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ORIGINAL ARTICLE

Bortezomib-based strategy with autologous stem cell transplantation for newly diagnosed multiple myeloma: a phase II study by the Japan Study Group for Cell Therapy and Transplantation (JSCT-MM12)

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Abstract

Background The Japan Study Group for Cell Therapy and Transplantation (JSCT) organized a phase II study to evaluate the efficacy and safety of a treatment protocol (JSCT-MM12) for multiple myeloma (MM) patients who were previously untreated and transplantation-eligible. Since bortezomib-based therapy is known to be effective for MM, the protocol is intensified more than the previous protocol (JSCT-MM10) and comprised the subsequent treatments: bortezomib + cyclophosphamide + dexamethasone (VCD) induction; bortezomib + high-dose-melphalan (B-HDM) conditioning with autologous stem cell transplantation (ASCT); bortezomib + thalidomide + dexamethasone (VTD) consolidation; and lenalidomide (LEN) maintenance.

Methods Sixty-four symptomatic patients aged between 20 and 65 years were enrolled for treatment and received three cycles of VCD, followed by cyclophosphamide administration for autologous stem cell harvest and B-HDM/ASCT, and subsequently two cycles of VTD, after that LEN for 1 year.

Results Complete response (CR)/stringent CR (sCR) rates for induction, ASCT, consolidation, and maintenance therapies were 20, 39, 52, and 56%, respectively. The grade 3/4 toxicities (≥ 10%) with VCD treatment included neutropenia (27%), anemia (19%), and thrombocytopenia (11%). There was no treatment-related mortality. After median follow-up of 41 months, estimated 3-year progression-free survival (PFS) and overall survival (OS) rates were 64% and 88%, respectively. The high-risk group revealed lower CR/sCR, PFS, and OS than the standard-risk group.

Conclusions The study revealed that the treatment protocol consisting of VCD induction, B-HDM/ASCT followed by VTD consolidation, and LEN maintenance could produce highly beneficial responses and favorable tolerability in newly diagnosed MM. However, future study is required for improving treatment in the high-risk group.

Keywords Bortezomib · Thalidomide · Lenalidomide · Autologous stem cell transplantation · Consolidation · Maintenance

Introduction

High-dose therapy (HDT) with autologous stem cell transplantation (ASCT) is a standard initial treatment for symptomatic patients with multiple myeloma (MM). However, further improvement is essential as many patients' relapse. Combination therapies of thalidomide (THAL), bortezomib (BTZ), and lenalidomide (LEN) with several different strategies, such as 2- or 3-drug induction regimens [1–6], systematic consolidation, and maintenance therapies [7–14], improved patient's responses. In Japan, a study for newly diagnosed MM (NDMM) was organized by the Japan Study Group for Cell Therapy and Transplantation (JSCT-MM10) and showed improved outcomes by the regimen consisting of 2-drug induction (BTZ + dexamethasone [DEX]), 2-drug consolidation (LEN + DEX), and LEN maintenance therapies [15]. The Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA) reported promising outcomes of employing BTZ + THAL + DEX (VTD) induction and

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consolidation therapies [2]. This suggested a combination of proteasome inhibitor-based consolidation therapy, HDT/ASCT, and maintenance treatment was advantageous for younger patients with MM.

High-dose melphalan (HDM) course is the only approved regimen for conditioning. Intensified pre-transplant conditioning to improve transplant outcomes increased the treatment-related toxicity events and did not increase survival rate [16–19]. Synergistic effects of BTZ and melphalan were reported from in vitro [20, 21] and in vivo [22, 23] studies. The Intergroup Francophone du Myélome (IFM) indicated that a combination of BTZ + HDM (B-HDM) was safer and produced higher complete response (CR) rate than HDM alone [24]. We planned a phase II study (JSCT-MM12) for using BTZ to evaluate efficacy and safety of BTZ + cyclophosphamide (CY) + DEX (VCD) as induction, B-HDM/ASCT and VTD as consolidation, and LEN as maintenance in NDMM. In this JSCT-MM12, we used more intensified BTZ induction, pre-transplant conditioning, and consolidation regimens than those in the JSCT-MM10.

Patients and methods

Patient recruitment

Between March 2012 and January 2013, 64 patients from 24 Japanese hospitals were enrolled into the study. Inclusion criteria were (1) treatment-naive MM, meeting the International Myeloma Working Group (IMWG) criteria; (2) 20–65 years old, expected to survive for more than 3 months; (3) performance status (PS) of the Eastern Cooperative Oncology Group (ECOG): 0–2 (acceptable for the higher scores if pain came from myeloma); and (4) no severe organ damage (hepatic, renal, cardiac, or pulmonary functions; absolute neutrophil count (ANC): 1.0×10^9/L or more; and platelet (PLT) count: 75×10^9/L or more). Exclusion criteria were (1) plasma cell leukemia or non-secretory MM, meeting the IMWG criteria; (2) positive for anti-human immunodeficiency virus, hepatitis B surface antigen, or anti-hepatitis C virus; (3) comorbidities including cardiac, respiratory, hepatic, or renal disease, and/or severe diabetes mellitus, hypertension, mental disorders, or infection; (4) pregnancy and lactation; and (5) active advanced malignancies.

Study design

In this multicenter, non-comparative, and open-label study, the subjects initially received three cycles of VCD induction therapy. BTZ, CY, and HDM were administered intravenously, whereas DEX and THAL were administered orally. Subcutaneous administration of BTZ was not approved by social insurance in Japan at that time. In the first 3 weeks, VCD therapy (BTZ: 1.3 mg/m^2 on Days 1, 4, 8, and 11; CY: 500 mg/m^2 on Days 1 and 8; and DEX: 40 mg on Days 1, 4, 8, and 11) was given. Then, two 5-week cycles of VCD therapy (BTZ: 1.3 mg/m^2 on Days 1, 8, 15, and 22; CY: 300 mg/m^2 on Days 1, 8, 15, and 22; and DEX: 40 mg on Days 1, 8, 15, and 22) were applied. A new cycle was initiated if ANC was 1×10^9/L or more, PLT was 75×10^9/L or more, and non-hematologic adverse events (AEs) were grade 2 or less. The treatment was terminated if there was 3-week delay in the schedule. Acyclovir was recommended during BTZ treatment and BTZ-associated peripheral neuropathy was managed with the established dose modifications [25]. CY (3 g/m^2) followed by administration of granulocyte-colony stimulating factor (G-CSF; filgrastim: 200–400 μg/m^2/day) was used to mobilize peripheral blood stem cell (PBSC). Mobilization procedure was scheduled for subjects with PS scores of 0–2, acceptable major organ functions, and no progressive disease (PD). PBSCs were collected by apheresis and later ASCT was performed at day 0, according to the transplant procedure [26]. The target number of PBSC yield was 1.0×10^6 or more CD34-positive cells/kg of recipient body weight. As ASCT preconditioning, B-HDM (BTZ: 1.3 mg/m^2 on Days −4 and −1; and HDM: 100 mg/m^2 on Days −3 and −2) were administered to subjects with PS scores of 0 or 1, no PD, 1×10^9/L or more ANC, 50×10^9/L or more PLT, normal major organ functions, and 1×10^6/kg or more preserved CD34-positive cells. On day 100, subjects without PD received two cycles of consolidation therapies consisting of VTD (BTZ: 1.3 mg/m^2 on Days 1, 8, 15, and 22; THAL: 100 mg every day; and DEX: 40 mg on Days 1, 8, 15, and 22). Subsequently, 4-week cycles of LEN alone (10 mg daily) were administered for 1 year. Consolidation and maintenance treatments were initiated in subjects with PS score of 0 or 1, no PD, 1×10^9/L or more ANC, 75×10^9/L or more PLT, and acceptable major organ functions. LEN was reduced, if patients developed bone marrow suppression or renal impairment. Aspirin was administered as anticoagulant prophylaxis during LEN treatment.

The study protocol was approved by the institutional review boards of participating hospitals. Written informed consents were obtained from all patients. This study was conducted according to the principles of the Declaration of Helsinki and the International Conference on Harmonization Guidelines of Good Clinical Practice. UMIN-CTR registration number was 000007216.

Efficacy and safety

Responses to VCD induction, B-HDM/ASCT, VTD consolidation, and LEN maintenance were assessed at the time points according to the IMWG Uniform Response Criteria [27]. Progression-free survival (PFS) was defined as

duration from the enrollment to the date of progression, relapse, or death from any cause (whichever occurred first). Overall survival (OS) was defined as duration from the enrollment to the date of death or the date when the subject was last known to be alive [27]. Adverse events (AEs) were monitored throughout the study and graded according to the Common Terminology Criteria for Adverse Events (version 4.0).

Bone marrow plasma cells

Bone marrow plasma cells purified with anti-CD138-coated magnetic beads (EasySep Human CD138 Positive Selection Kit, STEMCELL technologies, CAN) were analyzed by fluorescence in situ hybridization (FISH). Deletion of chromosome 17p (del(17p)) was detected with a locus-specific identifier (LSI)17p13.1 probe combined with 17α-satellite DNA centromere probe. An LSI Immunoglobulin H (*IgH*)/fibroblast growth factor receptor 3 dual fusion translocation probe (*FGFR3*, 4p16) was used to detect *IgH*/*FGFR3* fusion resulting from *t*(4;14)(p16; q32), and an LSI *IgH*/*c-maf* (*MAF*, 16q23) was used to detect *IgH*/*MAF* fusion resulting from *t*(14;16)(q32; q23).

Statistical approach to endpoints

The primary endpoint was set as response rate of complete response (CR)/stringent CR (sCR) after VTD consolidation therapy because CR is significantly associated with OS prolongation after ASCT [28]. The secondary endpoints included response rates of CR/sCR after induction therapy, ASCT and maintenance therapy, along with PFS, OS, and safety. Statistical analysis was conducted by SAS (SAS Institute, Cary, NC, USA) version 9.4. Fisher's exact test was employed to compare response rates. The Kaplan–Meier method was adopted to estimate PFS, OS, 50% survival period, and 1-year survival rate. One-group binominal test with 0.05 one-sided significance level had 80% power detecting differences between the null hypothesis proportion ($p_0 = 0.3$) and the alternative proportion ($p_1 = 0.5$) when setting the sample size of 39. Considering 25% off-study rate after the registration and 5% off-study rate due to lack of CD34-positive cells at PBSC harvesting, at least 56 subjects were required for conducting a reliable statistical analysis.

Results

Treatment procedures

The patient demographics and characteristics are summarized at baseline (Table 1). FISH analysis was not performed in 24 cases because sufficient marrow plasma cells were not obtained. High-risk cytogenetic profiles [del(17p) in ≥ 20% of screened plasma cells, *t*(4;14), and/or *t*(14;16)] were observed in 13 patients.

Table 1 Patient background ($n = 64$)

Age (years)	
Median	58
Range	34–65
Gender, *n*	
Male	38
Female	26
Performance status, *n*	
0–1	45
≥ 2	19
International staging system, *n*	
I	20
II	30
III	14
Type of M protein, *n*	
IgG	34
IgA	11
IgM	1
IgD	1
IgE	2
Light chain	9
IgG+ light chain	5
IgA+ light chain	1
β_2-microglobulin (mg/L)	
Median	3.2
Range	1.3–116.5
Cytogenetics, *n*	
No cytogenetic abnormality	27
t(4;14)	9
t(14;16)	1
del(17p)	3
Unknown	24

The patients underwent the treatment procedures shown in Fig. 1. After VCD induction, three patients developed PD, six patients had AEs (hepatobiliary disorders, CMV infection, pulmonary embolism, or neutropenia), and one patient withdrew the consent. Three patients did not receive ASCT because of poor mobilizer (less than 1.0×10^6 CD34-positive cells/kg). Four patients did not receive B-HDM/ASCT because of PD ($n = 1$), depression ($n = 1$), and deviation from the criteria to start the next treatment ($n = 2$). Four patients did not receive LEN because of PD ($n = 1$), AEs ($n = 2$: Herpes Zoster and VZV encephalitis), withdrawal of consent ($n = 1$), and deviation from the criteria to start the next treatment ($n = 1$). During LEN maintenance, three patients developed PD and 1 patient developed AE (cerebral infarction)

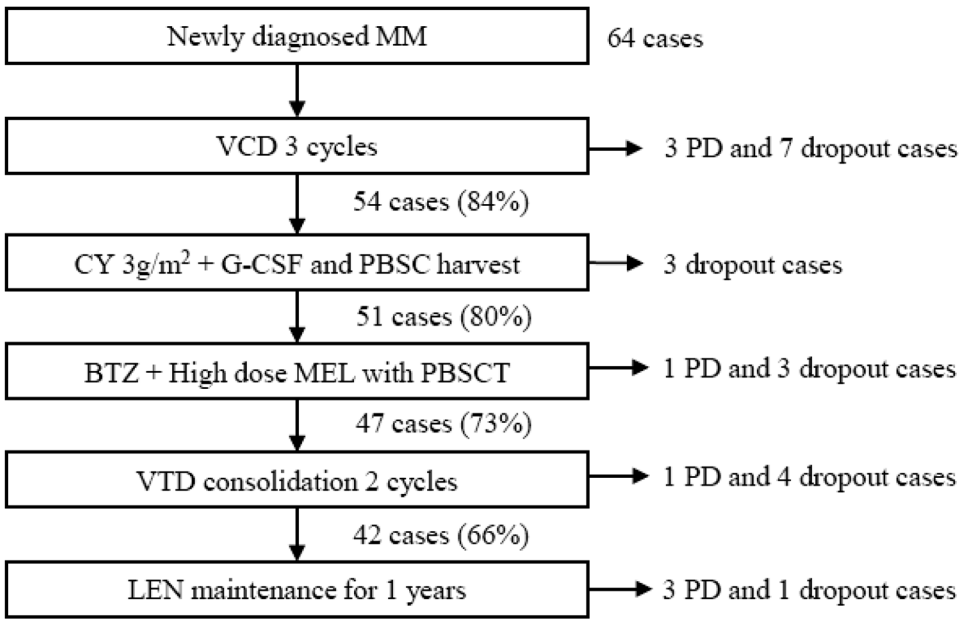

Fig. 1 Treatment procedures. *MM* multiple myeloma; *VCD* bortezomib, cyclophosphamide, dexamethasone; *CY* cyclophosphamide; *G-CSF* granulocyte-colony stimulating factor; *PBSC* peripheral blood stem cell; *MEL* melphalan; *PBSCT* peripheral blood stem cell transplantation; *VTD* bortezomib, thalidomide, dexamethasone; *LEN* lenalidomide; *PD* progressive disease

and withdrew consent. Four patients developed PD after the completion of LEN maintenance.

Autologous transplantation

The number of CD34-positive cells collected by the first cytapheresis was 3.54×10^6 cells/kg (median [range 0.02×10^6 to 16.1×10^6 cells/kg]). Eight out of 54 patients required the second cytapheresis. Three patients did not achieve the target yield and did not receive ASCT. Fifty-one patients received B-HDM/ASCT as scheduled. The number of CD34-positive cells infused was 3.17×10^6 cells/kg (median [range 1.0–11.5 cells/kg]). Rapid engraftment was observed in all patients after 11.5 days (median [range 9–20 days], ANC: $\geq 0.5 \times 10^9$/L; and PLT: $\geq 20 \times 10^9$/L).

Treatment response

The response rates after induction, ASCT, consolidation, and maintenance treatments were evaluated (Table 2). At the primary endpoint, the response rate of CR/sCR after consolidation was 52% (33/64 cases [95% CI 39–64]), including sCR rate of 39%. At the secondary endpoints, the response rates of CR/sCR after induction, ASCT, and maintenance were 20, 39, and 56%, respectively, and those of sCR were 14, 30, and 45%, respectively. The response rates increased as the treatment process proceeded. Eight patients (13%) developed PD.

At the median follow-up of 41 months (range 20–47 months), the estimated PFSs at 2 and 3 years were 77.0% (95% CI 64–85%) and 64% (95% CI 51–75%), respectively (Fig. 2a). The estimated OSs at 2 and 3 years were 97% (95% CI 88–99%) and 88% (95% CI 88–99%), respectively (Fig. 2b).

Table 2 Response rates (intent-to-treat analysis) ($n = 64$)

Response	Induction		Auto-PBSCT		Consolidation		Maintenance	
	No.	%	No.	%	No.	%	No.	%
sCR	9	14	19	30	25	39	29	45
CR	4	6	6	9	8	13	7	11
VGPR	12	19	10	16	10	16	8	13
PR	26	41	19	30	12	19	11	17
CR/sCR	13	20	25	39	33	52	36	56
≥VGPR	25	39	35	55	43	67	44	69
≥PR	51	80	54	84	55	86	55	86

CR complete response, *sCR* stringent CR, *VGPR* very good partial response, *PR* partial response

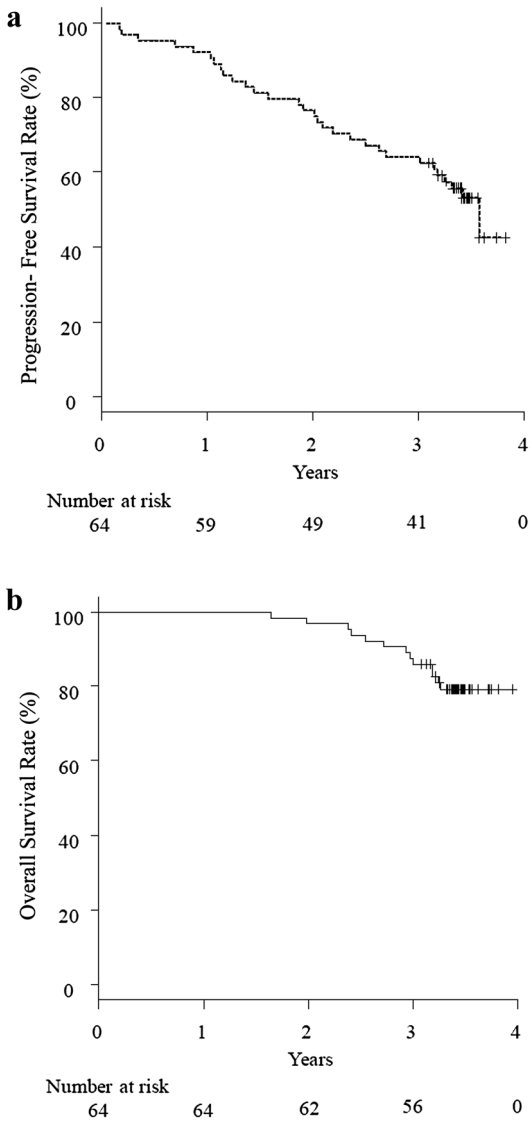

Fig. 2 **a** Progression-free survival rate and **b** overall survival rate (Kaplan–Meier estimates)

The best response rates of CR/sCR, very good partial response or better (≥ VGPR), estimated 2-year PFS, and OS for patients with high-risk cytogenetic profiles such as *t*(4;14), *t*(14;16) or del(17p), were 38, 63, 62, and 85%, respectively, and those of standard-risk patients were 63, 78, 89, and 100%, respectively. The best responses in high-risk group tended to be lower than those in standard-risk group, but no significant difference was observed between the two groups. However, the survival outcomes of the high-risk group were significantly lower than those of standard-risk group (Table 3).

Table 3 Best response and survival outcome for standard and high-risk cytogenetics patients

	Standard-risk ($n=27$)		High-risk ($n=13$)		p
	%	95% CI	%	95% CI	
Best response					
CR/sCR	63	42–81	38	14–68	0.19
≥ VGPR	78	58–91	62	32–86	0.45
2-year PFS	89	69–96	62	31–82	0.04
2-year OS	100		85	51–96	0.04

CR complete response, *sCR* stringent CR, *VGPR* very good partial response, *PFS* progression-free survival, *OS* overall survival

Toxicity

Drug dosage was reduced when needed. Reasons of reduction were (1) during VCD induction, BTZ: peripheral sensory neuropathy ($n=5$) and hepatobiliary disorders ($n=2$), CY: hepatobiliary disorder ($n=2$), DEX: hepatobiliary disorder ($n=2$); and (2) during VTD consolidation, BTZ: peripheral sensory neuropathy ($n=3$) and thrombocytopenia (grade 3/4: $n=1$), THAL: creatine phosphokinase elevation ($n=1$) and thrombocytopenia (grade 3/4: $n=1$). Full-dose LEN maintenance therapy was given to 42 patients (65%). The reasons for LEN modification were neutropenia or thrombocytopenia (grade 3/4: $n=5$) and non-hematological AEs (grade 2/3: $n=3$).

Severe hematological AEs (grade 3/4) were observed (excluding CY for PBSC harvest and B-HDM/ASCT): neutropenia ($n=17$), thrombocytopenia ($n=7$), and anemia ($n=12$) during VCD induction therapy; neutropenia ($n=3$) and thrombocytopenia ($n=3$) during VTD consolidation therapy; and neutropenia ($n=11$), thrombocytopenia ($n=4$), and anemia ($n=1$) during maintenance therapy. The severe non-hematological AEs (grade 3/4) were also observed (Table 4). Two life-threatening AEs were reported: sepsis after ASCT and VZV encephalitis during VTD consolidation therapy. No treatment-related mortality was observed. One patient developed a second primary cancer of prostate after completing the maintenance.

Discussion

In this study, we investigated the efficacy and safety of more intensified BTZ induction, pre-transplant conditioning, and consolidation regimens compared with the previous study [15]. We chose VCD induction therapy based on the research conducted by Reeder et al.'s highly effective triplet regimen of VCD induction for transplant-eligible patients [4]. They also reported that once- or twice-weekly intravenous BTZ administrations had similar benefits, but once-weekly

Table 4 Non-hematologic adverse events (Grade 3/4)

Adverse events	VCD induction ($n=64$)		CY with PBSCH ($n=54$)		HDT with auto-PBSCT ($n=51$)		VTD consolidation ($n=47$)		LEN maintenance ($n=42$)	
	G3	G4	G3	G4	G3	G4	G3	G4	G3	G4
Anorexia	0	0	6	0	21	0	0	0	0	0
Nausea and vomiting	0	0	5	0	17	0	0	0	0	0
Diarrhea	0	0	2	0	6	0	0	0	0	0
Stomatitis	0	0	0	0	4	0	0	0	0	0
Febrile neutropenia	1	0	14	0	24	0	0	0	0	0
Gastrointestinal disorders	2	0	0	0	0	0	0	0	0	0
Hepatobiliary disorders	5	0	0	0	0	0	0	0	0	0
Hyperglycemia	1	0	0	0	0	0	0	0	0	0
Hyponatremia	1	0	1	0	0	0	0	0	0	0
Hypokalemia	0	0	0	0	2	0	0	0	0	0
Fatigue	0	0	1	0	0	0	0	0	0	0
Peripheral neuropathy	0	0	0	0	0	0	1	0	0	0
HSV infection	1	0	0	0	0	0	0	0	0	0
CMV infection	2	0	0	0	0	0	0	0	0	0
CRP increased	0	0	1	0	0	0	1	0	0	0
Infection	0	0	2	0	2	1[a]	2	1[b]	1[c]	0
Pancreatitis	1	0	0	0	0	0	0	0	0	0
Pulmonary embolism	1	0	0	0	0	0	0	0	0	0
Cellulitis	1	0	0	0	0	0	0	0	0	0
Eruption	0	0	0	0	0	0	1	0	1	0
Pruritus	0	0	0	0	0	0	0	0	1	0

[a]Sepsis

[b]VZV encephalitis

[c]Herpes Zoster

administration caused less AEs [29]. In the JSCT-MM10, frequent peripheral neuropathy incidences were reported from patients who were intravenously administered BTZ twice-weekly [15]. Thus, in this JSCT-MM12, BTZ was administered twice-weekly in the beginning to reduce the tumor rapidly, after that administered once-weekly to reduce AEs. Compared with the JSCT-MM10 result [15], VCD induction therapy produced a higher CR/sCR rate (JSCT MM12: 20% versus JSCT MM10: 3%), with reducing AEs. Fifty-four (90%) out of 60 NDMMs (except for three cases with PD and 1 case who withdrew the consent) completed VCD induction therapy and showed a favorable tolerability. Moreau et al. reported that achievement of VGPR after induction therapy was an important prognostic factor for prolonging PFS [30]. The VGPR-or-better rate after VCD induction therapy in this study (39%) was comparable to that in the JSCT-MM10 study (37%). In spite of the reduced BTZ dose and the treatment cycles (three cycles in this JSCT MM12 versus four cycles in the JSCT-MM10), intensification of BTZ made it possible for this study to achieve almost the same rate. Moreau et al. also indicated that subcutaneous administration significantly reduced peripheral neuropathy rate compared with intravenous administration [31]. As the twice-weekly subcutaneous administrations have a potential to safely increase the dose intensity of BTZ and improve VGPR-or-better rate and from December 2012, the Japanese health insurance has covered BTZ subcutaneous therapy, further studies are expected.

Combination of CY with G-CSF was employed to mobilize PBSCs in MM. PBSC harvest with reduced CY (1.2–3 g/m^2) revealed milder toxicity, compared with 4 g/m^2 CY [32–34]. In the JSCT-MM10 where 4 g/m^2 CY was administered, six out of 34 patients withdrew the study due to AEs [15]. In this JSCT-MM12, 3 g/m^2 CY was administered and severe AEs (grade 3/4: anorexia, nausea, and vomiting) were reduced compared with the treatment where 4 g/m^2 was administered. No patients in the 3 g/m^2 group withdrew due to AEs. However, the number of CD34-positive cells harvested with 3 g/m^2 CY (median: 3.54×10^6 cells/kg) was lower than that with 4 g/m^2 CY (median: 6.87×10^6 cells/kg) [15]. Eight out of 54 patients were required for the second cytapheresis and 3 patients withdrew due to poor mobilization. A recent report suggested that bortezomib could promote stem cell egress and

bortezomib-based PBSC mobilization had a higher yield of CD34-positive cells [35]. BTZ + CY could be effective for collecting sufficient CD34-positive cells. Thus, a further trial was planned in the JSCT-MM14 protocol.

This study revealed safety and feasibility of the B-HDM/ASCT treatment. Engraftment was not affected by adding BTZ. However, no significant improvement was observed in CR/sCR rates for the JSCT-MM12 (data not shown) after ASCT, compared with those for JSCT-MM10. This suggested that the unsuppressed residual MM cells could grow rapidly, compared with the IFM report that BTZ after ASCT suppressed the proliferation [23]. Further study is required to confirm the efficacy of adding BTZ after ASCT.

We achieved good responses after the VTD consolidation therapy. Interestingly, the response continuously increased throughout the treatments. This observation suggested that a sequential treatment approach incorporating BTZ-based therapies for induction, pre-transplant conditioning, and post-transplant consolidation could improve overall response rates after ASCT. This was consistent with GIMEMA trial [2] and the IFM's retrospective study [36]. Three patients (one case with PD and two cases with VZV infection) withdrew during VTD consolidation therapy, and the patients with VZV infection did not receive prophylactic antiviral drug. The fact that patients tolerated well to the toxicities from the VTD consolidation therapy also supported the feasibility and efficacy of the treatment in Japanese patients.

Consistent with previous studies [6, 13, 14, 27], LEN maintenance therapy increased the CR rate while maintaining tolerability in this study, although a few patients were required for dose modification or discontinuation of LEN, or showed secondary primary cancer development. Recently, meta-analysis demonstrated a significant OS benefit and confirmed the benefits of PFS with LEN maintenance after ASCT in NDMM [37]. In many randomized controlled trials for NDMM, LEN maintenance was continued until PD. However, duration of maintenance therapy requires additional considerations and trials for standardizing a treatment procedure.

This study demonstrated the high CR/sCR rates after VTD consolidation, good PFS and OS at 3 years, which were 52, 64, and 88%, respectively. Cavo et al. reported that CR rates, 3-year PFS and OS after VTD induction therapy followed by ASCT and VTD consolidation therapy in GIMEMA trial, were 49, 68, and 88%, respectively [2]. These results indicated VCD induction followed by ASCT and VTD consolidation was feasible in NDMM. Although we aimed to intensify the JSCT-MM10 protocol in this study, no significant improvement was observed in CR/sCR rates (52% [95% CI 39–64%] versus 47.3% [95% CI 31.0–64.2%]), 2-year PFS (77% [95% CI 64–85] versus 76.3% [95% CI 59.4–86.9%]) and OS (97% [95% CI 88–99%] versus 92.1% [95% CI 77.4–97.4%]). The reason why the PFS and OS of JSCT-MM12 was not improved compared with that of JSCT-MM10 may be that the CR/sCR rate after LEN maintenance of JSCT-MM12 was poorly improved compared with JSCT-MM10 (56% vs. 52.6%). We speculate that failure to achieve CR/sCR after consolidation by the intensified regimen such as JSCT-MM12 may be difficult to achieve CR/sCR after LEN maintenance.

Chromosomal abnormalities could play an important role for prognosis. FISH techniques, focusing on identified plasma cells, revealed that some specific abnormalities indicated distinct poor outcomes [38, 39]. In our results, patients with high-risk cytogenetics, such as *t*(4;14), *t*(14;16) or del(17p) showed poorer outcomes than standard-risk patients. Similar results were obtained from patients with *t*(4;14) alone (data not shown). It was generally suggested that BTZ-based regimens might improve treatment outcomes in patients with *t*(4;14) [40, 41] Some reports indicated that patients with 1q gain or del(1p32) at *t*(4;14) had poor prognosis [42, 43]. Although we did not evaluate 1q gain and del(1p32) in this study, these cytogenetic profiles could have some influence on the prognosis. The treatment outcomes of high-risk group were not improved by intensifying the BTZ-based regimen. Recent reports suggested that employing LEN + BTZ + DEX (RVD) for consolidation and maintenance treatments after ASCT might improve PFS in high-risk group [44, 45]. There were also a few favorable outcome reports using next-generation novel agents in high-risk group [46–48].

In conclusion, we demonstrated the efficacy and safety of sequential treatment strategy on VCD induction, B-HDM/ASCT, and VTD consolidation followed by LEN maintenance in transplant-eligible NDMM. The treatment outcomes of the JSCT-MM12 were not superior to those of the JSCT-MM10. A further study incorporating RVD and next-generation novel agents is expected to improve prognosis of NDMM, especially for high-risk group.

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Compliance with ethical standards

Conflict of interest Kazutaka Sunami received research funding from Ono Pharmaceutical, MSD, Celgene, Abbvie, Takeda pharmaceutical, Sanofi, Bristol-Myers Squibb, Daiichi Sankyo, Janssen, Novartis, Alexion Pharma and GlaxoSmithKline, and received honoraria from Ono Pharmaceutical, Celgene, Takeda Pharmaceutical, and Bristol-Myers Squibb. Morio Matsumoto received honoraria from Janssen, Celgene and Ono Pharmaceutical. Shin-ichi Fuchida received honoraria from Takeda Pharmaceutical. Hiroyuki Takamatsu received honoraria from Janssen and Celgene. Toru Kiguchi received research funding from Daiichi Sankyo, Bristol-Myers Squibb, Otsuka Pharmaceutical, Kyowa Hakko Kirin, MSD, Astellas, Nippon Shinyaku, Novartis, Sumitomo Dainippon, Janssen, Celgene, Symbio Pharma-

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