

Analysis of the efficacy and safety of bortezomib for treating newly diagnosed multiple myeloma through different administration methods

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Background: This study aims to compare the efficacy and adverse reactions of bortezomib for treating newly diagnosed multiple myeloma (MM) through two different administration methods: intravenous (IV) injection and subcutaneous (SC) injection.

Methods: A retrospective analysis was performed in 205 patients with newly diagnosed MM, who were treated by the Department of Hematopathology, Henan Cancer Hospital, from June 2009 to December 2017. These patients were divided into two groups according to the treatment methods: IV injection group, IV injection of bortezomib; SC injection group, SC injection of bortezomib.

Results: After the first course of treatment, the effect of very good partial remission (VGPR) or above (\geq VGPR) in the IV injection group (IV group) and SC injection group (SC group) was 31.0% and 14.3%, respectively ($P=0.004$), while the overall response rate (ORR) was 72.0% and 49.5%, respectively ($P=0.001$). From the 2nd course to the 6th course of treatment, the ORR was not statistically different between these two groups. No significant difference was found in median progression-free survival (37 vs 45 months) and overall survival (63 vs 59 months). A lower frequency of adverse events, especially Grade 3 peripheral neuropathy, was observed in SC group compared with the IV group.

Conclusion: Compared with IV administration, SC bortezomib can provide a better balance between efficacy and toxicity.

Keywords: multiple myeloma, bortezomib, intravenous injection, subcutaneous injection

Introduction

Multiple myeloma (MM), the malignant tumor of the plasma cells, comprises of approximately 1.8% of cancers and 17% of hematological malignancies. At present, this disease has remained incurable with a high recurrence rate.¹ The use of proteasome inhibitor bortezomib and glucocorticoids is the standard scheme for newly diagnosed and recurrent/refractory MM, and it can improve the effect of MM significantly.²⁻⁴ The traditional administration method of bortezomib adopts intravenous (IV) injection. However, during the treatment process, some patients would suffer from adverse reactions, such as hematological toxicity, infection, peripheral neuropathy (PN), herpes zoster and digestive tract symptoms, and further treatments would be mostly affected by PN. In order to reduce the occurrence of PN, other countries attempted a new administration method, subcutaneous (SC) injection.^{5,6} SC administration of bortezomib was reported could reduce toxicity without loss of efficacy compared with the conventional intravenous (IV) bolus

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injections.⁶ But there are very limited data available about the safety and efficacy profile of SC bortezomib in Chinese and Asian patients with newly diagnosed MM.

The present study performs a retrospective comparison of the efficacy and safety of bortezomib for treating newly diagnosed MM in China through SC injection and IV injection.

Materials and methods

Case data

The clinical data of 205 patients with MM, who were diagnosed by the Department of Hematopathology, Henan Cancer Hospital, and treated with bortezomib from June 2009 to December 2017, were collected. The diagnosis, periodization and efficacy evaluation of MM were based on the MM NCCN diagnosis and treatment guidelines.⁷ All patients took the initial treatment, but the hematopoietic stem cell transplantation was not carried out due to the economy, age and physical condition. At least six courses of treatment were completed. This study was conducted in accordance with the declaration of Helsinki and approved by the Ethics Committee of our hospital. The written informed consent was obtained from all participants.

Treatment scheme

There are three schemes: VD (bortezomib and dexamethasone), VCD (bortezomib, cyclophosphamide and dexamethasone) and VAD (bortezomib, doxorubicin and dexamethasone). A total of 100 patients received bortezomib through IV injection (IV group): bortezomib, 1.3 mg/m², which was performed at the 1st, 4th, 8th and 11th day; 21 days were considered one course of treatment. A total of 105 patients received bortezomib through SC injection (SC group): bortezomib, 1.3 mg/m², which was performed at the 1st, 4th, 8th and 11th day; 21 days were considered one course of treatment. If the patient suffered from level 1–3 PN, paralytic bowel infarction, severe infection and other severe adverse reactions after the use of bortezomib, the dose of bortezomib was allowed to adjust to 1.0 mg/m², or the weekly dosage regimen was adopted. Cyclophosphamide through IV injection was given at a dose of 900 mg/m² on day 1 at each cycle. Doxorubicin through IV injection was given at a dose of 9 mg/m² on days 1 through 4 at each cycle.

Follow-up

Clinical and telephone follow-ups were mainly performed, and the follow-up deadline expired on November 30, 2018.

Evaluation of efficacy and adverse reactions

The evaluation of the efficacy was performed after every course of treatment, including complete remission (CR), very good partial remission (VGPR), partial remission (PR), minor remission (MR), stable disease (SD) and progression of disease (PD), in accordance with the International Myeloma Working Group's uniform response criteria for MM.^{5,7} Overall survival (OS) time: from the patient's treatment to death or loss to follow-up. Progression-free survival (PFS) time: from the patient's treatment to the progression or death caused by any reason. The evaluation of the adverse reactions was performed from the aspect of hematological toxicity, digestive tract symptoms, PN, pulmonary infection/upper respiratory infection, herpes zoster and hepatic injury.

Statistical process

The SPSS21.0 software was used for analysis, χ^2 -test was used for comparing among categorical data groups, the Kaplan–Meier method was used to describe the PFS and OS curve and log-rank test was used for comparisons among groups. $P < 0.05$ was considered statistically significant.

Results

Basic clinical features of patients

Among the 205 patients, 122 patients were male and 83 patients were female, and their median age was 61 years (range: 27–82 years). Immunophenotyping: 22 patients were tested to be IgA k type, 28 patients were IgA λ type, 48 patients were IgG k type, 57 patients were IgG λ type, 1 patient was IgD k type, 15 patients were k type, 33 patients were λ type and 1 patient had no secreting type. Furthermore, a total of 46 patients suffered from renal insufficiency. The differences in gender, age, typing, periodization and cytogeneticity among the patients of these two groups were not statistically significant (Table 1), but were comparable.

Efficacy and outcome

In the IV injection group, the overall response rate (ORR = CR + VGPR + PR) was 72.0%, 75.0% and 77.0%, respectively, after the 1st, 2nd and 3rd courses of treatment, 81.0% after the 4th course of treatment, 82.0% after the 5th course of treatment and 83.0% after the 6th course of treatment. In the SC injection group, the ORR was 49.5%, 72.4% and

Table 1 Baseline characteristics of patients in the IV group and the SC group

Characteristics	IV Group (N=100)	SC Group (N=105)	CHI ²	P-value
Gender (male/female)	58/42	64/41	0.185	0.667
Age, y	62 (32–82)	59 (27–81)	2.694	0.101
M-spike isotype			3.567	0.613
IgA	27 (27.0)	23 (21.9)		
IgG	52 (52.0)	53 (50.5)		
IgD	-	1 (0.9)		
K	6 (6.0)	9 (8.6)		
λ	14 (14.0)	19 (18.1)		
Non-secretory	1 (1.0)	-		
DS			1.119	0.571
I	5 (5.0)	9 (8.6)		
II	21 (21.0)	23 (21.9)		
III	74 (74.0)	73 (69.5)		
ISS			0.495	0.781
I	25 (25.0)	22 (21.0)		
II	38 (38.0)	43 (40.9)		
III	37 (37.0)	40 (38.1)		
Regimen			0.472	0.790
VD	50 (50.0)	56 (53.3)		
VCD	33 (33.0)	30 (28.6)		
VAD	17 (17.0)	19 (18.1)		
Reduction or delay of treatment	38 (38.0)	31 (29.5)	1.648	0.199

Notes: VD (bortezomib and dexamethasone), VCD (bortezomib, cyclophosphamide and dexamethasone), and VAD (bortezomib, doxorubicin and dexamethasone).

Abbreviations: IV, intravenous; SC, subcutaneous; DS, Durie–Salmon System; ISS, International Staging System.

78.1%, respectively, after the 1st, 2nd and 3rd courses of treatment, 80.0% after the 4th course of treatment, 81.0% after the 5th course of treatment and 81.9% after the 6th course of treatment. After the 1st course of treatment, the remission rate of VGPR or above (\geq VGPR) in the IV injection group and SC injection group was 31.0% and 14.3%, respectively, and the difference was statistically significant ($P=0.004<0.05$). The ORR was 72.0% and 49.5%, respectively, and the difference was statistically significant ($P=0.001<0.05$). From the 2nd to 6th courses of treatment, the ORR was not statistically different between these two groups ($P>0.05$, Table 2).

The median follow-up time for the IV injection group and SC injection group was 42 months (range: 2–105 months) and 24 months (range: 1–96 months), respectively.

Table 2 The response after every cycle

	IV Group, N (%)	SC Group, N (%)	CHI ²	P-value
Cycle 1				
CR	15 (15.0)	13 (12.4)	0.298	0.585
\geq VGCR	31 (31.0)	15 (14.3)	8.222	0.004
\geq PR	72 (72.0)	52 (49.5)	10.826	0.001
Cycle 2				
CR	16 (16.0)	17 (16.2)	0.001	0.970
\geq VGCR	35 (35.0)	28 (26.7)	1.671	0.196
\geq PR	75 (75.0)	76 (72.4)	0.181	0.670
Cycle 3				
CR	21 (21.0)	29 (27.6)	1.217	0.270
\geq VGCR	37 (37.0)	44 (41.9)	0.516	0.473
\geq PR	77 (77.0)	82 (78.1)	0.035	0.851
Cycle 4				
CR	29 (29.0)	33 (31.4)	0.143	0.705
\geq VGCR	49 (49.0)	52 (49.5)	0.006	0.940
\geq PR	81 (81.0)	84 (80.0)	0.033	0.857
Cycle 5				
CR	34 (34.0)	41 (39.0)	0.562	0.453
\geq VGCR	52 (52.0)	53 (50.5)	0.048	0.827
\geq PR	82 (82.0)	85 (81.0)	0.037	0.847
Cycle 6				
CR	40 (40.0)	50 (47.6)	1.207	0.272
\geq VGCR	54 (54.0)	59 (56.2)	0.099	0.753
\geq PR	83 (83.0)	86 (81.9)	0.042	0.837

Abbreviations: IV, intravenous; SC, subcutaneous; CR, complete response; VGPR, very good partial response; PR, partial response.

The median PFS was higher in the IV injection group than in the SC injection group (37 months vs 45 months), but the difference was not statistically significant ($X^2=0.082$, $P=0.774$). The median OS was higher in the IV injection group than in the SC injection group (63 months vs 59 months), but the difference was not statistically significant ($X^2=0.185$, $P=0.667$) (Figures 1 and 2).

Adverse reactions (Table 3)

Hematological toxicity

Compared with the SC injection group, the incidence of leukopenia was higher in the IV injection group, while the incidence of hemoglobin decrease and thrombocytopenia was lower in the IV injection group, but both were not statistically significant. After the chemotherapy, blood routine examination was carried out for a number of times, and the hemogram rose, when compared with the period of treatment after the symptomatic and supportive treatment.

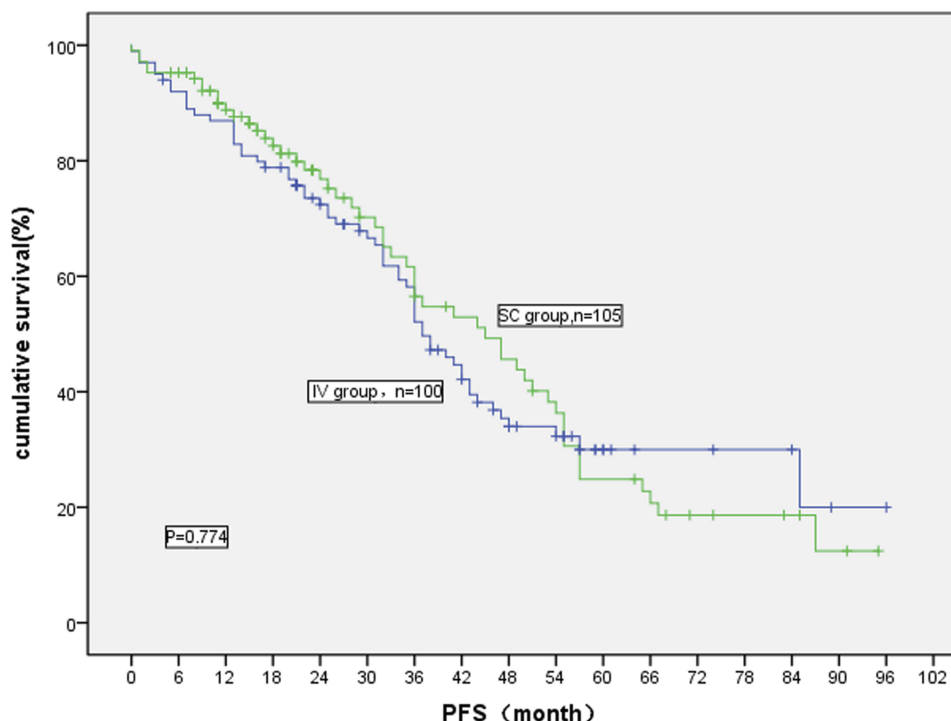


Figure 1 Comparison of progression-free survival for MM patients treated by bortezomib through different administration methods.

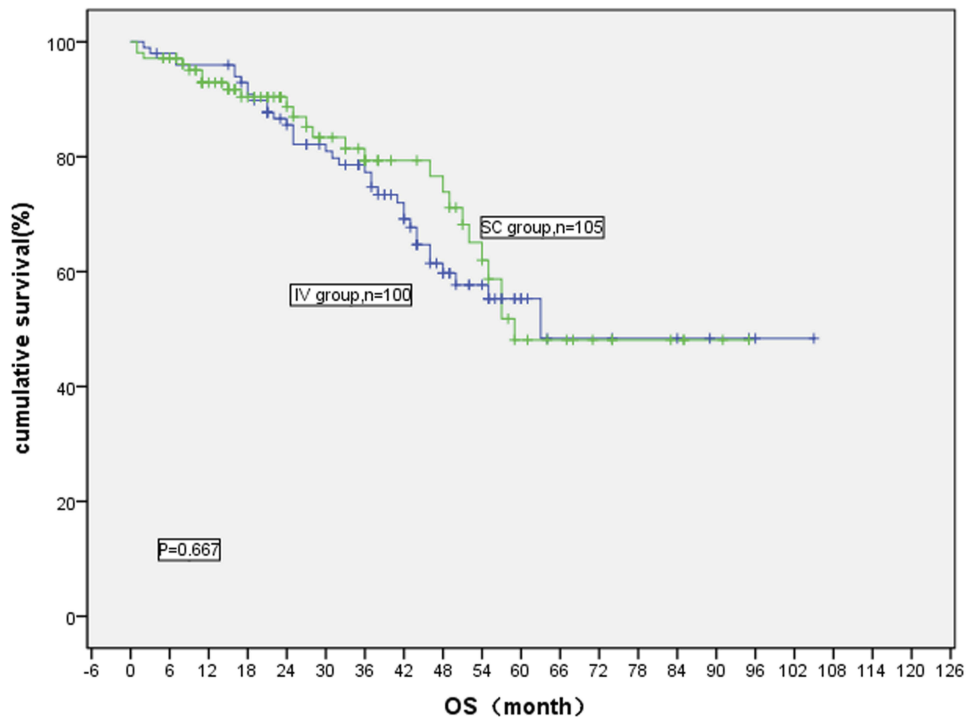


Figure 2 Comparison of overall survival for MM patients treated by bortezomib through different administration methods.

Peripheral neuropathy

This occurred more after the 3rd course of treatment in the IV injection group, while this occurred more after the 4th

course of treatment in the SC injection group. This mainly manifested as numbness of the distal limbs, pain, and abnormal sense of warmth and sense of touch. A total of

Table 3 Summary of other adverse events

Adverse events	IV Group, N (%)	SC Group, N (%)	CHI ²	P-value
Leukopenia ≥Grade 3	47 (47.0) 21 (21.0)	48 (45.7) 16 (15.2)	0.034 1.150	0.854 0.284
Thrombocytopenia ≥ Grade 3	53 (53.0) 20 (20.0)	56 (53.3) 28 (26.7)	0.002 1.269	0.962 0.260
Anemia ≥ Grade 3	48 (48.0) 22 (22.0)	51 (48.6) 18 (17.1)	0.007 0.769	0.935 0.380
Peripheral neuropathy	51 (51.0)	37 (35.2)	5.194	0.023
Grade 1	20 (20.0)	28 (26.6)	1.269	0.260
Grade 2	17 (17.0)	7 (6.7)	5.291	0.021
Grade 3	11 (11.0)	2 (1.9)	7.134	0.008
Grade 4	3 (3.0)	0 (0.0)	–	–
Pulmonary infection	71 (71.0)	68 (64.8)	0.913	0.339
≥Grade 3	10 (10.0)	11 (10.5)	0.013	0.911
Gastrointestinal symptoms	59 (59.0)	60 (57.1)	0.073	0.788
Nausea	21 (21.0)	24 (22.9)	0.103	0.748
Constipation	12 (12.0)	19 (18.1)	1.483	0.223
Diarrhea	20 (20.0)	18 (17.1)	0.277	0.599
Abdominal pain	8 (8.0)	5 (4.8)	0.904	0.342
Bloating	33 (33.0)	32 (30.5)	0.151	0.698
Paralytic ileus	7 (7.0)	5 (4.8)	0.466	0.495
Herpes zoster	30 (30.0)	21 (20.0)	2.741	0.098
Liver damage	23 (23.0)	19 (18.1)	0.756	0.384
Urinary tract infection	11 (11.0)	12 (11.4)	0.009	0.923

Abbreviations: IV, intravenous; SC, subcutaneous; PN, peripheral neuropathy.

51 patients (51.0%) in the IV injection group suffered from the PN, including 14 patients with level 3–4 PN. A total of 37 patients in the SC injection group suffered from PN, including two patients with level 3 PN, while the remaining patients had level 1–2 PN. The total incidence of PN in the IV injection group was apparently higher when compared with the SC injection group, and the difference was statistically significant ($P=0.023<0.05$). It is noteworthy that the incidence was apparently higher in the IV injection group than in the SC injection group ($P<0.05$) in the case of $PN \geq 2$, and the difference was statistically significant.

Pulmonary infection/upper respiratory infection

This occurs more from the 1st to 2nd courses of treatment, and this mainly manifests as fever, cough and sputum, and

pharyngeal cavity inflammation, and it shows the change in pulmonary inflammation according to the imageological examination. A total of 71 patients (71.0%) in the IV injection group suffered from the pulmonary infection/upper respiratory infection, including 10 patients with severe pneumonia. A total of 68 patients (64.8%) in the SC injection group suffered from pulmonary infection/upper respiratory infection, including 11 patients with severe pneumonia. After treated by antibacterial, antifungal and antiviral drugs, the infection of the majority of patients was controlled, but this deteriorated to bacteremia for the minority of patients, which could even lead to death.

Digestive tract symptoms

This mainly manifests as anorexia, nausea and vomiting, constipation, diarrhea, abdominal pain, abdominal distension and paralytic bowel infarction. A total of 59 patients (59.0%) in the IV injection group suffered from digestive tract symptoms, including seven patients with paralytic bowel infarction. A total of 60 patients (57.1%) in the SC injection group suffered from digestive tract symptoms, including five patients with paralytic bowel infarction. After the occurrence of bowel infarction, the positive expectant treatment relieved the symptoms.

Herpes zoster

A total of 30 patients (30.0%) in the IV injection group suffered from herpes zoster, including one patient who suffered from herpes zoster twice. A total of 21 patients (20.0%) in the SC injection group suffered from herpes zoster. These patients got better after the antiviral treatment.

Hepatic injury

This mainly manifests as an increase of transaminase. A total of 23 patients (23.0%) in the IV injection group suffered from hepatic injury. A total of 19 patients (18.1%) in the SC injection group suffered from hepatic injury. The majority of patients got better after the liver protection treatment.

Urinary system infection

This mainly manifests as odynuria, urgent urination and growth of bacteria in the urine culture. A total of 11 patients (11.0%) in the IV injection group suffered from urinary system infection. A total of 12 patients (11.4%) in the SC injection group suffered from hepatic injury. These patients got better after the anti-infective treatment.

Others

One patient in the IV injection group presented with epilepsy symptoms after six courses of treatment, while one patient in the SC injection group suffered from delirium after two courses of treatment. These patients got better after the expectant treatment, and these patients no longer had the above symptoms after further treatment, according to the original scheme. However, the mental disorder caused by bortezomib could not be reversed.

Discussion

MM is a kind of malignant plasmacyte cloning disease. At present, this remains as an incurable hematological system disease and is characterized by marrow plasmacyte clonal expansion, monoclonal immune globulin in the urine, a decrease in immunity and damage of the blood system, bone, kidney and other related target organs.^{8,9} Newly diagnosed patients should immediately receive treatment. The traditional clinical chemotherapy regimen includes MP (melphalan and prednisone), VAD (vincristine, doxorubicin and dexamethasone) and CTD (cyclophosphamide, thalidomide and dexamethasone). These can improve the remission rate and lifetime of MM patients, but have a high recurrence rate, and can easily lead to drug resistance to chemotherapy. Bortezomib is a kind of boracic acid peptide compound that belongs to the reversible proteasome inhibitor. It can realize the reversible inhibition of the activity of chymotrypsin and trypsin with the 26S sigma subunit in the proteasome of the mammalian cell through selective combination with the threonine in the active site of the proteasome. This can subsequently inhibit the genetic expression related to cell proliferation, delay tumor cell growth, induce cell apoptosis and inhibit angiogenesis.¹⁰⁻¹² Meanwhile, bortezomib can increase the sensitivity of the chemotherapy drug and overcome the resistance of myeloma cells to dexamethasone, doxorubicin, melphalan and other drugs. Various studies have revealed that bortezomib can act on many human tumor cell lines and have a significant effect on hematological malignancy.¹³ Furthermore, bortezomib can produce a significant effect on newly diagnosed and recurrent/refractory patients with myeloma and effectively improve abnormal renal function.^{14,15} However, the PN caused by this would bring great pain to these patients and limit the application of drugs. In order to reduce the incidence of neurotoxicity, the clinical administration method was changed from IV injection to SC injection.

The research data show that the ORR and \geq VGPR in the IV injection group were significantly higher, when compared with those in the SC injection group, after the first course of treatment, and the difference was statistically significant. Studies have shown that the difference in pharmacokinetics and pharmacodynamics between SC injection and IV injection is larger.¹⁶⁻¹⁸ The blood concentration-time area under the curve of these two groups was basically same within 72 hrs, namely, the dose of the drug absorbed into the blood was basically same within 72 hrs. However, compared with SC injection, the SC injection of bortezomib has a higher C_{max} (maximum plasma concentration) and shorter T_{max} (time to peak), which may partially explain the faster and deeper response observed in the IV injection group. With the continuation of treatment, the remission rate of ORR and VGPR or above in these two groups were basically the same, and the median PFS and OS were also basically the same. This indicates that the IV injection group exhibited a faster response and deeper remission degree, when compared with the SC injection group. With the increase of the course of treatment, the effect was basically the same, which is basically consistent with the results of the retrospective study conducted by Xu et al.¹⁹

The present study also reveals that the overall incidence of PN in the SC injection group was significantly lower than that in the IV injection group (35.2% vs 51.0%, $P=0.023$). In the case of $PN \geq 2$, the SC injection group was also significantly lower than the IV injection group (level 2: 6.7% vs 17.0%, $P=0.021$; level 3 1.9% vs 11.0%, $P=0.008$; level 4: 0.0% vs 3.0%). The difference in the incidence of other adverse events between these two groups was not statistically significant ($P>0.05$). In addition, the incidence of PN also increased with the increase in the accumulated dose of bortezomib. The IV injection group and SC injection group reach its peak in the 4th and 6th cycles. When the accumulated dose of bortezomib reached 20.8 mg/m², the incidence of PN in the SC injection group is significantly lower than that in the IV injection group (18.0% vs 36.6%, $P=0.027$). The present study shows that PN is the adverse reaction correlated to the dose of bortezomib. This may occur in the 1st cycle, reach the peak in the 5th cycle with an increase of its accumulated dose, and subsequently enter a plateau period.²⁰⁻²² In summary, the SC injection approach is a safer and more effective administration method.

The present study provides novel findings. These two administration methods have their respective advantages and disadvantages. However, it remains to be determined

whether a balance can be reached between effect and toxicity while avoiding the disadvantages. For newly diagnosed MM patients and MM patients with renal insufficiency, the IV injection approach can enable a faster and deeper response and rapidly reduce the tumor load. Subsequently, the SC injection approach can provide better tolerance and bring the most benefit for patients. Indeed, more clinical researches are needed to verify these.

In conclusion, we report that, compared with IV administration, SC administration of bortezomib results in significantly reduced toxicity and similar ORR, PFS and OS. This study demonstrated the point that SC bortezomib can provide a better balance between efficacy and toxicity, supported the view that high-risk patients who have previously suffered from nervous system disease, or patients who may develop PN should prefer the SC injection approach.

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Disclosure

The authors report no conflicts of interest in this work.

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