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Maintenance Therapy With Bortezomib and Dexamethasone for Transplant-ineligible Patients With Multiple Myeloma

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Abstract. *Background/Aim: Here, we investigated whether bortezomib as a maintenance therapy affected outcomes in transplant-ineligible patients with multiple myeloma (MM). Patients and Methods: Following induction therapy with bortezomib, maintenance therapy with bortezomib (1.3 mg/m^2) and dexamethasone (20 mg) was administered once or twice every 4 weeks until disease progression. The endpoints of this study were time to next treatment and overall survival. Results: Seventy-six newly diagnosed, transplant-ineligible patients were treated with a bortezomib-based regimen; 28 discontinued induction therapy, 27 did not receive maintenance therapy after induction therapy (the non-maintenance group), and 21 did (the maintenance group). In the three groups, the median times to the next required treatment were 3, 14, and 37 months, respectively. The 3-year overall survival rates were 55%, 69%, and 85%, respectively. There were no significant differences in patient characteristics between the non-maintenance and maintenance groups, except for poorer estimated glomerular filtration rates in the maintenance group. Conclusion: Bortezomib maintenance therapy may be a useful option for transplant-ineligible patients with MM.*

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Key Words: Multiple myeloma, bortezomib, maintenance therapy, prognosis.

Bortezomib, a first-in-class proteasome inhibitor, was approved for relapsed/refractory multiple myeloma (RRMM) in October 2006. In Japan, it has also been used to treat untreated MM since December 2011. The Assessment of Proteasome Inhibition for Extending Remissions trial, which assessed the efficacy of bortezomib in patients with RRMM by comparing it with high-dose dexamethasone therapy, demonstrated superior outcomes in the bortezomib-treated group (1). In addition, the Velcade as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone (VISTA) study, which compared melphalan plus prednisolone (previous first-line treatment) alone and with bortezomib, showed that the initial use of bortezomib improved progression-free survival and overall survival (OS) of transplant-ineligible patients with newly diagnosed MM (2). Induction therapy with a bortezomib-containing regimen is also highly effective for transplant-eligible patients and is recommended as a first-line treatment in this setting (3). Thus, bortezomib-based therapy has been established for patients with MM regardless of treatment setting, and it is widely used in clinical practice. However, MM remains incurable, and relapse is difficult to avoid despite the advent of novel agents. Therefore, maintenance therapy has been attempted in patients treated according to the VISTA trial protocol or with autologous hematopoietic stem cell transplantation (ASCT). Two phase III clinical trials, HOVON-65/GMMG-HD4 and

GEM05MENOS65, investigated bortezomib maintenance therapy post ASCT (4). These trials compared bortezomib and thalidomide (HOVON-65/GMMG-HD4), and bortezomib plus thalidomide, single-agent thalidomide, and interferon therapy (GEM05MENOS65), with both trials reporting that bortezomib-containing maintenance therapy significantly prolonged progression-free survival (5, 6). Several trials on bortezomib maintenance therapy have been conducted in transplant-ineligible patients; however, the GIMEMA-MM-03-05 trial is the only study to compare maintenance therapy with and without bortezomib (7). This study compared bortezomib combined with melphalan, prednisolone and thalidomide therapy with bortezomib with melphalan and prednisolone therapy without maintenance therapy. However, the induction therapy differed between the groups, and thalidomide was used concomitantly as a maintenance therapy. Although a small prospective trial that evaluated maintenance therapy with bortezomib alone in transplant-ineligible patients newly diagnosed with MM has already been published (8), it is difficult to interpret treatment efficacy because the study was single-arm and contained no comparative data. To date, there have been no controlled studies on the efficacy of bortezomib maintenance therapy in transplant-ineligible patients. Importantly, patients with MM tend to be frail because of bone lesions, severe renal impairment, and reduced daily activities due to older age, and most patients are not candidates for the clinical studies described above. In this retrospective study, we investigated the efficacy of bortezomib maintenance therapy in transplant-ineligible patients in clinical settings.

Patients and Methods

Patients. We retrospectively analyzed the medical records of patients with MM who were initially treated at Nihon University Itabashi Hospital between September 2011 and September 2019. Patients who were able to complete the initially planned bortezomib-containing regimen for ≥24 weeks were allocated to the treatment completion (TC) group and those who were unable to comprised the treatment interruption (TI) group. The TC group was further stratified into bortezomib maintenance and non-maintenance groups, depending on whether bortezomib maintenance therapy was administered. The decision to implement maintenance therapy was made by the physician, at the patient's request. This study was conducted in accordance with the Institutional Clinical Research Review Board of Nihon University Itabashi Hospital (identifier: RK-180710-28, approved June 2018, updated June 2020).

Treatment. Newly diagnosed patients with MM treated with a bortezomib-containing regimen as the initial therapy were eligible. The initial treatments comprised bortezomib plus dexamethasone (BD), cyclophosphamide plus BD, and melphalan and prednisolone plus bortezomib regimens (9-11). While combination therapies including alkylating agents were allowed, regimens involving lenalidomide or other novel agents were excluded. Bortezomib was administered intravenously until the approval of subcutaneous administration in December 2012 (12). In the BD, and cyclophosphamide plus BD therapies, bortezomib was administered on days 1, 4, 8, and 11 every 3 weeks and days 1, 8, 15, and 22 days every 5 weeks, respectively. Dexamethasone was administered orally at 20 mg/day on the same days as bortezomib injection, and treatment doses were adjusted according to the patient's condition. Patients who received a single course of high-dose dexamethasone therapy before bortezomib administration were included. Patients who were considered transplant-eligible at the time of diagnosis but were unable to receive ASCT due to insufficient mobilization of peripheral blood stem cells were also included. Maintenance therapy consisted of the same dose of BD, and it was administered weekly (four times every 5 weeks), biweekly, or monthly until disease progression.

Assessment for treatment response. Treatment response was assessed according to the International Myeloma Working Group criteria and classified into very good partial remission, partial remission, and stable disease (13). As the immunofixation method for the detection of M-protein was unavailable until 2016, we did not assess the achievement of complete remission. However, the serum free light chain (sFLC) ratio was routinely evaluated.

Study endpoints. The time to next treatment (TNT) was defined as the time from the start of the bortezomib-containing regimen to the start of the next therapy, death by any cause, or the final date of observation without administration of subsequent MM therapy. Furthermore, OS was defined as the time from the start of the bortezomib-containing regimen to the date of death or final confirmation of survival.

Statistical analysis. Fisher test and one-way analysis of variance were used to compare probabilities and variables between the maintenance and non-maintenance groups. TNT and OS were estimated using the Kaplan–Meier method, and statistical significance was evaluated using the log-rank test. EZR (Saitama Medical Center, Jichi Medical University, Japan), a graphical user interface for the R programming language (The R Foundation for Statistical Computing), was used for these analyses (14).

Results

Patients. The characteristics of the patients enrolled in this study are shown in Table I. There were 76 eligible patients; their median age was 70 years, and 39 were men. Induction therapy was based on BD in 66 patients, and an alkylating agent was added to the regimen of 10 patients at the start of therapy and nine patients thereafter. The TI group comprised 28 patients with treatment interruption due to complications, adverse drug events, treatment resistance, disease progression, or death. Of the 48 patients who completed the planned induction therapy (the TC group), 21 received maintenance therapy and 27 did not. As maintenance therapy, bortezomib was administered to two, 15, and four patients weekly, biweekly, and monthly, respectively.

Outcomes. As shown in Figure 1A, the median TNT for the entire cohort was 10 months, and it was significantly better in the maintenance group than in the others (Figure 1B). The

Table I. *Baseline characteristics of the patients enrolled in this study (n=76).*

Characteristic	Value
Age, years	
Median (range)	70 (36-83)
Gender, n (%)	
Male	39 (51.3)
Hb, g/dl	
Median (range)	9.55 (5.0-15.2)
Corrected calcium, n (%)	
<11.5 mg/dl	69 (90.8)
≥11.5 mg/dl	4 (5.3)
Missing data	3 (3.9)
Immunoglobulin subtype, n (%)	
IgG	37 (48.7)
IgA	20 (26.0)
IgM	1 (1.3)
IgD	1 (1.3)
Light chain only	16 (21.1)
Non-secretory	1 (1.3)
eGFR, n (%)	
≥40 ml/min/1.73 m^2	48 (63.2)
<40 ml/min/1.73 m^2	28 (36.8)
International Staging System classification, n (%)	
I	19 (25.0)
II	20 (26.3)
III	30 (39.5)
Missing data	7 (9.2)
Initial therapy, n (%)	
BD	66 (86.8)
BCD	9 (11.8)
MPB	1 (1.3)
Cytogenetics (available only), n (%)	
CCND1	7 (9.2)
FGFR3	2 (2.6)
MAF	0 (0)
P53	6 (7.9)
Chr 13 deletion	6 (7.9)
Observation period, months	
Median (range)	24 (1-97)

BCD: Cyclophosphamide plus bortezomib plus dexamethasone; BD: bortezomib plus dexamethasone; CCND1: cyclin D1; eGFR: estimated glomerular filtration rate; FGFR3: fibroblast growth factor receptor 3; MAF: v-maf musculoaponeurotic fibrosarcoma oncogene homolog; MPB: melphalan and prednisolone plus bortezomib.

median TNT was 3 months for the TI group, 14 months for the non-maintenance group, and 37 months for the maintenance group ($p<0.0001$ among the three groups; $p=0.0063$ between the non-maintenance and maintenance groups). The 3-year OS for the entire cohort was 68% (Figure 2A), and it was also significantly better for the maintenance group (85%) than for the TI (55%) and non-maintenance (69%) groups ($p=0.0153$ among the three groups; $p=0.0194$ between the non-maintenance and maintenance groups, Figure 2B). Furthermore, we investigated whether there were any differences in patient characteristics between the groups (Table II). However, there were no significant differences in patient age, sex, hemoglobin level, corrected calcium, immunoglobulin subtype, International Staging System classification, and cytogenetic abnormalities (detected by fluorescence *in situ* hybridization) between the non-maintenance and maintenance groups. Furthermore, myeloma cell expression of mature plasma cell 1 and CD45 antigen, both of which influence TNT in patients treated with bortezomib (15), did not significantly differ. However, patients with a poor estimated glomerular filtration rate were more frequent in the maintenance group ($p=0.0383$).

Cause of treatment cessation and response to bortezomib therapy. We assessed the cause of treatment cessation in the TI group and response to therapy in the non-maintenance and maintenance groups. The causes of treatment cessation in the TI group were treatment resistance in 18, death in six, adverse events in three (two with neuropathy and one with infection), and at the patient's request in one. As shown in Table III, there were no significant differences in treatment response between the non-maintenance and maintenance groups, but it tended to be better in the latter group. In the non-maintenance group, 17 patients proceeded to the subsequent therapy and two died after treatment completion. In the maintenance group, 11 patients proceeded to the subsequent therapy and 10 were on bortezomib as maintenance therapy. Importantly, bortezomib maintenance therapy was tolerated by all patients, and none discontinued treatment due to adverse events. Furthermore, among 11 patients who did not achieve normalization of the sFLC ratio during the induction therapy, four finally reached a normal level of the sFLC ratio during the maintenance therapy.

Discussion

Several studies have reported that the introduction of novel agents for MM, such as bortezomib, has improved patient prognosis (16-18). In particular, based on the results of the VISTA study, induction therapy with a bortezomib-containing regimen is recommended for transplant-ineligible patients (3). However, evidence regarding the efficacy of maintenance therapy after bortezomib-based induction therapy remains insufficient. In this study, conducted in transplant-ineligible patients, bortezomib maintenance therapy after the completion of induction therapy with the same drug significantly prolonged TNT and OS compared with no maintenance therapy, indicating the clinical usefulness of bortezomib maintenance therapy.

MM frequently occurs in elderly individuals and is often accompanied by renal failure or bone lesions, resulting in worsening of the general condition of patients. Because

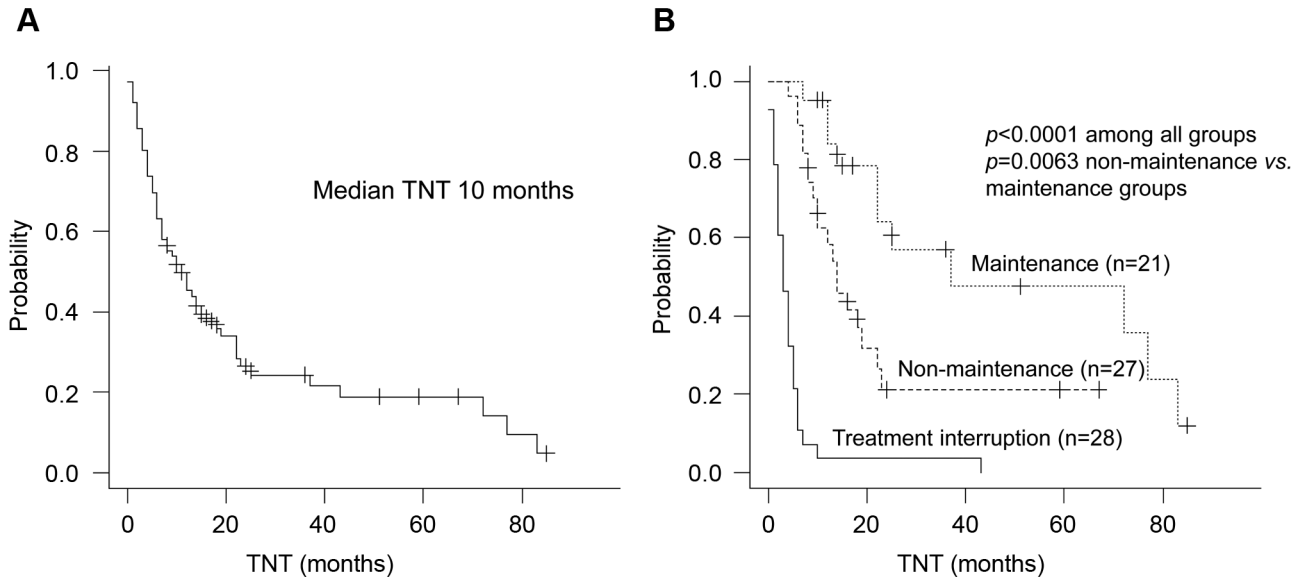

Figure 1. *Kaplan–Meier curves showing the time to next treatment (TNT) for the entire cohort (A) and for the treatment interruption, non-maintenance, and maintenance groups (B).*

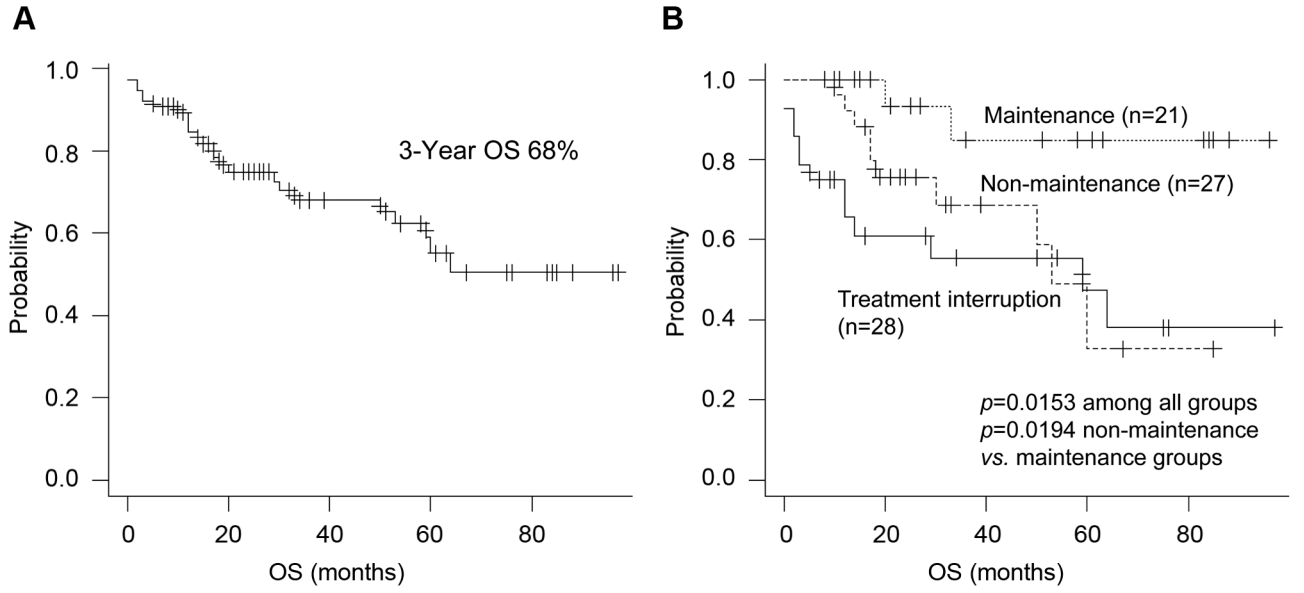

Figure 2. *Kaplan–Meier curves showing the overall survival (OS) for the entire cohort (A) and for the treatment interruption, non-maintenance, and maintenance groups (B).*

patients with severe organ damage or deteriorated general condition are excluded from clinical trials, it is difficult to conclude whether the results of clinical trials can be extended to these patients. Therefore, to more precisely evaluate treatment modalities and clinical outcomes in these patients, retrospective examinations of clinical data are required. As transplant-eligible patients were excluded from our study, our patients may have had worse performance status or more severe organ failure than patients enrolled in clinical trials. Despite this, none of the patients discontinued maintenance therapy due to intolerance, and the major reasons for bortezomib cessation were other events, such as

Table II. *Comparison of patient characteristics at treatment initiation.*

Factor		Maintenance group (n=21)	Non-maintenance group (n=27)	*p*-Value
Age, years	Median (range)	72 (48-88)	70 (58-82)	0.801
Gender, n	Male	11 (52.4)	12 (44.4)	0.772
Hb, g/dl	Median (range)	9.8 (5.3-14.5)	10 (7.5-15.2)	0.832
Corrected calcium, n	<11.5 mg/dl	20	27	0.438
	≥11.5 mg/dl	1	0	
Immunoglobulin subtype, n	IgG	6	14	
	IgA	7	8	
	IgM	0	0	
	IgD	1	0	
	Light chain only	7	5	
	Non-secretory	0	0	
eGFR, n	≥40 ml/min/1.73 m^2	10	21	0.0383
	<40 ml/min/1.73 m^2	11	6	
International Staging System classification, n	I	4	9	0.133
	II	5	9	
	III	10	5	
	Missing data	2	4	
Cytogenetics (available only), n	CCND1	3	2	
	FGFR3	0	2	
	P53	1	1	
	Chr 13 deletion	2	3	
Alkylating agents (during bortezomib therapy), n	Yes	8	5	0.410

CCND1: Cyclin D1; eGFR: estimated glomerular filtration rate; FGFR3: fibroblast growth factor receptor 3; MAF: v-maf musculoaponeurotic fibrosarcoma oncogene homolog. Patients with missing data were excluded from the statistical analysis.

Table III. *Response of patients in the maintenance and non-maintenance groups to bortezomib-based induction therapy.*

Response	Maintenance group (n=21)	Non-maintenance group (n=27)	*p*-Value
Partial response or better, n (%)	19 (90.5)	19 (70.4)	0.088
Very good partial response or better, n (%)	12 (57.1)	8 (29.7)	0.079
Normalization of sFLC ratio, n (%)	9 (42.9)	8 (29.7)	0.362

sFLC: Serum free light chain.

disease progression. These favorable results suggest that long-term bortezomib maintenance therapy is safe for patients who are able to complete bortezomib-based induction therapy, even with poor general health. Bortezomib can be used in patients with renal failure, and is useful for improving renal function and alleviating bone lesions (19, 20). The UPFRONT study, a community-based prospective study for transplant-ineligible patients, examined three different bortezomib-based induction regimens and bortezomib maintenance therapy after the completion of induction. Our observations are consistent with their report that bortezomib maintenance therapy was tolerable, although that study also included patients who did not meet the eligibility criteria of general clinical trials (10). Because switching treatment regimens increases the risk of new adverse drug events, continuous administration of a tolerable and effective drug is a logically conceivable treatment approach. Furthermore, our maintenance therapy was administered with previously reported duration-fixed regimens (4) and was continued until disease progression was detected. The long-term use of an active and tolerable agent may help explain the better treatment results. It should be noted that four patients achieved sFLC normalization during maintenance therapy, implying an additive effect of long-term use of bortezomib. On the contrary, although it was statistically insignificant, the better treatment response to bortezomib therapy in the maintenance group than in the non-maintenance group might have affected the favorable

outcomes in the former group. Recently, Mina *et al*. (21) conducted a phase II trial on RRMM in which patients were randomly assigned to three different strategies: Follow-up only, BD maintenance (administered every 2 weeks), and re-initiation of BD after biochemical relapse (administered weekly). The study showed that the median time to biochemical relapse and OS tended to be longer in the BD maintenance group than in the follow-up group. However, the authors of the study cautioned that the study lacked statistical power because of a protocol amendment due to a limited number of patients and delayed study enrollment. However, it is worth noting that the continuous administration of intermittent BD therapy in their study was safe and effective, which our findings are consistent with.

In this study, the TI group comprised patients who discontinued bortezomib therapy due to the incidence of adverse events such as peripheral neuropathy, despite the drug being effective. Although it has been reported that the evaluation of frailty is essential to determine the optimal dosage of bortezomib (22), frailty at onset was not evaluated in our patients, and most of them received the standard dose of bortezomib (1.3 mg/m^2). Evaluation of frailty to determine the optimal bortezomib treatment intensity may be effective in increasing the probability of patients completing induction therapy. Frailty should be considered at diagnosis, particularly for patients who will be treated with bortezomib-based regimens.

There are some limitations to this study. Firstly, whether the patients received maintenance therapy was based on the physician's discretion and the patient's request. Secondly, this was a single-center retrospective study with a small number of patients, and it lacked a formal evaluation of treatment responses. Thirdly, the treatment regimens were not uniform, with variations in the duration of induction therapy and the use of alkylating agents. Therefore, the efficacy of bortezomib maintenance therapy in clinical practice should be validated in a larger-scale study using a uniform treatment regimen.

Although MM prognosis has continuously improved due to the increased availability of various novel agents, the development of effective and safe treatment options adapted to clinical practice is still warranted. Our results indicate that bortezomib maintenance therapy may be a useful option for improving the prognosis of transplant-ineligible patients with MM in clinical practice.

Conflicts of Interest

NI received honoraria and speaker fees from Bristol-Myers Squibb, Takeda Pharma Co., Ltd., and Ono Parma Co., Ltd. KM received honoraria and speaker fees from Takeda Pharma Co., Ltd., and Ono Parma Co., Ltd. HT, MN, and TH reports honoraria and speaker fees from Bristol-Myers Squibb. YH received speaker fees and honoraria from Janssen Pharmaceutical K.K., Bristol-Myers Squibb, Takeda Pharma Co., Ltd., and Ono Parma Co., Ltd. MT received honoraria from Janssen Pharmaceutical K.K., Bristol-Myers Squibb, Takeda Pharma Co., Ltd., and Ono Parma Co., Ltd.; supports for extension lectures from Bristol-Myers Squibb; and scholarship funds from Takeda Pharma Co., Ltd. and Ono Parma Co., Ltd. Furthermore, MT is a part of an international clinical trial on investigational drug that was developed by Bristol-Myers Squibb for the treatment of Sjögren's syndrome. The remaining co-authors declare no competing financial interests.

Authors' Contributions

YN and NI contributed equally to this study. YN, NI, and TY analyzed and interpreted the results. KM, YH, TN, and MT assisted in interpreting the result. YN, NI, HT, YU, MN, and YH designed the research and wrote the article. YN, NI, HT, YU, MN, TH, KI, TK, KK, TE, and YH collated patient data. All Authors read and approved the final article.

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