Bortezomib with or without dexamethasone in relapsed multiple myeloma following allogeneic hematopoietic cell transplantation

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We retrospectively evaluated the efficacy of bortezomib in 23 patients with multiple myeloma who had relapsed after allografting. Bortezomib was given as single agent to 9 patients (39%) and in combination with steroids in the other 14 (61%). Major toxicities were thrombocytopenia (10/23, 43%) and peripheral neuropathy (12/23, 52%). The overall response rate was 61% (14/23), including 22% (5/23) immunofixation-negative complete remissions. No significant differences in toxicity and response rates were seen between patients treated with bortezomib plus steroids and bortezomib alone. After a median follow-up of 6 months, progression free survival was 6 months. Twenty-one patients are alive, two and five in continuous very good partial and complete remissions, respectively.

Key words: multiple myeloma, allogeneic transplantation, bortezomib.

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Relapse rates after allogeneic hematopoietic cell transplantation in patients with multiple myeloma (MM) remain high regardless of the intensity of the conditioning regimen. Post-transplant donor lymphocyte infusions (DLI) have been used to re-induce remission. Response rates vary from 30% to 50%, but very few durable complete remissions are achieved and the incidence of acute and chronic graft-versus-host disease (GVHD) is as high as 57% and 47%, respectively.[1-3] Clinical trials of recently developed drugs with molecular targets have reported promising response rates in patients with relapsed/refractory MM.[4] Bortezomib (Velcade™) has a very high affinity and specificity for the catalytic activity of the proteasome in the cell cytoplasm and blocks migration of NF-kB into the nucleus by preventing the degradation of its inhibitory partner protein, IκB, in the proteasome complex.[6,7] Thus, the functions of NF-κB, constitutively active in MM, are inhibited.[6,7] Proteosome activity is also involved in several T-cell functions and recent murine studies indicate that NF-κB is important in the pathophysiology of GVHD.[8,10] Pre-clinical and clinical findings provide the rationale for phase I-II studies aimed at evaluating the safety and efficacy of bortezomib in the setting of allogeneic hematopoietic cell transplantation. We assessed the toxicity profile and anti-myeloma activity of bortezomib in patients who had relapsed after allogeneic hematopoietic cell transplantation.

Design and Methods

This retrospective study included 23 patients with MM, whose median age at transplant was 53 years (range 31-66). Informed consent was obtained from all patients on entry to the study. The study was conducted according to the Declaration of Helsinki. Briefly, 13 (57%) patients underwent allogeneic hematopoietic cell transplantation as part of their initial treatment plan, seven (30%) at first relapse, and three (13%) at second relapse, from HLA identical related (n=20), unrelated (n=2) and syngenic (n=1) donors. Twenty-one patients had received at least one autologous transplant before allografting. Cytogenetic evaluation had been performed in five of the 23 (22%) patients at diagnosis, and three of them carried the chromosome 13 deletion. At the time of allografting, one patient was in complete remission (CR), two were in electrophoresis-negative partial remission (EN-PR); 12 in partial remission (PR); seven had refractory disease and one had progressive disease. Conditioning regimens were myeloablative in four, reduced-intensity in five and based on non-myeloablative low-dose (200 cGy) total body irradiation in 14. Bortezomib was administered at the dose of 1 mg/m^2 (n=6) or 1.3 mg/m^2 (n=17) on days 1, 4, 8, and 11 of each monthly course either alone (9 patients, (39%) or with dexamethasone 20 mg [n=8] or 40 mg (n=4) on days 1, 4, 15, and 18, in 13 patients (57%), plus prednisone 75 mg daily in one (4%). Doses were adjusted by the attending physician in the light of each

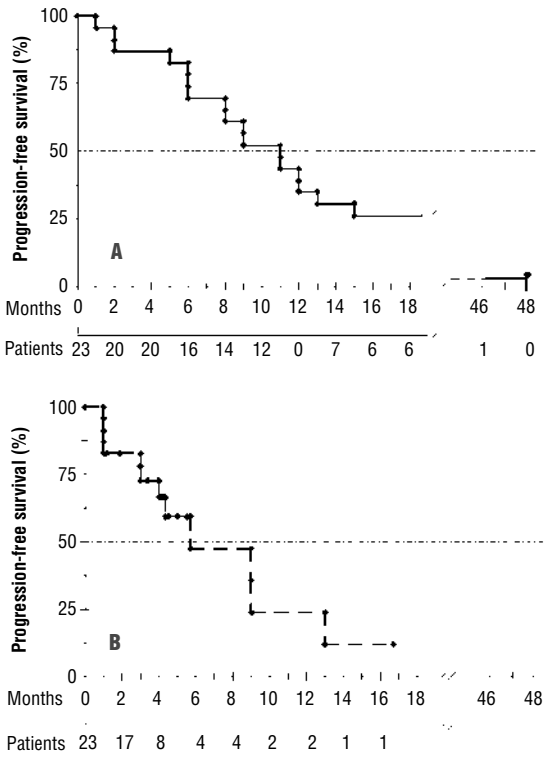

Figure 1. A. Progression-free survival after allografting B. Progression-free survival after salvage treatment with bortezomib.

patient's clinical conditions and the center's guidelines. Bortezomib was administered as first-line salvage treatment in three patients (12%), after DLI or combinations of DLI and chemotherapy in ten (44%), and after chemotherapy alone in the other ten (44%). Moreover, 15 patients (65%) had received thalidomide prior to bortezomib. No patient had active GVHD at the time of bortezomib administration. Twenty patients had progressive disease and three were in PR after having received thalidomide. Furthermore, two patients were treated for extramedullary relapse.

Toxicity was defined according to the NCI Common Toxicity Criteria. Disease response was assessed using the EBMT/IBMDR criteria with the following modifications.[11] CR was defined as the disappearance of the serum and urine monoclonal paraproteins on standard protein electrophoreses and presence of clear bands on immunofixation; less than 1% marrow plasma cells without evidence of clonal disease by flow cytometry; and no increase in the size or number of osteolytic lesions. EN-PR required the above criteria with no clear bands on immunofixation. PR was defined as a >50% reduction in the levels of serum monoclonal protein, 90% reduction in 24-hour urinary Bence-Jones protein excretion, and no increase in the size or number of lytic bone lesions. A minimal response was considered to be >25% reduction of the monoclonal protein. Progression-free survival was calculated using the Kaplan-Meier method.

Table 1. Toxicity and response rates in patients treated with bortezomib plus steroids or single agent bortezomib.

	*Bortezomib plus dexamethasone**	*Single agent bortezomib*
Number of patients	14	9
Hematologic toxicity		
Grade 1-2 thrombocytopenia	2 (14%)	2 (22%)
Grade 3-4 thrombocytopenia	4 (29%)	2 (22%)
Grade 1-2 neutropenia	0	1 (11%)
Grade 3-4 neutropenia	1 (7%)	1 (11%)
Non-hematologic toxicity		
Grade 1-2 peripheral neuropathy	5 (36%)	4 (44%)
Grade 3-4 peripheral neuropathy	1 (7%)	2 (22%)
Allergic reaction	1 (7%)	1 (11%)
Response to bortezomib		
Complete remission	2 (14%)	3 (33%)
EN-partial remission	3 (21%)	1 (11%)
Partial remission	2 (14%)	2 (22%)
Minimal vesponse	1 (7%)	0
Stable disease	2 (14%)	1 (11%)
Progression	4 (29%)	2 (22%)

**one patient received daily prednisone; EN: electrophoresis-negative.*

Results and Discussion

The median time from allografting to relapse or disease progression was 11 months (range 1-48) (Figure 1A). The median time from transplantation to the start of bortezomib therapy was 20 months (range 5-81). Overall, patients had received a median of four (range 1-8) bortezomib courses at the time of this analysis. Hematologic toxicity consisted of grade 1-2 thrombocytopenia in four patients (17%), grade 3-4 thrombocytopenia in six patients (26%) and neutropenia in three (13%). Major non-hematologic toxicities consisted of grade 1-2 and grade 3-4 peripheral neuropathy in nine (39%) and three (12%) patients, respectively, and skin rash in two (9%). Two patients completed only one course because of grade 3 peripheral neuropathy. Neither of these two patients was receiving cyclosporine or thalidomide. Bortezomib had to be discontinued after the first infusion in another patient because of persistent pancytopenia with grade 4 neutropenia. Flaring of prior chronic limited GVHD was observed in one patient who developed mild liver GVHD. The overall response rate was 61% (14/23) with 22% (5/23) immunofixation-negative CR, 17% (4/23) EN-PR, 17% (4/23) PR and 5% (1/23) minimal response. Three patients had stable disease and six progressed. Of the three patients with chromosome 13 deletion, one obtained durable EN-PR. Of the two patients with extramedullary relapse, one obtained an initial EN-PR with complete disappearance of the extramedullary masses and relapsed after 11 months, and one did not respond. The median progression-free survival from the start of salvage therapy with bortezomib was 6 months (Figure 1B). Twenty-one patients (91%) are alive at a median of 6 months from the start of bortezomib. Of the five patients who achieved CR, two underwent a second allogeneic transplant and have been previously

described.[12] Overall, all five patients in CR and two additional patients in EN-PR showed durable responses after a median follow-up of 3 months (range 2-15). Two patients refractory to bortezomib died of disease progression. Toxicity and response rates in patients treated with bortezomib alone or in combination with steroids are summarized in Table 1.

The curative potential of allografting primarily relies upon graft-versus-myeloma effects through donor T cells.[13-14] Relapse is likely due to mechanisms which allow the myeloma cells to escape the immune surveillance of donor cells. DLI are commonly employed as adoptive immunotherapy to re-induce remission, but durable responses are rare.[1-3,15] In a study by Mohty *et al.*, thalidomide was employed as salvage therapy in 31 patients post-allografting.[16] An overall response of 30% was documented. However, no immunofixation-negative CR were obtained. In another study by Kroger *et al.*, low dose thalidomide was associated with DLI in 18 patients.[17] The overall response rate was 67%, including CR in 22%, but *de novo* chronic GHVD developed in 13% of patients and 38% had signs of limited chronic GVHD.[17] In our study bortezomib led to a remarkable overall response with a high rate of CR that compares favorably with that obtained with thalidomide alone. Importantly, in 20 patients (87%), bortezomib was used after at least one previous salvage treatment such as thalidomide or DLI. Moreover, 20 patients (87%) had progressive disease. The toxicity profile was acceptable with only six patients developing grade 3-4 thrombocytopenia and three grade 3-4 peripheral neuropathy. Interestingly, even though gastrointestinal toxicity, such as diarrhea, has been rather frequently reported in non-transplant patients, no signs or symptoms of flaring of gastrointestinal GVHD or other intestinal side effects were noted. The monthly schedule may have helped to reduce toxicity. Moreover, no significant differences in either toxicity or response rates were observed between patients receiving bortezomib alone and those receiving bortezomib plus steroids suggesting that bortezomib is extremely powerful (Table 1). This finding, however, may be due to the low statistical power of the two small cohorts of patients and should be confirmed in prospective control studies.

In conclusion, our study indicates that bortezomib induces disease response and remissions in relapsed heavily pre-treated patients with MM who have been transplanted. Prospective studies are warranted to evaluate the optimal dosage and timing of use of this proteasome inhibitor.

BB, CC conceived and designed the study; BB, FP, RS interpreted the data and wrote the manuscript; DM, VM, JP, FB, MTP, GM, SG, LG, MR performed the clinical aspects of the research; RF, MB reviewed the manuscript. The final version was approved by all the authors. The authors declare that they have no potential conflicts of interest.

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