectively), neutropenia (12%, 15%, and 17%, respectively) peripheral neuropathy (11%, 9%, and 13%, respectively), dyspnea (1%, 4%, and 12%, respectively), and weakness (6%, 5%, and 10%, respectively). Comparing the incidence of reported adverse events between patients with creatinine clearance > 80 mL/minute and patients with creatinine clearance ≤ 50 mL/minute, Grade ≥ 3 weakness, diarrhea, dyspnea,

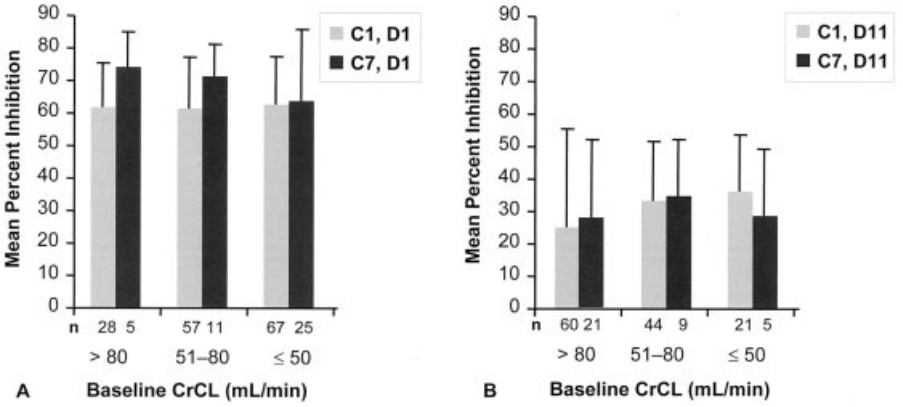


**FIGURE 2.** Maximal inhibition of proteasome activity observed at 1 hour after the first dose of bortezomib at Cycle 1 (C1) and C7 (A) and recovery of proteasome activity observed before last dose of bortezomib at C1 and C7 (B) by baseline creatinine clearance (> 80 mL/minute, 51–80 mL/minute, or ≤ 50 mL/minute). D: day.

pyrexia (2%, 5%, and 6%, respectively), and constipation (2%, 1%, and 4%, respectively) showed a trend toward a higher frequency in patients with worse renal function, whereas limb pain showed a trend toward a lower frequency (9%, 8%, and 4%, respectively), but the only adverse event that was statistically significant was dyspnea ($P = 0.01$; Fisher exact test). In five of six patients with dyspnea, an acute medical event that could have predisposed to severe dyspnea occurred concurrently, including a possible pulmonary embolism in a patient with chronic obstructive pulmonary disease, Klebsiella pneumonia with congestive heart failure in one patient, congestive heart failure in one patient, pneumonia in one patient, and pneumonitis with congestive heart failure in one patient.

Among the 10 patients with creatinine clearance < 30 mL/minute, adverse events Grade ≥ 3 included constipation ($n = 1$ patient), nausea ($n = 1$ patient), gastrointestinal hemorrhage ($n = 1$ patient), thrombocytopenia ($n = 4$ patients), neutropenia ($n = 3$ patients), weakness ($n = 1$ patient), fatigue ($n = 1$ patient), pyrexia ($n = 1$ patient), peripheral neuropathy ($n = 3$ patients), arthralgia ($n = 2$ patients), bone pain ($n = 1$ patient), neck pain ($n = 1$ patient), dyspnea ($n = 1$ patient), pneumonia ($n = 1$ patient), fracture ($n = 2$ patients), drug hypersensitivity ($n = 1$ patient), pelvic pain ($n = 1$ patient), and deep venous thrombosis ($n = 1$ patient). Dyspnea was reported in a patient with underlying hypertension and chronic obstructive pulmonary disease who had a possible pulmonary embolism 4 days earlier along with fluid retention and was deemed unrelated to bortezomib.

There was no association between inhibition and recovery of proteasome activity and renal function (Fig. 2). Recovery of nearly 70% of baseline proteasome activity was observed on Day 11 (3 days after the previous bortezomib dose) and did not appear to be affected by creatinine clearance. The mean maximal proteasome inhibition postdose did not change between Cycle 1 on Day 1 and Cycle 7 on Day 11 across defined creatinine clearance groups.

## DISCUSSION

In this subset analysis of patients with recurrent and/or refractory myeloma who were treated on two Phase II studies with bortezomib, renal function did not appear to have a major impact on response rates to bortezomib alone, toxicity, or the ability to complete the full eight cycles of treatment per protocol. The majority of these patients had dexamethasone added during their course. The proportion of patients receiving dexamethasone was higher than that observed in the Phase II trials overall.[12] The implication of this observation in this setting is unclear.

Patients with myeloma and concomitant renal failure represent a group at high risk for increased morbidity. Indeed, renal failure is generally a complication of high tumor burden and portends a worse prognosis.[4] Patients with renal failure who were treated with bortezomib in this study had signs of increased tumor burden.[13–15] For example, the percentage of patients with baseline thrombocytopenia was higher in these patients than in the overall SUMMIT and CREST populations. Nonetheless, although there were relatively few patients with severely impaired renal function in those studies, the observation of 2 PRs and 1 MR in the 10 patients who had creatinine clearance < 30 mL/minute was encouraging. Although a trend was observed in which patients with higher baseline creatinine clearance (> 80 mL/minute) had higher response rates than patients with lower values, clinical experience is limited to relatively few patients with low creatinine clearance and will require further study.

Bortezomib had a manageable toxicity profile in these studies. Although a greater frequency of adverse events may be expected in this high-risk population,

only minor differences in the incidence of reported adverse events were observed relative to renal function. However, there was a trend toward a higher frequency of serious adverse events with decreasing renal function. The overall frequency of discontinuation was similar regardless of baseline renal function.

Patients with renal impairment represent a therapeutic challenge in multiple myeloma. Response rates have been lower, and safety has been a significant concern, depending on the treatment regimen. With conventional chemotherapy, lower response rates have been reported in patients who have renal function abnormalities compared with patients who are without renal impairment. The differences have been attributed primarily to early mortality.[16] With autologous stem cell transplantation, the dose of melphalan may need to be lowered because of toxicity; but, otherwise, renal failure does not prejudice stem cell collection or affect engraftment.[17] However, poor performance status and very high creatinine levels (> 5 mg/dL) are considered exclusion criteria for such treatment.[18]

In summary, the initial clinical experience with bortezomib in this limited subgroup of patients with renal impairment suggests that these patients can respond to treatment, that the toxicity profile is tolerable, and that measures of proteasome inhibition and recovery are not affected by reductions in renal function. A Phase I study assessing the safety, pharmacokinetics, and pharmacodynamics of treatment with bortezomib in patients with myeloma who have reduced renal function is ongoing (National Cancer Institute study NCI-5874)[19] and is expected to contribute more information toward understanding the use of bortezomib in this clinical setting.

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