Increasing Diluent Volume Decreases Bendamustine-Induced Venous Irritation without Reducing the Therapeutic Efficacy

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The intravenous injection of bendamustine often induces venous irritation, which reduces patients’ QOL. We previously reported that the dilution of the final volume of bendamustine from 250 to 500 mL significantly decreased the incidence of venous irritation. However, the influence of this change on the therapeutic efficacy of bendamustine remains unclear. Therefore, the aim of this study was to evaluate the efficacy and safety profiles of bendamustine at different dilutions of the final volume, comparing with the correspondences of previous studies. Thirty-four patients, who received a total of 161 courses of bendamustine and rituximab chemotherapy, were included in this study. The overall response rate of this regimen was 94.1% in this study, which was comparable to that reported in the BRB study (94.2%, a phase II study of bendamustine plus rituximab therapy in Japanese patients). Additionally, the median progression-free survival was not inferior to that reported in the BRB study. Bendamustine-induced venous irritation was observed in 17.6% of the patients during the first treatment cycle administered at a final volume of 500 mL, and was found to be lower than that observed in the control, where bendamustine was administered at a final volume of 250 mL (85.7%). These results suggest that diluting bendamustine to 500 mL, but not to 250 mL, reduces the incidence of venous irritation without a negative impact on its therapeutic efficacy; thus, this simple strategy may be beneficial to ensure efficacy and safety in patients receiving regimens including bendamustine.

Key words bendamustine; therapeutic efficacy; venous irritation; diluent volume

INTRODUCTION

Bendamustine is a widely used anticancer drug that has various cell-killing mechanisms, including alkylating, apoptosis activation,2 and mitotic catastrophe induction.2 Recently, bendamustine combined with rituximab chemotherapy has rapidly become a standard frontline strategy for patients with follicular lymphoma.11 Bendamustine has also shown clinical efficacy against various hematological malignancies, including other subtypes of non-Hodgkin’s lymphoma (NHL)3–8 and chronic lymphocytic leukemia.9,10 Particularly, in Japanese patients, a phase II study of bendamustine plus rituximab therapy (BRB study)10 showed an overall response rate (ORR) of 94.2% in patients with relapsed or refractory indolent B-cell NHL and mantle cell lymphoma (MCL) previously treated with rituximab, with a median progression-free survival (PFS) of 17.95 months for patients with indolent B-cell NHL; these results were comparable to that obtained in another phase II study conducted in North America.12 However, the intravenous injection of bendamustine often causes venous irritation (e.g., erythema, pain at the site of injection, and phlebitis), which may reduce patients’ tolerability to chemotherapy and their QOL.

Although the mechanisms underlying bendamustine-induced venous irritation have not been fully elucidated, the effect of the administered concentration is assumed to correlate with an infusion-related complication. Upon drug approval, the reported incidence of bendamustine-induced venous irritation was 30.8% in Japan (TREAKISYM® injection),13 whereas it was less common (<10%) in the United States (TREANDA® injection).14 According to the package insert of the TREAKISYM® injection, the recommended final volume of the bendamustine injection is 250 mL,13 while that of the TREANDA® injection recommends a final volume of 500 mL, with a final concentration of 0.2–0.6 mg/mL.14 We previously reported a significant decrease in the incidence of venous irritation induced by bendamustine when its final volume was changed from 250 to 500 mL.15 However, the influence of this dilution of bendamustine volume on the therapeutic efficacy remains uncertain, because no study has revealed the therapeutic efficacy of bendamustine prepared in a 500 mL diluent, especially among Japanese patients. Therefore, in this study, we examined the therapeutic efficacy, as well as the incidence of bendamustine-induced venous irritation, with a lower final concentration.

PATIENTS AND METHODS

Patients The present study included 34 patients with relapsed or refractory indolent B-cell NHL and MCL, who received a total of 161 courses of bendamustine (only dissolved in 500 mL of normal saline as a final volume) and rituximab (B-R) chemotherapy from January 2013 to December 2017 at Kyushu University Hospital. According to predefined criteria, patients were excluded from this investigation if they had no prior history of chemotherapy.

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The study was conducted in accordance with the Declaration of Helsinki and its amendments, and the protocol was approved by the Ethics Committee of Kyushu University Graduate School and Faculty of Medicine (Institutional Review Board approval no. 30-243).

**Study Protocol and Data Collection** Bendamustine (TREAKISYM® injection, 90 mg/m² for B-R therapy) was administered intravenously in a final volume of 500 mL normal saline over 120 min on days 1 and 2 of the therapeutic regimen. Rituximab (375 mg/m²) was administered once on any single day of days 0 to 3. Modifications in the method of bendamustine preparation (diluted in normal saline with a final volume of 500 mL) and administration (infused over 120 min) were approved by the Cancer Chemotherapy Review Committee of Kyushu University Hospital.

All data were retrospectively collected from electronic medical charts and nursing records. The ORR and PFS were measured to assess the therapeutic efficacy of the modified administration of bendamustine. According to the International Working Group Response Criteria for NHL, the overall treatment responses were classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), and the ORR was calculated as the number of patients who achieved CR or PR divided by the total number of patients receiving B-R therapy. PFS, defined as the interval from the time of bendamustine administration until progression of the disease or death from any cause, was estimated using the Kaplan–Meier method. Patients who received allogeic hematopoietic stem cell transplantation as a subsequent treatment were censored on the day of transplantation, and those who received subsequent bendamustine administration at another hospital were censored on the final follow-up day at our hospital. Venous irritation was assessed based on the presence of the following symptoms: pain at the site of injection, swelling, or redness.

**Study Design** To evaluate the therapeutic efficacy of bendamustine with the modified administration, the ORR and PFS (median PFS and one-year PFS rate) obtained from the collected data of 34 patients were compared with those in the BRB study, a phase II study which included 52 Japanese patients with relapsed or refractory indolent B-cell NHL and MCL with prior history of rituximab treatment. In the BRB study, bendamustine was diluted in normal saline to a final volume of 250 mL. As in this study, the overall treatment responses in the BRB study were classified according to the International Working Group Response Criteria for NHL.

Further, to assess the safety of bendamustine with the modified administration, the incidence of venous irritation in this study was compared with previous data for 14 patients reused from our study, in which bendamustine was diluted in normal saline to a final volume of 250 mL.

**Data Analyses** The Kaplan–Meier method was used for the estimation of median PFS. All data were analyzed using JMP 13.0.0 (SAS Institute Inc., Cary, NC, U.S.A.).

**RESULTS**

The characteristics of patients in our cohort and in the BRB study are listed in Table 1. We did not compare these characteristics of patients between the two arms statistically, because statistical comparison of data between our study and BRB study are listed in Table 1. We did not compare these characteristics of patients between the two arms statistically, because statistical comparison of data between our study and BRB study is described here means the sum of CR (40.4%) and CRu (complete response unconfirmed, 30.8%). ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease.

Data of the BRB study were cited from Matsumoto et al. ECOG-PS, Eastern Cooperative Oncology Group Performance Status; B-R, bendamustine and rituximab; S.D., standard deviation; MALT, Mucosa-associated lymphoid tissue; FLIPI, Follicular Lymphoma International Prognostic Index.

Data of the BRB study were cited from Matsumoto et al. CR of the BRB study described here means the sum of CR (40.4%) and CRu (complete response unconfirmed, 30.8%). ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease.
previous report would be meaningless.

The ORR in the present study was 94.1% (70.6% of CR, 23.5% of PR, 2.9% of PD, and 2.9% of unevaluable; Table 2), which corresponded to 94.2% obtained in the BRB study (40.4% of CR, 30.8% of CR unconfirmed (CRu), and 23.1% of PR). Patient data collection was completed on October 25, 2018, and the median follow-up period was 28 (0.5–64) months. A Kaplan–Meier PFS curve of all patients is shown in Fig. 1. The median PFS, another index of therapeutic efficacy of bendamustine, remained unattained (95% confidence interval (CI), 29.2 months to unknown, as the upper arm of the CI had not been reached), and the one-year PFS rate was 94.0%.

The incidence of bendamustine-induced venous irritation is shown in Fig. 2. Venous irritation developed in 17.6% of all the patients (95% CI 8.3–33.5%) during the first treatment cycle (Fig. 2A). This result was lower than that observed with a final volume of 250 mL (85.7, 95% CI 60.1–96.0%) in previous data reused from our study.15) Similarly, during overall treatment cycles, venous irritation developed in 41.2% of all the patients (95% CI 26.4–57.8%, Fig. 2B), which was lower than that observed in the previously obtained data (92.9, 95% CI 68.5–98.7%).15)

**DISCUSSION**

In the present study, we evaluated the efficacy and safety profiles of bendamustine prepared in a 500 mL diluent. We showed that although the therapeutic efficacy, such as ORR, median PFS, or 1-year PFS rate, of the diluted bendamustine is retained, there is a reduction in the incidence of venous irritation induced by bendamustine when administered in a 500 mL diluent.

To examine whether the efficacy of the B-R regimen with a modified bendamustine final volume was preserved, we performed this retrospective comparative analysis. The previous data from our own institute would have been the ideal data for comparison; however, all except three patients in the previous study underwent bendamustine treatment with both the 250 mL and 500 mL dilutions. Therefore, we decided that the results of other previous clinical trials could be exploited as alternative comparative data to investigate the effect of bendamustine dilution volume accurately.

One of these clinical trials was the BRB study,11) in which the safety and efficacy of B-R regimen among 52 Japanese patients with relapsed/refractory indolent B-cell NHL or MCL were evaluated. The ORR obtained in the BRB trial was 94.2% in all cases. The median PFS was 17.95 months (95% CI, 15.91 months to unknown, as upper limit had not been reached), and the 1-year PFS rates were approximately 80% for patients with indolent B-cell NHL. The present study reconfirmed this high efficacy: the ORR and the median or 1-year PFS in the present study were similar to those obtained in the BRB study. The StiL2 study,17) another phase III clinical trial for relapsed indolent NHL or MCL, showed an ORR of 82.5% (94 of 114 patients) with bendamustine prepared in a 250 mL diluent. Based on these findings, we could expect a similar response rate from the B-R regimen with the standard dilution and the modified dilution, at least among Japanese patients.

Since only patients who strictly fit the inclusion and exclusion criteria were enrolled in the clinical trial, the therapeutic efficacy expected in clinical practice was generally lower than that of standard clinical trials. Nonetheless, we observed a high ORR, even in clinical practice, which was comparable to that obtained in these clinical trials, as mentioned above. In addition, the PFS observed in this study was not inferior to that reported in the BRB study. Although we did not perform a matched-pair analysis, the number of cycles of the B-R regimen completed in this study was marginally higher than that of the BRB study (Table 1), which might contribute to obtaining an efficacy similar to that in a clinical trial. However, the optimal cycles of the B-R treatment remain unclear, and hence, the results of this comparative analysis should be carefully interpreted.

To assess the safety of bendamustine with the modified administration, the incidence of venous irritation in this study was compared with the data for 14 patients reused from our previous study,15) but not with those in the previous phase III clinical trials. Previous data reused from our study were obtained at our own institute, and therefore, these results were
thought to be more relevant for the evaluation of the incidence of venous irritation.

Our previous study clearly demonstrated that the incidence of bendamustine-induced venous irritation could be effectively prevented by diluting the final volume to 500 mL, and the final bendamustine concentration infused was below 0.4 mg/mL. We could reproduce this effect in the present study, with the development of venous irritation in 17.6% (the first treatment cycle) and 41.2% (overall treatment cycles) of the patients. In general, increasing the volume of diluents reduces the concentration of a solution, thereby leading to the reduction in osmotic pressure and the risk of venous irritation. Nakashima et al. reported, in a case series with three follicular lymphomas, that the coadministration of 250 mL 5% glucose solution with bendamustine (dissolved in 250 mL saline, total volume: 500 mL) reduced the grade of vascular pain. In addition, vinorelbine reportedly induced vascular endothelial cell damage in a dose-dependent manner. Based on the results from our group and others, we recommended a lower concentration of bendamustine solution (≤0.4 mg/mL) to avoid the risk of venous irritation, although prolonged infusion time would be problematic in some patients.

In conclusion, we identified, in the settings of B-R treatment, bendamustine administered with a final volume of 500 mL had an equivalent therapeutic potential and showed a lower incidence of venous irritation than bendamustine prepared in a final volume of 250 mL. This simple but useful strategy could be adapted for all patients receiving a regimen including bendamustine. Our findings are limited given the single-center, retrospective design in a small number of patients; thus, further studies are required to confirm the results.

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Conflict of Interest The authors declare no conflict of interest.

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