Original Study

Tolerance, Kinetics, and Depth of Response for Subcutaneous Versus Intravenous Administration of Bortezomib Combination in Chinese Patients With Newly Diagnosed Multiple Myeloma

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Abstract

This retrospective investigation compared the efficacy and safety of bortezomib administration via subcutaneous and intravenous dosing in 307 patients with newly diagnosed multiple myeloma from a single Chinese center. Subcutaneous bortezomib is associated with better tolerance. However, intravenous 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:** We retrospectively analyzed 307 patients with newly diagnosed multiple myeloma from a single Chinese center, receiving Btz-based regimens administered either via SC injection (SC group, n = 167) or intravenous (IV) infusion (IV group, n = 140). The efficacy and safety of Btz administration via SC and IV were then compared. **Results:** Most baseline characteristics were similar between these 2 groups. A lower frequency of adverse events, especially grade ≥ 3 PN ($P = .002$), was observed in the SC group compared with the 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 owing to adverse events in the SC group compared with the IV group. The overall response rate (≥ partial response [PR]) was comparable (94.8% vs. 96.2%). However, patients in the IV group required fewer cycles to achieve PR, whereas a larger proportion of patients in the IV group achieved ≥ very good PR. After a median follow-up of 23 months (range, 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 patients with newly-diagnosed multiple myeloma.

Clinical Lymphoma, Myeloma & Leukemia, Vol. ■, No. ■, ■-■
Keywords: Bortezomib, Intravenous administration, Multiple myeloma, Response, Subcutaneous administration

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

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Submitted: Aug 21, 2017; Revised: Jan 11, 2018; Accepted: Mar 9, 2018

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2152-2650/$ - see frontmatter
https://doi.org/10.1016/j.clml.2018.03.006

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 administration 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 life.[9] 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 patients with relapsed or refractory MM (RRMM). This study also assessed the safety and efficacy of these 2 administration routes. The plasma concentration of Btz and the percent inhibition of 20S proteasome were measured on days 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 injection.[10] These outcomes were subsequently confirmed in the randomized, prospective MMY-3021 study involving patients with RRMM,[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 MM (NDMM).[16-19] Few studies with small cohorts compared the 2 administration routes in Asian patients.[20,21]

Promising results from our preliminary studies showed that SC Btz significantly decreases and delays peripheral neuropathy (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 the Btz (also named as PS341) combined with adriamycin and dexamethasone (PAd) group compared with the SC group. This has significant relevance in practice. This is also the largest cohort of Asian patients and demonstrates the relevance of SC versus IV administration of Btz 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 patients with NDMM treated with a Btz-based regimen at the Lymphoma and 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 or Btz combined with cyclophosphamide (CTX) and dexamethasone (BCd) (Btz 1.3 mg/m^2 on days 1, 4, 8 and 11; adriamycin 9 mg/m^2 intravenously on days 1-4; or CTX 500 mg/m^2, 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 IV (historical control IV group) before Feb 28, 2012 or SC injection (SC group) after March 1, 2012. The IV injections were administered at a concentration of 1 mg/mL as a 3- to 5-second intravenous push, whereas SC injections were administered at 2.5 mg/mL to limit total volume. All treatments were repeated every 3 to 4 weeks. After at least 4 cycles of treatment, patients underwent consolidation therapy with either autologous stem cell transplant (if patient was $<$ 65 years old and without contraindication to autologous stem cell transplant) combined with the original chemotherapy regimen or only the original chemotherapy regimen. After up to 9 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 to 2 months. All patients received prophylactic acyclovir.

Patients who completed $\geq$ 1 dose of Btz were included in this study, and the data on their demographic characteristics and disease profiles (including gender; age; M-protein type and quantity; Durie Salmon [DS], International Staging System [ISS], and Revised ISS [R-ISS][22] 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 PN and diabetes mellitus 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 $\geq$ 1 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 studies.[9] As for SC patients, an updated stricter dose-modification guidelines was used.[23]

Efficacy analysis was based on all patients who completed $\geq$ 1 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 $\pm$ standard deviation (SD). Independent samples of nonparametric tests were used to compare the difference between the 2 groups. The Spearman association and