Efficacy and Safety of Bortezomib plus Dexamethasone Therapy for Refractory or Relapsed Multiple Myeloma: Once-weekly Administration of Bortezomib may Reduce the Incidence of Gastrointestinal Adverse Events

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Abstract. *Background: To establish the clinical use of bortezomib with fewer adverse events, we retrospectively analyzed the efficacy and safety of bortezomib plus dexamethasone (BD) therapy for relapsed or refractory multiple myeloma. Patients and Methods: Patients received bortezomib (1.3 mg/m^2) as an intravenous bolus on days 1, 4, 8 and 11 in a 3-week cycle (twice-weekly administration), or on days 1, 8, 15 and 22 in a 5-week cycle (once-weekly administration). Dexamethasone (20 mg) was given on the day of and day after bortezomib treatment. Results: From January 2007 to July 2010, 22 patients began to receive BD therapy. Initially, bortezomib was administered twice-weekly, but some severe adverse events developed; therefore, from January 2008, bortezomib was administered twice-weekly for the first two courses, followed by once-weekly for the subsequent courses. Patients who were expected to have severe adverse events beforehand were treated initially with once-weekly administration. Of the 22 patients, 14 were treated with twice-weekly followed by once-weekly administration, five with only twice-weekly administration and three with only once-weekly administration. Seventeen patients (77.3%) achieved at least partial response, including three with complete response and seven with very good partial response. The median progression-free survival and the median overall survival of 22 patients were 512 days and not reached, respectively. The median progression-free survival and the median overall survival of 17 patients who received at least one course of once-weekly administration were 615 days and not reached, respectively. The most frequent ≥grade 3 adverse events with twice-weekly administration were gastrointestinal, especially paralytic ileus and constipation. Among seven patients who developed ≥grade 3 gastrointestinal adverse events with twice-weekly administration, all four patients changed the schedule to once-weekly were able to continue BD therapy. Conclusion: Once-weekly administration of bortezomib in BD therapy may reduce the incidence of gastrointestinal adverse events without reducing the clinical efficacy of this therapy for refractory or relapsed multiple myeloma.*

Multiple myeloma (MM) is a hematological malignancy characterized by monoclonal proliferation of plasma cells and the presence of monoclonal immunoglobulin in serum and urine. Its common clinical features are anemia, renal dysfunction, osteolysis and hypercalcemia (1-3). In the past decade, there have been major advances as a result of new anti-myeloma agents (2, 3). A proteasome inhibitor, bortezomib, is one of these new agents (4, 5) and has been successfully used for the treatment of MM. Bortezomib plus dexamethasone (BD) therapy has been established as one of the most promising therapies for refractory or relapsed MM. On the other hand, the use of bortezomib is associated with some severe adverse events, with 22% and 37% of patients being unable to continue bortezomib therapy due to adverse events in the SUMMIT and APEX study, respectively (6, 7).

Bortezomib-melphalan-prednisolone (VMP) therapy has also been established as a standard chemotherapy for newly diagnosed MM patients who were not eligible for high-dose therapy followed by autologous peripheral blood stem cell transplantation (auto-PBSCT); however, 46% of patients

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experienced severe adverse events and 34% of patients discontinued VMP therapy or bortezomib administration due to adverse events (8). It is considered that the continuation of chemotherapy is one of the crucial factors in obtaining a favorable response and long-term survival for MM patients. For the purpose of establishing the clinical use of bortezomib with fewer adverse events, we retrospectively analyzed the efficacy and safety of BD therapy for relapsed or refractory MM patients treated in our institute.

Patients and Methods

Patients. We retrospectively analyzed the medical records of 22 patients with relapsed or refractory MM who began BD therapy in Kanazawa Medical University Hospital between January 2007 and July 2010. The diagnosis of MM was confirmed using the International Myeloma Working Group (IMWG) criteria (1). The clinical stage was determined by the International Staging System (ISS) (9).

Treatment. Patients received bortezomib (1.3 mg/m^2) as an intravenous bolus on days 1, 4, 8 and 11 in a 3-week cycle (twice-weekly administration), or on days 1, 8, 15 and 22 in a 5-week cycle (once-weekly administration). Dexamethasone at 20 mg was given intravenously or orally on the day of and day after bortezomib treatment. BD therapy was continued until achieving a complete response (CR), disease progression or the development of severe adverse events. If patients were eligible for high-dose therapy, hematopoietic stem cells were harvested by high-dose cyclophosphamide (3 g/m^2), and high-dose melphalan (140 mg/m^2) was given followed by auto-PBSCT.

Assessments. Response to BD therapy was assessed using the IMWG uniform criteria (10). Progression-free survival (PFS) and overall survival (OS) were defined as the time from starting BD therapy until the date of disease progression and death, respectively. Adverse events were graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0 (11).

Statistical analysis. Response rates and the incidence of any adverse events were compared using Fisher's exact test. Time-to-event analysis was performed according to the Kaplan–Meier method, and the log-rank test was applied to assess differences between subgroups. A value of $p<0.05$ was considered statistically significant.

Results

Patients' characteristics. Table I shows the characteristics of the 22 patients. The median age was 69 years (range 42-81 years). Performance status (PS) of all patients was ≥2, including PS 3 in seven patients and PS 4 in three patients. Six patients had plasmacytomas. Three patients had renal impairment (serum creatinine ≥2 mg/dl). The median time from diagnosis to starting BD therapy was 10 months (range 1-180 months). The median number of prior therapies was two (range 1-4, radiotherapy was counted as one regimen).

Table I. *Characteristics of patients (n=22).*

Characteristics	Value
Age, years	
Median	69
Range	42-81
Gender	
Male	13
Female	9
Type of M-protein	
IgG	11
IgA	1
IgD	2
Bence-Jones	8
International Staging System	
1	7
2	5
3	10
ECOG performance status	
2	12
3	7
4	3
Plasmacytoma	6
Renal impairment	3
Time to BD therapy from diagnosis (months)	
Median	10
Range	1-180
Number of prior therapies	
1	9
2	10
3	2
4	1

Twenty-one had received corticosteroids, and five had received corticosteroids alone. Fifteen had received melphalan-containing therapy. One had received high-dose melphalan followed by auto-PBSCT. Two had received thalidomide. Three had received radiotherapy.

Treatment. Initially, bortezomib was administered twice-weekly, but some severe adverse events developed; therefore, from January 2008, bortezomib was administered twice-weekly for the first two courses, followed by once-weekly for subsequent courses. Furthermore, patients who were expected to have severe adverse events beforehand were treated initially with once-weekly administration. When severe adverse events developed or expected with once-weekly administration, the dose of bortezomib and/or dexamethasone was reduced. Of the 22 patients, 14 were treated with twice-weekly followed by once-weekly administration, five with only twice-weekly administration, and three with only once-weekly administration. Bortezomib was administered at a dose of 1.3 mg/m^2 for all courses for 10 patients, while the dose was reduced to ≤1.0 mg/m^2 for some or all courses for eight patients due to development of adverse events and for four

Table II. *Impact of patients' characteristics on response (≥very good partial response), progression-free survival (PFS) and overall survival (OS).*

Characteristics		*p*-Value		
		Response	PFS	OS
Age, years	70< *vs.* ≥70	0.415	0.428	0.757
Sex	Female *vs.* male	0.666	0.278	0.437
Performance status	2 *vs.* 3-4	0.231	0.645	0.430
International Staging System	1-2 *vs.* 3	0.691	0.043	0.330
Hb	≥10 g/dl *vs.* <10 g/dl	1.000	0.118	0.223
Serum Ca	<10 mg/dl *vs.* ≥10 mg/dl	0.675	0.063	0.0068
C-Reactive protein	<0.3 mg/dl *vs.* ≥0.3 mg/dl	1.000	0.021	0.279
Existence of plasmacytoma	No *vs.* yes	0.162	0.873	0.425
Time from diagnosis	<1 year *vs.* ≥1 year	1.000	0.394	0.597
Number of prior therapies	1 *vs.* ≥2	0.192	0.259	0.232

patients due to expectation to have severe adverse events. The median follow-up from starting BD therapy was 631 days (range 111-1,311 days) for surviving patients. Patients received a median of 8 courses of BD therapy (range 1-26 courses). The median cumulative bortezomib dose was 36.0 mg/m^2 (range 5.2-114.8 mg/m^2). At data cut-off, seven patients had discontinued BD therapy due to disease progression. Two patients and one patient had discontinued BD therapy with twice-weekly administration due to gastrointestinal adverse events and due to peripheral neuropathy (PN), respectively. Two patients received high-dose melphalan followed by auto-PBSCT after 8 courses of BD therapy.

Response and survival. Of the 22 patients, seventeen (77.3%) achieved at least partial response, including three with CR and seven with very good partial response (VGPR). Stable disease, progression and treatment-related death were four, zero and one, respectively. The median time to first response was 22 days (range 8-64 days) in the responding patients. The response (≥VGPR) to BD therapy was not influenced by age, sex, PS, ISS, Hb, serum Ca, C-reactive protein (CRP), existence of plasmacytoma, the time from diagnosis to starting BD therapy or the number of prior therapies in univariate analysis (Table II). The median PFS and the median OS of 22 patients were 512 days and not reached, respectively. The 2-year PFS and the 2-year OS of 22 patients were 39.6% and 54.2%, respectively (Figure 1). ISS (1-2 *vs.* 3, the median PFS was not reached and was 442 days, respectively) and CRP (<0.3 mg/dl *vs.* ≥0.3 mg/dl, the median PFS was not reached and was 442 days, respectively) were detected as prognostic factors for PFS, and serum Ca (<10 mg/dl *vs.* ≥10 mg/dl, the median OS was not reached and was 429 days, respectively) was detected as a prognostic factor for OS in univariate analysis (Table II). The median PFS and median OS of 17 patients who received at least one course of once-weekly administration was 615 days and not reached, respectively. The 2-year PFS and the 2-year OS of these 17 patients were 45.5% and 58.7%, respectively (Figure 2). The clinical course of one patient with relapsed MM with multiple plasmacytomas who achieved CR by BD therapy was published as a case report (12).

Table III. *Incidence (%) of ≥grade 3 adverse events of BD therapy.*

	Total (n=22)	Twice-weekly (n=19)	Once-weekly (n=17)
Constipation	18.2	21.1	0
Paralytic ileus	31.8	31.6	5.9
Anorexia	4.5	0	5.9
ALT elevation	4.5	5.3	0
Peripheral neuropathy	18.2	15.8	17.6
Leukocytopenia	4.5	0	5.9
Thrombocytopenia	13.6	10.5	5.9
Herpes zoster	18.2	15.8	11.8
CMV infection	4.5	0	5.9
Sepsis	13.6	5.3	11.8

Adverse events. Table III lists ≥grade 3 adverse events occurring during the first to fourth course of BD therapy. The most frequent ≥grade 3 adverse events with twice-weekly administration were gastrointestinal, especially paralytic ileus and constipation. One patient died due to severe paralytic ileus and sepsis on day 12 of the first course of BD therapy with twice-weekly administration. Among seven patients who developed ≥grade 3 gastrointestinal adverse events with twice-weekly administration, all four patients changed the schedule to once-weekly were able to continue BD therapy. While ≥grade 3 PN developed in four patients, one with twice-weekly, one with once-weekly and two with each twice-weekly and once-weekly administration, only one patient treated with twice-weekly administration was unable

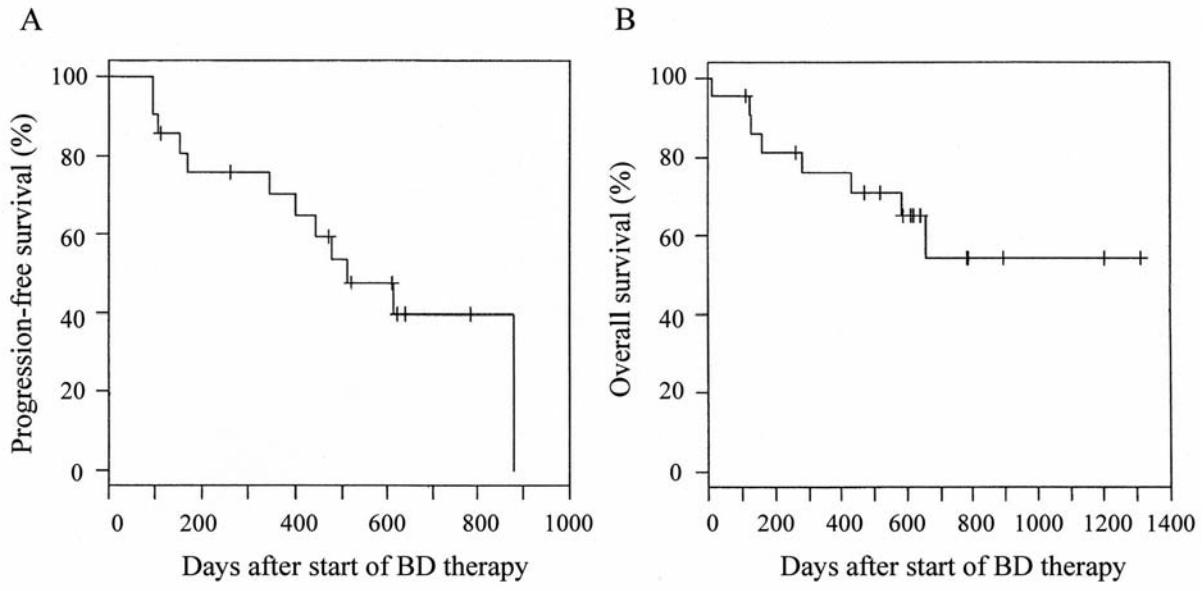

Figure 1. *Kaplan-Meier curves for progression-free (A) and overall survival (B) of 22 patients.*

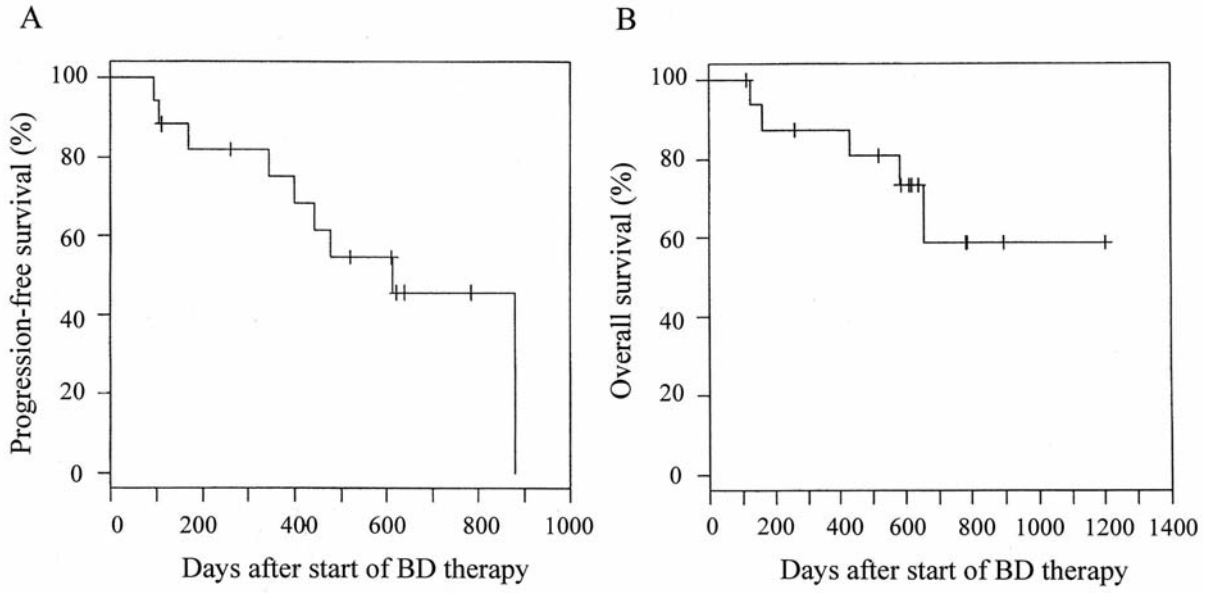

Figure 2. *Kaplan-Meier curves for progression-free (A) and overall survival (B) of 17 patients who received at least one course of once-weekly administration.*

to continue BD therapy due to PN. Pulmonary, cardiac and dermatologic ≥grade 3 adverse events did not develop. Herpes zoster developed in four patients without prophylaxis, two with twice-weekly, one with once-weekly and one with each twice-weekly and once-weekly administration, but did not develop in patients who received prophylactic 500 mg valaciclovir administration.

Discussion

Our efficacy data regarding the response rate, PFS and OS were almost equal or slightly superior to those of other retrospective investigations of BD therapy for Japanese patients with refractory or relapsed MM (13, 14). As CR has been considered to be a surrogate marker of the clinical

benefit of bortezomib (7, 15), our treatment approach planned to continue BD therapy until CR. After the schedule change to once-weekly administration, the incidence of severe gastrointestinal adverse events decreased and gastrointestinal adverse events did not prevent any patients from continuing BD therapy. No additional severe adverse events associated with long-term BD therapy were observed. The median number of courses of BD therapy was 8, which was more than that of other reports. These findings suggest that continuous and many courses of BD therapy resulted in the more favorable clinical efficacy in our study.

While PN often induced dose reduction or discontinuation of bortezomib, gastrointestinal adverse events were also frequent and severe. The incidence of gastrointestinal adverse events in our study was higher than that in other previous reports (13, 14). This may have been because many patients with poor PS were included in our study. Although it is difficult to make a comparison because of differences in disease status or the general condition of each patient at the time of BD therapy, the incidences of severe paralytic ileus and constipation were less frequent with once-weekly than twice-weekly administration.

Recently, once-weekly administration has been implemented to reduce adverse events of bortezomib (16, 17). In a randomized, phase 3 Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) trial, bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide (VMPT-VT) demonstrated superior efficacy to VMP for untreated MM patients who were not eligible for high-dose therapy followed by auto-PBSCT (18). In this GIMEMA study, the protocol was changed from twice-weekly to once-weekly administration because of the frequent discontinuation of chemotherapy due to adverse events. According to their non-randomized post-hoc analysis, once-weekly administration was found to be equally effective and better tolerated than twice-weekly administration. The incidence of grade 3/4 PN and gastrointestinal adverse events was less frequent with once-weekly than twice-weekly administration (19).

Twice-weekly administration was determined based on the pharmacodynamic profile of bortezomib (20). On the other hand, Ogawa *et al*. investigated the plasma bortezomib concentration–time profiles on days 1 and 11 obtained from 16 patients enrolled in a phase I study of bortezomib in Japanese patients with MM. They demonstrated that repeated administration of bortezomib produced a higher plasma concentration after administration (C_0, estimated value) and a higher area under the plasma concentration–time curve of bortezomib on day 11 than on day 1 (21). Delayed elimination of bortezomib from plasma may produce severe adverse events with twice-weekly administration.

In conclusion, once-weekly administration of bortezomib in BD therapy may reduce the incidence of gastrointestinal adverse events without reducing the clinical efficacy for refractory or relapsed MM patients. Initial twice-weekly followed by once-weekly administration may also be a practical valuable treatment schedule of BD therapy.

Conflict of Interest

The Authors declare they have no conflicts of interest.

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