Post-transplantation Consolidation and Maintenance Therapy with Lenalidomide for Japanese Patients with Multiple Myeloma

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Abstract. *Background: Post-autologous stem cell transplantation (ASCT) consolidation and maintenance therapies in multiple myeloma (MM) have recently been the central focus of studies. However, there have been no reports of Japanese patients with MM treated with post-ASCT consolidation/maintenance therapies. Patients and Methods: We retrospectively evaluated eight Japanese patients with newly-diagnosed symptomatic MM who received ASCT after high-dose melphalan, and three to four courses of bortezomib-plus-dexamethasone and two courses of lenalidomide-plus-dexamethasone followed by maintenance lenalidomide for 6-24 months. Results: Four patients achieved complete response (CR) after ASCT, and five patients (63%) achieved stringent CR after the consolidation and maintenance therapy; two out of these five were in molecular CR. At the median follow-up of 38 months, all patients were alive and only one patient had disease progression following post-ASCT therapy. Conclusion: Post-ASCT consolidation and maintenance therapy using lenalidomide may be effective in the treatment of Japanese patients with MM.*

Prognosis for multiple myeloma (MM) is dramatically improved since autologous stem-cell transplantation (ASCT) in conjunction with new therapeutics such as bortezomib, thalidomide, and lenalidomide are implemented. However, MM is an incurable disease, and relapse following ASCT is the main cause of death. Therefore, consolidation and the maintenance of response have been the central focus of current studies. A study conducted by the Intergroupe Francophone du Myelome (IFM) showed that progression-free survival (PFS) was significantly improved by lenalidomide-plus-dexamethasone (RD) consolidation and lenalidomide maintenance therapy (1). The Cancer and Leukemia Group B (CALGB) revealed that both PFS and overall survival (OS) were significantly improved by lenalidomide maintenance therapy (2). In addition, a study conducted at the Dana-Faber Cancer Institute (DFCI) reported high tolerability and efficacy of lenalidomide-bortezomib-dexamethasone (RVD) therapy for the treatment of newly-diagnosed myeloma (3). At present, the IFM and DFCI groups are performing a phase III clinical study to establish the efficacy of RVD induction and consolidation followed by lenalidomide maintenance therapy in patients with newly diagnosed MM. However, there have been no reports of Japanese patients with MM who were treated with high-dose chemotherapy and ASCT followed by consolidation and maintenance therapies. In the present study, we retrospectively analyzed the outcome of consolidation with RD followed by maintenance with lenalidomide after ASCT and bortezomib-dexamethasone (VD) therapy in Japanese patients with MM.

Patients and Methods

A total of 29 Japanese patients with newly-diagnosed symptomatic MM underwent ASCT between January of 2006 and June of 2012, and we started this post-ASCT consolidation and maintenance therapy from May of 2008 after the approval of the study protocol by the Institutional Review Board of NTT WEST Kanazawa

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Table I. *Patients' characteristics*.

Patient number	Age	Gender	Type	D-S, ISS	Chromosome G-band; FISH*	Therapy	MRD in autograft by patient-specific PCR	Post-ASCT response	Post-consolidation & maintenance treatment response	Disease progression (days)	Follow-up time post-ASCT (days)	Adverse effects during consolidation & maintenance treatment
1	58	F	IgG-κ, BJP-κ	IIIA, I	46, XX; ND	VAD#3→CY→ Mel 200 ASCTx2→ VD1#4→ RD#2→R#18	NA	VGPR	sCR	–	2619	PN (G2), AST/ALT (G2), anemia (G2)
2	55	M	IgG-λ	IIIA, I	46, XY; ND	VAD#3→CY→ Mel 200 ASCTx2 →VD1#4→ RD#2→R#24	+	CR	sCR (mCR)	–	2202	non
3	60	F	BJP-κ	IIIA, II	complex*; ND	VAD#3→CY→ Mel 200 ASCT→VD1#4→ RD#2→R#6	NA	CR	sCR	–	2041	neutropenia (G4), anemia (G3), PN(G3), rash (G1)
4	57	F	BJP-κ	IA, I	46, XX; non	VAD#2→VD2#3→ Mel 200 ASCT→ RD#2→R#6	NA	VGPR	VGPR	–	1390	PN (G2)
5	51	M	BJP-κ	IIA, I	46, XY; ND	D#1→VD2#4 →CY→Mel 200 ASCT→ RD#2→R#22	–	VGPR	VGPR	–	872	PN (G2), neutropenia (G3), leukocytopenia (G2)
6	57	M	BJP-λ	IIIA, I	46, XY; non	D#1→VD2#4→ RD#1→CY→ Mel 200 ASCT→ RD#2→R#17	+	sCR	sCR (mCR)	–	690	rash/ desquamation (G1)
7	61	F	IgG-λ	IIIA, II	complex**; t(4;14)	D#1→VD2#4→ CY→Mel 200 ASCT→ RD#2→R#6	+	VGPR	VGPR	312	606	non
8	40	F	BJP-κ	IA, I	46, XX; non	D#2→VD2#1→ VCD#3→Mel 200 ASCT→ RD#2→R#6	NA	sCR	sCR	–	445	non

D-S, Durie-Salmon classification; ISS, International Staging System; FISH*, high-risk cytogenetics [any of t(4;14), t(14;16), or del (17p)]; complex*, 46, XX, add(1)(q32), add(1)(q42), del(13)(q12q22), add(14)(q32); complex**, 44, X, -X, der(8;21)(q10;q10), -13, -14, der(21)t(1;21)(q12;p13), +der(?)t(?;1)(?;q12), +mar1; ND, not done; ASCT, autologous stem cell transplantation; Mel 200, melphalan 200 mg/m^2; VAD, vincristine (0.4 mg/d continuous infusion; days 1-4 of a 28-day cycle), doxorubicin (9 mg/m^2/d continuous infusion; days 1-4 of a 28-day cycle) plus dexamethasone (40 mg/d; days 1-4 and 9-12 and 17-20 of a 28-day cycle); CY, cyclophosphamide (4 g/m^2); D, dexamethasone (40 mg/d x 4-12); VD1, bortezomib (0.7-1.3 mg/m^2/d weekly *i.v.* infusion for four out of five weeks) plus dexamethasone (40 mg/d weekly for four out of five weeks); VD2, bortezomib (1.0-1.3 mg/m^2/d *i.v.* infusion; days 1, 4, 8, and 11 of a 21-day cycle) plus dexamethasone (20-40 mg/d; days 1-4 and 8-11 of a 21-day cycle);VCD, bortezomib (1.0 mg/m^2/d *i.v.* infusion; days 1, 8, 15, 22 of a 35-day cycle), cyclophosphamide (350 mg/m^2/d *p.o.*; days 1, 8, 15 of a 35-day cycle) plus dexamethasone (20 mg/d *p.o.*; days 1, 8, 15, 22 of a 35-day cycle); RD, lenalidomide (10-25 mg/d for three of four weeks) plus dexamethasone (40 mg/d weekly for four of four weeks) ; R, lenalidomide (5 mg/2 d or 5-10 mg/d for three of four weeks); MRD, minimal residual disease; NA, not applicable; +, positive; –, negative; CR, complete response; VGPR, very good partial response; sCR, stringent CR; mCR, molecular CR; PN, peripheral neuropathy; AST, aspartate aminotransferase; ALT, alanine aminotransferase; G, grade; #, number of performed therapies.

Hospital (Approval number H20-1). The eight Japanese patients (3 men and 5 women; median age at ASCT=57 years; age range=40-61 years) with newly-diagnosed symptomatic MM underwent ASCT between July of 2006 and June of 2012 (Table I). MM diagnosis was made according to the International Myeloma Working Group (IMWG) criteria (4) and response to therapy was assessed by International Uniform Response Criteria (5). Molecular complete response (mCR) was defined by at least two consecutive negative results at more than six-month intervals by polymerase chain reaction (PCR) with patient-specific primers. PCR using patient-specific primers was performed as described elsewhere (6). The sensitivity of this patient-specific PCR was 0.01%-0.001% and no false-positives were detected with DNA from normal tonsil cells of healthy donors. Patient-specific primers were designed for four patients (no. 2, 5, 6 and 7). In the present study, we investigated the efficacy of and tolerability to

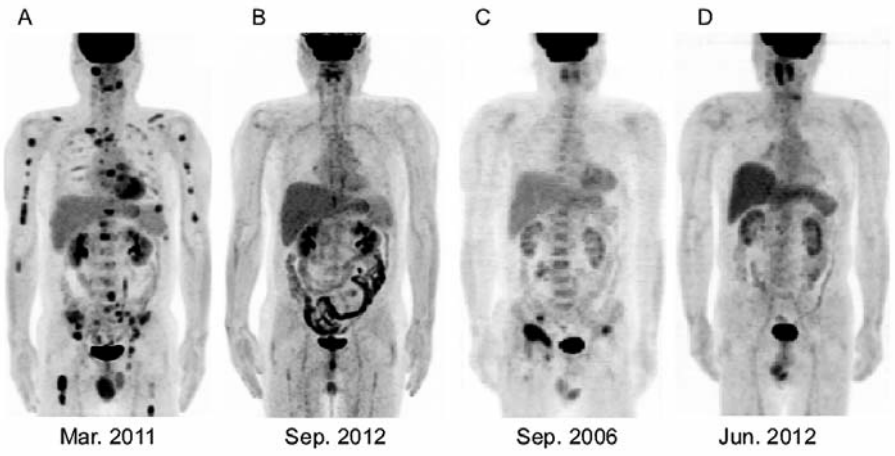

Figure 1. *Maximum-intensity projection images of whole body ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) of two patients with multiple myeloma: Patient 6 at diagnosis (A) and post-consolidation and maintenance therapy (B); patient 2 at diagnosis (C) and post-consolidation and maintenance therapy (D). All multiple ^{18}F- FDG uptake areas disappeared completely after the therapy in patient 6, and these in the pelvic regions responded well after the therapy in patient 2.*

lenalidomide consolidation and maintenance therapy after ASCT and VD therapy in Japanese patients with MM.

All patients achieved at least a very good partial response after high-dose melphalan-based therapy (melphalan 200 mg/m^2) and ASCT with peripheral blood stem cell (PBSC) support (Table I). PBSCs were collected after administration of high-dose cyclophosphamide (4 g/m^2) and granulocyte-colony stimulating factor (G-CSF) except that PBSCs were collected using only G-CSF in two (no. 4 and 8) out of eight patients. Patients underwent a single ASCT with PBSC support, except for tandem ASCT in two patients (no. 1 and 2). Consolidation and maintenance therapy consisted of four courses of bortezomib (0.7-1.3 mg/m^2/d weekly *i.v.* infusion for four out of five weeks) plus dexamethasone (40 mg/d weekly for four out of five weeks) and two courses of lenalidomide (10-25 mg/d for three out of four weeks) plus dexamethasone (40 mg/d weekly for four out of four weeks) followed by lenalidomide (5-10 mg/d for three out of four weeks for 6-24 months) in three patients who received vincristine, doxorubicin, and dexamethasone (VAD) induction therapy (7). In five patients who received bortezomib (1.0-1.3 mg/m^2/d *i.v.* infusion; days 1, 4, 8, and 11 of a 21-day cycle) plus dexamethasone (20-40 mg/d; days 1-4 and 8-11 of a 21-day cycle) induction therapy and one patient who received bortezomib (1.0 mg/m^2/d *i.v.* infusion; days 1, 8, 15, 22 of a 35-day cycle), cyclophosphamide (350 mg/m^2/d *p.o.*; days 1, 8, 15 of a 35-day cycle) plus dexamethasone (20 mg/d *p.o.*; days 1, 8, 15, 22 of a 35-day cycle), consolidation and maintenance therapy consisted of two courses of lenalidomide (25 mg/d for three out of four weeks) plus dexamethasone (40 mg/d weekly for four out of four weeks) followed by lenalidomide (5 mg/2 d or 5-10 mg/d for three out of four weeks for 6-22 months). Consolidation and maintenance therapy was started at day 30 or later post-ASCT. All patients were given antiviral prophylaxis and aspirin to prevent thrombosis. PFS was defined as the survival period from ASCT until relapse or death from any cause; OS was calculated from the time of ASCT, and the median follow-up period was 38 months. The main study endpoints were post-maintenance therapy response, PFS and OS.

Results

Consolidation and maintenance therapy was associated with various grade 1-3 non-haematological toxicities. These toxicities included peripheral neuropathy (4/8 patient), alanine transaminase and aspartate transaminase elevation (1/8 patients), and skin rash (2/8). One patient (no. 3) developed grade 3 peripheral neuropathy, which required temporary cessation of bortezomib. Grade 3/4 neutropenia occurred in 2/8 patients, but no episodes of febrile neutropenia were observed. Grade 2/3 anemia occurred in 2/8 patients, which resolved rapidly without transfusion. None of the patients developed varicella zoster virus infection or venous thromboembolism. Two patients (no. 3 and 4) discontinued the lenalidomide maintenance therapy due to their wishes. There were no signs of secondary malignancies during the follow-up period of between 15 and 87 months. Minimal residual disease in autograft was positive in 3/4 patients by PCR using patient-specific primers. Four out of eight patients achieved CR after ASCT. These four patients, as well as one out of the four non-CR patients, also achieved stringent CR after ASCT at the completion of consolidation and maintenance therapy, and two (no. 2 and 6) were in molecular CR. The three patients (no. 2, 4 and 6) who had ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) positive lesions before treatment achieved PET-CR after the consolidation and maintenance therapy (Figure 1). At the median follow-up of 38 months (range=15-87 months), all patients were alive and only one patient (no. 7) had disease progression after post-ASCT therapy (Table I).

Discussion

Recently, to achieve deeper response such as immunophenotypic CR and molecular CR, the treatment strategy for transplant-eligible patients with MM has evolved with the use of the novel agents as consolidation and maintenance therapies after ASCT. Cavo *et al*. demonstrated in a randomized phase III study that superior CR/near CR rates and extended PFS were achieved with bortezomib-thalidomide-dexamethasone (VTD) *versus* thalidomide-dexamethasone (TD) as induction therapy and consolidation after double ASCT for newly-diagnosed patients with MM (8). Furthermore, Ladetto *et al*. investigated how detection of minimal residual disease by qualitative and real-time quantitative PCR influenced the prognosis of patients with MM who received a post-ASCT consolidation regimen including VTD. Among 31 patients who received four VTD courses, one (3%) achieved molecular CR after ASCT, and six (18%) after VTD; no patients in molecular CR relapsed during the median follow-up of 42 months (9). The IFM 2008 study also showed that RVD consolidation and lenalidomide maintenance therapy after ASCT extended remission and was well tolerated by patients with *de novo* MM (10). Several clinical trials are currently underway to confirm this finding [*e.g*. IFM/DFCI 2009 (ClinicalTrials.gov Identifier: NCT01191060), Hovon-95/EMN02 (ClinicalTrials.gov Identifier: NCT01208766), and BMT CTN0702 (ClinicalTrials.gov Identifier: NCT01109004]. Because the RVD regimen used in the IFM 2008 study induced grade 3/4 neutropenia in 43%, grade 3/4 thrombocytopenia in 10%, and varicella zoster virus infection in 10% of the patient population. Since the RVD regimen is difficult to use in some countries, such as Spain and Italy, due to limitations imposed by healthcare insurance systems, the sequential two-drug regimen (*e.g*. VD and RD) used in this study may be as equally effective as the RVD regimen. According to the high positive rate of minimal residual disease in autograft in this study, it is crucial to administer post-ASCT consolidation and maintenance therapy in order to achieve molecular CR and long-term disease-free survival. Our consolidation and maintenance therapy using VD and/or RD, followed by lenalidomide treatment after ASCT, continues to maintain profound remission in seven out of eight patients with MM. However, the lower proportion of International Staging System stage I (75%) and stage II (25%) observed in this study group may have affected the treatment outcome. The small-scale clinical results obtained in this study warrant larger-scale prospective studies assessing post-ASCT consolidation and maintenance therapy using bortezomib and lenalidomide in Japanese patients with MM.

Conflicts of Interest

The Authors have no competing financial interests.

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