Bortezomib, Dexamethasone, and High-Dose Melphalan as Conditioning for Stem Cell Transplantation in Young Japanese Multiple Myeloma Patients: A Pilot Study

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Abstract Autologous stem cell transplantation is recommended for younger patients with newly diagnosed multiple myeloma because of a high complete response rate and better survival. Bortezomib shows a synergistic effect with melphalan and has no prolonged hematologic toxicity, and the complete response rate after autologous stem cell transplantation is improved by combining bortezomib with melphalan for conditioning. Twelve patients were enrolled in a phase 2 study between February and November 2010, receiving bortezomib ($1 \text{ mg/m}^2 \times 4$), dexamethasone ($20 \text{ mg/body} \times 8$), and melphalan (200 mg/m^2) for conditioning. No toxic deaths occurred. Neutrophils (absolute neutrophil count $\geq 0.5 \times 10^9/\text{L}$) and platelets ($\geq 20 \times 10^9/\text{L}$ without transfusion) recovered after a median of 5 days (range: 4–6 days) and 7 days (range: 4–8 days), respectively. No patient was admitted for exacerbation of peripheral neuropathy. Four patients obtained a stringent complete response, three patients obtained a complete response, and three patients showed a very good partial response. These results suggest that this conditioning regimen is safe and promising for young Japanese multiple myeloma patients. A prospective multicenter trial of this regimen combined with suitable induction and consolidation therapy should be performed.

Keywords Multiple myeloma · Stem cell transplantation · Bortezomib · Melphalan · Conditioning regimen

Introduction

Multiple myeloma (MM) is a clonal plasma cell disorder characterized by lytic bone disease, renal dysfunction, abnormal hematopoietic function, and the presence of a monoclonal paraprotein in the blood or urine [1, 2]. Conventional chemotherapy rarely achieves a major response, so high-dose chemotherapy with autologous stem cell transplantation (ASCT) is the standard treatment for MM patients under 65 years old [3, 4]. After ASCT, a number of patients achieve prolonged progression-free survival [3–8]. Among several conditioning regimens, high-dose melphalan (HDM; 200 mg/m^2) is the recommended standard regimen for use before ASCT, because of its efficiency and acceptable toxicity [9]. Bortezomib is a first-generation proteasome inhibitor that has been proven to be effective for MM [10, 11]. Bortezomib has also shown a synergistic effect with melphalan in a clinical trial [12], and some groups have recently reported that combining bortezomib with HDM provides safe and effective conditioning for ASCT [13–15].

Corticosteroids have a very important role in the treatment of MM, with the most common regimen being melphalan and prednisone [16, 17]. High-dose dexamethasone is also effective [18]. In addition, combining dexamethasone with bortezomib to treat relapsed or refractory MM showing a suboptimal response to bortezomib alone achieves a better response without prohibitive toxicity [19]. Accordingly, we considered that the complete remission rate might be improved if conditioning for ASCT was done by combining bortezomib and dexamethasone with

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high dose melphalan (BD-HDM). Therefore, we performed a phase 2 study in young Japanese MM patients who underwent conditioning with BD-HDM before ASCT.

Materials and Methods

Eligibility Criteria

According to the International Myeloma Working Group (IMWG) criteria [20], patients younger than 65 years with symptomatic MM were eligible for this trial. The exclusion criteria were a serum creatinine level ≥ 2.05 mg/dL at time of high-dose therapy (HDT), liver dysfunction (e.g., a serum total bilirubin level ≥ 2.0 mg/dL, or serum aspartate/alanine aminotransferase or alkaline phosphatase levels more than 2.5 times the upper limit of normal), grade 3 or worse peripheral neuropathy, significant comorbidity that would preclude ASCT, poor performance status ($\geq$ grade 3), and a history of any other malignancy with the exception of basal cell carcinoma and stage I cervical cancer. The institutional review board of our hospital approved the study protocol and written informed consent was obtained in accordance with the Declaration of Helsinki. Between January 2010 and January 2011, 12 patients with symptomatic MM were enrolled in this study and received BD-HDM at our center.

Treatment Protocol

Peripheral blood hematopoietic progenitor cells were collected by apheresis after chemo-mobilization in conjunction with lenograstim (10 μ g/kg/day). The method of cell collection was using cyclophosphamide 4 g/m² divided in 2 days. This phase 2 study was performed to assess the safety and efficacy of bortezomib and dexamethazone combined with HDM (BD-HDM) as the conditioning regimen. Bortezomib (1 mg/m²) was administered intravenously on days -6, -3, 1, and 4, according to IFM protocol [13]. Dexamethazone (20 mg) was administered orally on days -6, -5, -3, -2, 1, 2, 4, and 5, according to SUMMIT protocol [10]. Melphalan was administered intravenously at a dose of 200 mg/m² on day -2.

Peripheral blood stem cells ($\geq 2 \times 10^6$ CD34⁺ cells/kg) were infused on day 0 (Table 1). Patients received filgrastim, 5 μ g/kg/day, from day 5 until neutrophil count more than 1.0×10^9 /L was achieved. All patients also received standard supportive care, including blood transfusions, prophylactic/therapeutic antibiotics, and prophylactic antifungal therapy.

Evaluation

The primary objective was to assess the safety of the BD-HDM regimen based on the frequency of grade 3 or 4 toxicity and treatment-related mortality. The secondary end-point was the efficiency of this conditioning regimen as assessed by IMWG criteria, including the stringent complete response (sCR) rate, complete response (CR) rate, and very good partial response (VGPR) rate at 3 months after ASCT [21]. Initial diagnostic and staging evaluations, initial therapy, and disease status at enrollment were documented for all patients. Laboratory investigations included assessment of chromosomal abnormalities by fluorescence in situ hybridization analysis (FISH), measurement of β_2 -microglobulin and albumin, serum and urine electrophoresis plus immunofixation, and imaging studies (skeletal survey, total spine magnetic resonance imaging, and positron emission tomography). Patients were staged by the Durie–Salmon staging system [22] and by the International Staging System (ISS) [23] at the time of diagnosis. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria of Adverse Events (version 4.0). Definitions of response and relapse were based on the IMWG uniform response criteria, including bone marrow evaluation [21]. Responses were evaluated before ASCT and at 3 months after ASCT. All patients were followed up to the reference date (April 30 2011).

Results

Patient Profile

Between January 2010 and January 2011, 12 patients with symptomatic MM were enrolled in this trial and their

Table 1 The BD-HDM regimen

Days	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5
Bortezomib (1 mg/m ²) i.v.	●			●				●			●	
Dexamethasone (20 mg) P.O.	●	●		●	●			●	●		●	●
Melphalan (200 mg/m ²) i.v.					●							
Stem cells ($\geq 2 \times 10^6$ CD34 ⁺ cells/kg)							●					

Table 2 Profile of the subjects

Characteristic	(<i>n</i> = 12)
Sex, M/F	9/3
Median age, year (range)	57 (41–62)
Isotype, <i>n</i>	
IgG	8
IgA	2
LC	2
ISS stage, <i>n</i>	
I	2
II	4
III	6
Durie-Salmon stage, <i>n</i>	
I	0
II (A/B)	5 (5/0)
III (A/B)	7 (5/2)
Median creatinine level, mg/dL (range)	0.7 (0.4–4.8)
Median β_2 -microglobulin level, mg/dL (range)	4.4 (1.2–17.3)
Median albumin level, g/dL (range)	33 (17–50)
FISH analysis	
del (13q)	5
t (4;14)	1
First line therapy	
BD	10
Two or more prior regimens	2
Clinical response before SCT	
CR	0
VGPR	6
PR	4
SD	2

Ig immunoglobulin, *LC* light chain, *ISS* international staging system, *FISH* fluorescence in situ hybridization, *BD* bortezomib and dexamethasone, *CR* complete response, *VGPR* very good partial response, *PR* partial response, *SD* stable disease

characteristics are shown in Table 2. All patients had abnormal free light chain (FLC) at diagnosis. FISH was informative in all patients, identifying a 13q deletion in 5 patients and a t (4;14) translocation in 1 patient. Induction therapy was not specified by the study protocol and was selected on an individual basis by the treating clinician. Patients received four cycles of bortezomib (1.3 mg/m²) on days 1, 4, 8, and 11 plus dexamethasone (20 mg orally) on days 1, 2, 4, 5, 8, 9, 11, and 12 (BD regimen) or more than 2 other regimens before mobilization (one patient received VAD, high dose melphalan with ASCT, MP, thalidomide, and BD; another patient received MP, VAD, and BD). One of the patients who received more than 2 other regimens was given melphalan at 140 mg/m² with ASCT and relapsed before receiving BD-HDM.

Engraftment

All patients underwent the full BD-HDM conditioning regimen and then received a median of 2.5×10^6 CD34⁺ cells/kg (range: $2\text{--}4 \times 10^6$ CD34⁺ cells/kg). All patients received infusion of filgrastim at 300 $\mu\text{g}/\text{m}^2/\text{day}$. There was no engraftment failure. Recovery of neutrophils (ANC $\geq 0.5 \times 10^9/\text{L}$) and platelets ($\geq 20 \times 10^9/\text{L}$ without transfusion) was achieved after a median of 5 days (range: 4–6 days) and 7 days (range: 4–8 days), respectively. The median time to reach a platelet count $\geq 50 \times 10^9/\text{L}$ was 9 days (range: 7–14 days) (Table 3).

Treatment-Related Toxicities

Treatment-related toxicities are listed in Table 4. There were no treatment-related deaths. Bacteremia was documented in one patient and was due to *Staphylococcus epidermidis*. No patient died of sepsis. The most frequent grade 3 non-hematologic toxicity was mucositis (5 patients). No exacerbation of peripheral neuropathy was observed. Grade 1–2 treatment-related toxicities included diarrhea (91 %), dermatologic reactions such as skin rash and erythrodermia (4 patients), and fatigue (4 patients). Peripheral neuropathy was present before ASCT in 6 patients and did not deteriorate after the BD-HDM regimen.

Response

Within 3 months after conditioning with BD-HDM and ASCT, 83 % of patients achieved at least VGPR, with 4 patients having sCR, 3 patients having CR, and 3 patients showing VGPR (Table 5). Adverse cytogenetics had no effect on the response. Among 5 patients with 13q deletion, 2 achieved VGPR and 2 had CR.

Discussion

HDM (200 mg/m²) with ASCT is the standard treatment for younger patients with MM [9], but whether ASCT is

Table 3 Engraftment (*n* = 12)

Median duration of neutropenia (ANC $<0.5 \times 10^9/\text{L}$)	5 days (range: 4–6 days)
Median duration of thrombocytopenia	
Platelets $<20 \times 10^9/\text{L}$	7 days (range: 4–8 days)
Platelets $<50 \times 10^9/\text{L}$	9 days (range: 7–14 days)
Median no. of platelet transfusions	2 (1–5)
Median no. of red blood cell transfusions	2 (0–6)

Table 4 Transplantation-related toxicities ($n = 12$)

Mucositis	
All grades	11
Grades 3	5
Dermatologic or allergic reactions (grades 1 or 2)	4
Peripheral neuropathy (all grades)	0
General fatigue (grades 1 or 2)	4
Diarrhea	
All grades	11
Grade 3	1
Bacteremia	1
Toxic death	0

Table 5 Summary of the clinical response

Response	<i>n</i>
sCR	4
CR	3
VGPR	3
PR	2
SD	0

sCR stringent complete response, CR complete response, VGPR very good partial response, PR partial response, SD stable disease

beneficial for the majority of MM patients or only certain subsets remains unclear. It seems that achieving CR is crucial for a long-lasting response and prolonged survival [7]. Patients who achieve immunofixation-negative CR after ASCT have significantly longer event-free survival and overall survival than those who remain in partial remission (PR) [5]. Thus, several approaches have been tried to enhance the response to transplantation, but there have been problems with higher morbidity and mortality compared to HDM, which remains the recommended regimen [24–26]. Recently, the Intergroupe Francophone du Myelome phase 2 trial showed that conditioning with bortezomib plus melphalan achieved CR or VGPR in almost 70 % of patients with no toxic deaths [13]. Several other groups have subsequently reported similar results [14, 15]. However, these trials did not include patients who achieved sCR after ASCT.

Preclinical evidence provides a rationale for combining bortezomib with dexamethasone, suggesting that the effects of these two agents could be additive and that bortezomib may overcome resistance of MM cell lines to dexamethasone [27]. In two previous trials, bortezomib (1.0 or 1.3 mg/m²) was administered intravenously twice weekly for 2 weeks of a 3-week cycle for up to 8 cycles to patients who had failed second line therapy [10, 11, 28]. In these trials, patients with progressive disease after 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. This combination improved the response of patients with relapsed and/or refractory who had shown a less than optimal response to bortezomib monotherapy, and dexamethasone had no adverse influence on the safety profile of bortezomib [19]. Thus, we speculated that addition of dexamethasone to high-dose melphalan and bortezomib (BD-HDM) would be more effective without additional toxicities.

This phase 2 study demonstrated that BD-HDM is a useful conditioning regimen for ASCT that was well tolerated with no treatment-related mortality or increased toxicity. All patients received the full BD-HDM regimen. Graft failure was not observed and engraftment was not affected by the addition of bortezomib and dexamethasone to HDM. Recovery of the neutrophil count (ANC $\geq 0.5 \times 10^9/L$) and the platelet count ($\geq 20 \times 10^9/L$ without transfusion) occurred after a median of 5 days (range: 4–6 days) and 7 days (range: 4–8 days), respectively, while the median time until a platelet count $\geq 50 \times 10^9/L$ was 9 days (range: 7–14 days). Furthermore, 83 % of patients achieved at least VGPR, 4 patients obtained sCR, and three patients had CR. Accordingly, the combination of bortezomib and dexamethasone with HDM (BD-HDM) is a safe and promising conditioning regimen.

In this study, we did not specify the induction therapy in the protocol. According to multivariate analysis, a response of less than VGPR after induction therapy or after ASCT were both adverse prognostic factors for progression-free survival, but the most important factor was a response of less than VGPR after induction [29].

Conclusion

In conclusion, further prospective studies of induction therapies containing new drugs and BD-HDM are warranted.

Disclosure All authors disclose no financial or personal relationship with other people or organizations that could inappropriately influence their work.

Conflict of interest None.

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