High response rate and improved graft-versus-host disease following bortezomib as salvage therapy after reduced intensity conditioning allogeneic stem cell transplantation for multiple myeloma

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ABSTRACT

We describe the results of 37 myeloma patients who received bortezomib following reduced intensity allogeneic stem cell transplantation (RIC-allo-SCT). Grade 1-2 peripheral neuropathy (35%), mild thrombocytopenia (24%) and fatigue (19%) were the most frequent adverse events, while there was no worsening of graft-vs-host disease symptoms. Twenty-seven patients (73%; 95% CI, 59-87%) achieved an objective response. With a median follow-up of 9 months from bortezomib initiation, the estimate of overall survival was 65% at 18 months while this was significantly higher (p=0.002) in the 27 patients achieving an objective response, suggesting that bortezomib is a safe and efficient option for myeloma patients after RIC-allo-SCT.

Key words: bortezomib, allogeneic stem cell transplantation, multiple myeloma.

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Introduction

An increasing number of clinical studies has demonstrated that bortezomib had anti-tumor activity in refractory and relapsed multiple myeloma (MM). Clinical data also suggest that an allogeneic graft-versus-myeloma (GVM) effect can be induced against MM.[1] Unfortunately, the benefit of this is usually offset by an unacceptable rate of transplant-related mortality. The advent of reduced intensity conditioning (RIC) regimens as a possibly less toxic alternative to standard myeloablative allogeneic stem cell transplantation (allo-SCT) has renewed interest in allo-SCT in MM.[2] However, despite progress in terms of transplant-related mortality, a significant proportion of patients may still progress after RIC-allo-SCT.[3,4] Current approaches used to salvage these patients may include chemotherapy, thalidomide, and/or donor lymphocyte infusions (DLI).[5,6] Bortezomib may represent another potentially valid option. Therefore, this retrospective study aimed to assess the results of 37 patients who received bortezomib as a salvage therapy after RIC-allo-SCT.

Design and Methods

Study design

This was a retrospective study from 3 centers (Marseille, n=18; Lyon, n=13; and Tel-Hashomer, n=6). Investigators reported on patients who received bortezomib as a salvage treatment after MM relapse or progression following RIC-allo-SCT. Thirty-seven patients treated between November 2003 and March 2007 met these eligibility criteria. The study was performed according to institutional guidelines and was approved by the Institutional Review Board of the Institut Paoli-Calmettes (Marseille, France). The primary aim of the study was to analyze disease response to bortezomib. The study also aimed to determine toxicity and incidence of GVHD.

Transplant procedures and treatments

Allo-SCT was performed after RIC regimens as previously described.[3,7] Except for 3 patients who received a graft from a matched-unrelated donor, all other donors were HLA-A-, HLA-B-, and HLA-DR-identical siblings. Patients underwent RIC-allo-

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SCT as part of their second line (or beyond) treatment strategy. Conditioning regimens have been described elsewhere.[3,8] Supportive care was performed according to the standard procedures of each center. Patients received bortezomib 1.3 (n=33; 89%) or 1.0 mg/m^2 (n=4; 11%) by intravenous bolus on days 1, 4, 8, and 11 of a 21-day cycle, without (n=11; 30%) or associated to (n=26; 70%) dexamethasone 20 mg/day on days 1, 2, 4, 5, 8, 9, 11 and 12. If patients had progressive disease after 2 cycles, the drug was discontinued. Patients were also required to have liver transaminases values no more than three times above the normal limit, no active infections, and platelet counts of at least 30×10^9/L. Patients were scheduled to receive up to 8 cycles. Adverse events were reported as previously described.[9] Bortezomib doses were adjusted according to individual patient's clinical condition and the center's guidelines. Patients developing signs and/or symptoms of PN were treated symptomatically, and the bortezomib dose was reduced according to previously established guidelines.[10]

Clinical outcomes and assessment of response

Clinical outcomes collected included demographic and disease characteristics, GVHD status, time to progression, dose, toxicity, duration, response, and survival. GVHD assessment was made according to standard criteria. Disease response (complete, partial, or very good partial remission; CR, PR; VGPR) was assessed as previously described.[11,12]

Statistical analysis

Overall survival from initiation of bortezomib therapy was calculated using the Kaplan-Meier method. Comparisons were performed using the Log-Rank test. The SEM software (SILEX, Mirefleurs, France) was used for data management.

Results and Discussion

Patient and disease characteristics

Patient and disease baseline characteristics are shown in Table 1. Median time from diagnosis of MM to allo-SCT was 11 (range, 6-96) months. Before initiation of bortezomib, 14 patients (38%) received and failed DLI. Also, 20 patients (54%) received and failed thalidomide (either because of disease progression or toxicity).

Bortezomib treatment features and toxicities

Features of bortezomib salvage therapy, bortezomib-associated toxicities and response after RIC-allo-SCT are summarized in Table 2. Thirty-two patients (86%) received bortezomib in progressive disease and 5 (14%) in residual disease. The median time between allo-SCT and initiation of bortezomib was 20 (range, 1-65) months. At initiation of bortezomib, the majority of patients (n=26; 70%) did not have symptoms of chronic GVHD, while 8 patients (22%) had some form of limited chronic GVHD, and 3 patients (8%) had extensive signs. The median number of bortezomib cycles administered was 6 (range, 1-15). Furthermore, 7 responding patients continued to receive bortezomib as a maintenance therapy beyond the initially scheduled 8 cycles on the decision of the attending physician. Peripheral neuropathy was the most frequent adverse event observed after bortezomib (n=13; 35%; four grade 2 and nine grade 1). Median time to onset of peripheral neuropathy was 83 (range, 32-182) days. Mild thrombocytopenia not requiring platelet transfusions was observed in 9 cases (24%). Fatigue was also a common side effect observed in 7 patients (19%). None of the patients had to discontinue the treatment because of a life-threatening adverse event, and no treatment-related toxic deaths were reported. In terms of GVHD, only 2 patients experienced reactivation or worsening of GVHD symptoms. Interestingly, 2 of the 3 patients with extensive GVHD signs at the beginning of bortezomib therapy experienced a significant improvement in GVHD and were staged as limited chronic GVHD at last follow-up. The other 8 patients with limited chronic GVHD did not require any additional immunosuppressive therapy, and in 1 patient GVHD symptoms were no longer observed. Of note, the two patients with some worsening of GVHD symptoms (from *none* to *limited*, and from *limited* to *extensive*) did not require additional immunosuppressive therapy, indirectly highlighting rather mild symptoms.

Table 1. Baseline characteristics and treatments received prior to bortezomib salvage therapy.

Characteristic	*N (%)*
Median age (range, years)	49 (27-64)
Sex (Male/Female)	21 (57) / 16 (43)
Myeloma stage at diagnosis[a]	
I	1 (3)
II	4 (11)
III	32 (86)
Monoclonal component	
IgG	20 (54)
IgA	9 (24)
Light chain	7 (19)
Bence Jones urine paraprotein	1 (3)
Induction therapy at diagnosis	
VAD	33 (89)
Dexamethasone alone	1 (3)
Other	3 (8)
History of autologous stem cell transplantation prior to allo-SCT	
1	37 (100)
2	6 (16)
Salvage treatments received after allo-SCT and prior to bortezomib	
Thalidomide[b]	20 (54)
Dexamethasone alone	14 (38)
Donor lymphocytes infusion (DLI)	14 (38)
Chemotherapy (VAD, MP)	5 (14)

[a]According to Salmon and Durie classification; FISH analysis was performed in 14 patients, with 7 chromosome 13 deletion, 2 with a complex caryotype, and 5 with a normal caryotype. 24 patients (65%) had a high (>2.5 mg/dL) serum beta-microglobulin at diagnosis. [b]Median duration of thalidomide treatment was 10 (range, 1-15) months after allo-SCT. Median thalidomide dose received was 200 (range, 100-600) mg. Abbreviations: VAD, vincristine, adriamycin, dexamethasone; MP, melphalan, prednisone.

Table 2. Features of bortezomib salvage therapy, bortezomib-associated toxicities and response to bortezomib after reduced intensity conditioning allo-SCT.

Clinical feature	*N (%)*
Median time (range) between allo-SCT [and bortezomib initiation (m.)	20 (1-65)
Disease status at time of bortezomib initiation	
Progressive disease	32 (86)
Partial response	5 (14)
GVHD status at time of bortezomib initiation	
No GVHD signs	26 (70)
Limited GVHD	8 (22)
Extensive GVHD	3 (8)
Immunosuppressive therapy at time of bortezomib initiation	
None	32 (86)
Corticosteroids	3 (8)
CSA or MMF alone	2 (6)
Median number of bortezomib cycles administered (range)[a]	6 (1-15)
Bortezomib-associated toxicities after allo-SCT	
Thrombocytopenia	9 (24)
Fatigue	7 (19)
Other (skin reaction)	1 (3)
Peripheral neuropathy[c]	13 (35)
Median time (days) to onset of peripheral neuropathy	83 (32-182)
Best response to bortezomib achieved after allo-SCT	
CR	7 (19)
VGPR	7 (19)
PR	13 (35)
Stable disease	4 (11)
Progressive disease	6(16)
Causes of death	
Disease progression	8 (80)
Infection	1 (10)
Other	1 (10)

[a]Patients received bortezomib 1.3 (n=33; 89%) or 1.0 mg/m² (n=4; 11%), by intravenous bolus on days 1, 4, 8, and 11 of a 21-day cycle, without (n=11; 30%) or associated to (n=26; 70%) dexamethasone 20 mg/day on days 1, 2, 4, 5, 8, 9, 11 and 12. 18 patients who started at the dose of 1.3 mg/m² were dose reduced to 1.0 mg/m² by the attending physician during the course of therapy to limit toxicity (mainly symptoms of PN, or because of thrombocytopenia).[10] [b]Only grade 1 and 2 toxicities were observed. [c]Four grade 2 PN and nine grade 1 PN were observed. PN: peripheral neuropathy; CSA: cyclosporine A; MMF, mycophenolate mofetil; GVHD, graft-versus-host disease; allo-SCT: allogeneic stem cell transplantation; CR, complete remission; PR: partial response; VGPR, very good partial response.

Disease response to bortezomib after allo-SCT

Altogether, 27 patients (73%; 95%CI, 59%-87%) achieved an objective disease response after bortezomib (7 CR, 7 VGPR, and 13 PR; Figure 1A). Prior use of thalidomide and/or DLI did not influence disease response to bortezomib. Neither was there any difference in disease response when using bortezomib in combination or without dexamethasone. With a median follow-up of 9 (range, 3-42) months from initiation of bortezomib, 25 patients (68%; 95%CI, 53%-83%) still had a sustained objective disease response (5 CR, 5 VGPR, and 15 PR). Ten patients (27%) died and 27 are still alive with a median overall follow-up after allo-SCT of 80 (range, 18-153) months. The majority of deaths were directly attributed to disease progression (n=8; 80% of all deaths). Figure 1B shows the rates of overall survival in the whole cohort from initiation of bortezomib salvage therapy (Kaplan-Meier estimate of overall survival is 65% at 18 months; 95% CI, 44-82%). Most importantly, patients achieving an objective disease response (CR, VGPR or PR) after the introduction of bortezomib enjoyed a significantly higher overall survival compared with non-responding patients (p=0.002). Despite the high risk of relapse after RIC-allo-SCT, there are no established guidelines or post-transplant strategies for patient management. A commonly used salvage therapy is DLI. In a European survey on the effect of DLI after RIC-allo-SCT for MM patients with relapse or persistent disease, it was shown that 19% of the patients achieved PR, and 19% CR.[13] To enhance the anti-myeloma effect of DLI, low-dose thalidomide in combination with DLI could achieve an overall response rate of 67% with 22% CR.[5] Some recent reports showed that bortezomib might be efficient for MM relapse after allo-SCT.[14-16] This report shows an impressive objective disease response rate of 73%, achieved in a group of heavily pre-treated patients, comparing favorably with results obtained with bortezomib in different settings. These favorable results were achieved and sustained with a relatively low rate of toxicity. Indeed, the rate of adverse events in our study was relatively lower than that observed by Kroger *et al.*[14] This difference might be explained by the earlier use of bortezomib after allo-SCT in that study.[14] (median time, 8 vs. 20 months), and the concomitant use of cyclosporine A, since bortezomib and cyclosporine are both metabolized by cytochrome p450 liver microenzymes.[14] Furthermore, the absence of systemic immunosuppressive therapy in the majority of our patients (86%) at initiation of bortezomib, may also

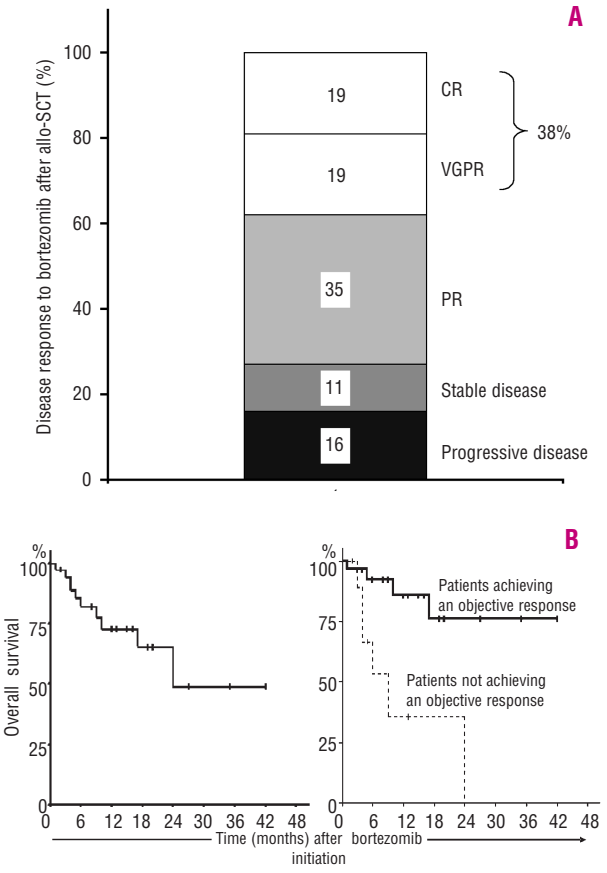

Figure 1. A. Disease response to bortezomib after reduced intensity conditioning allo-SCT. B. Overall survival in the study population after bortezomib salvage therapy initiation.

explain the absence of those serious infectious complications observed by Korger *et al.*[14] Another major limitation of any salvage therapy after allo-SCT is the risk of GVHD. Despite a remarkable efficacy, the use of bortezomib after allo-SCT was not associated with GVHD reactivation, in contrast to results obtained with, for example, thalidomide.[17] Indeed, *in vitro* results demonstrated that bortezomib may be of benefit in the management of GVHD.[18] This was also shown in mice, where bortezomib proved effective for GVHD prevention while retaining an anti-tumor effect.[19] At present, the optimal schedule, dosing, duration, and timing for initiation of bortezomib after allo-SCT has still to be prospectively investigated. However, given the promising results showing that a combination of planned autologous transplantation followed by RIC-allo-SCT can lead to a high rate of objective disease responses and decreased rate of procedure-related toxicities,[20] *global* anti-MM approaches may merit further development. A combination of prior high dose therapy, and an RIC-allo-SCT, including strategies to generate myeloma-specific effectors, followed by maintenance therapy with targeted drugs such as bortezomib, might allow clinicians to use the GVM effect as a potential cure for this challenging disease.

Authorship and Disclosures

J E-C: conceived and designed the study, collected and analyzed data, provided clinical care, carried out bibliographic research, and helped write the manuscript. MM provided patients, analyzed data and approved the final version of the manuscript. H de L: collected data, carried out bibliographic research and reviewed the manuscript. MS: collected data and reviewed the manuscript. AN, FN, AS, CF, DR, IH, SF, DB: recruited patients, provided clinical care and reviewed the manuscript. MM: conceived and designed the study, collected and analyzed data, provided clinical care, performed statistical analysis, provided financial support, carried out bibliographic research, and wrote the manuscript.

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