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Once-weekly bortezomib had similar effectiveness and lower thrombocytopenia occurrence compared with twice-weekly bortezomib regimen in treating patients with newly diagnosed multiple myeloma in China

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Abstract

The study aims to examine the treatment effect and adverse reactions of patients with newly diagnosed MM receiving different bortezomib-based regimens.

This was a retrospective study of patients with newly diagnosed MM and who were treated with bortezomib-based combined chemotherapy at the Department of Hematology of the 2 affiliated hospitals of Wenzhou Medical University between July 2009 and May 2016. Cox proportion hazard multivariate analyses were carried out to assess the differences in treatment effect and adverse events between standard (1.3 mg/m^2 on days 1, 4, 8, 11) and weekly (1.6 mg/m^2 on days 1, 8, 15) cohorts, as well as the differences between intravenous injection and subcutaneous injection therapy. Progression-free survival (PFS) and overall survival (OS) were assessed using Kaplan–Meier method and the log-rank test.

Among the 117 patients, 78 patients were treated with bortezomib standard therapy and 39 patients were treated with bortezomib weekly therapy (all with intravenous injection). In all patients, the treatment strategy was not independently associated with PFS or OS. The patients in the weekly therapy group had less thrombocytopenia events than those in the standard therapy group. The subcutaneous route had similar treatment effect as the intravenous route, but the incidence of peripheral neuropathy was lower.

The once-weekly bortezomib regimen was similar in effectiveness to standard therapy in treating patients with newly diagnosed MM, but the incidence of thrombocytopenia was lower with the weekly regimen compared with the standard regimen.

Abbreviations: DS = Durie-Salmon, IMWG = International Myeloma Working Group, ISS = International Staging System, MM = multiple myeloma, OS = overall survival, PFS = progression-free survival, PN = peripheral neuropathy.

Keywords: bortezomib, multiple myeloma, once-weekly, peripheral neuropathy, standard therapy, subcutaneous injection

1. Introduction

Multiple myeloma (MM) is a common malignant plasma cell disease, ranking second as the most common hematologic cancer after non-Hodgkin lymphoma, accounting for about 10% of hematologic cancers.[1–3] Median age at presentation is 66 years and 38% of the patients are >70 years of age at diagnosis, only 2% being <40 years of age.[4,5]

The overall risk of progression from asymptomatic state is 10% for the first 5 years and declines thereafter.[1–3] Since 2000, the median overall survival (OS) of patients with newly diagnosed MM is 44.8 months compared with 29.9 months before 2000.[6] This is due to the emergence of various new drugs, such as immunomodulators (thalidomide and lenalidomide), proteasome inhibitors (bortezomib and carfilzomib), histone deacetylase inhibitors, and monoclonal antibodies, and the development of stem cell transplantation.[7]

As the first artificially synthesized proteasome inhibitor, bortezomib has been confirmed by many clinical trials to significantly prolong the survival time of patients with MM[6–11] and combination therapy based on bortezomib is also recommended for the treatment of newly diagnosed and relapsed, refractory MM patients.[12] Currently, based on pharmacodynamics and a large number of preclinical studies,[8,13–20] the recommended standard regimen for bortezomib is still twice a

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week, that is, bortezomib 1.3 mg/m^2 by intravenous injection on days 1, 4, 8, and 11.[7,8,21,22] Although the standard bortezomib regimen shows more significant effects than the traditional chemotherapy regimens, its adverse reactions including thrombocytopenia, leukopenia, severe peripheral neuropathy (PN), gastrointestinal reactions, herpes zoster, and various infections[23] often lead to the reduction of the dose and even to the termination of treatment, affecting the efficacy and prognosis.[24] Therefore, alternative less toxic regimens are being sought, such as changing from twice weekly to once weekly[22,25–27] or from the traditional intravenous administration to subcutaneous injection.[28,29] So far, the studies suggest that the efficacy of the bortezomib once weekly regimen was relatively good and with low toxicity.

Nevertheless, data are still lacking in various populations. Therefore, the aim of the present retrospective study was to examine the treatment effect and adverse reactions of patients with newly diagnosed MM receiving different bortezomib-based regimens and routes of administration in 2 hospitals in China.

2. Methods

2.1. Study design and patients

This was a retrospective study of patients with newly diagnosed MM and who were treated with bortezomib-based combined chemotherapy at the Department of Hematology of the 2 affiliated hospitals of Wenzhou Medical University between July 2009 and May 2016. The study was approved by the ethics committee of Wenzhou Medical University (approval No. L-2018–41). The need for individual consent was waived by the committee because of the retrospective nature of the study.

The inclusion criteria were:

(1) received at least 1 cycle of treatment;
(2) diagnosis of MM in accordance with the International Myeloma Working Group (IMWG) MM diagnostic criteria;[30] and
(3) no missing data among the pre-planned variables to collect (as shown in the Tables).

The Durie-Salmon (DS) and International Staging System (ISS) were used for staging and grouping.[31]

2.2. Therapeutic regimens

All patients received a combined chemotherapy regimen based on bortezomib and dexamethasone. Additional drugs, such as anthracycline (epirubicin hydrochloride), thalidomide, and cyclophosphamide could be used according to the specific condition of each patient.

The patients in the standard therapy group were treated with bortezomib 1.3 mg/m^2 by intravenous or subcutaneous injection on days 1, 4, 8, and 11, and with dexamethasone 40 mg/d by intravenous infusion on days 1 to 2, 4 to 5, 8 to 9, and 11 to 12. A cycle was 21 days. The patients in the weekly therapy group received bortezomib 1.6 mg/m^2 by intravenous injection on days 1, 8, and 15, and dexamethasone 40 mg/d by intravenous infusion on days 1 to 2, 8 to 9, and 15 to 16. A cycle was 28 days. Supportive treatments were provided as needed. If adverse reactions occurred during the treatment, the drug dose was adjusted or treatment was delayed according to the specific situation.

2.3. Data collection

Demographics (age, sex), clinical characteristics (M protein type, DS staging, ISS staging, creatinine, β2-microglobulin, blood calcium, hemoglobin, albumin, percentage of bone marrow plasma cells, genotypes), treatment effect and adverse reactions were extracted from the medical charts.

Treatment effect was evaluated according to the IMWG unified standard,[32] which was divided into complete remission (CR), very good partial remission (VGPR), partial remission (PR), stable disease (SD), and progressive disease (PD). Response to treatment was assessed after the end of each cycle of treatment. The overall response rate (ORR) was the sum of the PR, VGPR, and CR rates.

The end of follow-up was death of the patient or January 1, 2017. OS was defined as the time from the start of bortezomib treatment to the last follow-up or death. Progression-free survival (PFS) was defined as the time from the start of bortezomib treatment to disease relapse or progression or death. The criteria for progression or recurrence were based on the current guidelines.[1,2,7,32]

The adverse reactions are routinely graded using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), based on the version that was current when the adverse reactions occurred. These data were extracted from the medical charts.

2.4. Statistical analysis

SPSS 21.0 (IBM, Armonk, NY) was used for statistical analysis. The Kolmogorov-Smirnov test was used to determine whether the continuous variables were normally distributed or not. Normally distributed continuous data were presented as means ± standard deviation and analyzed using the Student *t* test. Non-normally distributed data were presented as medians (range) and analyzed using the Mann–Whitney *U* test. Categorical data were presented as frequencies and analyzed using the chi-square test or Fisher exact test. PFS and OS were computed using the Kaplan–Meier method and compared using the log-rank test. The Cox model was used to perform multivariable analysis. Two-sided *P* values $<.05$ were considered statistically significant.

3. Results

3.1. Characteristics of the patients

From July 2009 to May 2016, 117 patients with newly diagnosed MM were treated with bortezomib-based therapy and included in this study. Among the 117 patients, 78 were treated with bortezomib standard therapy, including 57 patients (64.0%) with intravenous injection, 21 patients (23.6%) with subcutaneous injection; there were 39 patients who received the bortezomib weekly therapy (all with intravenous injection).

The characteristics of the patients are shown in Table 1. The patients in the weekly therapy group were older (68.6 ± 10.0 vs 62.6 ± 10.3 years, $P = .036$). The median number of treatment cycles in the standard and weekly therapy groups were 4 (1–8) and 4 (1–6), respectively. Of the 78 patients in the standard therapy group, 2 (2.6%) received VTD (bortezomib + thalidomide + dexamethasone), 9 (11.5%) received VD (bortezomib + dexamethasone), 17 (21.8%) received VCD (bortezomib + cyclophosphamide + dexamethasone), and 50 (64.1%) received PAD (bortezomib + epirubicin hydrochloride + dexamethasone).

Table 1

Baseline clinical characteristics of patients with multiple myeloma with initial treatment.

Clinical characteristics	Standard therapy (n = 78)		Weekly therapy (n = 39)	P*
	Intravenous injection (n = 57)	Subcutaneous injection (n = 21)		
Age (mean ± SD)	62.6 ± 10.3		68.6 ± 10.0	.036
<65 yr, n (%)	32 (56.1)	12 (57.1)	14 (35.9)	
≥65 yr, n (%)	25 (43.9)	9 (42.9)	25 (64.1)	
Sex				.581
Male	38 (66.7)	12 (57.1)	27 (69.2)	
Female	19 (33.3)	9 (42.9)	12 (30.8)	
M protein type				.095
IgG	28 (49.1)	7 (33.3)	16 (41.0)	
IgA	12 (21.1)	6 (28.6)	11 (28.2)	
IgM	0	0	3 (7.7)	
IgD	0	0	1 (2.6)	
Light chain type	13 (22.8)	4 (19.0)	7 (17.9)	
No secretion type	2 (3.5)	3 (14.3)	1 (2.6)	
Undetermined	2 (3.5)	1 (4.8)	0	
DS staging				.186
Stage I	4 (7.0)	2 (9.5)	1 (2.6)	
Stage II	16 (28.1)	2 (9.5)	5 (12.8)	
Stage III	37 (64.9)	17 (81.0)	33 (84.6)	
Group A	44 (77.2)	18 (85.7)	27 (69.2)	.220
Group B	13 (22.8)	3 (14.3)	12 (30.8)	
ISS staging				.588
Stage I	3 (5.3)	2 (9.5)	4 (10.2)	
Stage II	32 (56.1)	15 (71.4)	20 (51.3)	
Stage III	22 (38.6)	4 (19.1)	15 (38.5)	
Creatinine (μmol/L, median, range)	89 (41–1288)	130 (48–601)	140 (37–612)	.515
β2 microglobulin (mg/L, median, range)	7.3 (2–30)	5.5 (2–19.7)	7.6 (1–54)	.079
Blood calcium (mmol/L, median, range)	2.31 (1.62–3.59)	2.32 (1.80–3.07)	2.28 (1.43–3.39)	.404
Hemoglobin (g/L, mean ± SD)	89.9 ± 23.9	98.45 ± 28.1	90.5 ± 24.6	.677
Albumin (g/L, mean ± SD)	33.5 ± 7.3	32.1 ± 7.6	29.2 ± 6.4	.007
% of bone marrow plasma cells (mean ± SD)	0.38 ± 0.25	0.34 ± 0.22	0.28 ± 0.28	.049
Karyotype and FISH test	27	10	16	
Del(13q14), n (%)	17 (45.9%)		5 (31.3%)	
RB1, n (%)	17 (45.9%)		5 (31.3%)	
1q21, n (%)	22 (59.5%)		9 (56.3%)	
IgH, n (%)	27 (72.9%)		8 (50.0%)	
P53, n (%)	8 (21.6%)		3 (18.8%)	
FISH normal n (%)	4 (10.8%)		3 (18.8%)	

* Weekly therapy vs standard therapy (including intravenous injection and subcutaneous injection).

Of the 39 patients in the weekly therapy group, 37 (94.9%) received VTD and 2 (5.1%) received PAD. Nine patients were treated with autologous stem cell transplantation in the standard treatment group and only one patient underwent autologous stem cell transplantation in the weekly therapy group.

Percentage of bone marrow plasma cells ($P = .049$) and albumin levels ($P = .007$) were lower in the weekly therapy group. In the standard therapy group, 37 patients underwent routine chromosome and FISH detection and the patients with normal FISH accounted for 10.8% (4/37). In the weekly therapy group, 16 cases underwent routine chromosome and FISH detection and patients with normal FISH accounted for 18.8% (3/16) (Table 1). There were 4 patients with maintenance hemodialysis in the standard therapy group and 3 patients in the weekly therapy group.

3.2. Treatment effect

The ORR of the standard and weekly therapy groups was 70.5% and 71.8%, respectively ($P = .886$) (Table 2). The ORR in the 57 patients with intravenous injection in the standard therapy group was 63.2%, which was lower than in the patients who received subcutaneous injection (90.5%) ($P = .019$) (Table 2). The SD rate in patients with intravenous injection was 35.1%, while the SD rate in patients with subcutaneous injection was only 9.5%. There were no differences regarding the CR, VGPR, and PR rates.

3.3. Survival

The median follow-up was 21 (range, 0.6–82.6) and 23 (range, 2–82) months in the standard and weekly therapy groups, respectively ($P = .277$). The patients in the standard therapy group had a median PFS of 17.5 (range, 0.6–71) months and a median OS of 19 (range, 0.6–81) months, which were 19 (range, 0.4–79.7) and 22 (range, 1.1–80.0) months, respectively, in the weekly therapy group (PFS, log-rank $P = .143$; OS, log-rank $P = .730$) (Fig. 1).

The median PFS of patients who received intravenous and subcutaneous injection in the standard therapy group was 18 months (range, 0.6–71) and 16 months (range, 1–34), respectively ($P = .621$), and the median OS was 22 (range, 0.6–81) months and 17 months (range, 1–34), respectively ($P = .240$) (Fig. 2). There was no significant difference in PFS (log-rank $P = .621$) and OS (log-rank $P = .240$) between the 2 groups.

Table 2

Comparison of therapeutic effects in patients with multiple myeloma with initial treatment.

Therapeutic effects	Standard therapy (n = 78)		Weekly therapy (n = 39)	$P^{\dagger}$
	Intravenous injection (n = 57)	Subcutaneous injection (n = 21)		
ORR	36 (63.2)*	19 (90.5)*	28 (71.8)	.886
CR	15 (26.3)	9 (42.9)	14 (35.9)	–
VGPR	1 (1.8)	1 (4.7)	3 (7.7)	–
PR	20 (35.1)	9 (42.9)	11 (28.2)	–

ORR (overall response rate) = CR+VGPR+PR rate.

* Intravenous injection vs subcutaneous injection: ORR rate, $P = .019$.

† Weekly therapy vs standard therapy (including both intravenous injection and subcutaneous injection).

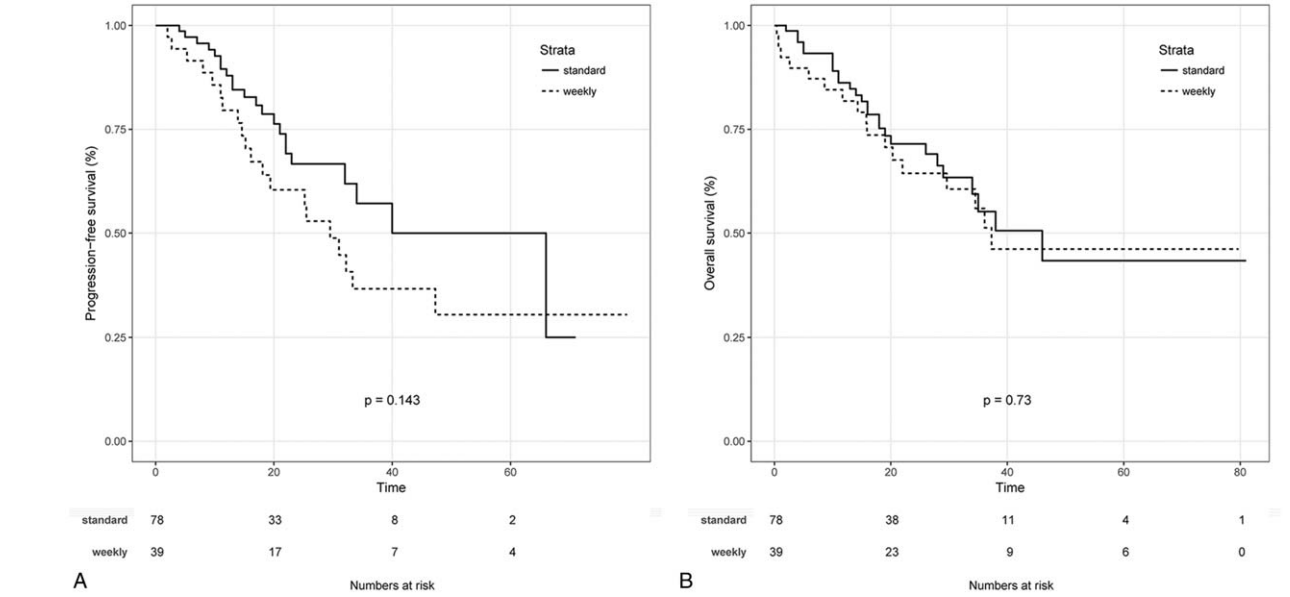

Figure 1. PFS and OS analysis of patients in the standard therapy group and the weekly treatment group. There were no differences in PFS and OS between the standard and weekly therapy groups. (A) PFS. (B) OS. PFS = Progression-free survival, OS = overall survival.

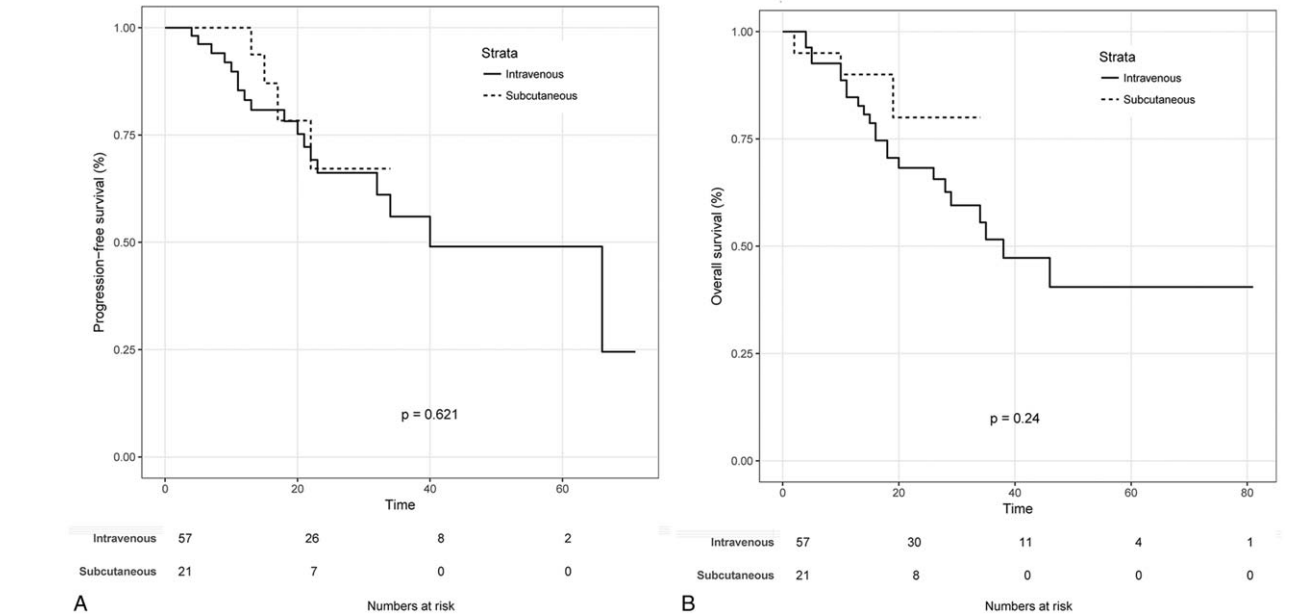

Figure 2. PFS and OS analysis of patients in intravenous and subcutaneous injections in the standard therapy group. There were no differences in PFS and OS between the subcutaneous and intravenous routes. (A) PFS. (B) OS. PFS = Progression-free survival, OS = overall survival.

Table 3

Multivariate Cox analysis of all patients.

Clinical characteristics		Progression-free survival			Overall survival		
		HR	95% CI	P	HR	95% CI	P
Age	≥65 vs <65	0.651	(0.335,1.266)	.206	1.19	(0.622,2.274)	.599
Sex	Male vs female	1.208	(0.616,2.368)	.583	1.153	(0.583,2.277)	.683
DS stage				.07			.573
	I	1	–	–	1	–	–
	II	2.009	(0.519,7.784)		1.791	(0.374,8.568)	
	III	0.755	(0.211,2.700)		1.191	(0.267,5.311)	
DS stage (Group)	B vs A	2.799	(1.309,5.989)	.008	2.696	(1.341,5.421)	.005
Treatment strategy	Weekly vs standard	1.963	(1,3.854)	.06	0.954	(0.492,1.851)	.89

DS = Durie-Salmon.

During follow-up, 34 patients (43.6%) died in the standard therapy group and 17 patients (43.6%) died in the weekly therapy group ($P = 1.000$). The cause of death was mainly disease progression, various serious infections, renal failure, or heart failure.

3.4. Multivariable analyses

In all patients, B DS stage was the only factor independently associated with PFS (HR = 2.799, 95%CI: 1.309–5.989, $P = .008$) and OS (HR = 2.696, 95%CI: 1.341–5.421, $P = .005$); the treatment strategy was not independently associated with PFS or HR (Table 3). In patient with the standard therapy, no factor was found to be independently associated with PFS and OS; specifically, no differences were found in PFS and OS between the intravenous and subcutaneous routes (Table 4).

3.5. Adverse reactions

There were no differences regarding the adverse effects between the standard and weekly therapy groups except regarding thrombocytopenia (all grades: 61.5% vs. 41.0%, $P = .04$; grades 3–4: 38.5% vs 17.9%, $P = .03$). In the standard therapy group, those with intravenous injection had higher rates of PN than those receiving subcutaneous injection (all grades: 54.4% vs 9.5%, $P < .05$; grades 3–4: 12.3% vs 0%, $P = .18$) (Table 5).

Table 4

Multivariate Cox analysis of patients with standard therapy.

Clinical characteristics		Progression-free survival			Overall survival		
		HR	95% CI	P	HR	95% CI	P
Age	≥65 vs <65	0.747	(0.298,1.875)	.535	1.336	(0.581,3.073)	.495
Sex	Male vs female	0.802	(0.296,2.175)	.665	0.684	(0.257,1.823)	.448
DS stage				.99			.84
	I						
	II	0.954	(0.175,5.214)		0.688	(0.124,3.826)	
	III	0.909	(0.19,4.351)		0.926	(0.195,4.391)	
DS stage (Group)	B vs A	1.104	(0.289,4.211)	.885	2.423	(0.892,6.578)	.082
Treatment strategy	Subcutaneous vs intravenous	0.714	(0.229,2.228)	.562	0.494	(0.140,1.737)	.271

DS = Durie-Salmon.

Table 5

Comparison of adverse reactions in patients with multiple myeloma with initial treatment.

	Standard therapy (n = 78)						
	Intravenous injection (n = 57)		Subcutaneous injection (n = 21)		Weekly therapy (n = 39)		*
	All grades n (%)	Grade 3–4 n (%)	All grades n (%)	Grade 3–4 n (%)	All grades n (%)	Grade 3–4 n (%)	P
Leukocytopenia	40 (70.2)	11 (19.3)	15 (71.4)	2 (9.5)	21 (53.9)	4 (10.3)	.075
Thrombocytopenia	39 (68.5)	27 (47.4)	9 (42.9)	3 (14.3)	16 (41.0)	7 (17.9)	.036
Lung infection	27 (47.4)	22 (38.6)	14 (66.6)	12 (57.1)	17 (43.6)	16 (41.0)	.360
Urinary tract infection	2 (3.5)	0	1 (4.8)	0	2 (5.1)	0	.747
Herpes zoster	10 (17.5)	0	2 (9.5)	0	7 (18.0)	1 (2.6)	.723
Peripheral neuropathy†	31 (54.4)	7 (12.3)	2 (9.5)	0	13 (33.3)	0	.349
Constipation	10 (17.5)	0	4 (19.0)	0	5 (12.8)	0	.478
Diarrhea	6 (10.5)	0	4 (19.0)	0	9 (23.1)	3 (7.7)	.156
Nausea	8 (14.0)	0	6 (28.6)	0	2 (5.1)	0	.057
Ileus	3 (5.3)	2 (3.5)	0	0	2 (5.1)	1 (2.6)	.747

* Weekly therapy vs standard therapy (including intravenous injection and subcutaneous injection).

† Intravenous injection vs subcutaneous injection, $P < .05$.

4. Discussion

Although the efficacy of bortezomib in the treatment of MM is widely recognized,[21,27,32] its adverse reactions cannot be overlooked. The most common adverse reactions of standard therapy regimens (bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11) include hematological toxicity, digestive tract reactions, various infections, herpes zoster, PN, and fatigue. The occurrence of PN is associated with the dose of bortezomib and is the most common factor leading to drug reduction or termination of treatment.[24,27] The VISTA trial showed that patients >75 years of age are more likely to discontinue treatment because of drug toxicity when receiving intravenous bortezomib, while severe neuropathy persists in one third of patients.[33] Hence, the aim of alternative bortezomib regimens is to reduce adverse reactions while ensuring efficacy.[19,34] So far, the studies suggest that the efficacy of the bortezomib once weekly regimen is relatively good and with low toxicity in patients with MM,[22,25–27] but data are still lacking in various populations.

Therefore, this study aimed to examine the treatment effect and adverse reactions of patients with newly diagnosed MM receiving different bortezomib-based regimens (twice-weekly vs once-weekly) in 2 hospitals in China, as well as to examine the route of administration (intravenous vs subcutaneous) in those receiving the standard twice-weekly regimen. The results strongly suggest that the once-weekly bortezomib regimen was similar in efficacy to standard therapy in treating newly diagnosed patients with MM, but the incidence of thrombocytopenia was lower with the weekly regimen compared with the standard regimen. Among those receiving the standard regimen, treatment effect was similar, but the occurrence of PN was lower with the subcutaneous route. Those results mean that once-weekly bortezomib could improve tolerability without compromising effectiveness in Chinese patients with MM. In addition, the administration of intravenous bortezomib once weekly should be associated with lower patient burden in terms of visits to the hospital and costs compared with the twice-weekly regimen, but this will have to be confirmed by a pharmacoeconomics study.

Some clinical trials[10,35] showed that extending bortezomib to once a week could reduce the incidence of PN without changing the efficacy. Reeder et al[35] treated newly diagnosed MM patients with a VCD regimen in a phase II clinical trial: 33 patients received intravenous bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11, and 30 patients received intravenous bortezomib 1.5 mg/m^2 on days 1, 8, 15, and 22; after completing 4 cycles, the ORR was 96% and 93%, respectively, the CR rate was 46% and 48%, and the effectiveness ≥VGPR rate was 71% and 63%, respectively. The effectiveness of the above 2 regimens was similar, but the incidence of grade 3 to 4 adverse reactions in once-weekly bortezomib administration group was significantly lower than that in the twice-weekly group. In the GIMEMA trial,[10] bortezomib was administered intravenously twice-weekly at 1.3 mg/m^2 for cycles 1 to 4 and once-weekly at the same dose for cycles 5 to 9; the ORR of patients receiving twice-weekly and once-weekly administration was 86% and 85%, respectively, and the CR rate was 35% and 30%, respectively. In terms of adverse reactions, the grade 3 to 4 non-hematologic toxicity of the once-weekly administration group was significantly lower than that of the twice-weekly administration group. The incidence of grade 3 to 4 PN decreased from 28% to 8%, and the number of patients who discontinued treatment due to PN decreased from 15% to 5%. Taken together, those results support the results of the present study: similar treatment effect and lower toxicity for the once-weekly regimen compared with the twice weekly regimen.

Nevertheless, compared with the literature, the median PFS, OS, and 1- and 2-year PFS and OS rates were lower in the 2 groups in the present study. Indeed, Bringhen et al[10] reported that the 3-year PFS rates for patients receiving bortezomib twice- and once-weekly in the GIMEMA trial were 47% and 50%, respectively, and the 3-year OS rates were 89% and 88%, respectively. Mateos et al[36] compared the efficacy and safety of the VMP and VTP regimens in the induction treatment of elderly MM patients with initial treatment. Bortezomib was administered once a week in this trial. The ORR in the 2 groups was above 80%, the median PFS in the 2 groups was 34 months and 25 months, respectively, and the 3-year OS rate was 74% and 65%, respectively. In the present study, the 2-year PFS and OS rate of the standard therapy group and the weekly therapy group was only 36.0% and 38.5%, 46.1% and 46.2%, respectively. Several reasons could account for the discrepancies. First, in the present study, the median number of cycles in both groups was 4. Taking the above VISTA and GIMEMA trials as examples, both groups were required to complete nine cycles of induction treatment.[10,33] Therefore, previous studies had a higher cumulative dose than in the present study. Taking the GIMEMA trial[10] as an example, the total cumulative dose per square meter of patients receiving the weekly treatment was 39.4 mg/m^2, while the median cumulative dose of patients receiving weekly treatment in the present study group was only 19.2 mg/m^2. Based on the VISTA study, Mateos et al[32] found that increasing the cumulative dose of bortezomib could improve the OS. Secondly, in the present study, the percentage of patients with treatment effect ≥VGPR in the standard and weekly therapy groups was 33.7% and 43.6%, respectively, while in the study of Reeder et al.,[35] the percentage of patients with effectiveness ≥VGPR in the 2 groups was 71% and 63%, respectively. Many large-scale clinical trials showed that the rate of remission after induction treatment of MM was closely related to prognosis.[36,37] There was a significant correlation between CR or at least VGPR and long-term benefits of MM patients.[36] The VISTA study confirmed that bortezomib full-course treatment could achieve maximum remission.[33] The APEX study also confirmed that full-course bortezomib treatment could maximize efficacy in patients with relapsed MM.[38] In the present study, the number of patients who completed the full course of chemotherapy was very small. In the standard therapy group, 22 patients (24.7%) had more than 6 cycles of treatment and only 5 patients (5.6%) had completed 8 cycles of treatment. In the weekly therapy group, no patients completed 8 cycles of induction treatment and only 4 patients (10.3%) completed 6 cycles of treatment. This could be attributed to a number of possible reasons, including the cost of treatment for patients without insurance, smaller tolerable dose of bortezomib in Asian populations, and the higher frequency of elderly patients in the present study. Nevertheless, taken together, those results indicate that completing the entire treatment course is important to ensure optimal treatment effect and survival.

This study also compared the effects of intravenous and subcutaneous injections of bortezomib on the effectiveness of patients with newly diagnosed MM. In a phase III clinical trial (MMY-3021), Moreau et al[28] compared the efficacy and safety of bortezomib twice-weekly with intravenous and subcutaneous injections in the treatment of relapsed MM patients. The median course of treatment was 8 in both groups. After 8 cycles of induction treatment, the ORR of both subcutaneous and intravenous injection groups was 52%, the CR rate was 20% and 22%, respectively, and the rate of ≥VGPR was both 25%

($P > .05$). The median PFS of subcutaneous injection group and intravenous injection group was 10.2 months and 8 months, respectively ($P > .05$), and the 1-year OS rate were 72.6% and 76.7%, respectively ($P > .05$). Merz et al,[39] Liu et al,[40] and Wu et al[41] showed better tolerability and similar treatment response of subcutaneous vs intravenous bortezomib. On the other hand, Minarik et al[42] reported similar effectiveness but also similar adverse reactions of subcutaneous and intravenous bortezomib. In addition, Xu et al[43] highlighted that subcutaneous bortezomib is associated with better tolerability, intravenous bortezomib achieves faster and deeper response. Nevertheless, these results strongly suggest that subcutaneous and intravenous injections had similar effectiveness and prognosis in the treatment of MM patients. In the present study, the ORR of the subcutaneous injection group was significantly higher than that of the intravenous injection group, while the SD rate of the intravenous injection group was 35.1%, which was higher than that of the subcutaneous injection group. This could be explained by the different median numbers of cycles between the 2 groups (4 vs 5). There were no significant differences in PFS and OS between the 2 groups, suggesting that different administration routes did not affect the prognosis of patients with newly diagnosed MM, despite a difference in the ORR rate between the 2 groups. This discrepancy could be due to the small sample size or to a good initial response that did not translate into survival benefits. Nevertheless, the results suggest some benefits of the subcutaneous route, which could be worthy of further investigation.

The thrombocytopenia frequency in the standard therapy group was significantly higher than in the weekly therapy group, probably because 77% of patients in the standard therapy group were treated with the PAD or VCD regimen. Indeed, anthracycline and cyclophosphamide can induce thrombocytopenia, leukopenia and other hematological adverse reactions; if combined with bortezomib in the treatment of MM patients, the incidence of thrombocytopenia would be significantly increased.[7] In a phase II trial, Reeder et al[44] used the VCD regimen to treat newly diagnosed patients with MM and the results showed that the incidence of grade 3 to 4 thrombocytopenia was 25%. In the present study, the frequency of PN was similar in the 2 groups (standard vs weekly), but the difference was significant between the subcutaneous and intravenous routes (9.5% vs 54.4%). This is supported by the MMY-3021 trial,[28] in which the frequency of PN in patients with intravenous and subcutaneous injection was 53% and 38%, respectively, the incidence of grade ≥2 neuropathy was 41% and 24%, respectively, and the incidence of grade ≥3 neuropathy was 16% and 6%, respectively.

The present study has some limitations. This was a retrospective study, with all the inherent limitations. Of the 117 patients in this study, only 53 underwent routine chromosome and FISH detection, but the testing revealed that the rate of abnormalities was high in both groups. The treatment effects and adverse events could not be compared by genetic risk stratification due to the small sample size. Limited by economic conditions, many patients could not complete the full course of treatment, leading to low ORR, PFS, and OS. Future studies will have to address those issues.

5. Conclusions

Bortezomib once-weekly and twice-weekly have similar treatment effect compared with standard therapy in patients with newly diagnosed MM. Bortezomib once-weekly can reduce the incidence of thrombocytopenia. Subcutaneous injection and intravenous injection of bortezomib have similar treatment effect in the treatment of patients with newly diagnosed MM, but the subcutaneous route leads to less PN than the intravenous route.

Author contributions

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