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RESEARCH

Modified Bortezomib, Adriamycin and Dexamethasone (PAD) Regimen in Advanced Multiple Myeloma

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Abstract The PAD regime, composed of bortezomib, adriamycin and dexamethasone, improves the outcomes of patients with advanced multiple myeloma (MM), but at the same time produces high frequency of serious toxic side effects. For the first time, we evaluated the efficacy and safety of a bortezomib-dose-reduced PAD regime in the treatment of relapsed/refractory MM in this clinical study. Forty-five patients were treated with two to six 21-day cycles of PAD, comprising bortezomib at 1.3 mg/m^2 (P_1AD, n=21) or 1.0 mg/m^2 (P_2AD, n=24) (days 1, 4, 8, 11), adriamycin at 9 mg/m^2 (days 1–4) and dexamethasone at 40 mg/day (days 1–4). Overall, 36 patients (80 %) showed at least partial remission (PR), in which 9 cases (20 %) showed complete remission (CR) and 10 cases (22 %) showed very good partial remission (VGPR). The efficacy of PAD regimen in advanced MM patients was not related to the traditional prognostic factors. There was no significant difference between P_1AD and P_2AD in the rates of PR, CR or VGPR, 1.5-year progression-free survival (PFS), and overall survival (OS) (81 % vs. 79 %, 48 % vs. 38 %, 64 % vs. 59 %, and 85 % vs. 73 %, respectively). However, the grade 3–4 toxic effects, including thrombocytopenia (13 % vs. 38 %), peripheral neuropathy (8 % vs. 33 %) and 3–4 grade gastrointestinal reaction (13 % vs. 43 %), were markedly inhibited after P_2AD compared to P_1AD (P<0.05). The bortezomib-dose-reduced PAD regime reduced the incidence of adverse reactions without affecting the treatment efficacy in patients with advanced MM.

Keywords Modified PAD regimen · Bortezomib · Advanced multiple myeloma · Efficacy and safety

Introduction

Multiple myeloma (MM) is an incurable malignant plasma cell disorder which is characterized by the clonal proliferation of bone marrow plasma cells and abnormal secretion of immunoglobulins [1]. For patients with relapsed and refractory MM, the progression-free survival (PFS) is generally difficult to exceed 6 months, and overall survival (OS) is difficult to sustain for over one year [2]. However, introduction of novel agents improves the efficacy and long-term outcomes of advanced MM [3]. About 35 to 38 % patients with relapsed or refractory MM for single-agent treatment of bortezomib/PS341, an inhibitor of 26S proteasome, achieved partial or complete remission (PR or CR) [2, 4]. Clinical treatment employing bortezomib in combination with other conventional anti-myeloma drugs have shown synergistic activity in patients with relapsed or refractory MM [5–9]. It has been reported that 55 % of the patients with relapsed or refractory MM achieved at least partial response after receiving bortezomib and dexamethasone treatment [10]. The overall response rate after the treatment of bortezomib, melphalan and dexamethasone is increased to 62–68 % [6, 9]. A modified regimen of pegylated liposomal doxorubicin, bortezomib, and dexamethasone is also effective with an overall response rate of 55.5–61 % [5, 8]. Therefore, it is important to explore the synergistic anti-myeloma effects of bortezomib with other anti-myeloma drugs and to design or verify new combined

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therapeutic regimens containing bortezomib for the treatment of relapsed or refractory MM [11].

Recently, a multi-center clinical study found that 67 % patients (43 out of 67) with relapsed or refractory MM achieved at least a PR response after PAD treatment that comprises bortezomib, adriamycin and dexamethasone, and more than half of the patients had PFS and OS for more than 1 year [12]. Refractory plasmacytoma patients, who once had ineffective treatment of autologous hematopoietic stem cell transplantation, had a CR effect after PAD treatment [13]. The above studies show that PAD treatment may significantly improve the efficacy and prognosis of patients with relapsed or refractory MM.

Despite the good efficacy of PAD regimen, severe toxic effects were produced in the MM patients at the same time [14]. The efficacy and toxicity of two different doses (1.3 and 1.0 mg/m^2) of bortezomib were evaluated in patients with newly diagnosed MM [15]. No significant difference in efficacy was found, and the one-year survival rate was roughly equal (100 % vs. 95 %). Nevertheless, the latter regimens (with 1.0 mg/m^2 bortezomib) had lower toxicity [15]. However, the efficacy and safety of different doses of bortezomib in PAD programs in patients with relapsed or refractory MM have not been reported. In this study, PAD regimens containing of 1.3 and 1.0 mg/m^2 bortezomib (P_1AD and P_2AD, respectively) were studied in Chinese patients with relapsed or refractory MM.

Patients and Methods

Patients

From September 2007 to September 2012, 45 consecutive patients with relapsed or refractory MM hospitalized in the Hematology Department of Xijing Hospital and the Hematology Department of the 309th Hospital of People's Liberation Army (PLA) were enrolled in this study. The inclusion criteria were as follows: patients achieved at least a minor response, but relapsed or progressed during treatment, or patients experienced progression within 60 days after their last therapy; patients should be more than 18 years old with adequate cardiac function. Exclusion criteria included grade 3–4 peripheral neuropathy, platelet count $<75\times10^9$/L, the presence of another cancer, and hypersensitivity to bortezomib, boron, mannitol, adriamycin or dexamethasone. Previous treatment with bortezomib or anthracycline was permitted. The International Staging System for MM was used in this study [16].

All patients provided written informed consent to participation in the study. The study was performed in adherence to the Declaration of Helsinki, and was approved by the ethics committees of the 309th Hospital of PLA and the Fourth Military Medical University.

Treatment Plan

According to the previous studies [15, 14], a modified PAD regimen was designed and given continuously for six 21-day cycles as the following: bortezomib 1.3 mg/m^2 (P_1AD) or 1.0 mg/m^2 (P_2AD) for rapid intravenous injection at the 1st, 4th, 8th, and 11th day; adriamycin 9 mg/m^2 for intravenous infusion from the 1st to 4th day; dexamethasone 40 mg/m^2 for intravenous infusion at the 1st to 4th day. Patients were randomly assigned to the two groups. Consequently, 21 and 24 patients were assigned to receive P_1AD and P_2AD treatment, respectively. Ciprofloxacin and acyclovir were recommended for antibiotic prophylaxis. During the treatment, if the patients had drug-related grade 4 hematologic toxicity or grade 3–4 non-hematologic toxicity (according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v3.0), the treatment was delayed until remission of the toxicity. The bortezomib dose in P_1AD and P_2AD was then decreased to 1.0 and 0.7 mg/m^2, respectively. If ≥ grade 3 non-hematologic toxicity still occurred after the dose-reduced treatment, the treatment was postponed until the toxicity was reduced to ≤ grade 2. Treatment was discontinued if the patients failed to achieve at least a minor response or suffered from heart and lung failure, or grade 3–4 toxic effects failed to be relieved and maintained during the therapy.

Efficacy and Toxicity Evaluation

The assessment of therapeutic efficacy was based on the International Uniform Response Criteria for Multiple Myeloma published in 2006 [17]. Briefly, complete response (CR) was defined as negative immunofixation on the serum and urine, disappearance of any soft tissue plasmacytomas and plasma cells in bone marrow ≤5 %. Very good partial response (VGPR) was defined as detectable serum and urine M-proteins by immunofixation but not on electrophoresis or a ≥90 % reduction in serum M-protein with urinary M-protein excretion <100 mg per 24 h. Partial response (PR) was defined as a ≥50 % reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90 % or to < 200 mg per 24 h. Progressive disease (PD) was defined as a ≥25 % increase of serum and/or urinary M-protein or bone marrow plasma cells, an increase in the size of existing bone lesions or soft tissue plasmacytomas or development of new ones, or development of hypercalcemia. The disease was considered as stable (SD) if the criteria for CR, VGPR, PR or PD were not met. The toxicity was graded according to NCI CTCAE v3.0 criteria. The efficacy and toxicity was evaluated before the start of every PAD regimen. MM patients with extramedullary plasmacytoma received CT scan of tumor sites to assess changes in tumor volume before and after the treatment.

Statistical Analysis

Analyses were performed with SAS 9.0 software (SAS Corp, Cary, NC, USA). Overall survival (OS) was calculated from the time of PAD treatment until the date of death or the date the patient was last known to be alive. Progression-free survival (PFS) was calculated from the time of PAD treatment until the date of progression, relapse, death or the date the patient was last known to be in remission. Time-to-event and OS analyses were performed using the Kaplan-Meier method. Fisher's exact test was used to compare data between groups. Log-Rank test was used for the survival analysis. The significant P value was set at 0.05.

Results

Patients' Characteristics

Forty-five advanced MM patients were enrolled in this study and treated using PAD regimen; 21 received P_1AD and 24 received P_2AD. The characteristics of patients were summarized in Table 1. One patient in P_1AD and P_2AD had received prior bortezomib-based regimens, respectively. No patients received an autologous stem cell transplant in the prior treatments or during our PAD treatment.

Forty patients received PAD regimen for 4–6 cycles. Four patients in P_1AD and one in P_2AD only received treatment for 2–3 cycles and then discontinued the assigned treatment: 1 patient in P_1AD and the patient in P_2AD stopped treatment because of failure to achieve at least a PR response; 2 in P_1AD because of grade 3–4 toxic effects; and 1 patient in P_1AD because of economic scarcity.

The Overall Efficacy of PAD Regime

After receiving PAD treatment, 36 out of 45 relapsed or refractory MM patients (80 %) achieved at least a PR response, while 6 (13 %) and 3 (7 %) patients had a SD and PD response, respectively (Table 2). The cycles required to achieve the best response was 1.6 cycles (range 1 to 3 cycles) of treatment.

The Relationship Between PAD Efficacy and the Prognostic Factors of Conventional Chemotherapy

There was no significant difference among patients who achieved different PAD efficacy in the conventional chemotherapy prognostic factors, such as β2 microglobulin, serum albumin, the percentage of tumor cells, serum calcium, and the number of pre-chemotherapy regimen ($p>0.05$) (Table 3), suggesting that the efficacy of PAD regimen in advanced MM patients was not related to the traditional prognostic factors.

The Efficacy of PAD Treatment for Relapsed or Refractory Patients with Extramedullary Plasmacytoma

A total of 8 MM patients were diagnosed as extramedullary plasmacytoma (4–10 cm diameter) (4 patients for P_1AD and 4 patients for P_2AD). After the 1st cycle of PAD treatment, 5 patients achieved CR or VGPR response, and all the 8 patients had at least PR efficacy (2 CR, 3 VGPR, and 3 PR) after the complete PAD treatment (Table 4). In the patients who received P_1AD treatment, 1 had a CR, 1 had a VGPR, and 2 had a PR, while in the patients who received P_2AD treatment, CR was achieved in 1 patient, VGPR in 2 and PR in 1 (Table 4).

Comparison of Efficacy of Two Regimes: P_1AD and P_2AD

In the 21 patients who received the P_1AD regimen, 17 (81 %) achieved a PR or better therapeutic response including 10 (48 %) with a CR or VGPR response and 7 (33 %) with a PR response, 3 patients (14 %) achieved SD and 1 patient (5 %) achieved PD (Table 5). For the 24 patients given the P_2AD regimen, 19 patients (79 %) had at least a PR effective response including 9 (38 %) with a CR or VGPR response and 10 (41 %) with a PR response, 3 patients (13 %) achieved SD and 2 patient (8 %) achieved PD. There were no significant differences in CR or VGPR rate and at least PR response rate between P_1AD and P_2AD groups ($P=0.359$ and 0.590, respectively) (Table 5).

Time-to-Events Analyses

The median time of follow-up was 18 months (range 6–23 months). 1.5-year PFS after P_1AD and P_2AD was 52 % vs. 50 % ($P=0.766$), respectively (Fig. 1). 1.5-year OS were 66 % vs. 67 % ($P=0.883$), respectively (Fig. 2).

The Main Side Effects of the P_1AD and P_2AD

The types and severity of adverse reactions of the P_1AD and P_2AD treatments are listed in Table 6.

The major hematological side effect in 45 patients was thrombocytopenia and leucopenia. The thrombocytopenia rate and leucopenia rate in P_1AD and P_2AD groups were 62 % vs. 38 % ($p=0.091$) and 48 % vs. 29 % ($p=0.167$), respectively. The III-IV grade thrombocytopenia for P_1AD and P_2AD treatment were 38 % vs. 13 % ($p=0.049$). Eight patients in the P_1AD group required platelet transfusion, while it was required for only two patients in the P_2AD group. Six patients in the P_1AD group needed G-CSF adjuvant therapy, while this was not required in the P_2AD group.

The main non-hematological side effects were peripheral neuropathy (15 out of 45 patients, 33.3 %), presenting as numbness, paresthesia, and pain. The symptoms in 76 % of patients occurred in the first one to two cycles of PAD

Table 1 The clinical characteristics of patients before PAD treatment

Characteristics	P_1AD (N=21)	P_2AD (N=24)
Age, median y (range)	58 (30–75)	61 (33–81)
Sex, n (%)		
Male	13 (62)	15 (63)
Female	8 (38)	9 (37)
ISS Stage, n (%)		
I	2 (10)	3 (12)
II	9 (43)	10 (42)
III	10 (47)	11 (46)
Myeloma isotype, n [κ:λ] (%)		
IgG	12 [7:5] (57)	13 (8:5) (54)
IgA	7 [3:4] (33)	8 (4:4) (33)
Bence Jones protein	2 [1:1] (10)	3 (1:2) (13)
Karnofsky performance status, n (%)		
No higher than 50 %	5 (24)	8 (33)
50–80 %	11 (52)	10 (42)
More than 80 %	5 (24)	6 (25)
BM plasmacytosis, median % (range)	46 (13–90)	51 (15–73)
Extramedullary plasmacytoma, n (%)	4 (19)	4 (17)
Prior treatments		
Chemotherapy times, median (range)	4.5 (2–13)	4.1 (3–11)
Anthracycline chemotherapy, n (%)	8 (38)	10 (42)
Conventional chemotherapy and Thalidomide, n (%)	6 (29)	8 (33)
Bortezomib-based regimen, n (%)	1 (5)	1 (4)
Laboratory values, mean (range)		
LDH, U/L	312 (106–755)	289 (122–713)
β_2 microglobulin, mg/L	6.1 (1.5–23)	5.7 (1.7–21)
Albumin, g/L	28 (23–40)	31.1 (25–43)
Hemoglobin, g/L	98 (51–142)	95 (55–136)
Platelets, $\times 10^9$/L	94 (65–220)	101 (61–270)
Creatinine, μmol/L	96 (61–421)	115 (65–580)
Calcium, mmol/L	2.1 (1.8–3.5)	2.3 (1.9–3.3)
Grade 1–2 peripheral neuropathy, n (%)	1 (5)	1 (4)

BM bone marrow, *LDH* lactate dehydrogenase

treatment. The peripheral neuropathy rates in the P_1AD and P_2AD groups were 52 and 17 % (P=0.013), while grade III-IV peripheral neuropathy were 33 % vs. 8 % (p=0.042). All the 9 patients with grade III-IV peripheral neuropathy received the neurological nutrition treatment by taking vitamin B1 and B12, as well as other suitable treatments. Among them, 3 patients in the P_1AD group went into remission and the toxicity was reduced to ≤ II grade. Then, P_1AD treatment with 25 % dose reduction of bortezomib was continued for four to six cycles, and the symptom of peripheral neuropathy did not worsen. No patient experienced a cardiac-related adverse event despite the use of an anthracycline. The gastrointestinal side effects included nausea, vomiting, abdominal distension, and diarrhea. The grade III-IV gastrointestinal reaction rates in the two groups were 43 % vs. 13 % (P= 0.024), respectively. The fatigue rates in the two groups were 43 % vs. 21 % (P=0.102). No patient treated with prophylactic acyclovir had viral infections. However, 8 patients without antiviral prophylaxis developed herpes zoster infections.

Table 2 The efficacy of the PAD treatment for 45 patients with relapsed or refractory MM

Efficacy	N	Percentage (%)
CR	9	20
VGPR	10	22
PR	17	38
SD	6	13
PD	3	7

CR complete remission, *VGPR* very good partial remission, *PR* partial remission, *SD* stable disease, *PD* progression of disease

Table 3 The relationship between PAD efficacy response and the prognostic factors of conventional chemotherapy (mean ± standard deviation)

Efficacy	Case (n)	β_2-MG (mg/L)	Albumin (g/L)	Tumor cell (%)	Serum calcium (mmol/L)	Previous chemotherapy (times)
CR	9	8.8±3.2	31.1±3.3	48.8±4.5	2.2±0.9	3.8±2.2
VGPR	10	10.6±2.6	27.9±4.1	50.2±6.1	2.1±1.2	5.1±2.7
PR	17	6.9±3.7	30.6±3.5	47.9±7.2	2.3±0.8	4.2±2.9
SD + PD	9	7.5±4.1	28.5±6.8	49.5±4.3	2.1±1.1	4.1±2.5
P value		0.0512	0.1023	0.874	0.973	0.501

CR complete response, *VGPR* very good partial response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *β_2-MG* β_2 microglobulin

Among them, 3 patients developed grade 1–2 herpes zoster infections and 3 developed grade 3–4 infections in the P_1AD group, while the 2 patients in the P_2AD group suffered from grade 1–2 herpes zoster infections. The remission of adverse reactions was achieved after supportive treatment, or the reduction of bortezomib dose.

After the fifth P_1AD treatment, one patient who suffered from past chronic bronchitis, with PR efficacy assessment, had respiratory failure. His oxygen saturation dropped to 20 %, and interstitial lung disease was diagnosed based on CT scan. The patient died even after comprehensive rescue treatments of anti-bacteria, anti-virus and anti-fungus drugs, and inhaling of high concentrations of oxygen.

Discussion

In this study, we evaluated the efficacy and safety profile of a bortezomib-dose-reduced PAD regime in patients with relapsed or refractory MM in China. Compared with the conventional PAD regime, dose reduction of bortezomib had similar efficacy, but significantly relieved the side effects.

Efficacy of PAD Treatment Varies in Different Races

Bortezomib is oxidatively metabolized by cytochrome P450 enzymes which present various polymorphisms between populations of Asia and Europe-America [18, 19], indicating that the efficacy and safety of PAD therapy for the relapsed or refractory MM patients might be different in different races. Therefore, it is very important to explore the efficacy and safety of PAD treatment in the Chinese population, which has a relatively high incidence of MM.

Our results showed that 80 % of the relapsed or refractory MM patients had at least a PR effect after PAD treatment, in which the CR or VGPR rate was 42 %. The efficacy was higher than that in the European patients with the relapsed or refractory MM (67 % of the patients exhibited at least a PR effect; CR or VGPR rate was 25 %) [12]. The difference might be related with the fact that 27 % of the latter patients received prior bortezomib treatment and 58 % previously underwent autologous hematopoietic stem cell transplantation treatment, respectively. On the other hand, the Chinese refractory or relapsed MM patients may be more sensitive to the PAD therapy.

Combined, PAD treatment in Chinese patients with relapsed or refractory MM had the following characteristics: quick effectiveness with 1–3 cycles (an average of 1.6 cycle) to achieve the best efficacy and high remission quality.

Efficacy of PAD Regimen in MM Patients with Extramedullary Plasmacytoma Might be Related to Protein Synthesis Rate in Myeloma Cells

There is no report of systematic research on the treatment of extramedullary plasmacytoma in patients with refractory MM.

Table 4 The clinical characteristics and efficacy response of 8 patients with extramedullary plasmacytoma

Sex	Age (y)	Diagnosis	Location of extramedullary plasmacytoma	PAD regimen	Efficacy
Male	45	IgGIIB	back soft tissue shadow	P_1AD	PR
Male	57	IgGGIIIB	right chest wall	P_1AD	PR
Female	63	IGAIIIA	right chest wall	P_1AD	VGPR
Male	59	IgGIIIB	left middle tibia	P_1AD	CR
Female	69	IgGIIA	right middle tibia	P_2AD	PR
Female	43	IgAIIIA	upper right side of the head temporal	P_2AD	VGPR
Male	60	K light chain IIB	left chest wall (hepatosplenomegaly)	P_2AD	VGPR
Male	67	IgGIIA	right chest wall	P_2AD	CR

Table 5 Response of patients with relapsed/refractory MM receiving P_1AD and P_2AD regimen

Efficacy	P_1AD n (%)	P_2AD n (%)
CR	5 (24 %)	4 (17 %)
VGPR	5 (24 %)	5 (21 %)
PR	7 (33 %)	10 (41 %)
SD	3 (14 %)	3 (13 %)
PD	1 (5 %)	2 (8 %)

CR complete remission, *VGPR* very good partial remission, *PR* partial remission, *SD* stable disease, *PD* progression of disease

A patient with primary extramedullary plasmacytoma of the pancreas had been reported to reach a near complete remission after treated with bortezomib and hyper-dose dexamethasone [20]. However, the benefits of bortezomib as well as other anti-myeloma drugs in the efficacy and long-term survival of patients with extramedullary plasmacytoma need further observation.

In this study, eight MM patients with extramedullar plasmacytoma (4–10 cm diameter) reached an effect of PR or better after the first cycle of PAD treatment. The mechanism responsible for the efficacy of PAD treatment for extramedullary plasmacytoma is not clear. It is well known that extensive immunoglobulin proteins are synthetized in myeloma cells accompanied by unfolded proteins, which need to be degraded by the ubiquitin-proteasome system [21]. As an inhibitor of 26S proteasome, bortezomib inhibits protein degradation and induces apoptosis in various malignant cells, especially in the immunoglobulin-high cells [22]. We found

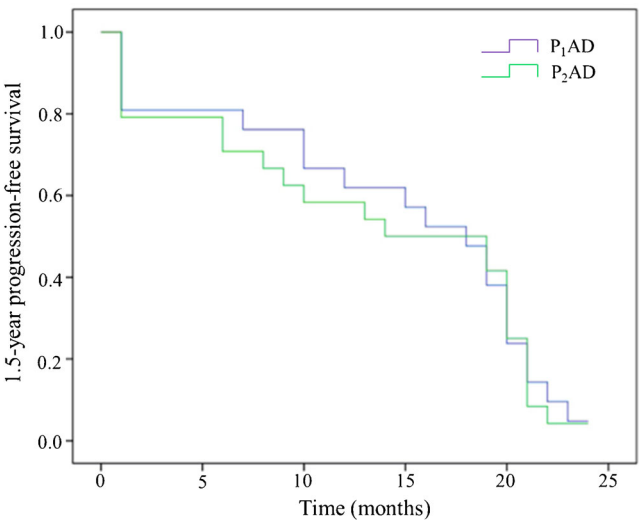

Fig. 1 Progression-free survival (PFS) from the start of PAD regimen in patients receiving P_1AD (bortezomib 1.3 mg/m^2; n=21) and P_2AD (bortezomib 1.0 mg/m^2; n=24)

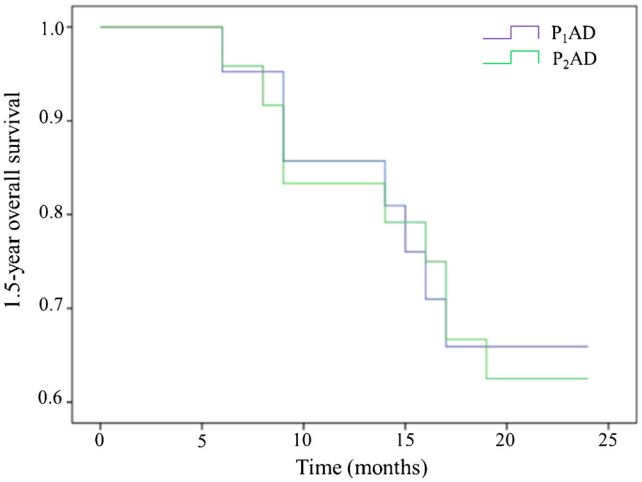

Fig. 2 Overall survival (OS) from the start of PAD regimen in patients receiving P_1AD (bortezomib 1.3 mg/m^2; n=21) and P_2AD (bortezomib 1.0 mg/m^2; n=24)

that compared to the patients with stable or progressive disease, the level of tumor proteins were significantly higher in the 8 patients with extramedullary plasmacytoma (86±12 vs. 53±7 g/L). Thus, we hypothesized that the high level of tumor proteins in the 8 patients may contribute to the exceptional efficacy of PAD regimen, which required to be confirmed in the further research. Besides, in 7 out of the 8 patients, the plasma cell infiltration sites were in the bone tissues of the proximal marrow or in the soft tissues near bone. Location of the plasma cell may be another important factor that affects the efficacy of PAD regiment in MM patients with extramedullary plasmacytoma.

Furthermore, in this study, curative effect on patients with extramedullary plasmacytoma seems to be better in the P_2AD group than that in the P_1AD group. Due to the limitation of small simple size, more patients will be enrolled in our future study to explore this question.

A Bortezomib-Dose-Reduced PAD Regime is More Suitable for Chinese Patients with Advanced MM

The dose of bortezomib in the PAD regimen (1.3 mg/m^2) was set mainly based on the efficacy and safety trials from European and American studies. However, this dose is not suitable for Asian patients with myeloma. In Japan, 15.2 % patients who received PAD treatment with this dose of bortezomib had serious complications of respiratory failure [23, 24]. Based on one report in China, 1.3 mg/m^2 bortezomib causes herpes simplex virus infection in 60 % of patients [25].

It has been reported that reduction of treatment frequency of bortezomib in the regimen employing bortezomib and dexamethasone could reduce the incidence of grade 3 and 4 neuropathies in patient with advanced MM [7]. Beside, in the

Table 6 The types and severity of adverse reactions of the P_1AD and P_2AD treatments

Adverse side effects	P_1AD (n)		P_2AD (n)		P_1AD	P_2AD	*p*
	I–II	III–IV	I–II	III–IV	n (%)	n (%)	
Thrombopenia	5	8	6	3	13 (62 %)	9 (38 %)	0.091
Leukopenia	5	5	5	2	10 (48 %)	7 (29 %)	0.167
Peripheral neuropathy	4	7	2	2	11 (52 %)	4 (17 %)	0.013
Fatigue	7	2	4	1	9 (43 %)	5 (21 %)	0.102
Nausea, vomiting	3	5	4	2	8 (38 %)	6 (25 %)	0.266
Abdominal distention, diarrhea	2	4	3	1	6 (29 %)	4 (17 %)	0.274
Herpes zoster virus infection	3	3	2	0	6 (29 %)	2 (8 %)	0.083

treatment of relapsed or refractory MM with bortezomib alone, similar treatment efficacy was achieved after the treatment of 1.3 or 1.0 mg/m^2 dose of bortezomib, while the rate of treatment-emergent adverse events was lower in the 1.0 mg/m^2 dose group [26, 27]. Similar results were demonstrated in the newly diagnosed MM patients treated with bortezomib-dose-reduced PAD regimen [15]. Thus, it is necessary to study the efficacy and safety of the PAD regimen with conventional and reduced doses of bortezomib for Chinese patients with relapsed or refractory MM.

In this study, PAD treatments consisting of two different doses of bortezomib, 1.3 mg/m^2 (P_1AD) or 1.0 mg/m^2 (P_2AD) were used to treat 45 patients with relapsed or refractory MM. No significant difference between the two regiments was determined in the overall efficacy response rate, CR or VGPR response rate, and 1.5-year PFS and OS. Therefore, the reduction of bortezomib dose in the PAD regimen did not affect the efficacy for Chinese patients with relapsed or refractory MM.

The adverse side effects of PAD are closely related with bortezomib dosage. Hematological toxicity manifested as thrombocytopenia and leukopenia, consistent with previous study [28]. The incidence of thrombocytopenia and leukopenia in the P_1AD regimen group was similar as that reported in the literature (62 % vs. 66 %; 48 % vs. 45 %) [12]. The incidence of III-IV thrombocytopenia in the P_2AD regimen was significantly reduced in comparison with that in the P_1AD regimen (13 % vs. 38 %, p=0.049). The mechanism of thrombocytopenia in this treatment might be related to the interference of NF-κB activity by bortezomib, which interferes with megakaryocytes maturation and platelet production [29].

Compared to the P_1AD regimen, the P_2AD regimen could reduce the following common non-hematological toxicity rates: peripheral neuropathy and III-IV grade gastrointestinal reactions. The grade of herpes zoster virus infection after P_2AD treatment was relatively higher than that after the P_1AD regimen. Considering the significant inhibitory effect of bortezomib on $CD4^+$ T cell function [30], the impaired T-cell-mediated immune system may responsible for the higher virus infection rate in the P_1AD group.

One MM patient with chronic bronchitis (PR effective response) had hypoxemia during the 5th P_1AD treatment, and eventually died of respiratory failure after ineffectual emergency treatment. In 46 Japanese MM patients who received 1.3 mg/m^2 bortezomib treatment, 7 patients (15.2 %) had respiratory failure and 3 of them died after ineffectual emergency treatment. Six of these seven patients had lung injury history in the early course of hematopoietic stem cell transplantation [23, 24]. These results indicated that a dose of 1.3 mg/m^2 bortezomib might induce higher pulmonary toxicity in Asian MM patients. Basic pulmonary disease might be a high risk factor for this serious complication. This compilation was relatively rare in Europe and America, where bortezomib is more commonly used. Therefore, the Asian population might be more susceptible to this adverse side effect.

However, limitation of our study might be the relatively small sample size, which limited the power of this study to show the benefits of bortezomib-dose-reduced PAD regime in patients with relapsed or refractory MM, especially in the patients with extramedullary plasmocytoma.

Conclusion

In summary, the PAD regimen is an effective form of treatment for Chinese patients with relapsed or refractory MM. PAD regimen with dose-reduced bortezomib did not affect its efficacy, while it significantly reduced the incidence of common adverse reactions. A bortezomib-dose-reduced PAD regimen might be more suitable for Chinese patients with relapsed or refractory MM.

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Conflict Interest All authors have no conflicts of interest.

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