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Tolerance, kinetics and depth of response for subcutaneous versus intravenous administration of bortezomib combination in Chinese newly diagnosed multiple myeloma patients

Yan Xu^{1,2,*}, Shuhui Deng^{1,*}, Xuehan Mao¹, Gang An¹, Zengjun Li¹, Yafei Wang³, Mariateresa Fulciniti², Matthew Ho², Jianhong Lin², Weiwei Sui¹, Wei Liu¹, Dehui Zou¹, Shuhua Yi¹, Wenyang Huang¹, Hong Liu¹, Rui Lv¹, Jian Li¹, Tingyu Wang¹, Chenxing Du¹, Nikhil C Munshi², and Lugui Qiu¹

¹State Key Laboratory of Experimental Hematology, Institute of Hematology & Blood Diseases Hospital, Chinese Academic Medical Science & Peking Union Medical College, 288# Nanjing Road, Heping District, Tianjin, China, 300020

²Medical Oncology, Jerome Lipper Center for Multiple Myeloma Research, Lebow Institute for Myeloma Therapeutics, Dana Farber Cancer Institute, Harvard Medical School, 440 Brookline Avenue, Boston, USA, 02215

³Department of Hematology, Cancer Institute & Hospital, Tianjin Medical University, Binshui Road, Hexi District, Tianjin, China, 300040

Abstract

The retrospectively investigation compared the efficacy and safety of Bortezomib (Btz) administration via subcutaneous (SC) and intravenous (IV) in 307 newly-diagnosed multiple myeloma (NDMM) patients from a single Chinese center. SC Btz is associated with better tolerance. However, IV administration achieves a faster and deeper response in these patients.

Background—Peripheral neuropathy (PN) is an important toxicity that limits the use of Bortezomib (Btz). Attempts to reduce PN have included its subcutaneous (SC) administration.

Patients and methods—Here we retrospectively analyzed 307 newly-diagnosed multiple myeloma (NDMM) patients from a single Chinese center, receiving Btz-based regimens administered either via SC injection (SC group, n=167) or IV infusion (IV group, n=140). The efficacy and safety of Btz administration via SC and IV were then compared.

Correspondence to: Nikhil C Munshi; Lugui Qiu.

*The same contribution to this article.

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Disclosure

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Results—Most baseline characteristics were similar between these 2 groups. A lower frequency of adverse events (AEs), especially grade 3 peripheral neuropathy (PN) ($p=0.002$), was observed in SC compared to IV group. The estimated median Btz dosage when PN developed was higher (20.8 mg/m^2 vs 15.6 mg/m^2) and fewer patients reduced or discontinued Btz due to AEs in SC compared to IV group. The overall response rate (PR) was comparable (94.8% vs 96.2%). However, patients in IV group required fewer cycles to achieve partial response (PR) while larger proportion of patients in IV group achieved VGPR. After a median follow-up of 23 (1–84) months, no significant difference in median progression-free survival (not arrived vs 33.0 ± 2.735 months) and overall survival (not arrived vs 56.0 months) was noted.

Conclusion—SC Btz is associated with better tolerance; however, IV administration achieves a faster and deeper response in Chinese NDMM patients.

Keywords

multiple myeloma; bortezomib; subcutaneous; intravenous

Introduction

Multiple myeloma (MM) is an incurable plasma cell malignancy primarily affecting the elderly. The variety of clinical signs and symptoms profoundly impact the lives of patients and imposes a heavy burden on society. However, recent basic and clinical research developments have led to the use of novel therapeutic agents which have greatly improved overall survival (OS) and shifted treatment paradigms in MM.

The proteasome inhibitor bortezomib (Btz) is a potent agent used extensively in the treatment of both newly diagnosed and relapsed MM, and as part of induction, consolidation, conditioning and maintenance therapies^{1–8}. The standard administration route for Btz is intravenous (IV), but IV poses a therapeutic challenge in patients who have poor venous access. IV Btz administration is also limited by Btz-induced peripheral neuropathy (BIPN), which significantly impacts patients' quality of life⁹. In 2008, a French group reported the results of a randomized phase I study (CAN-1004) that compared the pharmacokinetics and pharmacodynamics of IV versus subcutaneous (SC) administration of Btz in relapsed or refractory MM (RRMM) patients. This study also assessed the safety and efficacy of these two administration routes. The plasma concentration of Btz and the percent inhibition of 20S proteasome were measured on day 1 and 11 of cycle 1. Btz systemic exposure was equivalent with SC versus IV which led to similar overall 20S inhibition in both arms. The safety profile and response rate of SC did not appear inferior to IV, and the local tolerance of SC injection was also good. Based on these exploratory findings, SC administration was deemed as a promising alternative to IV injection¹⁰. These outcomes were subsequently confirmed in the randomized, prospective MMY-3021 study involving RRMM patients^{11–13} which led to the 2012 approval of SC Btz in the United States and European Union. However, despite several other reports supporting the use of SC Btz,^{14, 15}, there is very limited data available about the safety and efficacy profile of SC Btz in Chinese and Asian patients with newly-diagnosed multiple myeloma (NDMM)^{16–19}. Few studies with small cohorts compared the two administration routes in Asian patients^{20, 21}.

Promising results from our preliminary studies showed that SC Btz significantly decreases and delays PN in RRMM and particularly in NDMM, prompting this follow-on study to look at a larger cohort of patients with NDMM. We report, for the first time, that patients with IV btz may have quicker and deeper response, especially in PAD group compared to SC group. This has significant relevance in practice. This is also the largest cohort of Asian patients and demonstrates the relevance of SC vs IV administration of bortezomib in this population.

Materials and Methods

Patients and study design

This retrospective, historical control study was conducted at a single center and its design was approved by the Institutional Review Board of the Blood Diseases Hospital at Tianjin, China. Informed consent was obtained from all patients included in this study. Data from 307 NDMM patients treated with a Btz-based regimen at the Lymphoma & Myeloma Center of this Blood Diseases Hospital between May 1, 2008, and December 31, 2014 was abstracted from the medical records and subsequently analyzed.

Patients were assigned to receive Btz-based regimens, including PAd/BCd [Btz 1.3 mg/m² on days 1, 4, 8 and 11; adriamycin 9 mg/m² intravenously on days 1–4; or CTX 500mg/m², orally on days 1, 8, 15, and dexamethasone 20 mg/day, orally or intravenously on days 1, 2, 4, 5, 8, 9, 11 and 12]. Btz was administered by either intravenous injection (IV) (historical control IV group) before Feb 28, 2012 or subcutaneous injection (SC group) after March 1, 2012. The IV injections were administered at a concentration of 1mg/mL as a 3–5s intravenous push, while SC injections were administered at 2.5mg/mL to limit total volume. All treatments were repeated every 3–4 weeks. After at least four cycles of treatment, patients underwent consolidation therapy with either autologous stem cell transplant (ASCT) (if patient was <65 years old and without contraindication to ASCT) combined with the original chemotherapy regimen or only the original chemotherapy regimen. After up to nine cycles of induction and consolidation chemotherapy, patients were maintained with either thalidomide or lenalidomide, plus dexamethasone. Where necessary, patients also received supportive treatment with zoledronic acid every 1–2 months. All patients received prophylactic acyclovir.

Patients who completed one dose of Btz were included in this study, and the data on their demographic characteristics and disease profiles [including sex, age, M-protein type and quantity, DS, ISS and RISS²² staging, percentage of plasma cells in bone marrow (BM) and peripheral blood (PB), cytogenetics characteristics detected by conventional karyotype and fluorescence in situ hybridization (FISH), etc] were collected. The presence or absence of peripheral neuropathy (PN) and diabetes mellitus (DM) at baseline was obtained before treatment. CD138-purified plasma cells were used to identify cytogenetic abnormalities in FISH analyses.

Assessment of treatment safety and efficacy

Safety analysis was based on all patients who received one dose of Btz. Safety was monitored for 30 days after the last dose by grading the toxicities based on the National Cancer Institute's Common Toxicity Criteria (version 3.0). Toxicity-related therapeutic adjustments were recorded along with the dose at which PN was induced or aggravated. For IV patients, PN was managed using a dose-modification guideline developed based on experience in phase II studies⁹. As for SC patients, an updated stricter dose-modification guidelines was used²³.

Efficacy analysis was based on all patients who completed one cycle of the Btz-based regimen. In both groups, disease status was assessed after every cycle of induction and consolidation chemotherapy, and once every 3 months during maintenance therapy, in accordance with the International Myeloma Working Group's uniform response criteria for MM, incorporating near complete response (nCR)²⁴. Progression-free survival (PFS) is defined as the time from the start of the treatment to disease progression or death (regardless of cause), whichever comes first. Overall survival (OS) is defined as the time elapsed between treatment initiation and death. The efficacy and safety of Btz administration via SC and IV were then compared.

Statistical considerations

The data are presented as median±standard deviation (SD). Independent samples of nonparametric tests were used to compare the difference between the two groups. Spearman association and logarithmic regression analyses were performed. Survival was estimated according to the Kaplan-Meier method, and survival curves were compared using the log-rank test. Two-tailed tests were used with p -value 0.05 indicating statistical significance. The SPSS 23.0 software package was used.

Results

Patients: Comparable baseline characteristics between IV and SC group

Among the total 307 patients enrolled in our study, 140 received IV Btz, while 167 received SC Btz. The summary of the baseline characteristics of all patients is listed in Table 1. Overall patients from 22 Chinese provinces were diagnosed and treated at the same Lymphoma & Myeloma Center of the Blood Diseases Hospital, with the majority (92.8%) from 10 northern provinces of China. The median age of the cohort was 56 (25–77) years. Patient demographics and all other baseline characteristics (including age, M-protein type and quantity, percentage of plasma cells in BM and PB, ISS, R-ISS, risk-group according to cytogenetics characteristics, PN and DM before treatment, etc.) were similar between the IV and SC groups. About 60.7% (85/140) of patients in the IV group and 61.1% (102/167) patients in the SC group received PAd regimen, while the remaining patients in both group received BCd ($p=0.948$).

Safety profile: SC Btz has a better safety profile and is associated with less severe PN

Adverse events (AEs) associated with IV Btz and SC Btz are listed in Tables 2 and 3. Patients who received IV Btz had more frequent grade 3 AEs compared to those who

received SC Btz. PN remained to be one of the most common and important Btz-related AE that greatly affects patients' quality of life. Although the overall incidence of PN was only slightly lower in patients receiving SC Btz than those receiving IV Btz (49.7% vs 57.1%, $p=0.154$), the frequency of grade 3 PN was significantly less in SC group (8.4% grade 3, none grade 4) compared to IV group (20.7% grade 3, 2.1% grade 4, $p=0.002$). Importantly, the median dosage of Btz associated with PN development was higher in SC group (Table 2, Figure 1). Compared with the risk of PN development in IV group, the risk in SC group is 0.561 (95% CI 0.411–0.765). When compared with the risk of grade 2 PN development in IV group, the risk in SC group is only 0.349 (95% CI 0.217–0.559). Subgroup analysis showed that patients tolerated significantly higher doses to develop/worse PN when Btz was administered SC versus IV independent of whether doxorubicin or cyclophosphamide was used. In patients with PN who received long-term follow-up, the resolution rate was not significantly different between the SC and IV groups. A total of 68.1% and 77.3% patients in SC and IV groups, respectively, showed improvement to a lower grade of PN, or even complete resolution ($p=0.215$). However, the median time to improvement was shorter in SC versus IV group (5 vs. 7.5 months, respectively; $p<0.001$). This was observed both in patients receiving PAd (5 vs. 10 months, respectively; $p<0.001$) or BCd (4.5 vs. 6.5 months respectively; $p=0.028$). There were also fewer patients who developed grade 3 fatigue, paralytic ileus, and constipation in SC group. These AEs may also be related to the neuropathic toxicity of Btz (Table 3). Additionally, there were significantly fewer grade 3 hematologic toxicities (i.e. leukopenia, anemia, thrombocytopenia) and infections in the SC group (Table 3). Notably, 11 out of 167 (6.6%) patients had one SC injection-site reactions reported as an adverse event that however did not require dose-adjustment. Based on these observations, SC Btz was found to have a better safety profile, especially with regards to PN.

Btz dosing: Patients in SC group received a higher dose of Btz

One hundred and forty individuals in IV group completed 466.5 cycles of Btz-based chemotherapy, with a median of 3 (0.5–9) cycles/patient; while 167 patients in SC group, completed 684.5 cycles of Btz-based chemotherapy with a median of 4 cycles (0.5–9) / patient. The rate of dose reduction or delay in administration of Btz was not significantly different between the SC and IV group (28.7% vs 29.3%, $p=0.917$) (Table 4). The median Btz dose at the time of first reduction or delay (if any at all) was higher in SC compared to IV group (15.6 mg/m² vs 7.8 mg/m², $p<0.001$). Fewer patients discontinued SC Btz (failed to complete at least 8 cycles) compared to IV Btz (71.9% vs 96.4%, respectively; $p<0.001$). Overall, the cumulative dose of Btz delivered was significantly higher in SC- compared to IV-treated patients (20.8mg/m² vs 15.6mg/m² respectively, $p<0.001$). No significant difference was noted between PAd and BCd groups.

IV Btz achieves similar ORR, PFS and OS but rapider response and higher VGPR rate compared to SC Btz

At median follow-up of 18.5 (1–41) months in the SC group, and 41 (1–84) months in the IV group, the median PFS and OS were similar between the 2 groups (PFS: not arrived vs 33.0±2.7 months respectively, $p=0.976$; and OS: not arrived vs 56.0 months respectively, $p=0.425$) (Figure 2). The median number of cycles to initial response was 1 (1–4) in both the IV and SC groups ($P=0.396$). The majority patients in both groups (92.3% in IV group, and

82.5% in SC group) achieved MR after only one cycle of Btz-based therapy. However, the depth of the initial response between these two groups was significantly different ($p=0.001$) with better response in the IV versus SC group after 1 cycle of chemotherapy [77.7% partial response (PR), with 22.3% very good partial response (VGPR) in IV Btz versus 61.7% PR, with 13.0% VGPR in SC Btz]. MR was achieved by 14.6% of the patients in IV group and 20.8% in SC group (Table 5). The ORR (PR) was similar between the 2 groups (96.2% vs 94.8%). However, VGPR or higher response was achieved more frequently with IV Btz versus SC Btz (75.0% vs 63.2% respectively; $p=0.014$) (Tables 5).

Discussion

Bortezomib-induced peripheral neuropathy (BIPN) is a major dose-limiting adverse effect which was first observed during phase I studies²⁵, and also corroborated in the later phases of clinical studies^{9, 26, 27}. Multiple interventions have been (and are being) investigated in a bid to decrease the incidence and severity of BIPN. The administration of Btz via SC route was one such intervention which was reported to be associated with a lower incidence of BIPN in a phase 3 study comparing IV versus SC Btz^{11, 13}.

In this context, our study is the first comparison of IV versus SC Btz in Chinese patients with NDMM. Our analysis confirmed that Btz administration via SC offers a comparable efficacy (ORR and survival), with the added advantage of an improved safety profile consistent with earlier reports (CAN-1004 and MMY-3021 trials for RRMM, GMMG-MM5 trial for NDMM)^{10–13, 28}.

Patients in our SC group tolerated Btz better than those in IV group. SC Btz was associated with lower incidence and severity of PN, consistent with the reported findings from MMY-3021 and GMMG-MM5. It is of note that we followed the updated stricter dose-modification guidelines for Btz-related neuropathic pain and/or peripheral sensory or motor neuropathy²³ in SC group. Importantly, fewer patients in SC group discontinued Btz because of AEs, especially due to PN, which allowed these patients to receive more cycles of chemotherapy and a higher total dosage of Btz. Regrettably, one of the main reasons for discontinuing Btz was the financial hardship brought about by the high cost of Btz coupled with the denial of medical insurance coverage in China. As a result, both the median number of cycles and total dose of Btz are lower in our study when compared to other published reports. Notably, one other retrospective study¹⁴ reported that SC Btz induces similar therapeutic response rates as intravenous Btz in MM without the reduction in incidence of PN. However, this study used once weekly Btz, and subgroup analysis revealed a higher percentage of patients had pre-existing neuropathy in the SC versus IV arm (18% in SC arm vs 13% in IV arm, $p=0.073$). In addition, the incidence and severity of non-PN AEs (especially hematological AEs) are also lower in our SC versus IV cohort. In our study, the incidence of grade 3 infection is much higher in IV group than in that in SC group. This phenomenon is in accordance with the significant higher incidence of grade leukopenia in IV group, which is the high-risk factor for severe infection.

In our analysis, IV Btz, on the other hand, has the advantage of bringing about quicker and deeper response compared to SC administration. After one cycle of chemotherapy, more

patients achieved PR in IV group than SC group. Even though the median number of cycles to initial response was 1 in both groups, the depth of initial response was better in IV versus SC group. As for the best response across all cycles, a greater percentage of patients in IV group achieved VGPR, even though median 1 more cycle of Btz-based chemotherapy was administrated in SC group compared to that in IV group. The MMY-3021 trial also reported a median time to initial response of 1.4 months in both groups (SC and IV) in RRMM patients; however, they did not illustrate the detailed depth of the initial response¹¹. In the GMMG-MM5 trial, subgroup analysis revealed that patients with baseline creatinine $\leq 2\text{mg/dL}$ who were treated with IV BCd had much higher rates of nCR/CR (47% in IV group vs. 11% in SC group, $p=0.03$), while patients with adverse cytogenetic abnormalities who were treated with IV PAD had much higher VGPR rates than those treated with SC Btz (45% in IV group vs. 29% in SC group, $p=0.05$). Similar phenomena were also noticed in the whole BCD arm (VGPR, 42% in IV group vs. 29% in SC group, $p=0.02$; nCR/CR, 27% in IV group vs. 14% in SC group, $p=0.01$)²⁸. Previous pharmacokinetics and pharmacodynamics studies have documented that the IV administration of Btz has a higher C_{max} and a shorter T_{max} compared to SC administration¹³. These two pharmacokinetic factors seem to have an impact on time to response and may partly explain the deeper response observed in our IV group. The comparable ORR could be due to the overall equivalent systemic exposure of Btz between the SC and IV groups^{10, 11}. This study raises interesting question about possible pharmacokinetics differences in Chinese population. We plan to study this in future. Importantly, it also brings about a point that IV may have quicker effect which may have clinical significance especially in newly-diagnosed patients and patients with renal dysfunction or aggressive disease where a quicker response may be advantageous. Whereas for patients with indolent diseases, SC Btz can get better balance between efficacy and toxicity. This phenomenon also provides us the possibility to administer Btz by IV first to rapid control disease, then followed by SC to get better tolerance.

We have observed higher ORR in our study compared to other studies comparing IV vs SC Btz mainly because, unlike other studies, we studied patients with NDMM and received three-drug regimens as initial therapy. Similar responses have been reported with other three-drug regimens such PAd, BCd, VRd, BCd-modified in NDMM (88–100%)^{4–6, 15, 29–31}.

There are some limitations to this study. First, this study is not a prospective randomized controlled trial. Second, Btz was not administrated during the same period in the IV and SC groups. Third, Subgroup analysis lack power as the cohort size is not sufficiently large especially for the different cytogenetic subgroups. Lastly, the differences in pharmacokinetics and pharmacodynamics between SC and IV administration of Btz in Chinese patients was not studied which represents a missed opportunity as race or ethnicity is known to play a key role in inter-patient variability in drug response³². Thus, a randomized controlled trial with a larger cohort of enrolled patients and longer follow-up times will be required to conclusively address these issues in the future.

Conclusion

In conclusion, we report that, compared with IV administration, SC administration of Btz, when combined with Adriamycin or cyclophosphamide, results in significantly reduced toxicity and similar ORR, PFS, and OS. Thus, SC administration is an acceptable alternative for Chinese NDMM patients due to its superior safety profile and similar ORR and survival. However, IV administration of Btz leads to rapider and deeper responses in these patients. This study raises the point that SC Btz can provide better balance between efficacy and toxicity, especially for patients with indolent diseases. While IV Btz may control tumor load more rapidly, which maybe preferred in patients with more aggressive diseases or renal failure.

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Clinical Practice Points

- The use of bortezomib (Btz) have greatly improved overall survival (OS) and shifted treatment paradigms in MM but peripheral neuropathy (PN) is an important toxicity. Attempts to reduce PN have included its subcutaneous (SC) administration.
- We retrospectively compared the efficacy and safety of Btz administration via SC and IV in 307 newly-diagnosed multiple myeloma (NDMM) patients from a single Chinese center.
- We found that the estimated median Btz dosage when PN developed was higher (20.8 mg/m² vs 15.6 mg/m²) and fewer patients reduced or discontinued Btz due to AEs in SC compared to IV group.
- The overall response rate (PR) and survival (PFS and OS) were comparable between these two groups.
- Patients in IV group required fewer cycles to achieve partial response (PR) and larger proportion of patients in IV group achieved VGPR, though higher totally Btz dosage was used in SC group.
- We report, for the first time, that SC Btz is associated with better tolerance, while quicker and deeper responses can be achieved by IV Btz in Chinese NDMM patients.

Figure 1. Median estimated bortezomib dosage to develop PN (left) and to develop grade2 PN (right). Median estimated bortezomib dosage to develop PN is (15.6±0.328) mg/m² in IV group and (20.8±0.328) mg/m² in SC group. Median estimated bortezomib dosage to develop grade2 PN is (26.0±4.346) mg/m² in IV group and NA (not arrived) in SC group.

Figure 2. Progression free survival (PFS, left) and overall survival (OS, right) of patients in IV group and SC group. After a median follow-up of 23 (1–84) months, no significant difference in median (PFS: not arrived vs 33.0±2.735 months, left) and OS (not arrived vs 56.0 months, right) was noted.

Table 1

Baseline characteristics of patients in IV group and SC group

Characteristics	Median value or percentage of patients (range)		
	IV group	SC group	p value
Gender (male/female)	95/45	95/72	0.049
Age	56 (26–77)	56 (25–76)	0.442
Albumin (ALB) (g/L)	34.4 (16.4–49.1)	35.8 (13.2–50.5)	0.214
β_2 -Microglobulin (mg/L)	5.135 (1.04–105.94)	5.05 (1.5–58.1)	0.245
Lactate dehydrogenase (LDH, IU/L)	157 (57–284)	169 (69–824)	0.088
Creatinine (umol/L)	84.3 (37–674)	90.45 (45–697)	0.337
Serum M-protein (g/L)	27.1 (1.88–152)	23.2 (1.7–184)	0.175
Plasma cell of BM (smear, %)	33 (0–93)	30 (0.5–93.5)	0.209
M-spike isotype			0.648
IgG	78 (55.7%)	82 (49.1%)	
IgA	23 (16.4%)	37 (22.2%)	
IgD	10 (7.1%)	6 (3.6%)	
IgM	1 (0.7%)	-	
Double colonies	-	1 (0.6%)	
Light Chain	25 (17.9%)	38 (22.8%)	
Non-secrete	3 (2.1%)	3 (1.8%)	
Conventional cytogenetics karyotype	n=108	n=134	
Hypodiploidy	11 (10.2%)	8 (6.0%)	0.637
Del(13)	9 (8.3%)	7 (5.2%)	0.131
del(13) in FISH	n=110	n=163	0.464
(+)	47 (42.7%)	77 (47.2%)	
del(17p) in FISH	n=106	n=164	0.380
(+)	12 (11.3%)	23 (15.1%)	
Amplification of 1q21 in FISH	n=88	n=148	0.739
(+)	43 (48.9%)	69 (46.6%)	
IgH translocation in FISH	n=108	n=163	0.521
(+)	56 (51.9%)	91 (55.8%)	
Type of IgH translocation	n=56	n=91	
IgH/CCND1	25 (44.6%)	28 (30.8%)	0.963
IgH/MAF	6 (10.7%)	9 (9.9%)	0.443
IgH/FGFR3	18 (32.1%)	25 (27.5%)	0.303

Characteristics	Median value or percentage of patients (range)		
	IV group	SC group	p value
CCND1/MAF/FGFR3(–)	3 (5.4%)	15 (16.5%)	
Not discriminated further	4 (7.1%)	14 (15.4%)	
International staging system (ISS)	n=135	n=160	0.941
I	24 (17.8%)	37 (23.1%)	
II	49 (36.3%)	43 (26.9%)	
III	62 (45.9%)	80 (50.0%)	
Risk group according to FISH ⁱ	n=99	n=153	0.810
High-risk	29 (29.3%)	47 (30.7%)	
Revised ISS ⁱⁱ	n=114	n=151	0.383
I	9 (7.9%)	21 (13.9%)	
II	71 (62.3%)	87 (57.6%)	
III	34 (29.8%)	43 (28.5%)	
PN	n=115	n=141	0.514
None	109 (94.8%)	136 (96.5%)	
Grade 1	5 (4.3%)	4 (2.8%)	
Grade 2	1 (0.9%)	1 (0.7%)	
Diabetes mellitus	n=110	n=155	0.364
Yes	9 (8.2%)	18 (11.6%)	

ⁱ Risk group according to FISH: high-risk CA, del(17p) and/or t(4;14) and/or t(14;16)]; standard risk (all others).

ⁱⁱ Revised ISS: ISS stage I, serum β 2-microglobulin level < 3.5 mg/L and serum albumin level $\geq$ 3.5 g/dL, no high-risk CA [del(17p) and/or t(4;14) and/or t(14;16)], and normal LDH level (less than the upper limit of normal range); R-ISS III, ISS stage III (serum β 2-microglobulin level > 5.5 mg/L) and high-risk CA or high LDH level; and R-ISS II, including all the other possible combinations.

Table 2

Summary of peripheral neuropathy (grade, developing time, and outcome)

	IV group	SC group	P value
incidence of peripheral neuropathy (PN)	n=140	n=167	
Any grade	80 (57.1%)	83 (49.7%)	0.154
Grade 1	34 (24.3%)	54 (32.2%)	0.121
Grade 2	14 (10.0%)	16 (9.6%)	0.902
Grade 3	29 (29.7%)	13 (7.8%)	0.002
Grade 4	3 (2.4%)		-
Median dosage of Btz when PN developed	(15.6±0.328)mg/m2	(20.8±1.017) mg/m2	<0.001
median dosage of btz when PN grade 2	(26.0±4.346)mg/m2	NA	<0.001
Outcome of PN	n=75	n=69	0.215
Not resolved	17 (22.7%)	22 (31.9%)	
Improved	58 (77.3%)	47 (68.1%)	
Time for recovery from PN (month)	7.5 (1–36)	5.0 (0.3–12)	<0.001

Table 3

Summary of other adverse events

Adverse events	IV group (466.5 cycles)	SC group (684.5 cycles)	p value
Infection: Any grade	98 (21.0%)	108 (15.8%)	0.154
grade 3	89 (19.1%)	38 (5.6%)	0.005
Leukopenia: Any grade	197 (42.2%)	138 (20.2%)	0.065
grade 3	103 (22.1%)	42 (6.1%)	0.006
Anemia: Any grade	175 (37.5%)	134 (19.6%)	0.098
grade 3	86 (18.4%)	38 (5.6%)	0.009
Thrombocytopenia: Any grade	249 (53.4%)	178 (26.0%)	0.041
grade 3	183 (39.2%)	73 (10.7%)	0.005
Fatigue: Any grade	144 (30.9%)	108 (15.8%)	0.235
grade 3	25 (5.4%)	15 (2.2%)	0.004
Constipation: Any grade	92 (19.7%)	89 (13.0%)	0.154
grade 3	26 (5.6%)	7 (1.0%)	0.003
Diarrhea: Any grade	37 (7.9%)	65 (9.5%)	0.207
grade 3	15 (3.2%)	7 (1.0%)	0.122
Abdominal distension: Any grade	58 (12.4%)	78 (11.4%)	0.650
grade 3	18 (3.9%)	12 (1.8%)	0.094
Paralytic ileus: Any grade	22 (4.7%)	26 (3.8%)	0.431
grade 3	17 (3.6%)	6 (0.9%)	0.001
Hypotension: Any grade	7 (1.5%)	1 (0.1%)	0.236
grade 3	5 (1.1%)	0	0.058
Hypertension: Any grade	30 (6.4%)	28 (4.1%)	0.945
grade 3	4 (0.9%)	2 (0.3%)	0.801
Hyperglycemia: Any grade	168 (36.0%)	215 (31.4%)	0.405
grade 3	27 (5.8%)	31 (4.5%)	0.275

Table 4

Reasons for reducing/delaying and discontinuing Btz treatment

	reduction or delay of Btz treatment		discontinuing Btz treatment	
	IV group (n, %)	SC group (n, %)	IV group (n, %)	SC group (n, %)
PN	21 (15.0%)	30 (18.0%)	59 (42.1%)	23 (13.8%)
Diarrhea or paralytic ileus	9 (6.4%)	3 (1.8%)	38 (27.1%)	17 (10.2%)
Infection	7 (5.0%)	5 (3.0%)	1 (0.7%)	-
Other AEs	2 (1.4%)	1 (0.6%)	6 (4.3%)	2 (1.1%)
Patients' intent	-	5 (3.0%)	13 (9.3%)	3 (1.8%)
Economics difficulty	2 (1.4%)	-	1 (0.71%)	1 (0.6)
Combined with itraconazole or voriconazole	-	4 (2.4%)	4 (2.9%)	6 (3.6%)
Patients' intent			10 (7.1%)	49 (29.3%)
Economics difficulty			61 (43.6%)	42 (25.1%)
Dead			1 (0.7%)	-

Table 5

The primary response after 1 cycle and the best response across all cycles

	primary response		best response across all cycles		
	IV group (n=130)	SC group (n=154)	p value	IV group (n=132)	SC group (n=155)
CR/nCR	22 (16.9%)	12 (7.8%)	0.018	60 (45.5%)	62 (40.0%)
VGPR	29 (22.3%)	20 (13.0%)	0.039	99 (75.0%)	98 (63.2%)
PR	101 (77.7%)	95 (61.7%)	0.004	127 (96.2%)	143(94.8%)
MR	120 (92.3%)	127 (82.5%)	0.014	128 (96.9%)	150 (97.4%)
					0.818