Bortezomib in combination with dexamethasone for the treatment of patients with relapsed and/or refractory multiple myeloma with less than optimal response to bortezomib alone

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Background and Objectives. The efficacy and safety of added dexamethasone were assessed in patients with relapsed and/or refractory multiple myeloma who had a suboptimal response to bortezomib alone.

Design and Methods. In two previously reported, open-label, multicenter phase 2 studies, bortezomib 1.0 or 1.3 mg/m^2 was administered intravenously twice weekly for 2 weeks of a 3-week cycle for up to 8 cycles to patients who had failed either ≥2 lines of therapy (SUMMIT, n=202) or first-line therapy (CREST, n=54). Patients with progressive disease after the first two cycles or stable disease after four cycles of bortezomib were eligible for addition of oral dexamethasone 20 mg on the day of and after each bortezomib dose. Responses were assessed by an Independent Review Committee using European Group for Blood and Marrow Transplantation criteria.

Results. Addition of dexamethasone to bortezomib was associated with improved responses in 13 of 74 evaluable patients (18%) in SUMMIT and 9 of 27 (33%) in CREST; eight of these 22 patients had been previously refractory to dexamethasone. There were 2 complete, 8 partial, and 12 minimal responses. Dexamethasone did not appear to alter the type or number of adverse events. Treatment-emergent adverse events reported in ≥ 20% of patients receiving combination therapy were fatigue (25%), thrombocytopenia (24%), insomnia (21%), and nausea (20%).

Interpretation and Conclusions. Addition of dexamethasone to bortezomib in patients with relapsed and/or refractory myeloma who had suboptimal responses to bortezomib alone was associated with improvement in responses without prohibitive toxicity.

Key words: multiple myeloma, bortezomib, dexamethasone, phase 2.

Haematologica 2006; 91:929-934

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Corticosteroids have long been a central component of the treatment for multiple myeloma, with the most commonly used regimens being melphalan and prednisone,[1,2] vincristine, doxorubicin, and dexamethasone (VAD),[3-5] thalidomide plus dexamethasone,[6-8] and high-dose dexamethasone alone.[9] The dose of dexamethasone used in the VAD regimen and as a single agent is typically 40 mg po on days 1-4, 9-12, and 17-20 of a 28- to 35-day cycle, for a total of 480 mg.

Bortezomib (VELCADE®, Millennium Pharmaceuticals, Inc. and Johnson & Johnson Pharmaceutical Research & Development, L.L.C.) is a potent, reversible inhibitor of the proteasome and is active in myeloma. Preclinical evidence provides a rationale for combining bortezomib with dexamethasone, suggesting that the therapeutic effects of the two agents could be additive and that bortezomib may overcome resistance to dexamethasone in multiple myeloma cells.[10] Adherence of myeloma cells to bone marrow stromal cells triggers nuclear factor (NF)-κB-dependent transcription and secretion of interleukin (IL)-6,[11,12] a growth and survival factor[11,13] that blocks dexamethasone-induced apoptosis in myeloma cells.[14] Bortezomib inhibits binding of multiple myeloma cells to bone marrow stromal cells, prevents activation of NF-κB, and inhibits the secretion of IL-6 *in vitro*.[10,15]

Bortezomib is approved for the treatment of myeloma patients who have relapsed after one prior therapy in the United States and European Union based predominantly on the results of two phase 2 clinical trials, SUMMIT and CREST,[16,17] and the randomized, phase 3 APEX trial.[18] In the European Union, patients must have already undergone bone marrow transplantation or be unsuitable for the procedure. Both phase 2 studies allowed for the addition of dexamethasone in patients with a suboptimal response to bortezomib alone. The response to and toxicity of bortezomib alone in these two trials were reported in previous publications.[16,17] We report here for the first time a detailed analysis of the contribution of dexamethasone when it is added to bortezomib in this patient population.

Design and Methods

In SUMMIT, 202 patients who had received at least two lines of therapy for myeloma and had progressed during or within 60 days after

completion of their last therapy (i.e., refractory myeloma) were enrolled to receive bortezomib monotherapy, 1.3 mg/m^2. In CREST, 54 patients who had progressed during or after completion of first-line therapy were randomized to receive bortezomib monotherapy, 1.0 or 1.3 mg/m^2. The methods used in the SUMMIT trial have been published in detail[17] and are generally similar to those of the CREST trial,[16] except that CREST patients presented at an earlier time in their disease treatment after failing only one prior treatment regimen and were randomized to receive one of two different doses of bortezomib.

Patient selection

All SUMMIT and CREST study patients were at least 18 years of age, had measurable relapsed and/or refractory myeloma, and had a life expectancy of ≥3 months. Measurable disease was defined as a monoclonal immunoglobulin (Ig) concentration on serum electrophoresis of ≥1 g/dL of IgG or ≥0.5 g/dL of IgA, or urinary excretion of ≥200 mg/24 h of monoclonal light chain; patients with non-measurable disease, defined as non-secretory or oligosecretory myeloma, had to have other measurable evidence of disease such as extramedullary plasmacytoma. Corticosteroid-refractory disease was defined as progression during a prior corticosteroid-containing regimen. Other inclusion criteria included a Karnofsky performance scale score of ≥60%, serum aspartate aminotransferase or alanine aminotransferase concentration ≤3 times the upper limit of normal, serum total bilirubin concentration ≤2 times the upper limit of normal, creatinine clearance of >30 mL/min (patients with a creatinine clearance >10 mL/min and <30 mL/min could be enrolled in the study if approved by the sponsor and local institutional review board), platelet count ≥50×10^9/L or ≥30×10^9/L if the bone marrow was extensively infiltrated by myeloma, hemoglobin level ≥8 g/dL, and absolute neutrophil count ≥0.5×10^9/L. Premenopausal women were required to have a negative pregnancy test result before enrollment, and all patients had to agree to use an acceptable method of birth control during the studies. All patients provided written informed consent before entering the studies, which were performed in accordance with the Declaration of Helsinki and approved by the institutional review board at each participating center.

Interventions

Bortezomib was administered by intravenous bolus over 3 to 5 seconds on days 1, 4, 8, and 11 of a 21-day cycle for up to eight cycles; the dose was 1.3 mg/m^2 for all patients in SUMMIT and, by random assignment, either 1.0 mg/m^2 (n=28) or 1.3 mg/m^2 (n=26) for patients in CREST. Patients who exhibited progressive disease after two cycles or no change after the first four cycles of bortezomib monotherapy as determined by the investigator were allowed to receive additional oral dexamethasone 20 mg on the day of and the day after each dose of bortezomib, for a total dose of 160 mg every 21 days. The decision to add dexamethasone based on the response criteria was at the discretion of the investigator.

Bortezomib treatment was withheld if non-hematologic adverse events were grade 3 or if hematologic adverse events were grade ≥4. After adverse events had resolved, bortezomib could be resumed at a dose of 1.0 mg/m^2 if adverse events had occurred at the 1.3 mg/m^2 dose, or at a dose of 0.7 mg/m^2 if adverse events had occurred at the 1.0 mg/m^2 dose (~25% dose reduction). There were no defined or prespecified dose interruptions or modifications with regard to dexamethasone. Patients with a complete response received two additional cycles of treatment beyond confirmation of the complete response. An extension protocol was available in which treatment was continued beyond eight cycles for patients who achieved a response or who, in the investigator's opinion, could potentially benefit from additional treatment.

Efficacy assessment

The intent-to-treat population was used for efficacy analysis in these studies, which included all patients who received at least one dose of study drug and had measurable disease at screening. An Independent Review Committee (IRC) consisting of three independent physicians with expertise in multiple myeloma, who were not investigators in the study, assessed data from each treatment cycle in which efficacy evaluations were conducted. IRC members were blinded to whether the patients received added dexamethasone. Patients with non-measurable disease at baseline with insufficient data available for the IRC were excluded from the analysis.

Responses, including improvements relative to the start of dexamethasone, were determined by an IRC according to the criteria of the European Group for Blood and Marrow Transplantation (EBMT).[19] Complete response was defined by a negative immunofixation test result for myeloma protein in serum and urine, absence of soft-tissue plasmacytomas, normal serum calcium concentration, stable skeletal disease, and <5% plasma cells in the bone marrow. Near complete response, a modification of the EBMT criteria, was defined as a positive immunofixation test result, absence of myeloma protein on serum and urine electrophoresis, stable skeletal disease, and normal serum calcium concentration. Measurements to confirm responses were required at least 6 weeks after the initial response was observed. Improved response was defined as improvement from at least no change or not evaluable during bortezomib monotherapy to minimal response or better during combination therapy with added dexamethasone. As prospectively defined, patients with progressive disease receiving bortezomib alone were considered to have progressive disease in the final response evaluation of the study, regardless of a possible response upon addition of dexamethasone.

Safety assessment

Adverse events were assessed and graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0).[20] All patients who received any study drug were included in the safety evaluation. Adverse events are reported as those that were treatment emergent and were defined as any adverse events that occurred after administration of the first dose of study drug(s) and through 20 days after the last dose of study drug(s), events that were considered drug-related (possibly or probably) regardless of the start date of the event, or events that were present at baseline but worsened in severity or were subsequently

considered drug-related by the investigator. Adverse events reported for bortezomib alone and for bortezomib combined with dexamethasone were assessed.

Statistics

Descriptive analyses were performed using SAS statistical software (version 8.2, SAS Institute). Time-to-event analyses were analyzed using Kaplan-Meier methodology: event times were calculated from the first dose of bortezomib until the occurrence of the first event in patients receiving either bortezomib alone or combination therapy. Adverse event summaries include all treatment-emergent events separated by start date, that is, based on the start date of the adverse event relative to the start date of the first dose of bortezomib alone, or the first dose with dexamethasone added. Any adverse event that started before combination therapy was attributed to bortezomib alone, and any event with a start date after the first dose of dexamethasone was attributed to the combination.

Results

Of the 256 patients with relapsed and/or refractory multiple myeloma who were enrolled in SUMMIT (n=202) or CREST (n=54), 106 (41%) had dexamethasone added to the initial bortezomib monotherapy. The demographics and disease characteristics of all patients at enrollment in both trials were similar to those of patients who later received the combination regimen (Table 1). All 106 patients who received dexamethasone had been treated with corticosteroids in a previous regimen. Figure 1A shows the cycle of bortezomib therapy at which dexamethasone was initiated in the 106 patients who received added dexamethasone. Dexamethasone was started at cycle 3 of bortezomib therapy in 20 of 78 (26%) SUMMIT patients and 7 of 28 (25%) CREST patients. Dexamethasone was started after the fourth cycle of bortezomib in 51 of 78 (65%) patients in SUMMIT and in 19 of 28 (68%) patients in CREST. Figure 1B shows the number of cycles in which the combination of bortezomib plus dexamethasone therapy was administered to patients in each study. The bars indicate the number of patients who were administered the combination by extent of exposure; all 106 patients were administered the combination in at least one cycle, whereas fewer received two or more cycles. Dexamethasone was administered for a median of 39 days (range 1-138 days) in SUMMIT and 54 days (range 5-117 days) in CREST. Twenty-eight of 106 patients who had received combination treatment with bortezomib plus dexamethasone in the parent trial subsequently received a median of three additional cycles of treatment in an extension trial that was designed to allow patients with the potential to benefit to receive additional therapy beyond eight cycles.

Activity

Ten of the 256 patients who were enrolled in SUMMIT or CREST had non-measurable disease at baseline or had insufficient data available for the IRC and were excluded from the analysis. In SUMMIT, 74 of 78 patients receiving bortezomib plus dexamethasone combination therapy were evaluable for response; 13 (18%) had improved responses during combination therapy, six of whom (46%) had been refractory to previous dexamethasone

Table 1. Baseline characteristics of all patients and the subset receiving the combination of bortezomib and dexamethasone.

	All patients SUMMIT and CREST (n=256)	*Combination bortezomib plus dexamethasone (n=106)*
Male, %	56	57
Median age, y (range)	60 (30-84)	62 (30-84)
Ethnicity, white, %	82	84
Karnofsky performance status ≤70%, %	19	14
Myeloma type, IgG/IgA/other, %	60/24/16	59/24/17
Median percentage of plasma cells in bone marrow biopsy	50	40
Abnormal cytogenetics, %	36	34
Median platelet count, 10^9/L	168	185
Median β_2-microglobulin, mg/L	3.6	3.2*
Number of previous regimens, median (range)	5 (1-15)	5 (1-15)
Prior steroid treatment, %	99	100

**Based on data from 91/106 patients.*

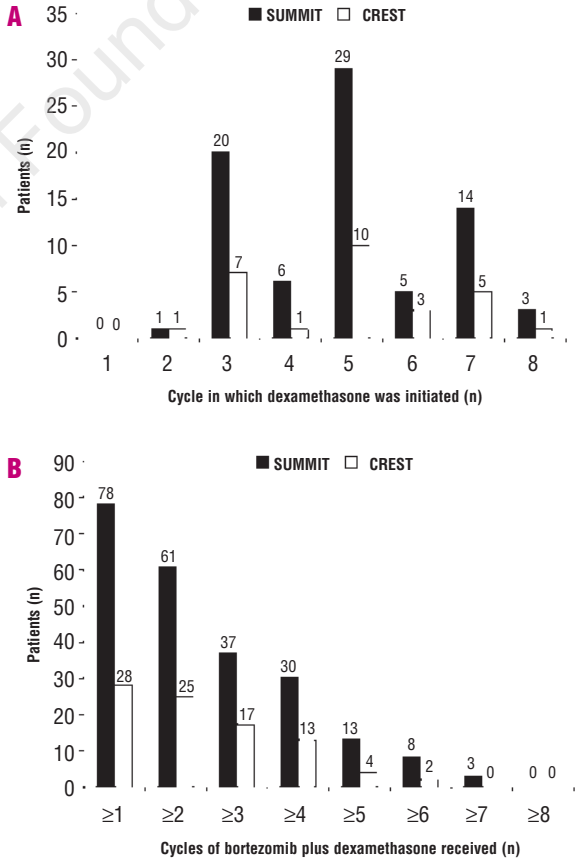

Figure 1. Timing of addition of dexamethasone by bortezomib treatment cycle (A) and number of patients receiving dexamethasone by number of cycles of combination treatment received (B) in SUMMIT and CREST.

Table 2. Improved responses following the addition of dexamethasone to bortezomib monotherapy.

Parameter	*SUMMIT*	*CREST*
Improved response on combination therapy, n/n (%)*	13/74 (18)	9/27 (33)
Improved response despite being refractory to prior dexamethasone, n/n (%)	6/13 (46)	2/9 (22)
Median time to improved response from start of dexamethasone, months	1.2	1.2
Median duration of response (CR + PR + MR), months (n)		
1.3 mg/m^2	5.1 (29)	NR (8)
1.0 mg/m^2	NA	4.7 (6)
Median time to progression among patients receiving bortezomib + dexamethasone, months†	5.3	6.8

**Improvement to MR or better from at least no change or not evaluable during bortezomib monotherapy. †From initial dose of bortezomib. CR, complete response; PR, partial response.MR, minimal response; NA, not applicable; NR, not reached.*

Table 3. Summary of changes in M-protein levels in patients evaluable for response who experienced an improved response or did not improve following the addition of dexamethasone to bortezomib monotherapy.

Percentage changes in M-protein levels	*Response following addition of dexamethasone*	
	Improved (n=22)	*Did not improve (n=79)*
Change between study enrollment and overall best M-protein response, median (range)	-57.7 (-100, -25.0)	-28.6† (-100, +359.9)
Change between study enrollment and best M-protein response on bortezomib alone, median (range)	-15.4* (-100, +5.3)	-17.1‡ (-100, +424.2)
Change between initiation of dexamethasone and best M-protein response on combination therapy, median (range)	-36.7 (-100, +42.9)	-9.0¶ (-100, +246.2)

**n=21, †n=78, ‡n=73, ¶n=72, patient data not available.*

(Table 2). Of these 13 patients, five achieved partial responses following minimal responses (n=2) or no change (n=3) on bortezomib alone. The response status improved to a minimal response in the remaining eight patients whose initial response to bortezomib alone was no change (n=7) or not evaluable (n=1). Response in the remaining 61 patients did not improve.

In CREST, 27 of 28 patients who received combination therapy were evaluable for response; nine (33%) had improved responses during combination therapy, two of whom had been refractory to previous dexamethasone. Of 15 patients who received bortezomib 1.0 mg/m^2, the response status improved to complete response in two patients whose initial response to bortezomib alone was minimal (n=1) or no change (n=1) and to minimal response in two patients whose initial response to bortezomib alone was no change. Responses in the remaining 11 patients did not improve.

Of 12 patients who received bortezomib 1.3 mg/m^2 in CREST, the response status improved to partial response in three patients whose initial response to bortezomib alone was minimal (n=2) or not evaluable (n=1) and to minimal response in two patients whose initial response to bortezomib alone was no change. Responses in the remaining seven patients did not improve.

Improvements in response were analyzed according to when dexamethasone was first added to bortezomib monotherapy. In patients who received dexamethasone either on or before cycle 4 of bortezomib therapy (n=34), five (14.7%) improved responses (one complete response, two partial and two minimal responses) were seen. In patients who received dexamethasone after cycle 4 of bortezomib therapy (n=67), 17 (25.4%) improved responses (one complete, six partial and ten minimal responses) were seen.

Data on change in M-protein level were analyzed in patients evaluable for response who received added dexamethasone. Table 3 shows the results for patients who experienced an improved response upon addition of dexamethasone and those who did not, in order to assess the relative impacts of bortezomib alone and the combination therapy. In patients who had an improved response with the combination therapy, the median reduction in M-protein level was 36.7% following the addition of dexamethasone, compared with a median reduction of 15.4% on bortezomib alone. As expected, the select patient population that received combination therapy after a less than optimal response to bortezomib alone had a shorter time to progression. In SUMMIT, the median time to progression was 6.9 months for all patients on bortezomib alone (n=202) and 5.3 months for the subset that received dexamethasone (n=78). In CREST, the median time to progression was 10.6 months for all patients on bortezomib alone (n=54) and 6.8 months for the subset that received dexamethasone (n=28).

Safety

Of 106 patients receiving dexamethasone, 100 (94%) had at least one treatment-emergent adverse event reported after the addition of dexamethasone. Most adverse events were mild to moderate in severity and did not usually lead to discontinuation because of toxicity. Adverse events leading to discontinuation occurred in 13 of 106 patients (11%), 12 in SUMMIT and one in CREST. Peripheral neuropathy was reported as a reason for discontinuation in four patients and was considered possibly or probably attributable to bortezomib in all instances. Other reasons for discontinuation included diarrhea (n=3; one of these patients also had neuropathy leading to discontinuation), dehydration (n=1), hyponatremia (n=1), syncope (n=1), and diverticulitis (n=1). One patient discontinued because of thrombocytopenia and tachycardia, and another because of dyspnea and dysautonomia. Table 4 lists the most common treatment-emergent adverse events by bortezomib dose group reported before and after the addition of dexamethasone. The most common

Table 4. Most frequently reported adverse events (>30% in any single group).

Adverse event	Patients (%)				
	Bortezomib 1.3 mg/m² (n=90)		Bortezomib 1.0 mg/m² (n=16)		
	Alone	After DEX added	Alone	After DEX added	All grade 3 or 4 events (n=106)
Fatigue	56	24	63	25	8
Nausea	52	21	44	13	7
Diarrhea	42	22	25	0	8
Thrombocytopenia	38	24	31	19	33
Pyrexia	32	12	13	25	2
Anemia	32	14	25	13	9
Insomnia	26	19	31	31	3
Constipation	27	14	25	31	3
Headache	24	8	38	0	4
Arthralgia	23	13	31	50	5
Pain in limb	17	12	31	6	6
Bone pain	13	8	38	0	2
Back pain	9	6	31	13	4
Peripheral edema	8	3	31	6	0

DEX: dexamethasone.

adverse events reported during treatment with bortezomib alone were fatigue, nausea, diarrhea, and thrombocytopenia. Thrombocytopenia was cyclical, occurring during the administration of bortezomib but recovering toward baseline during the rest period of each cycle. No serious bleeding events associated with thrombocytopenia occurred.

With the addition of dexamethasone, several adverse events appeared to be reported less frequently. Adding dexamethasone in patients initially receiving bortezomib 1.3 mg/m² was associated with a reduction in the reporting of fatigue (from 56% to 24%), nausea (from 52% to 21%), and diarrhea (from 42% to 22%). Of the most frequently reported adverse events, the only events that were reported more frequently during combination therapy were arthralgia, pyrexia, and possibly constipation, and these were limited to the group receiving bortezomib 1.0 mg/m². During therapy with bortezomib alone, peripheral neuropathy was reported in 22% (23/106) of patients; after dexamethasone was added, it was reported in 20% (21/106). Grade 3 or 4 peripheral neuropathy was reported in 12% (13/106). In the patient populations of SUMMIT and CREST, peripheral neuropathy was reported in 35% (90/256) of patients overall.

Neutropenia of any grade was reported as an adverse event in 20% (21/106) of patients receiving bortezomib alone and in 7% (7/106) after the addition of dexamethasone. Grade 3 or 4 neutropenia was reported in 13% (14/106) of patients based on adverse event reporting. No instances of febrile neutropenia were reported.

Discussion

Bortezomib is a novel antineoplastic agent approved for the treatment of multiple myeloma in patients who have received at least one prior therapy in the United States and European Union based primarily on the results of two phase 2 trials, SUMMIT and CREST,[16,17] and the phase 3 APEX trial.[18] Using rigorous EBMT criteria,[19] overall response rates (complete + partial + minimal responses) to bortezomib 1.3 mg/m² as monotherapy were 35% in SUMMIT[17] and 50% in less heavily pretreated patients who failed first-line therapy (CREST).[16]

Overall, 41% (106/256) of patients starting on bortezomib alone in these two phase 2 trials ultimately received treatment with the combination of bortezomib and dexamethasone because of suboptimal response to bortezomib alone. Following combination treatment with bortezomib and dexamethasone, improved responses were observed in 18% of heavily pretreated patients in the SUMMIT trial and in 33% of less heavily pretreated patients in the CREST trial who received the combination. These improved responses occurred in 22 patients (2 complete, 8 partial and 12 minimal responses), including eight with multiple myeloma who had been refractory to previous dexamethasone. The results of our analysis suggest that if the response to bortezomib as a single agent is less than optimal, even among patients previously treated with or refractory to corticosteroids, then the addition of dexamethasone may provide additional benefit. The improved responses (1 complete response, 4 partial responses) seen in patients who achieved minimal response to bortezomib alone suggest some degree of additive sensitivity. Additionally, although numbers are small, the data indicate a trend towards greater sensitivity to bortezomib combined with dexamethasone in patients with a better overall initial response to bortezomib monotherapy, i.e. those who had dexamethasone added later in their treatment (after cycle 4). Data on median changes in M-protein levels indicate that, in patients who had an improved response following the addition of dexamethasone, the majority of the overall reduction in M-protein level occurred during combination therapy.

These findings suggest initial clinical validation of additional benefit from dexamethasone in combination with bortezomib in multiple myeloma, as has been demonstrated in preclinical models.[10] However, the potential benefit of an earlier introduction of dexamethasone therapy could not be assessed. Moreover, the possibility that some of the improved responses may have represented a late response to bortezomib (and not a response to the combination with dexamethasone) or a response to high-dose dexamethasone itself could not be excluded in the absence of a control group and requires further study. In addition, although bortezomib combined with dexamethasone appeared to improve responses, the duration of response is less than optimal. Therefore, combination with other chemotherapeutic agents such as doxorubicin, which has clear synergy with bortezomib[21,22] should be considered. As expected, the median time to progression was shorter in patients for whom dexamethasone was added to the treatment regimen. Baseline demographics and disease characteristics of the subset that received combination therapy were similar to those of the overall population; this observation was surprising because these patients already had a less than optimal response to bortezomib alone by definition.

The combination of bortezomib and high-dose dexamethasone was associated with manageable adverse events that did not usually interfere with the ability to continue therapy. Adding high-dose dexamethasone did not appear to change the type of adverse events or increase their incidence compared with those associated with bortezomib alone. Indeed, the reporting of some adverse events was lower after the addition of dexamethasone than with monotherapy alone. For example, combination therapy was associated with an approximately 50% lower frequency of fatigue, nausea, and diarrhea. Because dexamethasone has long been known to have properties that alleviate nausea and fatigue,[23] even at oral doses as low as 4 or 8 mg twice daily,[24,25] the apparent decrease in the incidence of nausea is not unexpected. The safety profile of bortezomib and dexamethasone is noteworthy, because the spectrum and frequency of adverse events has been less favorable when dexamethasone is added to agents other than bortezomib for the treatment of multiple myeloma.[26,27] For example, adding dexamethasone to thalidomide resulted in several unusual adverse events, including vascular thrombosis.[26]

In conclusion, the combination of bortezomib and dexamethasone was associated with improved responses in patients with relapsed and/or refractory multiple myeloma who had a less than optimal response to bortezomib monotherapy. Adding dexamethasone did not appear to have an adverse effect on the safety profile of bortezomib. Additional studies are needed to assess the efficacy of this and other combinations and to identify patients most likely to benefit from these combinations. Clinical trials are ongoing to investigate these and related clinical issues.

SJ,: conception and design, acquisition of data, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content, final approval of the version to be published; PGR, BB, JRB, SS, DI, GS, DS, DLE, KA: conception and design, acquisition of data, analysis and interpretation of data, revising it critically for important intellectual content, final approval of the version to be published.

This study was supported by a grant from Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, and was presented in part at the 39th Annual Meeting of the American Society of Clinical Oncology, May 31-June 3, 2003, and at the 9th Congress of the European Hematology Association, June 10-13, 2004.

Manuscript received August 9, 2005. Accepted April 20, 2006.

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