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Efficacy and safety of bortezomib-containing induction chemotherapy for autologous stem cell transplantation-eligible Japanese multiple myeloma patients —A phase 2 multicenter trial—

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A phase II multicenter trial was conducted to analyze the efficacy and safety of a bortezomib-containing regimen for induction prior to autologous stem cell transplantation (ASCT) in newly-diagnosed multiple myeloma Japanese patients under the age of 65. The induction regimen consisted of one cycle of vincristine-doxorubicin-dexamethasone followed by 3 cycles of twice-weekly bortezomib-dexamethasone (BD). Responding patients underwent stem cell harvesting and ASCT. The primary endpoint was the post-induction response rate (RR). Forty-one patients were enrolled from September 2009 to December 2012. Post-induction RR was 85.4% including 17.1% CR, 4.9% nCR, and 34.1% VGPR. Three-year progression-free and overall survival were 51.9% and 90.3%, respectively. During induction, grade ≥3 hematologic adverse events (AEs) were frequent, of which infection was the most prevalent: 2 events during VAD and 7 events during BD. A total of 8 patients (19.5%) dropped out during induction due to AEs. Furthermore, 15 patients dropped out prior to ASCT, 10 of whom were due to AEs. Only 26 patients (63.4%) proceeded to ASCT, resulting in a relatively low RR after ASCT (58.5%, including 14.6% CR, 17.1% nCR, and 12.2% VGPR). Clinicians must be wary of possible serious AEs, both during and after BD induction, when applied to Japanese patients.

Key words: multiple myeloma, induction chemotherapy, bortezomib, autologous stem cell transplantation, adverse events

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Introduction

Despite the recent emergence of novel drugs, multiple myeloma (MM) remains an incurable plasma cell neoplasm. It is now widely accepted that high-dose therapy (HDT) combined with ASCT improves RR, progression-free survival (PFS), and overall survival (OS) in patients with newly diagnosed MM (NDMM) under the age of 65. Indeed, several randomized trials demonstrated the superiority of HDT over standard-dose therapy in this population of patients. Historically, the vincristine-doxorubicin-dexamethasone (VAD) regimen has long been a standard for induction therapy, due to its non-toxicity to normal bone marrow stem cells, allowing substantial stem cell mobilization. Moreover, the VAD regimen achieves reasonable responses [1–3]. A recent randomized trial with the VAD regimen as a control arm reported that VAD achieves a RR of 52%, including 14% very good PR (VGPR) and 8% complete response (CR) [4]. Meta-analyses of the HDT strategy further revealed that maximal response after completion of the induction is closely related to long-term outcome [5], suggesting the relevance of achieving deeper response in the induction phase before ASCT. Based on this notion, the majority of recent clinical studies have included novel drugs instead of VAD in the induction phase. One of these, bortezomib, is a reversible proteasome inhibitor which binds directly to the enzymatic complex of the proteasome, blocking its chymotrypsin-like activity and thus inhibiting the degradation of multiple proteins. Proteasome inhibition results in the disruption of various intracellular signaling pathways, leading to cell cycle arrest and apoptosis in myeloma cells, and inhibition of surrounding angiogenesis [6,7].

Considerable data have been accumulated demonstrating the significant clinical activity of bortezomib both as a conventional chemotherapy agent [8] and as an induction chemotherapy agent prior to HDT [9]. In the IFM phase III trial evaluating the efficacy of a BD regimen as an induction agent in comparison with VAD for ASCT-eligible NDMM, overall RR achieving at least PR was 78.5%, including 37.7% of VGPR and 14.8% of CR or near CR (nCR), after 4 cycles [10]. Superiority of BD over VAD in terms of event-free survival (EFS) and OS was reported to persist even after ASCT. In this IFM trial, total incidence of severe AEs was comparable between the VAD and BD groups, although peripheral neuropathy (PN) was more prevalent in the BD group. A meta-analysis integrating four phase III trials, including the IFM trial, confirmed the superiority of bortezomib-based induction chemotherapy with acceptable toxicity [11]. However, in Japan, little has been reported on the efficacy and safety of introducing bortezomib in the induction phase for ASCT-eligible NDMM. Because bortezomib had not been approved for the treatment of NDMM until September 2009 in Japan, the present study adopted a VAD/BD regimen consisting of one cycle of VAD followed by three cycles of BD for induction chemotherapy. The present study was thus designed to clarify the feasibility of introducing a bortezomib-containing regimen for induction therapy before ASCT as a daily general practice in Japanese patients.

Patients and Methods

Patients

Patients were eligible if they had NDMM defined by the International Myeloma Working Group (IMWG) criteria [12], Durie & Salmon stage II–III disease, and were aged 15–65 years. Key inclusion criteria were Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2 (patients with PS 3-4 due to myeloma pain were eligible), no previous anti-myeloma therapy, and adequate hepatic (bilirubin, AST, ALT < 2x normal upper limit), hematologic (white blood cell counts ≥ 3×10^9/L, absolute neutrophil counts ≥ 1.5×10^9/L, hemoglobin ≥ 8.0 g/dl, platelet counts ≥ 100×10^9/L), cardiac (EF ≥ 50%), pulmonary (FVC, $FEV_{1.0}$, DL_{CO} ≥ 50%, SaO_2 ≥ 90%), and renal (serum creatinine ≤ 4 mg/dl) function. RBC transfusion or usage of recombinant human erythropoietin prior to enrollment was allowed. Patients with ≥ grade 2 PN or neuropathic pain were excluded from the study.

Study design

This study was conducted as a phase II single-arm open-label multicenter trial of 11 institutions in Japan. The protocol was approved by the institutional review board of each institution. All patients provided written informed consent. Patients were enrolled from September 2009 to December 2012, and received induction chemotherapy with one cycle of VAD followed by 3 cycles of twice-weekly BD (VAD/BD). The VAD regimen consisted of a 28-day cycle of vincristine (0.4 mg/day, day 1–4) and doxorubicin (9 mg/m^2/day, day 1–4) by continuous intravenous (IV) infusion plus dexamethasone (40 mg, IV, day 1–4). BD consisted of 21-day cycles of bortezomib (1.3 mg/m^2, IV, day 1, 4, 8, and 11) plus dexamethasone (40 mg, IV or orally, day 1, 2, 4, 5, 8, 9, 11, and 12). Anti-varicella-zoster virus (VZV) prophylaxis was recommended during the BD induction. Approximately 4 weeks after the completion of the induction treatment, stem cells were mobilized by administrating cyclophosphamide (2 g/m^2, IV, day 1, 2) followed by lenograstim (10 μg/kg/day), starting the day the neutrophil count fell under 1×10^9/L. The target yield of stem cells was 4×10^6 CD34-positive cells/kg. Conditioning for ASCT was performed using melphalan (200 mg/m^2, IV, day –2). The second transplantation was performed by physician's decision if VGPR was not achieved after the first transplantation. Maintenance therapy

was not prescribed by the protocol.

Treatment with BD was prolonged with observation of grade 4 hematologic or grade ≥3 non-hematologic toxicity, excluding PN, until its recovery to ≤ grade 2. Management of PN was defined as shown below. After recovery from toxicity, treatment was restarted after stepwise dose-reduction of the responsible drug as follows: bortezomib, 1.3, 1.0, and 0.7 mg/m^2; and dexamethasone, 40, 30, and 23 mg/body. Further dose reduction was not permitted. When the toxicity was unable to be reduced to under grade 3 after 2 weeks' prolongation, or when grade 4 hematologic or grade ≥3 non-hematologic toxicity manifested even at the lowest dose level, the patient was withdrawn from the trial. Bortezomib-induced PN was managed following the established guideline exactly [13]: grade 1, no dose-reduction; grade 1 with pain or grade 2, stepwise dose-reduction (1.3, 1.0, and 0.7 mg/m^2); grade 2 with pain or grade 3, resuming the treatment at a dose of 0.7 mg/m^2 for a once-week schedule after the recovery of PN less than grade 2; and grade 4, withdrawal from the study.

This study was registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (http://www.umin.ac.jp/ctr/) as UMIN000002611.

Endpoints and assessment

The primary endpoint of this study was post-induction RR achieving at least PR. Secondary endpoints were OS, PFS, and safety of the VAD/BD induction chemotherapy. Therapeutic response was evaluated at post-induction and post-first ASCT according to the International Myeloma Working Group (IMWG) uniform response criteria [14]. nCR was defined as a condition achieving CR but with positive immunofixation test [15]. AEs were evaluated according to NCI-CTC version 3.0 criteria.

Statistical analyses

The present study was designed by employing a binominal distribution with a one-sided type I error of 0.05 and statistical power of 80%. Post-induction RR was initially estimated to be 80% due to a previous report stating RR with VAD was 63% [16]. All patients meeting the eligibility criteria who had started the first cycle of chemotherapy were evaluated for toxicity, response, and survival. The Kaplan-Meier method was used to estimate the distributions of PFS and OS. Times of observation were censored on June 30, 2014. Influence of each parameter on the achievement of post-induction RR was evaluated by Student's *t*-test or Fisher's exact test. Multivariate analysis was performed by a logistic model regression. A calculated *p* value of less than 0.05 was interpreted to indicate statistical significance. All analyses were performed with the STATA13 software (StataCorp LP, TX, USA).

Results

Patient characteristics

Characteristics of patients are summarized in Table 1. Forty-one patients were enrolled in this study. Median age was 59 years ranging from 40 to 65 years, and the male to female ratio was 23:18. Clinical stages were stages II and III by the Durie & Salmon system in 13 and 28 patients, respectively (n = 41), and stages I, II, and III by the International Staging System (ISS) in 12, 17, and 9 patients, respectively (n = 38). Three patients were excluded from the ISS analysis due to the unavailability of serum levels of β2 microglobulin. Chromosomal analysis of bone marrow cells was performed in all patients; however, the results were not available in 2 patients due to poor cell division. Among 39 available patients, 32 showed normal karyotype, and 7 showed abnormal karyotype, including 5 patients with hyperdiploidy and 2 patients with non-hyperdiploidy karyotypes. Deletion 13 was observed in 3 patients, and 2 of them showed hyperdiploid karyotypes. Because the use of

Table 1. Characteristics of patients

Characteristic	No. of Patients (n = 41)	%
Age, years		
Median (Range)	59 (40–65)	
Sex		
Male	23	56
Female	18	44
DS Stage		
II	13	32
III	28	68
ISS Stage		
I	12	29
II	17	41
III	9	22
NA	3	7
PS		
0–1	30	73
2–4	11	27
Immunoglobulin-type		
IgG	23	56
IgA	9	22
IgD	3	7
BJP	6	15
Karyotype		
Normal	32	78
Hyperdiploidy	5	12
non-Hyperdiploidy	2	5
NA	2	5
del(13)	3	7

DS, Durie & Salmon; ISS, International Staging System; PS, performance status; NA, not available.
Chromosomal analysis was performed by G-banding.

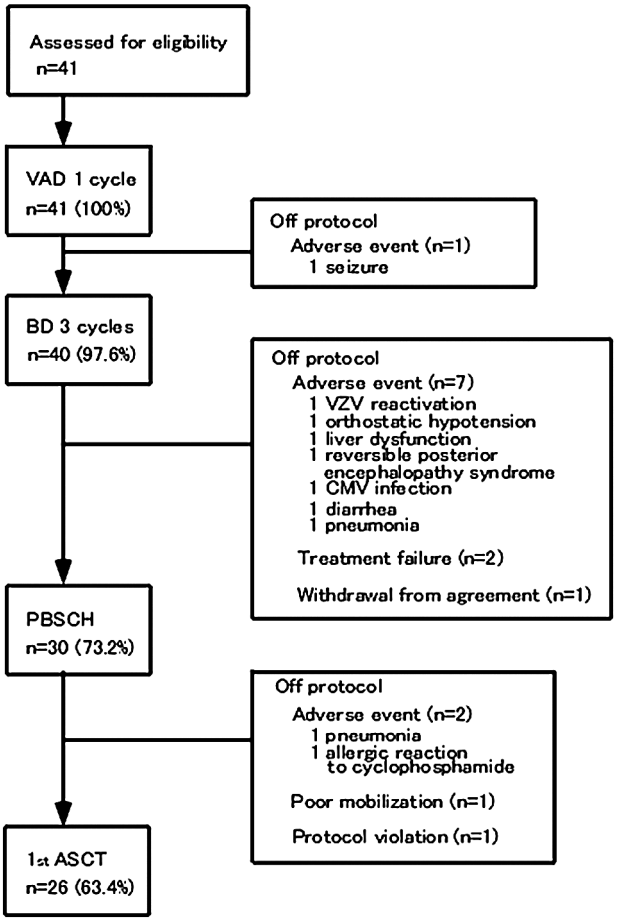

Figure 1. Flow diagram of patients enrolled in the trial.

fluorescent *in situ* hybridization (FISH) analysis was not mandatory in this study, its usage was dependent on each physician's decision. t(4;14) was observed in 1 out of 14 analyzed patients, del(17p) in 0 out of 5 patients, t(14;16) in 0 out of 2 patients, and del(13) in 7 out of 13 patients.

Patient disposition

The flowchart of patient disposition is shown in Figure 1. Among 41 enrolled patients, one patient dropped out during VAD because of an AE. Forty patients (97.6%) entered the induction phase with BD, and 30 patients (73.2%) completed 3 cycles. A total of 10 patients dropped out during BD, 7 due to AEs, 2 due to treatment failure, and 1 due to agreement withdrawal. Collectively, the drop-out rate due to AEs during the VAD/BD induction phase was 19.5% (8/41). Peripheral blood stem cell harvesting (PBSCH) and the first ASCT were performed in 30 (73.2%) and 26 (63.4%) of the 41 patients, respectively. During PBSCH, 4 patients dropped out: 2 due to AEs, one due to poor mobilization, and one due to protocol violation. The second ASCT was performed in 3 out of the 26 patients who completed the first ASCT. Although not prescribed by the protocol, 17 patients received maintenance therapy, 9 with thalidomide and 8 with lenalidomide.

Table 2. Therapeutic response

Response	Induction		1st ASCT		
	ITT (n = 41)		ITT (n = 41)		Per Protocol (n = 26)
	No.	%	No.	%	%
CR	7	17.1	6	14.6	23.1
nCR	2	4.9	7	17.1	26.9
VGPR	14	34.1	5	12.2	19.2
PR	12	29.3	6	14.6	23.1
≥PR	35	85.4	24	58.5	92.3
SD	3	7.3	1	2.4	3.8
PD	1	2.4	0	0.0	0.0
Not evaluable	2	4.9	1	2.4	3.9

ITT, intention to treat; ASCT, autologous stem cell transplantation.

Therapeutic response

Results of the response to treatment are summarized in Table 2. Post-induction RR was 85.4% with 17.1% CR, 4.9% nCR, and 34.1% VGPR by intention-to-treat (ITT) analysis. Univariate analysis identified pre-treatment level of serum albumin as a significant prognostic factor that positively influences post-induction achievement of ≥PR (p = 0.027) (Table 3). However, this was not validated by multivariate analysis (p = 0.201). RR after the first ASCT was 58.5% with 14.6% CR, 17.1% nCR, and 12.2% VGPR by ITT analysis, and 92.3% with 23.1% CR, 26.9% nCR, and 19.2% VGPR by per-protocol analysis. Although the second ASCT was performed in 3 patients, none of them achieved upgraded response. Efficacy of maintenance therapy was evaluated in 12 out of 17 patients excluding 4 patients who achieved CR after ASCT and 1 patient whose data were unavailable. Among these 12 patients, 5 patients achieved upgraded response.

Progression-free and overall survival

The median follow-up was 712 days. PFS and OS are shown in Figure 2. In total, 14 out of 41 patients experienced either disease progression (11 patients) or death (3 patients) during the follow-up period. PFS at 1, 2, and 3 years (95% confidence interval) were 84.5% (68.8–92.7), 67.5% (49.6–80.2), and 51.9% (27.1–72.0), respectively. OS at 1, 2, and 3 years were 97.4% (83.2–99.6), 90.3% (72.5–96.8), and 90.3% (72.5–96.8), respectively. Median PFS and OS have not yet been reached.

Safety

The safety profile during VAD (n = 41) and BD (n = 40) are summarized in Table 4. Grade ≥3 hematologic AEs were frequently observed. In particular, the incidence of cytopenia was

Table 3. Factors influencing therapeutic outcome

Variables	Univariate analysis			Multivariate analysis		
	≥PR (n = 35)	<PR (n = 6)	*p* value	Odds Ratio	95% CI	*p* value
Age, mean ± SD	57.3 ± 6.0	56.7 ± 5.2	0.814	0.95	0.74–1.22	0.705
Sex						
Male	19	4	0.679	1.5	0.05–44.7	0.814
Female	16	2				
PS						
0–1	8	3	0.316	0.53	0.34–8.46	0.656
2–4	27	3				
Alb, mean ± SD (g/dl)	3.4 ± 0.7	2.7 ± 0.5	0.027	4.75	0.43–52.0	0.201
β2MG, mean ± SD (mg/l)	4.8 ± 3.4	3.6 ± 1.8	0.503	1.47	0.65–3.34	0.357

Alb, albumin; β2MG, β2-microglobulin.

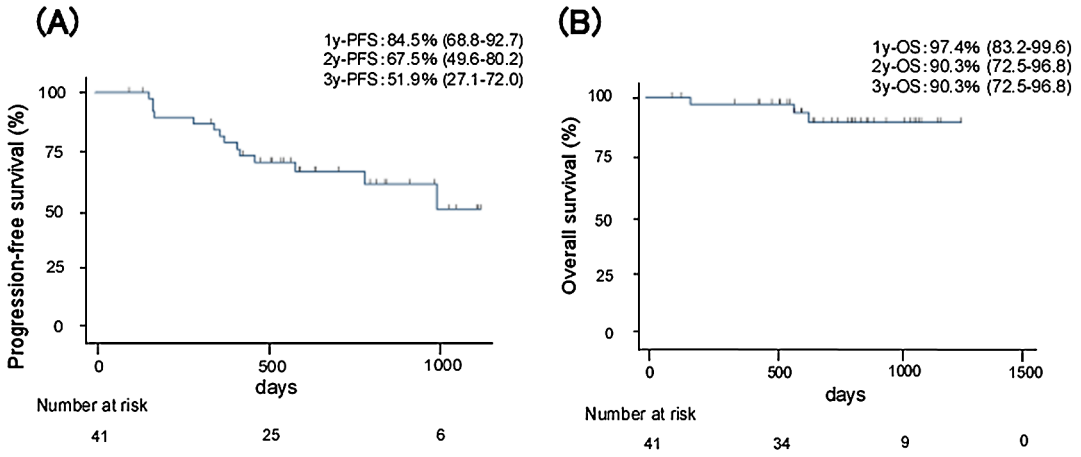

Figure 2. Progression-free survival and overall survival. Kaplan-Meier analysis of progression-free survival (A) and overall survival (B) in the ITT population.

high, with 26 events (19 out of 40 patients) during VAD and 13 events (11 out of 39 patients) during BD documented. However, grade 4 cytopenia rarely occurred during induction; only 1 event of anemia during VAD and 3 events of thrombocytopenia during BD were documented. For infections, grade ≥3 events were frequent; 2 events of sepsis during VAD and 7 events of infection, including 4 of sepsis, 2 of bacterial pneumonia, and 1 of VZV reactivation in a patient who didn't receive anti-VZV prophylaxis, during BD. On the other hand, incidence of grade ≥3 non-hematologic AEs was relatively low throughout the induction. Among non-hematologic AEs, neuropathy was documented in 12.2% of patients during VAD and 27.5% of patients during BD. However, grade ≥3 neuropathy was rarely experienced: no patients during VAD and 2 patients (one PN and one orthostatic hypotension) during BD were documented.

One patient dropped out during VAD due to seizures, and seven patients during BD (one each due to VZV reactivation, orthostatic hypotension, liver dysfunction, reversible posterior encephalopathy syndrome, cytomegalovirus (CMV) infection, diarrhea, and pneumonia). Furthermore, 2 patients dropped out during PBSCH (one due to pneumonia and one due to allergic reaction to cyclophosphamide).

Overall, 3 patients died during the study period. Two patients died after the first ASCT due to tumor progression, and one patient died during the first ASCT due to bacterial pneumonia.

Discussion

In the present study, we analyzed the efficacy and safety of a bortezomib-containing regimen for use as induction prior to ASCT in Japanese patients. Because the use of bortezomib had not been approved as a first-line therapy in Japan at the time of the study's commencement, a VAD/BD regimen was adopted for use in the present study instead of BD for induction. Thus, the present study was conducted for its use as a daily medical practice, according to the Japanese health ser-

Table 4. Safety profile during induction

	VAD (n = 40)				BD (n = 39)			
	Grade 3		Grade 4		Grade 3		Grade 4	
Hematologic AEs	No.	%	No.	%	No.	%	No.	%
Anemia	10	25	1	2.5	8	20.5	0	0
Leukopenia	13	32.5	0	0	1	2.6	0	0
Thrombocytopenia	2	5	0	0	1	2.6	3	7.7
Infection	2	5	0	0	7	17.9	0	0
Sepsis	2	5	0	0	4	10.3	0	0
Pneumonia	0	0	0	0	2	5.1	0	0
VZV reactivation	0	0	0	0	1	2.6	0	0

	VAD (n = 41)				BD (n = 40)			
	Grade 3		Grade 4		Grade 3		Grade 4	
Non-Hematologic AEs	No.	%	No.	%	No.	%	No.	%
Neuropathy	0	0	0	0	2	5	0	0
Peripheral neuropathy	0	0	0	0	1	2.5	0	0
Orthostatic hypotension	0	0	0	0	1	2.5	0	0
Fatigue	0	0	0	0	1	2.5	0	0
Anorexia	0	0	0	0	1	2.5	0	0
Constipation	0	0	0	0	1	2.5	0	0
Glucose intolerance	1	2.4	1	2.4	0	0	0	0
Liver dysfunction	0	0	1	2.4	0	0	1	2.5
Seizure	1	2.4	0	0	1	2.5	0	0

	VAD (n = 41)		BD (n = 40)	
Neuropathy	No.	%	No.	%
Grade 1	5	12.2	4	10
2	0	0	5	12.5
3	0	0	2	5
4	0	0	0	0

AEs, adverse events; VZV, varicella-zoster virus.

vice system. We observed that post-induction RR in Japanese patients was found to be comparable with that of preceding trials performed in foreign countries. A previous meta-analysis integrating 4 randomized trials concluded that the bortezomib-containing induction regimen achieves CR/nCR, ≥VGPR, and ≥PR rates of 23%, 47%, and 83%, respectively[11]. One of these trials, the IFM 2005-01 trial which adopted a BD regimen as induction treatment, achieved CR/nCR, ≥VGPR, and ≥PR rates of 14.8%, 37.7%, and 78.5%, respectively[10]. Because CR/nCR, ≥VGPR, and ≥PR rates in the present study were 22.0%, 56.1%, and 85.4%, respectively, the bortezomib-containing regimen may be equally as effective in Japanese patients. Furthermore, because the median age was 59 years and the percentage of patients with ISS stage ≥II disease was 63.0%, the characteristics of the patients in the present study appeared to be comparable or even disadvantageous in comparison with those in the IFM 2005-01 trial.

However, contrary to the favorable therapeutic outcome achieved by the VAD/BD induction regimen, post-ASCT RR was unexpectedly low. By ITT analysis, the CR/nCR, ≥VGPR, and ≥PR rates after the first ASCT were 31.7%, 43.9%, and 58.5%, respectively, whereas the IFM 2005-01 trial reported values of 35.0%, 54.3%, and 80.3%, respectively[10], and similar results were obtained in a recent French study[16]. Therefore, the RR after the first ASCT in the present study was particularly low. We hypothesized that relatively high drop-out rate during and after the VAD/BD induction chemotherapy, namely 8 and 2 out of 41 patients, respectively, adversely affected the post-ASCT therapeutic outcome.

In our preceding trial, our study group adopted 3 courses of VAD as the induction followed by harvesting with either cyclophosphamide or etoposide and ASCT. Patients' backgrounds, in terms of age, sex, the Durie & Salmon and ISS stage, and serum level of β2 microglobulin, were comparable between

Table 5. Comparison of VAD (historical control) and VAD/BD induction

	VAD (n = 52)	VAD/BD (n = 41)	*p* value
	No. of Patients (%)	No. of Patients (%)	
Response to Induction			
≥VGPR (ITT)	15/52 (28.8)	23/41 (56.1)	0.011
Response to ASCT			
≥VGPR (ITT)	19/52 (36.5)	18/41 (43.9)	0.526
≥VGPR (Per Protcol)	19/40 (47.5)	18/26 (69.2)	0.127
Discontinuation during induction			
AEs	2 (3.8)	8 (19.5)	0.020
PD	6 (11.5)	2 (4.9)	0.459
Withdrawal from agreement/ Physician's choice	1 (1.9)	1 (2.4)	1.000

PD, progressive disease; ITT, intention to treat.

these 2 trials (data not shown). Because the VAD regimen achieved 28.8% of ≥VGPR and 73.1% of ≥PR after induction chemotherapy (our unpublished data) (Table 5), the VAD/BD regimen seems to be superior to VAD in terms of therapeutic response. However, the superiority of the VAD/BD regimen over VAD for induction didn't persist after the first ASCT (≥VGPR: 43.9% versus 36.5%, respectively). Although it may not be rational to directly compare the results of these two studies, it is highly possible that the favorable response achieved by the bortezomib-containing induction regimen was suppressed by relatively high incidence of adverse events during and immediately after the induction. To gain insight on principal factors contributing to the unfavorable outcomes after completion of the first ASCT in the present study, we analyzed the toxicity and safety of the bortezomib-containing induction regimen and the subsequent PBSCH with cyclophosphamide. Infectious episodes were frequently observed during VAD/BD induction, with 2 events during VAD and 7 events during BD, and 3 patients dropping out due to infection during induction. Given that the incidence of grade ≥3 infections observed during BD induction in previously published large-scale studies conducted in foreign countries was 12–14% [10,17], Japanese patients may be more vulnerable to infectious complications. High-dose dexamethasone prescribed in this study may have resulted in higher incidence of infection during the induction. Similar situation was previously reported in a lenalidomide-combined induction chemotherapy [18]. It should also be noted that 4 additional patients dropped out because of various non-hematologic AEs during VAD/BD induction. Consequently, drop-out rates due to AEs and disease progression during VAD/BD induction in this study were 19.5% and 4.9%, respectively, whereas those during VAD induction were 3.8% and 11.5%, respectively. Because 2 additional patients dropped out during PBSCH, only 63.4% of the patients proceeded to the first ASCT, which may have adversely affected the therapeutic outcome values. Reflecting the higher toxicity of the BD regimen and relatively higher incidence of drop-out throughout the period of chemotherapy prior to ASCT, ITT-based RR after the first ASCT was disappointing in this study. Indeed, differences in response achieving ≥VGPR between the VAD and VAD/BD induction regimens were trivial. Considering that a previous meta-analysis integrating 3 randomized trials comparing bortezomib-based and non-bortezomib-based induction regimens concluded that the post-ASCT rate of ≥VGPR was significantly higher in the bortezomib-based regimen (60% versus 41%, $p < 0.001$) [11], the present results (rate of ≥VGPR: 43.9%) are clearly inferior to those of the previous meta-analysis. Although the possibility cannot be denied that inclusion of VAD prior to BD in this study may have had adverse effects, we conclude that the use of the BD regimen itself as an induction is toxic to Japanese patients.

In conclusion, we believe that a BD-containing induction strategy, despite its durable therapeutic response, possesses problems in safety and feasibility of use. As its toxicity may result in the cessation of treatment, care must be taken in the management of toxicity when administering BD induction to Japanese patients. Although we employed criteria for prolongation and dose-reduction of chemotherapy in the present study referring to preceding foreign studies, these criteria may not be sufficient for Japanese patients. On the other hand, as the relevance of achieving deeper response in the induction phase before ASCT is now widely accepted, we should also bear in mind not to excessively diminish the therapeutic power of BD induction. From this standpoint, it may be rational to decrease the dose-intensity of BD for minimizing its toxicity, and instead include a third drug to increase the therapeutic power against myeloma without overlapping

toxicity[19–23]. In line with this scenario, we are now conducting a phase 2 trial of cyclophosphamide-bortezomib-dexamethasone (CyBorD) to prove its efficacy and safety as induction treatment prior to ASCT in Japanese patients.

Conflict of Interest

The authors declare that they have no conflict of interest.

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