Clinical Assessment of Bortezomib for Multiple Myeloma in Comparison with Thalidomide

Mitsutoshi Satoh[*1], Rieko Oguro[1], Chigusa Yamanaka[2], Katsutoshi Takada[2], Yasuhiro Matsuura[3], Toyomi Akiba[2], Nobuyuki Aotsuka[3], Yoshihiro Tani[2] and Hisashi Wakita[3]

[1]Department of Toxicology and Pharmacology, Faculty of Pharmaceutical Sciences, Toho University, 2-2-1 Miyama, Funabashi, Chiba, JAPAN.
[2]Department of Pharmacy, Japanese Red Cross Narita Hospital, 90-1 Iida-cyo, Narita-shi, Chiba, JAPAN.
[3]Department of Hematology and Oncology, Japanese Red Cross Narita Hospital, 90-1 Iida-cyo, Narita-shi, Chiba, JAPAN.

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ABSTRACT – Purpose. We studied the efficacy and safety of bortezomib (BOR) for treatment of multiple myeloma in comparison with thalidomide (THAL) by reference to adverse events, and searched for laboratory markers that could be used for prognostication of patients. **Methods.** Biochemical data of patients receiving BOR and THAL for treatment of multiple myeloma at the Japanese Red Cross Narita Hospital were investigated retrospectively, after obtaining Institutional Review Board approval. Judgment of curative effects complied with the effects criteria of the International Myeloma Working Group (IMWG) [1]. **Results.** BOR showed a higher rate of effectiveness than THAL for refractory multiple myeloma, and its effects were rapid. The overall survival of BOR-treated patients tended to be longer than that of THAL-treated patients. The efficacy of BOR was unrelated to patient age, the number of previous therapeutic regimens, or the disease period. After medication with BOR, patients in whom it had been effective tended to show an increase of the serum alkaline phosphatase (ALP) level. Thrombocytopenia (86.2%) and leucopenia (69.0%) were observed at high frequencies, but no previously unreported adverse events or fatalities were associated with BOR therapy. **Conclusion.** It is suggested that BOR has therapeutic efficacy for multiple myeloma as a first-line medical treatment and/or for patients with THAL resistance, and can improve prognosis and survival. Since serum ALP elevation was observed in many patients for whom BOR was effective, this may be a predictor of BOR efficacy.

INTRODUCTION

Multiple myeloma is a hematopoietic malignancy with a poor prognosis, and for which cure cannot be expected. Although the median survival of affected patients is about 6 to 12 months without treatment, chemotherapy can prolong survival up to about three years, the 5- and 10-year survival rates being about 25% and less than 5%, respectively [2]. Melphalan–prednisone (MP) consolidation therapy as a standard treatment for multiple myeloma is now the first choice. As the efficacy of vincristine – adriamycin–dexamethasone (DEX) (VAD) consolidation therapy and DEX high-dose therapy provide immediate, but transient, effects, they are generally used for emergency situations. High-dose chemotherapy with autologous stem-cell transplantation is also a more effective first-line treatment than standard chemotherapy in terms of response rate and progression-free survival for patients with multiple myeloma who are younger than 65 years of age [3], and it is used as one form of intensive treatment for this group of patients.

Multiple myeloma is an intractable disease characterized by repeated relapses, necessitating repeated treatment that provides only short periods of remission. Since this relapsing and remitting pattern cannot be broken by standard treatment, the development of drugs with new mechanisms of action has been needed in order to increase the choice of treatment further [4]. Bortezomib (BOR), which is a new drug, or thalidomide (THAL), have been compared with DEX high-dose therapy in an international phase III (APEX) trial for multiple myeloma patients who have already received 1 to 3 courses of medical treatment. BOR was found to be

Corresponding author: Dr. Mitsutoshi Satoh, Department of Toxicology and Pharmacology, Faculty of Pharmaceutical Sciences, Toho University. Miyama 2-2-1, Funabashi, Chiba 274-8510, Japan; E-mail: satoh@phar.toho-u.ac.jp

superior to DEX high-dose therapy in terms of response rate, progression-free survival, and overall survival [5].

BOR inhibits proteasomes selectively and reversibly, and exerts its anti-tumor effects by induction of apotosis in tumor cells [6], cell-growth suppression [7], and inhibition of angiogenesis [8]. However, the mechanisms involved have not been clarified completely, and it is reported that the anti-tumor effects of BOR are attributable to multiple mechanisms [9]. In multiple myeloma, proliferation of the myeloma cells is induced by the bone marrow microenvironment and mediated by cytokines and other endogenous substances. BOR inhibits the effects of cytokine release by preventing the activation of nuclear factor-kappa B (NF-k B). In addition, angiogenesis is inhibited through inhibition of VEGF and IL-6, which are produced by vascular endothelial cells of myeloma origin, and indirect anti-tumor effects resulting from gene silencing of RANKL (the receptor activator of the NF-k B ligand: osteoclast differentiation factor), which is an activation factor for osteoclasts, have been reported [10, 11]. Bone pain due to osteolytic lesions is the most frequent and troublesome clinical symptom of multiple myeloma, and is present initially in about 60% of patients. This is attributable to a collapse of bone turnover balance, resulting in accelerated bone resorption and differential inhibition of bone blast cells by osteoclasts. It has been suggested that BOR has an osteoblast activating effect, and that this is not a secondary action of the anti-tumor effect but rather a direct ameliorating effect on osteolytic lesions, resulting in an increase of bone-type ALP, which is a marker of bone formation [12].

BOR, in addition to THAL, is a drug that has brought a significant change to the treatment strategies for multiple myeloma through its multi-mechanism anti-tumor effect and amelioration of osteolytic pathological changes. In the present study, we investigated the response rate, survival period and medical efficacy of BOR in patients with multiple myeloma in comparison with those of patients receiving THAL as a control. Moreover, we searched for clinical factors or laboratory-data markers that might have potential use for prognostication of patients receiving BOR therapy, and evaluated the safety of BOR by investigation of adverse events.

METHODS

1. Patients

Twenty-nine patients with refractory multiple myeloma who were treated with BOR (VELCADE®) at the Department of Hematology and Oncology, Japanese Red Cross Narita Hospital, between October 2005 and November 2008, were surveyed. Moreover, 47 patients (except for seven in whom evaluation of efficacy was not possible) among 54 with refractory multiple myeloma who were treated with THAL at the same department between October 2002 and November 2008, were surveyed as controls.

2. Clinical data

We investigated the following data obtained from the clinical records of hospitalized and outpatients.

2-1. *Patient characteristics*

The age at the start of medication, sex, type of illness, period of illness in the D&S classification [13], the date of diagnosis of multiple myeloma, and the medical history relevant to multiple myeloma were investigated.

2-2. *Dosages*

The doses and administration dates of BOR or THAL and co-administered drugs were investigated.

2-3. *Laboratory parameters*

Leukocyte counts, hemoglobin levels, platelet counts, alkaline phosphatase (ALP), alanine aminotransferase (ALT), serum M protein and urinary protein were investigated.

2-4. *Efficacy evaluation*

The judgment of curative efficacy complied with the effects criteria of the International Myeloma Working Group (IMWG) [1]. In addition, since stringent complete response (sCR) and complete response (CR) could not be judged from the medical records, we used very good partial response (VGPR), partial respose (PR), stable disease (SD) and progressive disease (PD) instead of sCR and CR in the survey.

2-5. *Patient condition after treatment*

Progression-free survival, overall survival, and the subsequent medical treatment protocol were investigated.

2-6. *Adverse events and reasons for withdrawal*
Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events v3.0 (NCI-CTCAE) [14].

3. Statistical analysis
All data were analyzed using Stat View ver 5.0 (SAS Institute, Japan). Frequency analysis was performed using the Pearson X^2 test and Fisher's exact test. One-way analysis of variance and Kruskal-Wallis Statistic test (Scheffe's multiple comparison test) and Mann-Whitney U-test were used to compare the different parametric or nonparametric variables. Differences at $p < 0.05$ were considered to be statistically significant.

RESULTS

1. Patient characteristics
The numbers of patients, and their age, sex, illness type, and periods of BOR and THAL treatment are shown in Table 1. As the patients prescribed BOR included those who had or had not received THAL, in order to separate the effects of BOR, 31 patients excluding 15 who had been prescribed BOR after THAL treatment and one who had been prescribed BOR before THAL treatment were studied. There was no significant difference in patient characteristics between the BOR group and the THAL group.

2. Response rates
In the BOR group (29 patients), VGPR was seen in 4 patients (13.8%), PR in 14 (48.3%), SD in 7 (24.1%), and PD in 4 (13.8%). In the THAL group (31 patients), PR was seen in 11 patients (35.5%), SD in 12 (38.7%), and PD in 8 (25.8%). The BOR group and the THAL group were divided into responders (VGPR and PR) and non-responders (SD and PD), respectively, and the therapeutic effects were compared (Table 2). X^2 test demonstrated a significant difference in the response rate between the BOR group and the THAL group (p=0.039).

3. Period until response of therapeutic effects
In responders (VGPR and PR), the period (days) from start of a drug administration until effectiveness is shown in Table 3 for the BOR and THAL groups. A significant inter-group difference was evident in the period until a therapeutic effect was observed (p=0.029).

4. Effects of BOR on patients with THAL resistance
Previously, DEX high-dose therapy, MP consolidation therapy or ranimustine-vindesine-melphalan-prednisolone (MCNU-VMP) consolidation therapy were performed on patients with recurrent multiple myeloma who were ineligible for THAL therapy. The Kaplan-Meier survival curves of 15 patients who received BOR after THAL, 7 who received BOR-non-containing treatment (DEX high-dose therapy 4 patients, MP consolidation therapy 2 patients, and MCNU-VMP consolidation therapy one patient) and 22 patients who did not receive medical treatment for multiple myeloma are shown in Fig.1. The p value between those untreated and treated with BOR was p=0.072. On the other hand, the p value between those untreated and treated without BOR was p=0.110. Overall survival of the patients treated with BOR tended to be longer than that of those treated without BOR by log-rank test.

Table 1. Baseline characteristics of the patients

	BOR treated	**THAL treated**	***p* value**
Patient Number	29	31	
Age: years old	65.1±10.1	66.8±10.1	0.524
	[65, 44-81]	[68, 33-82]	
Sex: Male / Female	15/14	15/16	0.796
Clinical entity: IgG/IgA/IgD/BJP/NS	1/2/1/7/18	1/4/0/7/19	0.995
Stage: I / II / III	3/3/23	3/4/24	0.659

BOR: bortezomib, THAL: thalidomide, BJP: Bence Jones protein, NS: Non-secretory myeloma, Mean±S.D. [median, minimum-maximum]. Age comparison was carried out by Student's *t* test. Sex, clinical entity and stage analysis were carried out using the $\chi 2$ test.

Table 2. Efficacies of BOR and THAL on multiple myeloma patients.

	BOR treated	THAL treated	*p* value
Responder (VGPR, PR)	62.1%(18/29)	35.5% (11/31)	0.039
Non-responder (SD, PD)	37.9% (11/29)	64.5% (20/31)	

BOR: bortezomib, THAL: thalidomide, VGPR: very good partial response, PR: partial response, SD: stable disease:, PD: progressive disease. $\chi 2$ test.

Table 3. Period until therapeutic effects of BOR and THAL on multiple myeloma patients.

	BOR treated (n=18)	THAL treated (n=11)	*p* value
Duration (days)	52.6±47.3 [40, 13-217]	155.2±125.7 [87, 45-433]	0.029

BOR: bortezomib, THAL: thalidomide, Mean±S.D. [median, minimum-maximum] Student's *t* test.

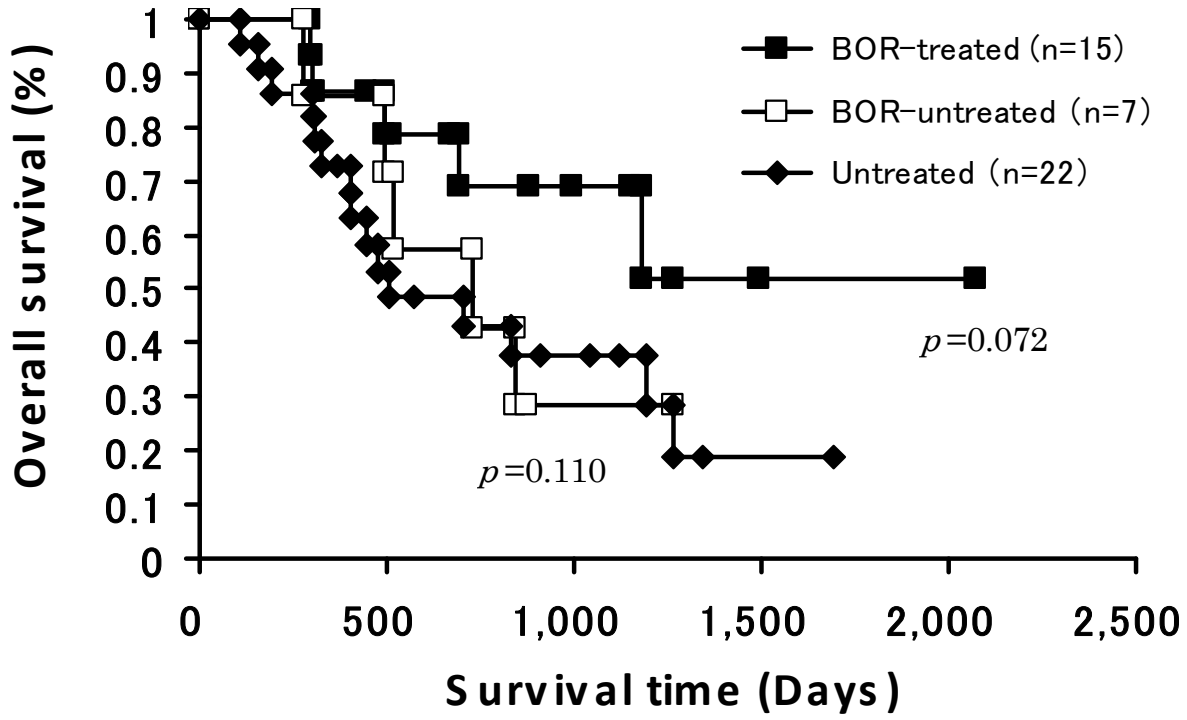

Figure 1. Kaplan-Meier estimates of overall survival for BOR-treated (n=15), BOR-untreated (n=7), and untreated (n=22) multiple myeloma patients after THAL treatment.

5. Age, number of previous regimens, and rate of BOR effectiveness according to disease duration
Age, number of previous regimens, and the rate of BOR effectiveness according to disease duration are shown in Table 4. In general, people who are over 65 years old are classed as being aged, and the mean of the patients in this study was 65 years. Therefore we separated the patients into two groups using an age of 65 years as the cut-off. There are three standardized therapies for multiple myeloma: DEX high-dose therapy, MP consolidation therapy, and MCNU-VMP consolidation therapy, and in addition THAL or lenalidomide can be used. We separated the two patient groups according to which of the three therapies they received. Also, as the mean disease duration in this study was about 3 years, we separated the two groups according to disease duration using 3 years as the cut-off. As no significant differences were evident, it was suggested that the efficacy of BOR was not dependent on patient age, the number of previous regimens, or disease duration.

6. Changes in ALP value in patients with ALP elevation
The efficacy of BOR in the patients who did and did not show ALP elevation is shown in Table 5. Fisher's exact test demonstrated significant differences in the therapeutic effects of BOR between the two patient groups (p= 0.265).

The time courses of the ALP and serum M protein values in a patient who showed ALP elevation and the effects of BOR are shown in Fig. 2. This patient received BOR therapy 3 times, and ALP elevation and a serum M protein decrease were observed each time. The ALP value increased from the baseline (121 U/L) to the peak level (1,018 U/L) at the first BOR treatment.

Table 4. Comparison of BOR efficacy among age, number of previous regimens and disease duration.

Categories		Cases (Total Numbers)	Response percentages (Number)	*p* value
Age	<65 years old	13	61.5% (8)	0.960
	65 years old ≤	16	62.5% (10)	
Number of previous resume	< 3 kinds	14	71.4% (10)	0.333
	3 kinds ≤	15	53.3% (8)	
Disease duration	< 3 years	17	70.6% (12)	0.277
	3 years ≤	12	50.0% (6)	

BOR: bortezomib. Student's t test.

Table 5. Influence of BOR in patients with and without elevation of the ALP level.

	ALP elevation	ALP non-elevation	*p* value
BOR effective (VGPR, PR)	11	3	0.246
BOR no-effective (SD, PD)	7	5	

ALP: alkaline phosphatase, BOR: bortezomib, VGPR: very good partial response, PR: partial response, SD: stable disease, PD: progressive disease. Fisher's exact test.

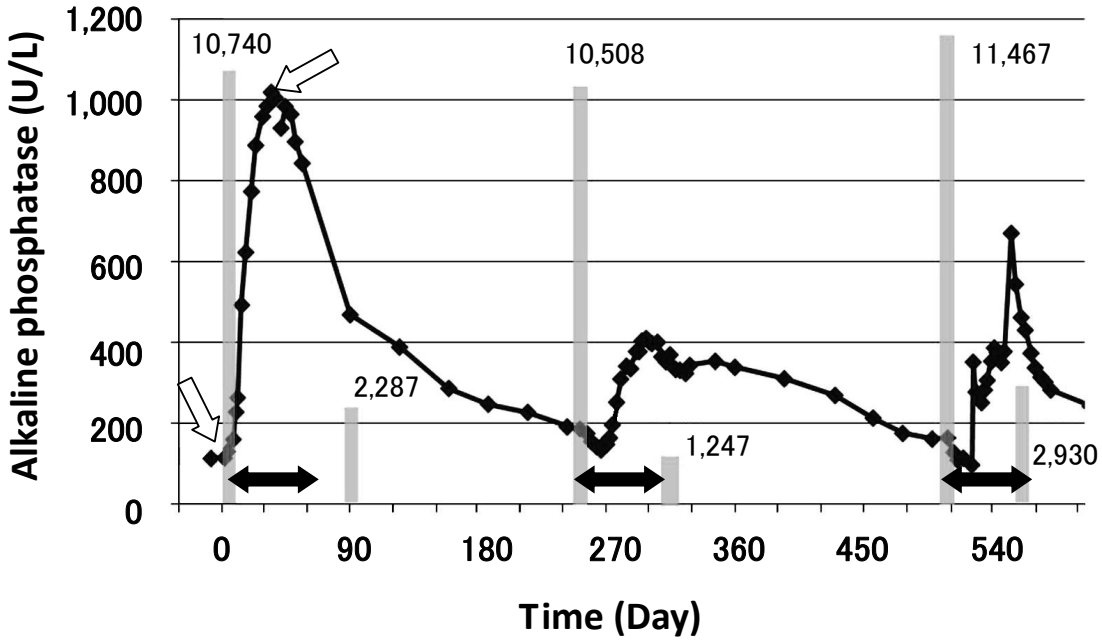

Figure 2. Time courses of ALP and serum M-protein concentrations in a patient for whom BOR was effective. This patient was 68 years old, with an IgG type clinical entity, III stage and PR based on the effects criteria of the IMWG. BOR therapy was administered 3 times. Double arrows represent BOR treatment. Diamonds represent the time course of ALP (U/L) and gray columns represent serum M-protein (mg/L). Clear arrows represent the ALP baseline (121 U/L) and peak level (1,018 U/L) at the first BOR treatment.

7. All adverse events induced by BOR

The types and frequency of the adverse events that occurred in the 29 patients prescribed BOR are shown in Fig.3. Thrombocytopenia occurred in 86.2% (25 patients), leucopenia in 69.0% (20 patients), fever in 55.2% (16 patients), peripheral neuropathy in 48.3% (14 patients), diarrhea in 48.3% (14 patients), nausea and vomiting in 24.1% (7 patients), pulmonary related events in 20.7% (6 patients), constipation in 10.3% (3 patients), rash in 10.3% (3 patients), shingles in 6.9% (2 patients), tumor lysis syndromes in 6.9% (2 patients), and mouth ulcers in 3.4% (1 patient). The grade classification of thrombocytopenia, leucopenia, fever and peripheral neuropathy was performed according to NCI-CTCAE v3.0 [14]. Thrombocytopenia (25 cases) included 3 cases of Grade 1 (12.0%), 8 cases of Grade 2 (32.0%), 8 cases of Grade 3 (32.0%) and 6 cases of Grade 4 (24.0%). Leukopenia (20 cases) included one case of Grade 1 (5.0%), 10 cases of Grade 2 (50.0%), 8 cases of Grade 3 (40.0%) and one case of Grade 4 (5.0%). Fever (16 cases) included 14 cases of Grade 1 (87.5%), and 2 cases of Grade 2 (12.5%). Peripheral neuropathy (14 cases) included 2 cases of Grade 1 (14.3%), 11 cases of Grade 2 (78.6%), and one case of Grade 3 (7.1%).

DISCUSSION

In the present study, the efficacy of BOR was compared with that of THAL, following approval of its use for recurrent and intractable multiple myeloma in Japan in October, 2008. THAL exerts therapeutic effects against multiple myeloma through inhibition of angiogenesis, direct suppression, prevention of stromal adhesion of multiple myeloma cells, and inhibition of cytokine secretion, among other mechanisms [1]. It is reported that about 30% of patients respond to

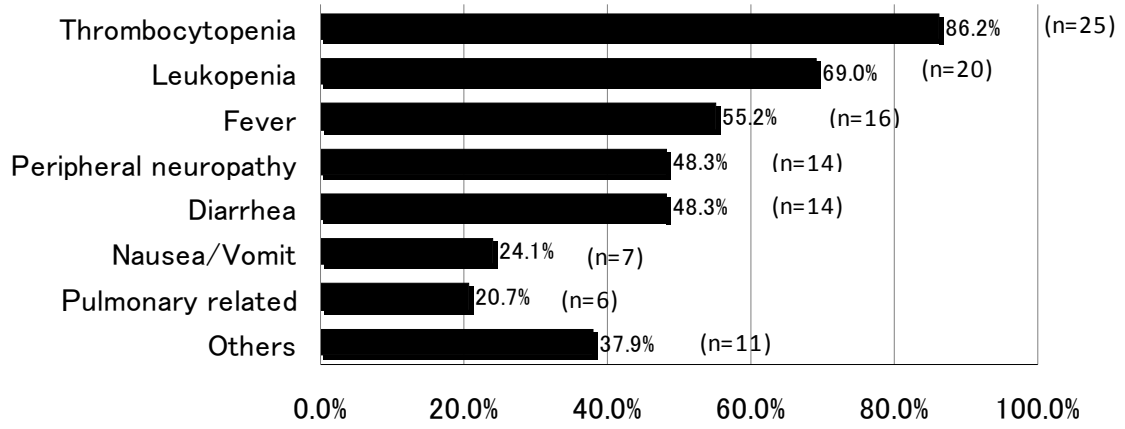

Figure 3. Frequencies of adverse events in BOR-treated patients (n=29).

THAL, whereas concomitant treatment with DEX gives a response rate of about 50% [15]. In the present study, the rate of response to THAL treatment was 35.5%, because the THAL group included patients that had been treated concomitantly with DEX in addition to THAL. On the other hand, the rate of response to BOR was 62.1%, but this included 10 patients who had received DEX concomitantly, and the BOR group had an intentionally high rate of effectiveness compared with the THAL group (Table 2). These results are supported by a meta-analysis of BOR and THAL, which found that the median rate of response to BOR (53%) was better than that (32%) for THAL [16].

Although BOR exerts anti-tumor effects against multiple myeloma cells independently [17], it also had excellent efficacy as a consolidation therapy with other medicines, such as MP consolidation therapy and liposomal doxorubicin [18-20]. In multiple myeloma the bone marrow stromal cells feed nutrient to the myeloma cells, which allows them to acquire resistance to chemotherapy. However, adhesion of myeloma cells to bone marrow stromal cells is inhibited by the action of BOR on the adhesion molecule. This leads to loss of drug resistance, and the myeloma cells regain their sensitivity to chemotherapy. Therefore, a synergistic effect can be expected if BOR is used in combination with other agents [21, 22]. As shown in Table 3, the median period until the appearance of therapeutic effects in the BOR group was about 40 days, whereas that in the THAL group was about 87 days. One explanation for this difference is that during close observation of the effects of THAL and possible adverse events, the dose of THAL is increased gradually from an initial 100 mg to 200 mg [23], whereas BOR is administered at a fixed dose (1.3 mg/m^2) at its introduction. Generally, it is reported that the median period until the appearance of the therapeutic effect of BOR is six weeks [24], whereas that for THAL is three months [25]. Thus, BOR yields prompt therapeutic effects.

Because two of the 29 patients in the BOR groups showed disease progression after initial improvement, retreatment with BOR was performed. The period until retreatment was 9 months in one patient, whereas the other received retreatment at 7 months followed by a second course of retreatment 7 months later. Retreatment with BOR was effective in these two patients. It has been reported that the effectiveness rate of BOR retreatment is 50%, and that the median period until retreatment is 5.1 months [26]. The effectiveness rate of BOR retreatment is also high for patients who show a good response to the initial medication [27]. Moreover, within one year after treatment with BOR or THAL, other forms of therapy for multiple myeloma were performed in 55.6% of the BOR group and 75.0% of the THAL group (data not shown). Four (44.4%) of the 9 patients treated with BOR group did not need other treatment, and

no fatality was observed. In two patients, more than three years passed without any need for chemotherapy after the BOR treatment. Thus it is suggested that BOR treatment is also able to prolong the treatment-free period for patients suffering repeated relapses of multiple myeloma. The overall survival period of BOR-treated patients tended to be longer than that of THAL-treated patients who did not receive BOR, although difference was not significant (Fig.1). These findings suggest that BOR has high efficacy for patients with multiple myeloma who show resistance to standard therapy such as MP consolidation therapy, and also those with resistance to THAL, thus delivering a survival benefit [28].

Previous data have indicated that the efficacy of BOR may differ according to individual patient characteristics. In the present study, we investigated patient age, the number of previous regimens used, reflecting the number of recurrences, and the disease period. BOR showed no significant differences in efficacy or patient responses between patients aged less than 65 years and those aged 65 years or more, between patients who had received less than three kinds of regimen and those who had received three or more, and those with a disease duration of three years or more and less than three years, respectively (Table 4). Richardson et al. [29] reported that the efficacy of BOR was not dependent on race, type of disease, hemoglobin concentration or beta 2-microglobulin level, which are known to be prognostic factors for multiple myeloma. Therefore, it was confirmed that efficacy of BOR was not affected by patient background factors such as age and the number of recurrences.

As mentioned above, in addition to its anti-tumor effects, BOR has an osteoblast-activating effect, and it is reported that the skeletal ALP concentration rises after BOR therapy [30-32]. ALP elevation of at least 25% or more for 6 weeks from the start of BOR medication has been shown to be a predictive indicator of BOR efficacy [33]. Therefore, in the present study, we investigated the relationship between ALP elevation and the BOR effectiveness rate. Although the difference was not significant, many patients in the ALP elevation group showed a tendency for treatment effectiveness (Table 5). Although the mechanisms responsible for ALP elevation by BOR are unknown, it is assumed that the phenomenon is due to induction of ALP in mesenchymal stem cells, the progenitors of osteoblastic cells, or fibroblastic colony-forming units (CFU-F) [34]. The time course of the ALP value in a patient who showed the typical changes in the levels of ALP and M protein is shown in Fig.2. Although this patient relapsed twice after BOR treatment and received BOR three times, elevation of ALP and reduction of M protein were observed after two retreatments. A case in which BOR was similarly effective after a rapid elevation of the ALP level, and a case that showed amelioration of the osteolytic pathological change on X-ray examination after treatment with a combination of BOR and DEX, have been reported [35]. As the individual ALP isozymes are not routinely measured in the hospital where this investigation was conducted, the isozyme of ALP was unknown and could include liver and skeletal-type ALP. Furthermore, the increase of ALP concentration may be low, because there were a small number of patients with MM and the proportion of elderly individuals was high. This is thought to explain why we did not observe a significant correlation between the elevation of ALP and the efficacy of BOR. Although marked ALP elevation is not observed in all patients, it is considered that elevation of the ALP level after first or second cycle of BOR treatment may be an early predictor of the therapeutic efficacy of BOR [14]. Measurement of the skeletal-type ALP isozyme appears to be useful for predicting the efficacy of BOR.

The adverse events observed in the previous study of BOR conducted in Japan (December 1st, 2006 - September 21st, 2007; 666 subjects) [36] included thrombocytopenia (39.49%), fever (23.57%), leukopenia (17.87%), diarrhea (10.81%), constipation (9.61%), peripheral neuropathy (8.11%), shingles (7.96%), tumor lysis syndrome (3.60%), and interstitial lung disease (3.00%). In the present study, thrombocytopenia (86.2%), leukopenia (69.0%), fever (55.2%) and peripheral neuropathy (48.3%) occurred at high frequency. No remarkable decrease of the hemoglobin level induced by BOR medication, compared with leukocytes or platelets, was evident, contrary to some cases in which the hemoglobin levels and hematopoietic functions recovered. In the present study, platelets showed a marked decrease resulting from BOR therapy (Fig.3), and this occurred in 25 of the 29 patients. As patients with multiple myeloma show marked hematopoietic compromise, it would expected that blood platelets, leukocytes

and hemoglobin would all be suppressed. Moreover, it has been reported that the frequency of drug-induced interstitial pneumonia caused by medicines other that BOR is higher in Japanese people [37], and one death due to interstitial pneumonia induced by BOR has been reported in a Phase II trial. Although there were six lung-related events in this survey, any causal relationship with BOR was unclear. Although interstitial shadows were evident on CT images in one patient, there was no elevation of interstitial pneumonia markers (KL-6, SP-A, SP-D), and this case was not diagnosed as interstitial pneumonia.

Fever accompanying the BOR treatment in 16 of the 29 patients was transient, and resolved spontaneously or after treatment with anti-pyretics. Though the pathogenesis of such fever is unknown, it does not seem to be attributable to inhibition by BOR of inflammatory cytokines through prevention of NF-k B activity. In a preliminary study of five patients, BOR did not increase the release of IL-6 from myeloma cells alone, but did so when the cells were co-cultured with bone marrow stromal cells [38]. Therefore, it is suggested that the inflammatory cytokines responsible for fever after BOR administration are secreted from bone marrow stromal cells, and not from myeloma cells.

Peripheral neuropathy was observed in 48.3% (14/29) of the present patients. This seems to have been due to the fact that many of the patients had received therapy with THAL and vinka [39]. However, there was no significant difference between the frequency of occurrence of peripheral neuropathy induced by BOR and that due to previous use of THAL or vinka (data not shown). In the international Phase III (APEX) trial, a similar tendency was shown (in that case for THAL, vinka, platinum and taxanes) [5], supporting the contention that the previous medical history of patients with multiple myeloma does not affect the development of peripheral neuropathy when BOR therapy is used. As previous reports [39, 40] have indicated that the peripheral neuropathy caused by BOR is related to various risk factors, such as the amount of cumulative medication, the medication period, and previous occurrence of peripheral neuropathy, it may be possible to predict patients who are at risk of peripheral neuropathy after BOR treatment. THAL causes irreversible peripheral neuropathy, and its incidence increases in relation to the dose and period of administration [38]. As the peripheral neuropathy associated with BOR is reversible, and can be improved by discontinuing the medication, BOR treatment before THAL treatment may be an advisable option.

Although 16 of the present 29 patients were 65 years old or more, the frequency of adverse events in the older patients was not high. Renal dysfunction due to an increase of serum M protein was a general feature, but one of the patients had undergone dialysis before treatment with BOR. These findings also suggest that BOR could be used effectively and safely for patients with poor renal function or who have received dialysis, as BOR is metabolized by the liver [41, 42].

BOR produces high response rates in patients with recurrent and intractable multiple myeloma through proteasome inhibition. BOR exerts indirect effects through subtle alterations of the microenvironment of myeloma cells, and also has activating effects on osteoblastic cells in addition to its anti-tumor effects against multiple myeloma cells. In the present study, BOR produced a significantly higher therapeutic response rate in comparison with THAL for multiple myeloma, but there was no significant difference in survival time between the BOR group and the THAL group. It was shown that BOR exerts therapeutic effects not only in cases that are resistant to chemotherapy but also in those that are recurrent or do not respond to THAL. Moreover, although it has been reported that the frequency of interstitial pneumonia in clinical trials conducted in Japan is higher than in the United States and Europe, no cases of interstitial pneumonia as an adverse event induced by BOR were observed. Currently, clinical studies of BOR for patients with non-treated multiple myeloma, and the effects of consolidation therapy, are being conducted. A few clinical studies [43-45] have reported the efficacy of a protocol that combines BOR and THAL for multiple myeloma. BOR undoubtedly has an important role to play in the treatment of patients with multiple myeloma, and when used together with THAL, it is expected that the life expectancy and quality of life of affected patients will be improved.

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REFERENCES

1. Barlogie B, Desikan R, Eddlemon P, Spencer T, Zeldis J, Munshi N, Badros A, Zangari M, Anaissie E, Epstein J, Shaughnessy J, Ayers D, Spoon D, Tricot G.: Extended survival in advanced and refractory multiple myeloma after single-agent thalidomide: identification of prognostic factors in a phase 2 study of 169 patients. *Blood*, 98: 492-494, 2001.
2. Oken MM.: Management of myeloma: current and future approaches. *Cancer Control,* 5: 218-225, 1998.
3. Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K, Brown J, Drayson MT, Selby PJ.: High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med*, 348: 1875-1883, 2003.
4. Ogawa Y, Tobinai K, Ogura M, Ando K, Tsuchiya T, Kobayashi Y, Watanabe T, Maruyama D, Morishima Y, Kagami Y, Taji H, Minami H, Itoh K, Nakata M, Hotta T.: Phase I and II pharmacokinetic and pharmacodynamic study of the proteasome inhibitor bortezomib in Japanese patients with relapsed or refractory multiple myeloma. *Cancer Sci,* 99: 140-144, 2008.
5. Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, Harousseau JL, Ben-Yehuda D, Lonial S, Goldschmidt H, Reece D, San-Miguel JF, Bladé J, Boccadoro M, Cavenagh J, Dalton WS, Boral AL, Esseltine DL, Porter JB, Schenkein D, Anderson KC.: Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med*, 352: 2487-2498, 2005.
6. Mitsiades N, Mitsiades CS, Poulaki V, Chauhan D, Fanourakis G, Gu X, Bailey C, Joseph M, Libermann TA, Treon SP, Munshi NC, Richardson PG, Hideshima T, Anderson KC.: Molecular sequelae of proteasome inhibition in human multiple myeloma cells. *Proc Natl Acad Sci USA*, 99: 14374-14379, 2002.
7. Hideshima T, Chauhan D, Richardson P, Mitsiades C, Mitsiades N, Hayashi T, Munshi N, Dang L, Castro A, Palombella V, Adams J, Anderson KC.: NF-kappa B as a therapeutic target in multiple myeloma. *J Biol Chem*, 277: 16639-16647, 2002.
8. Karin M, Yamamoto Y, Wang QM.: The IKK NF-kappa B system: a treasure trove for drug development. *Nat Rev Drug Discov*, 3: 17-26, 2004.
9. Rajkumar SV, Richardson PG, Hideshima T, Anderson KC.: Proteasome inhibition as a novel therapeutic target in human cancer. *J Clin Oncol*, 23: 630-639, 2005.
10. Fujii H, Kotobuki Y, Nomura S, Harada Y.: Pharmacological and clinical profile of bortezomib (Velcade®). *Nippon Yakurigaku Zasshi*, 130: 421-429, 2007.
11. Shibuya Y, Takimoto M, Kato Y, Saito T, Ogawa K, Miura I.: Proteasome inhibitors. *Biotherapy,* 21: 147-152, 2007.
12. Abe M, Matsumoto T.: Myeloma bone disease and its treatment. *Bone,* 21: 613-616, 2007.
13. Hotta T.: Classification, staging and prognostic indices for multiple myeloma. *Nippon Rinsho* 65: 2161-2166, 2007.
14. National Cancer Institute: Common Terminology Criteria for Adverse Events (NCI-CTCAE) v3.0, 2006.
15. Singhal S, Mehta J, Desikan R, Ayers D, Roberson P, Eddlemon P, Munshi N, Anaissie E, Wilson C, Dhodapkar M, Zeddis J, Barlogie B.: Antitumor activity of thalidomide in refractory multiple myeloma. *N Engl J Med,* 341: 1565-1571, 1999.
16. Prince HM, Adena M, Smith DK, Hertel J.: Efficacy of single-agent bortezomib vs. single-agent thalidomide in patients with relapsed or refractory multiple myeloma: a systematic comparison. *Eur J Haemat*o, 79: 93-79, 2007.
17. Mitsiades N, Mitsiades CS, Richardson PG, Poulaki V, Tai YT, Chauhan D, Fanourakis G, Gu X, Bailey C, Joseph M, Libermann TA, Schlossman R, Munshi NC, Hideshima T, Anderson KC.: The proteasome inhibitor PS-341 potentiates sensitivity of multiple myeloma cells to conventional chemotherapeutic agents: therapeutic applications. *Blood*, 101: 2377-2380, 2003.
18. Mateos MV, Hernández JM, Hernández MT, Gutiérrez NC, Palomera L, Fuertes M, Díaz-Mediavilla J, Lahuerta JJ, de la Rubia J, Terol MJ, Sureda A, Bargay J, Ribas P, de Arriba F, Alegre A, Oriol A, Carrera D, García-Laraña J, García-Sanz R, Bladé J, Prósper F, Mateo G, Esseltine DL, van de Velde H, San Miguel JF.: Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: results of a multicenter phase 1/2 study. *Blood*, 108: 2165-2172, 2006.
19. Orlowski RZ, Voorhees PM, Garcia RA, Hall MD, Kudrik FJ, Allred T, Johri AR, Jones PE, Ivanova A, Van Deventer HW, Gabriel DA, Shea TC, Mitchell BS, Adams J, Esseltine DL, Trehu EG, Green M, Lehman MJ, Natoli S, Collins JM, Lindley CM, Dees EC.: Phase 1 trial of the proteasome inhibitor bortezomib and pegylated liposomal doxorubicin in

patients with advanced hematologic malignancies. *Blood*, 105: 3058-3065, 2005.

20. Berenson JR, Yang HH, Sadler K, Jarutirasarn SG, Vescio RA, Mapes R, Purner M, Lee SP, Wilson J, Morrison B, Adams J, Schenkein D, Swift R.: Phase I/II trial assessing bortezomib and melphalan combination therapy for the treatment of patients with relapsed or refractory multiple myeloma. *J Clin Oncol*, 24: 937-944, 2006.
21. Sundar J.: The role of bortezomib in previously untreated myeloma. *Myeloma Today*, 6: 6-7, 2006.
22. Hideshima T, Richardson P, Chauhan D, Palombella VJ, Elliott PJ, Adams J, Anderson KC.: The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells. *Cancer Res*, 61: 3071-3076, 2001.
23. Japanese Society of Hematology, Evaluation committee for proper use of pharmaceuticals: The guideline for proper use of thalidomide for the patients with multiple myeloma.
24. Pieter S.: Bortezomib as treatment of MM: Analysis of efficacy and toxicity. *Myeloma Today,* 6: 5-7, 2005.
25. Cibeira MT, Rosiñol L, Ramiro L, Esteve J, Torrebadell M, Bladé J.: Long-term results of thalidomide in refractory and relapsed multiple myeloma with emphasis on response duration. *Eur J Haematol*, 77: 486-492, 2006.
26. Wolf J, Richardson PG, Schuster M, LeBlanc A, Walters IB, Battleman DS.: Utility of bortezomib retreatment in relapsed or refractory multiple myeloma patients: a multicenter case series. *Clin Adv Hematol Oncol*, 6: 755-760. 2008.
27. Conner TM, Doan QD, Walters IB, LeBlanc AL, Beveridge RA.: An observational, retrospective analysis of retreatment with bortezomib for multiple myeloma. *Clin Lymphoma Myeloma*, 8: 140-145, 2008.
28. Musto P, Falcone A, Sanpaolo G, Guglielmelli T, Zambello R, Balleari E, Catalano L, Spriano M, Cavallo F, La Sala A, Mantuano S, Nobile M, Melillo L, Scalzulli PR, Dell'Olio M, Bodenizza C, Greco MM, Carella AM Jr, Merla E, Carella AM, Boccadoro M, Cascavilla N, Palumbo A.: Bortezomib (Velcade) for progressive myeloma after autologous stem cell transplantation and thalidomide. *Leuk Res*, 30: 283-285, 2006.
29. Richardson PG, Barlogie B, Berenson J, Singhal S, Jagannath S, Irwin D, Rajkumar SV, Hideshima T, Xiao H, Esseltine D, Schenkein D, Anderson KC.: Clinical factors predictive of outcome with bortezomib in patients with relapsed, refractory multiple myeloma. *Blood*, 106: 2977-2981, 2005.
30. Ulrike H, Martin K, Christian M, Carsten-Oliver S, Christian J, Ivana Z, Jan E, Jan S, Lorenz K. Kurt P, Orhan S.: Treatment of bortezomib increases osteoblast function in patients with multiple myeloma. *Blood* (ASH Annual Meeting abstracts), 106: 3457, 2005.
31. Shimazaki C, Uchida R, Nakano S, Namura K, Fuchida SI, Okano A, Okamoto M, Inaba T.: High serum bone-specific alkaline phosphatase level after bortezomib-combined therapy in refractory multiple myeloma: possible role of bortezomib on osteoblast differentiation. *Leukemia*, 19: 1102-1103, 2005.
32. Heider U, Kaiser M, Müller C, Jakob C, Zavrski I, Schulz CO, Fleissner C, Hecht M, Sezer O.: Bortezomib increases osteoblast activity in myeloma patients irrespective of response to treatment. *Eur J Haematol*, 77: 233-238, 2006
33. Min CK, Lee MJ, Eom KS, Lee S, Lee JW, Min WS, Kim CC, Kim M, Lim J, Kim Y, Han K.: Bortezomib in combination with conventional chemotherapeutic agents for multiple myeloma compared with bortezomib alone. *Jpn J Clin Oncol*, 37: 961-968, 2007.
34. Ozaki S, Tanaka O, Fujii S, Shigekiyo Y, Miki H, Choraku M, Kagawa K, Asano J, Takeuchi K, Kitazoe K, Hashimoto T, Abe M, Matsumoto T.: Therapy with bortezomib plus dexamethasone induces osteoblast activation in responsive patients with multiple myeloma. *Int J Hematol.* 86: 180-185, 2007.
35. Ozaki S, Tanaka O, Fujii S, Shigekiyo Y, Miki H, Choraku M, Kagawa K, Asano J, Takeuchi K, Kitazoe K, Hashimoto T, Abe M, Matsumoto T.: Therapy with bortezomib plus dexamethasone induces osteoblast activation in responsive patients with multiple myeloma. *Int J Hematol,* 86: 180-185, 2007.
36. JANSSEN® PHARMACEUTICAL K.K.: VELCADE® (bortezomib) for Injection 3mg, Interim report, 2007.
37. Inoue A, Saijo Y, Maemondo M, Gomi K, Tokue Y, Kimura Y, Ebina M, Kikuchi T, Moriya T, Nukiwa T.: Severe acute interstitial pneumonia and gefitinib. *Lancet*, 361: 137-139, 2003.
38. El-Cheikh J, Stoppa AM, Bouabdallah R, de Lavallade H, Coso D, de Collela JM, Auran-Schleinitz T, Gastaut JA, Blaise D, Mohty M.: Features and risk factors of peripheral neuropathy during treatment with bortezomib for

advanced multiple myeloma. *Clin Lymphoma Myeloma,* 8: 146-152, 2008.

39. Umapathi T, Chaudhry V.: Toxic neuropathy. *Curr Opin Neurol,* 18: 574-580, 2005.
40. Argyriou AA, Iconomou G, Kalofonos HP.: Bortezomib-induced peripheral neuropathy in multiple myeloma: a comprehensive review of the literature. *Blood*, 112: 1593-1599, 2008.
41. Jagannath S, Barlogie B, Berenson JR, Singhal S, Alexanian R, Srkalovic G, Orlowski RZ, Richardson PG, Anderson J, Nix D, Esseltine DL, Anderson KC.: Bortezomib in recurrent and/or refractory multiple myeloma. Initial clinical experience in patients with impared renal function. *Cancer*, 103: 1195-1200, 2005.
42. Chanan-Khan AA, Kaufman JL, Mehta J, Richardson PG, Miller KC, Lonial S, Munshi NC, Schlossman R, Tariman J, Singhal S.: Activity and safety of bortezomib in multiple myeloma patients with advanced renal failure: a multicenter retrospective study. *Blood*, 109: 2604-2606, 2007.
43. Kaufman JL, Nooka A, Vrana M, Gleason C, Heffner LT, Lonial S.: Bortezomib, thalidomide, and dexamethasone as induction therapy for patients with symptomatic multiple myeloma: a retrospective study. *Cancer*, 116: 3143-3151, 2010.
44. Palumbo A, Bringhen S, Rossi D, Cavalli M, Larocca A, Ria R, Offidani M, Patriarca F, Nozzoli C, Guglielmelli T, Benevolo G, Callea V, Baldini L, Morabito F, Grasso M, Leonardi G, Rizzo M, Falcone AP, Gottardi D, Montefusco V, Musto P, Petrucci MT, Ciccone G, Boccadoro M.: Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib - melphalan - prednisone for initial treatment of multiple myeloma: a randomized controlled trial. *J Clin Onco*, 28: 5101-5109, 2010.
45. Mateos MV, Oriol A, Martínez-López J, Gutiérrez N, Teruel AI, de Paz R, García-Laraña J, Bengoechea E, Martín A, Mediavilla JD, Palomera L, de Arriba F, González Y, Hernández JM, Sureda A, Bello JL, Bargay J, Peñalver FJ, Ribera JM, Martín-Mateos ML, García-Sanz R, Cibeira MT, Ramos ML, Vidriales MB, Paiva B, Montalbán MA, Lahuerta JJ, Bladé J, Miguel JF.: Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. *Lancet Oncol*, 11: 934-941, 2010.