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\textsuperscript{2} on days 1, 4, 8, 11) and weekly (1.6 mg/m\textsuperscript{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\cite{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\cite{4,5}.

The overall risk of progression from asymptomatic state is 10% for the first 5 years and declines thereafter\cite{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\cite{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\cite{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\cite{6,11} and combination therapy based on bortezomib is also recommended for the treatment of newly diagnosed and relapsed, refractory MM patients\cite{12}.

Currently, based on pharmacodynamics and a large number of preclinical studies\cite{8,13,20}, the recommended standard regimen for bortezomib is still twice a
week, that is, bortezomib 1.3mg/m² by intravenous injection on days 1, 4, 8, and 11.\textsuperscript{[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\textsuperscript{[23]} often lead to the reduction of the dose and even to the termination of treatment, affecting the efficacy and prognosis.\textsuperscript{[24]} Therefore, alternative less toxic regimens are being sought, such as changing from twice weekly to once weekly\textsuperscript{[22,23,25]} or from the traditional intravenous administration to subcutaneous injection.\textsuperscript{[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;\textsuperscript{[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.\textsuperscript{[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 1.3mg/m² by intravenous or subcutaneous injection on days 1, 4, 8, and 11, and with dexamethasone 40mg/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 1.6mg/m² by intravenous injection on days 1, 8, and 15, and dexamethasone 40mg/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,\textsuperscript{[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.\textsuperscript{[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 once weekly regimen including 57 patients (64.0%) with intravenous injection, 21 patients (23.6%) with subcutaneous injection; there were 39 patients who received the bortezomib once weekly regimen, 17 (21.8%) received VCD (bortezomib + cyclophosphamide + dexamethasone), and 50 (64.1%) received PAD (bortezomib + epirubicin hydrochloride + dexamethasone).
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 \( (P = .730) \). 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 22 (range, 1–80.0) months, respectively, in the weekly therapy group (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 \( (P = .240) \), 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 1

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

| Standard therapy (n = 78) | Intravenous injection (n = 57) | Subcutaneous injection (n = 21) | Weekly therapy (n = 39) | \( P^* \) |
|-------------------------|-------------------------------|-------------------------------|-------------------------|--------|
| **Clinical characteristics** |                               |                               |                          |        |
| Age (mean ± SD)          | 62.6 ± 10.3                   | 68.6 ± 10.0                   | .036                    |        |
| <65 yr, n (%)            | 52 (96.6)                     | 12 (57.1)                     | 14 (35.9)               |        |
| ≥65 yr, n (%)            | 25 (43.9)                     | 9 (42.9)                      | 25 (64.1)               |        |
| Sex                      |                               |                               |                         |        |
| Male                     | 38 (66.7)                     | 12 (57.1)                     | 27 (69.2)               |        |
| Female                   | 19 (33.3)                     | 9 (42.9)                      | 12 (30.8)               |        |
| M protein type           |                               |                               |                         |        |
| 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         |                               |                               |                         |        |
| 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)                       |                         |        |
| 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 (41–1289) | 130 (48–601) | 140 (57–412) | .515   |
| β2 microglobulin (mg/L, median, range) | 7.3 (2–30) | 5.5 (2–19.7) | 7.6 (5–54) | .079   |
| Blood calcium (mmol/L, median, range) | 2.31 (1.62–3.53) | 2.32 (1.80–3.07) | 2.28 (1.43–3.39) | .404   |
| Hemoglobin (g/L, mean ± SD) | 89.9 ± 23.9 | 98.4 ± 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  |                               |                               |                         |        |
| 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).
Table 2
Comparison of therapeutic effects in patients with multiple myeloma with initial treatment.

| Therapeutic effects | Intravenous injection (n = 57) | Subcutaneous injection (n = 21) | Weekly therapy (n = 36) | P  |
|---------------------|-------------------------------|-------------------------------|------------------------|----|
| 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.
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).

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**Table 3**

| 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     | 1.190  | (0.622, 2.274) | .599     |
| Sex                      | 1.208  | (0.616, 2.368) | .563     | 1.153  | (0.583, 2.277) | .683     |
| DS stage                 | 2.009  | (0.519, 7.784) | .791     | 2.799  | (1.309, 5.989) | .008     |
| I                        | 1      | –            | –        | 1      | –            | –        |
| II                       | 0.755  | (0.211, 2.700) | .791     | 1.963  | (1.309, 5.989) | .008     |
| DS stage (Group)         | B vs A | 0.954 | (0.175, 5.214) | .99    | 2.739  | (1.309, 5.989) | .008     |
| Treatment strategy       | Weekly vs standard | 1.063 | (1.385) | .965  | (0.492, 1.851) | .89      |

DS = Durie-Salmon.

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**Table 4**

| 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) | .405     |
| Sex                      | 0.902  | (0.296, 2.175) | .665     | 0.684  | (0.257, 1.823) | .448     |
| DS stage                 | 1      | –            | –        | 0.926  | (0.195, 4.391) | .360     |
| I                        | 0.954  | (0.175, 5.214) | .99     | 2.423  | (0.892, 6.578) | .082     |
| II                       | 0.909  | (0.19, 4.351)  | .99     | 2.423  | (0.892, 6.578) | .082     |
| DS stage (Group)         | B vs A | 1.104 | (0.289, 4.211) | .885   | 0.494  | (0.140, 1.737) | .271     |
| Treatment strategy       | Subcutaneous vs intravenous | 0.714 | (0.229, 2.228) | .562   | 0.494  | (0.140, 1.737) | .271     |

DS = Durie-Salmon.

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**Table 5**

|                      | 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)       | .732 |
| Peripheral neuropathy | 10 (17.5)     | 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 |

1 Weekly therapy vs standard therapy (including intravenous injection and subcutaneous injection).
2 Intravenous injection vs subcutaneous injection, \(P < .05\).
4. Discussion

Although the efficacy of bortezomib in the treatment of MM is widely recognized, its adverse reactions cannot be overlooked. The most common adverse reactions of standard therapy regimens (bortezomib 1.3 mg/m² 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. 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. Hence, the aim of alternative bortezomib regimens is to reduce adverse reactions while ensuring efficacy. 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, 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 showed that extending bortezomib to once a week could reduce the incidence of PN without changing the efficacy. Reeder et al treated newly diagnosed MM patients with a VCD regimen in a phase II clinical trial: 33 patients received intravenous bortezomib 1.3 mg/m² on days 1, 4, 8, and 11, and 30 patients received intravenous bortezomib 1.5 mg/m² on days 1, 8, 15, and 22; after completing 4 cycles, the ORR was 96% and 93%, respectively, the CR rate was 46% and 46.2%, respectively, and the effectiveness ≥VGPR rate was 71% and 63%, respectively. The effectiveness of the above 2 regimens was similar, but the incidence of thrombocytopenia was lower with the twice-weekly regimen. In the present study, the number of patients who completed the full course 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 in the effectiveness of patients with newly diagnosed MM. In a phase III clinical trial (MMY-3021), Moreau et al 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 25%
The median PFS of subcutaneous injection group and intravenous injection group was 10.2 months and 8 months, respectively (P>0.05), and the 1-year OS rate were 72.6% and 76.7%, respectively (P>0.05). Mez et al, Liu et al and Wu et al showed better tolerability and similar treatment response of subcutaneous vs intravenous bortezomib. On the other hand, Minarik et al reported similar effectiveness but also similar adverse reactions of subcutaneous and intravenous bortezomib. In addition, Xu et al 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. In a phase II trial, Reeder et al 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, 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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References

[1] Pratt G, Jenner M, Owen R, et al. Updates to the guidelines for the diagnosis and management of multiple myeloma. Br J Haematol 2014;167:131–3.
[2] Snowden JA, Greenfield DM, Bird JM, et al. Guidelines for screening and management of late and long-term consequences of myeloma and its treatment. Br J Haematol 2017;176:885–907.
[3] Raab MS, Podar K, Breitbart I, et al. Multiple myeloma. Lancet 2009;374:324–39.
[4] Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 2003;78:21–33.
[5] Rajkumar SV, Kumar S. Multiple myeloma: diagnosis and treatment. Mayo Clin Proc 2016;91:101–19.
[6] Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood 2008;111:2516–20.
[7] Kumar SK, Callander NS, Alsina M, et al. Multiple myeloma, version 3.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2017;15:230–69.
[8] Leibma, Kedmi M, Duke A, et al. Bortezomib-cyclophosphamide-dexamethasone (VCD) versus bortezomib-thalidomide-dexamethasone (VTD) -based regimens as induction therapies in newly diagnosed transplant eligible patients with multiple myeloma: a meta-analysis. Br J Haematol 2014;166:702–10.
[9] Nieszynski R, Flinn IW, Ritkin R, et al. Community-based phase IIIb trial of three UPFRONT bortezomib-based myeloma regimens. J Clin Oncol 2015;33:3921–9.
[10] Bringhen S, Larocca A, Rossi D, et al. Efficacy and safety of once-weekly bortezomib in multiple myeloma patients. Blood 2010;116:4754–53.
[11] Nooka AK, Kaufman JL, Behera M, et al. Bortezomib-containing induction regimens in transplant-eligible myeloma patients: a meta-analysis of phase 3 randomized clinical trials. Cancer 2013;119:4119–28.
[12] Cavo M, Pantani L, Pezzi A, et al. Bortezomib-thalidomide-dexamethasone (VTD) is superior to bortezomib-cyclophosphamide-dexamethasone (VCD) as induction therapy prior to autologous stem cell transplantation in multiple myeloma. Leukemia 2015;29:2429–31.
[13] Sun CY, Li JY, Chu ZR, et al. Efficacy and safety of bortezomib maintenance in patients with newly diagnosed multiple myeloma: a meta-analysis. Biosci Rep 2017;37:doi:10.1042/BSR20170304.
[14] Zhu W, Chen W. Bortezomib-based treatment for multiple myeloma patients with renal impairment: a systematic review and meta-analysis of observational studies. Medicine (Baltimore) 2016;95:e5202.
[15] Liu X, He CK, Meng X, et al. Bortezomib-based vs non-bortezomib-based post-transplantation treatment in multiple myeloma patients: a systematic review and meta-analysis of Phase III randomized controlled trials. Onco Targets Ther 2015;8:1459–69.
[16] Gao M, Yang G, Han Y, et al. Single-agent bortezomib or bortezomib-based regimens as consolidation therapy after autologous hematopoietic stem cell transplantation in multiple myeloma: a meta-analysis of randomized controlled trials. Int J Clin Exp Med 2015;8:12202–10.
[17] Wang L, Xu YL, Zhang XQ. Bortezomib in combination with thalidomide or lenalidomide or doxorubicin regimens for the treatment of multiple myeloma: a meta-analysis of 14 randomized controlled trials. Leuk Lymphoma 2014;55:1479–88.
[18] Knopf KB, Duh MS, Lafaille LH, et al. Meta-analysis of the efficacy and safety of bortezomib re-treatment in patients with multiple myeloma. Clin Lymphoma Myeloma Leuk 2014;14:380–8.
Yao et al. Medicine (2019) 98:39

[19] Hainsworth JD, Spigel DR, Barton J, et al. Weekly treatment with bortezomib for patients with recurrent or refractory multiple myeloma: a phase 2 trial of the Minnie Pearl Cancer Research Network. Cancer 2008;113:765–71.

[20] Zeng Z, Lin J, Chen J. Bortezomib therapy alone and in combination with thalidomide, lenalidomide, or pomalidomide in newly diagnosed multiple myeloma: a systematic review and meta-analysis of randomized controlled trials. Ann Hematol 2013;92:935–43.

[21] Rajan AM, Rajkumar SV. Treatment of newly diagnosed myeloma: Bortezomib-based triplet. Semin Oncol 2016;43:700–2.

[22] Wang Y, Ai L, Cui G, et al. Once- versus twice-weekly Bortezomib induction therapy with dexamethasone in newly diagnosed multiple myeloma. J Huazhong Univ Sci Technolog Med Sci 2012;32:495–500.

[23] Jagannath S, Durie BG, Wolf J, et al. Bortezomib therapy alone and in combination with dexamethasone for previously untreated symptomatic multiple myeloma. Br J Haematol 2005;129:776–83.

[24] Schlafer D, Shah KS, Panjic EH, et al. Safety of proteasome inhibitors administered subcutaneously. Hematology Am Soc Hematol Educ Program 2016;2016:485–94.

[25] Tang Y, Yu YH, Yao YY, et al. Once-weekly 1.6 mg/m² bortezomib for patients with recurrent or refractory multiple myeloma: a phase 2 trial of the Minnie Pearl Cancer Research Network. Cancer 2008;113:765–71.

[26] Liu H, Xu R, Huang H. Peripheral neuropathy outcomes and efficacy of subcutaneous bortezomib when combined with thalidomide and dexamethasone for treatment of newly diagnosed multiple myeloma patients: an interim analysis from the prospective GMMG-MM5 trial. Haematologica 2015;100:964–9.

[27] Merz M, Salvendel H, Haenel M, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. Lancet Oncol 2011;12:431–40.

[28] Petracci MT, Finsinger P, Chissini M, et al. Subcutaneous bortezomib for multiple myeloma treatment: patients' benefits. Patient Prefer Adherence 2014;8:939–46.

[29] Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014;15:e538–48.

[30] Anderson KC, Alsina M, Atanackovic D, et al. Multiple Myeloma, version 2.2016: clinical practice guidelines in oncology. J Natl Compr Canc Netw 2015;13:1398–433.

[31] Mateos MV, Richardson PG, Dimopoulos MA, et al. Effect of cumulative bortezomib dose on survival in multiple myeloma patients receiving bortezomib-melphalan-prednisone in the phase III VISTA study. Am J Hematol 2015;90:314–9.

[32] Wildes TM, Rosko A, Tuchman SA. Multiple myeloma in the older adult: better prospects, more challenges. J Clin Oncol 2014;32:2531–40.