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Original Article

Bendamustine Plus Rituximab as Salvage Treatment for Patients with Relapsed or Refractory Low-grade B-cell Lymphoma and Mantle Cell Lymphoma: A Single-Center Retrospective Study

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Bendamustine plus rituximab (B-R) is an effective therapy for relapsed or refractory (r/r) low-grade B-cell lymphoma (LGBCL) and mantle cell lymphoma (MCL); however, clinical data from Japanese patients treated with B-R therapy are limited. We retrospectively evaluated the efficacy and safety of B-R therapy in 42 patients who received B-R therapy at our hospital for r/r LGBCL and MCL. All patients received intravenous (IV) rituximab 375 mg/m^2 on day 1 and IV bendamustine 90 mg/m^2 on days 2 and 3 every 28 days for up to 6 cycles. The common histologic subtypes were follicular lymphoma (n = 29, 70%), marginal zone lymphoma (n = 6, 14%), and MCL (n = 5, 12%). The overall response rate was 93%, with 62% complete response and complete response unconfirmed. The median progression-free survival (PFS) was 38 months (95% confidence interval [CI], 24.6 to not reached [NR]), and the median overall survival (OS) was 80 months (95% CI, 60.7 to NR). Patients receiving a cumulative dose of bendamustine ≥ 720 mg/m^2 showed a significantly longer PFS and OS. Grade 3/4 adverse events (≥ 10%) included neutropenia (55%), lymphopenia (69%), and nausea (24%). B-R therapy was effective and well tolerated, and the cumulative dose of bendamustine was associated with a favorable outcome.

Key words: bendamustine, low grade B-cell lymphoma, mantle cell lymphoma

According to the 2017 World Health Organization classification, low-grade B-cell lymphomas (LGBCLs) comprise follicular lymphoma (FL), marginal zone lymphoma (MZL), small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL), lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia (LPL/WM), and mantle cell lymphoma (MCL) [1]. This classification has been widely used in various clinical trials, and bendamustine is now commonly used as a treatment option for these diseases.

Bendamustine hydrochloride was designed in East Germany in the 1960s as a drug having both the nitrogen-mustard structure of an alkylator and a purine analogue-like structure. Bendamustine damages the double strands of DNA more strongly and more quickly than other alkylators. The DNA damage caused by bendamustine is not affected by the repair mechanisms induced by other DNA-damaging alkylators. Therefore, bendamustine has no cross-resistance with other alkylators [2-4].

A phase II clinical study evaluating the efficacy and safety of bendamustine plus rituximab (B-R) therapy for relapsed or refractory (r/r) LGBCL and MCL was reported in 2008. The overall response rate (ORR) and median progression-free survival (PFS) were 92% and 23 months, respectively. The treatment was well tolerated, with the primary adverse event being myelosup-

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pression; grade 3/4 neutropenia and leukopenia were observed in 36% and 30% of the patients, respectively [5]. Japan approved the use of bendamustine for r/r LGBCL and MCL in 2010. B-R therapy has been widely used since then, but there is a lack of clinical data from Japanese patients treated with B-R therapy. Therefore, we retrospectively evaluated the efficacy and safety of B-R therapy for r/r LGBCL and MCL patients at our clinical practice.

Patients and Methods

Patients. We registered 42 patients who had received B-R therapy for r/r LGBCL and MCL from September 2011 to March 2019 at the Department of Hematology, National Hospital Organization Okayama Medical Center. This study was conducted in accordance with the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects and was approved by the local ethics committee of the National Hospital Organization Okayama Medical Center (No. 2019-247).

Treatment. Patients received B-R therapy [intravenous (IV) rituximab 375 mg/m^2 on day 1 and IV bendamustine 90 mg/m^2 on days 2 and 3, administered every 28 days for up to 6 cycles]. The dose of bendamustine and schedule of B-R therapy were modified according to the discretion of the attending physician. Antibiotic (sulfamethoxazole: 80 mg/day, trimethoprim: 400 mg/day) and antiviral (acyclovir: 200-400 mg/day) prophylaxes were routinely administered to all patients. The dose of these drugs was adjusted according the patients' renal function.

Outcome assessment and statistical analysis. Response was defined according to the guidelines established by an international workshop to standardize response criteria for non-Hodgkin's lymphoma [6]. PFS was defined as the time from the start of treatment to disease progression or death. Overall survival (OS) was defined as the time from the start of treatment to death. The severity of adverse events (AEs) was graded according to the Common Terminology Criteria for Adverse Events, version 4.0. Relative dose intensity (RDI) of bendamustine was defined as the ratio of actual administered dose per protocol dose per unit time. PFS and OS were estimated using the Kaplan–Meier method and were compared between groups by log-rank test. Cox proportional hazards regression models were used to assess whether patient characteristics at treatment were predictive of PFS and OS. The ORR was compared between the 2 groups using Fisher's exact test. All tests were two-sided and the level of statistical significance for all analyses was defined as $p < 0.05$. Statistical analysis was performed using EZR software (ver. 1.35) [7].

Results

Patients characteristics. The patient characteristics are summarized in Table 1. The histologic subtypes were FL (n = 29, 70%), MZL (n = 6, 14%), SLL (n = 1, 2%), LPL (n = 1, 2%), and MCL (n = 5, 12%). Rebiopsy was not conducted because there were no patients suspected of histological transformation. The median patient age was 78.5 years (range, 41 to 87), the sex ratio was 24 : 18 (male: female), and 90% of the patients were diagnosed as being at an advanced stage. Bulky mass lesions (> 7 cm) were found in 4 patients, extranodal lesions were found in 10 patients, and high lactate dehydrogenase (LDH) levels (> 240 IU/l) were found in 30 patients. In 83% (n = 35) of patients, B-R therapy was second line. Four patients were considered refractory to the previous therapy. Most patients had received rituximab monotherapy or rituximab combination chemotherapy as the last therapy prior to the B-R regimen. Two patients had been administered rituximab maintenance therapy. However, none of our patients was treated with rituximab maintenance therapy after B-R therapy. The median number of cycles of B-R therapy was 4 (range, 1 to 6). The total number of cycles of B-R therapy administered was 196. The number of patients who completed each cycle and the median interval days per cycle are detailed in Table 1.

Efficacy. The ORR, complete response and complete response unconfirmed (CR/CRu) rate and partial response (PR) rate were 93%, 62%, and 31%, respectively (Table 2). For LGBCL, the ORR, CR/CRu rate, and PR rate were 92%, 65%, and 27%, respectively. For MCL, the ORR, CR/CRu rate, and PR rate were 100%, 40%, and 60%, respectively. With a median follow up of 53 months (range, 2.5-94), the median PFS and OS were 39.5 months (95% confidence interval [CI], 24 to "not reached" [NR]) and 80 months (95% CI, 60.7 to NR), respectively (Fig. 1). In MCL, the median PFS and OS were 39 (95% CI, 20.7 to NR) and 47 months (95% CI, 22 to NR), respectively. The 10 factors which could have influenced PFS—namely age,

Table 1 Patient characteristics

No. of patients	42
Median age (range)	78.5 (41 to 87)
Male/Female	24/18
Histologic subtypes	
Low grade B-cell lymphoma	
Follicular	29
grade 1	25
grade 2	3
grade 3a	1
Marginal zone	6
Small lymphocytic	1
Lymphoplasmacytic	1
Mantle cell lymphoma	5
Stage	
I–II	2
III–IV	38
Unknown	2
Bulky mass (>7 cm)	
Yes	4
No	38
Extranodal lesions ≥1	
Yes	10
No	32
LDH	
≤240	30
>240	12
Median months from initial diagnosis to start of B-R therapy (range)	92.5 (3 to 180)
Median no. of prior regimens (range)	1 (1 to 3)
Prior regimens	
Rituximab monotherapy	21
Rituximab + chemotherapy	23
Other	6
Last regimen before B-R therapy	
Rituximab monotherapy	20
Rituximab + chemotherapy	21
Disease status	
Relapse	38
Refractory	4
Median no. of cycles treated with B-R therapy (range)	4 (1 to 6)
Total no. of cycles treated with B-R therapy	196
No. of patients who completed the cycle (%)	
Cycle 1	42 (100)
Cycle 2	41 (98)
Cycle 3	34 (81)
Cycle 4	33 (79)
Cycle 5	25 (60)
Cycle 6	21 (50)
Median interval days per cycle (range)	
Cycles 1 to 2	35 (28 to 267)
Cycles 2 to 3	34 (28 to 98)
Cycles 3 to 4	36 (28 to 77)
Cycles 4 to 5	36 (28 to 103)
Cycles 5 to 6	35 (28 to 90)
Median RDI (%) of bendamustine (range)	64.4 (23.5 to 100)

B, bendamustine; R, rituximab; LDH, lactate dehydrogenase; RDI, relative dose intensity.

sex, histology, LDH, extranodal lesions, bulky mass, time from diagnosis to initiation of B-R therapy, regimen before B-R therapy, cumulative dose of bendamustine, and RDI of bendamustine—were analyzed using the log-rank test. The median values of cumulative dose of bendamustine and RDI of bendamustine were adopted as cut-offs. High LDH (95% CI, 3.02 to NR, $p<0.05$), extranodal lesions ≥1 (95% CI, 7.55 to 39.32, $p<0.05$), and cumulative dose of bendamustine <720 mg/m^2 (95% CI, 3.02 to 25.26, $p<0.05$) had significantly inferior PFS in the log-rank test (Table 3). These 3 factors were subjected to Cox proportional hazards regression analysis. High LDH and cumulative dose of bendamustine <720 mg/m^2 had significantly inferior PFS (Table 4). Furthermore, high LDH and cumulative dose of bendamustine <720 mg/m^2 had significantly inferior OS in the log-rank test and Cox proportional hazards regression models (Tables 3, 4). The patient characteristics for the cumulative bendamustine doses groups ≥720 mg/m^2 and <720 mg/m^2 are shown in Table 5. There were no significant differences in patient characteristics between these 2 groups. The reasons for receiving a cumulative dose of bendamustine <720 mg/m^2 were prolonged neutropenia (n=5, 42%), patient request (n=2, 17%), disease progression (n=2, 17%), and other (n=3, 25%); these events were not related to non-hematological AEs. The ORR was significantly better in the cumulative bendamustine dose ≥720 mg/m^2 group than in the <720 mg/m^2 group (100% vs. 75%, $p=0.02$). However, the CR/CRu rate was not significantly different between the 2 groups (Table 6). The RDI was not significantly related to PFS, OS, and ORR. The follicular lymphoma international prognostic index (FLIPI) (low vs. intermediate vs. high risk) [8] was significantly associated with the PFS ($p<0.01$, log-rank analysis) but not with the OS ($p=0.077$) in patients with FL (n=29).

Safety. The AEs of B-R therapy are shown in Table 7. The most frequently observed severe hematological AEs (grade 3/4) were neutropenia (n=23, 55%)

Table 2 Response with respect to pathological subtype

	n	Response, n (%)				
		ORR	CR/CRu	PR	SD	PD
All	42	39 (93)	26 (62)	13 (31)	1 (2)	2 (5)
Pathological subtype						
Low grade B-cell lymphoma	37	34 (92)	24 (65)	10 (27)	1 (3)	2 (5)
Mantle cell lymphoma	5	5 (100)	2 (40)	3 (60)	0 (0)	0 (0)

ORR, overall response rate; CR, complete response; CRu, complete response unconfirmed; PR, partial response; SD, stable disease; PD, progressive disease.

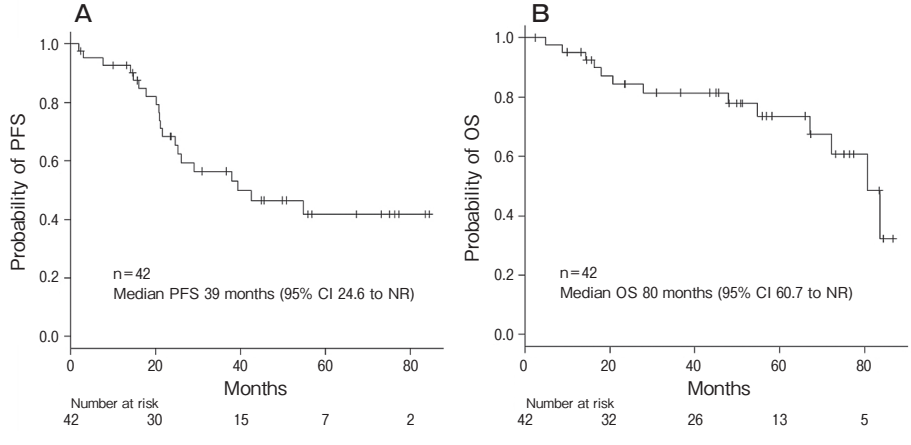

Fig. 1 Kaplan–Meier curve of progression-free survival (**A**) and overall survival (**B**) in all patients (n=42) receiving B-R therapy. PFS, progression-free survival; OS, overall survival; NR, not reached; CI, confidence interval; B, bendamustine; R, rituximab.

Table 3 Factors influencing survival (log-rank test)

	n	Median PFS (months)	95% CI	*P* value	Median OS (months)	95% CI	*P* value
Age							
≥75	14	25.2	14.09 to NR	0.17	80.2	14.29 to NR	0.53
<75	28	54.8	24.64 to NR		NR	67.22 to NR	
Sex							
Male	24	39.3	21.58 to NR	0.57	83.7	47.87 to NR	0.92
Female	18	NR	17.83 to NR		80.7	67.22 to NR	
Histology							
FL	29	NR	24.64 to NR	0.14	80.7	67.22 to NR	0.62
Others	13	37.9	14.09 to NR		83.7	17.84 to NR	
LDH (IU/L)							
>240	12	20.7	3.02 to NR	<0.05	20.7	8.74 to NR	<0.05
≤240	30	54.8	25.26 to NR		83.7	72.28 to NR	
ENLs							
Yes	10	24.6	7.35 to 39.32	<0.05	80.7	14.29 to NR	0.17
No	32	NR	25.26 to NR		NR	67.22 to NR	
Bulky mass (>7 cm)							
Yes	4	21.1	20.92 to NR	0.14	72.3	NR to NR	0.99
No	38	54.8	24.64 to NR		83.7	67.22 to NR	
Years from initial diagnosis to start of B-R							
≥2	20	NR	20.73 to NR	0.48	NR	47.87 to NR	0.36
<2	22	37.9	21.12 to NR		80.7	54.83 to NR	
Last regimen before B-R							
R monotherapy	21	NR	20.17 to NR	0.93	NR	28.8 to NR	0.67
R + CT	21	39.3	24.64 to NR		80.7	54.83 to NR	
Cumulative dose of bendamustine							
≥720 mg/m^2	30	NR	37.94 to NR	<0.05	83.7	67.22 to NR	<0.05
<720 mg/m^2	12	20.7	3.02 to 25.26		72.3	8.74 to NR	
RDI of bendamustine							
≥64.4%	21	42	24.64 to NR	0.469	NR	67.21 to NR	0.45
<64.4%	21	29	20.1 to NR		80.2	20.7 to NR	

PFS, progression-free survival; CI, confidence interval; NR, not reached; OS, overall survival; FL, follicular lymphoma; LDH, lactate dehydrogenase; ENL, extranodal lesion; R, rituximab; CT, chemotherapy; RDI, relative dose intensity.

Table 4 Factors influencing survival (Cox proportional hazards regression analysis)

	PFS			OS		
	HR	95% CI	*P* value	HR	95% CI	*P* value
LDH (>240 IU/L vs. ≤240 IU/L)	2.80	1.07 to 7.32	<0.05	3.31	1.05 to 10.43	<0.05
ENLs ≥1 (yes vs. no)	2.45	0.90 to 6.71	0.08	NE	NE	NE
Cumulative dose of bendamustine (<720 mg/m^2 vs. ≥720 mg/m^2)	6.70	2.20 to 20.45	<0.05	11.28	2.62 to 48.63	<0.05

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; ENL, extranodal lesion; NE, not evaluated.

and lymphopenia (n=29, 69%). Granulocyte-colony stimulating factor (G-CSF) was administered to 36 patients (85%). Grade 3/4 anemia (n=2, 5%) and thrombocytopenia (n=3, 7%) were rarely found. The most frequently observed non-hematological AEs were nausea (71%), constipation (52%), fatigue (38%), rash

Table 5 Patient characteristics by cumulative dose of bendamustine

	Cumulative dose of bendamustine		*P* value
	≥720 mg/m^2 (n=30)	<720 mg/m^2 (n=12)	
Age, n			
≥75	7	7	0.07
<75	23	5	
Sex, n			
Male	16	8	0.51
Female	14	4	
Bulky mass (>7 cm), n			
Yes	1	3	0.06
No	29	9	
Extranodal lesions ≥1, n			
Yes	6	4	0.43
No	24	8	
Follicular lymphoma, n			
Yes	21	8	1
No	9	4	
LDH (IU/L), n			
>240	7	5	0.27
≤240	23	7	
Last regimen before B-R, n			
Rituximab monotherapy	13	8	0.31
Rituximab + chemotherapy	17	4	

LDH, lactate dehydrogenase; B-R, bendamustine, rituximab.

Table 6 Response to the cumulative dose and RDI of bendamustine

	ORR, n (%)	*P* value	CR/CRu, n (%)	*P* value
Cumulative dose of bendamustine				
≥720 mg/m^2	30 (100)	<0.05	19 (63)	1
<720 mg/m^2	9 (75)		7 (58)	
RDI of bendamustine				
≥64.4%	21 (100)	0.23	13 (62)	1
<64.4%	18 (86)		13 (62)	

ORR, overall response rate; CR, complete response; CRu, complete response unconfirmed; RDI, relative dose intensity.

(19%), and infusion-related reactions (28%). Grade 3 non-hematological AEs were nausea, febrile neutropenia (FN), fatigue, and rash, of which nausea was the most frequent (n=10, 24%). FN was never observed more than once in the same patient. The other AEs were observed several times in some patients. These AEs quickly improved with supportive therapies, and B-R therapy was not discontinued. Cytomegalovirus reactivation was observed in 7% (3/42) of the patients, but responded rapidly to antiviral drug therapy.

Discussion

Bendamustine produced high response rates and durable responses in both LGBCL and MCL patients. A retrospective analysis of patients receiving bendamustine combined chemotherapy for r/r MCL has been reported from Spain. In that report, 83% of patients were treated with B-R therapy, and the ORR, CR/CRu rate, and median PFS were 84%, 53%, and 16 months, respectively. Only patients with CR/CRu had favorable PFS (median, 33 months) [9]. In a Japanese retrospective study of B-R therapy for r/r LGBCL and MCL,

Table 7 Adverse events in 42 patients treated with B-R therapy

Events	Any grade		Grade 3		Grade 4	
	n	%	n	%	n	%
Hematological AEs						
Lymphopenia	40	95	19	45	10	24
Neutropenia	36	86	13	31	10	24
Thrombocytopenia	24	57	2	5	1	2
Anemia	20	48	2	5	0	0
Non-hematological AEs						
Nausea	30	71	10	24	0	0
Constipation	22	52	0	0	0	0
Diarrhea	7	17	1	2	0	0
Vomiting	6	20	0	0	0	0
Fatigue	16	38	2	5	0	0
Rash	8	19	1	2	0	0
Alopecia	1	3	0	0	0	0
Infusion-related reaction	12	28	0	0	0	0
Febrile neutropenia	4	9	4	9	0	0

AE, adverse event.

Kawaguchi *et al.* reported that the ORR, CR/CRu rate, and 2-year PFS and OS rates were 81.1%, 39.6%, 59.7% and 74.9%, respectively [10]. In a prospective phase II clinical trial for r/r LGBCL and MCL (BRB study), the ORR, CR/CRu rate, and median PFS were 94%, 71%, and 18 months, respectively [11]; the maximum number of cycles of B-R therapy in that study was four. Furthermore, Sakai *et al.* reported the efficacy of B-R therapy for r/r follicular lymphoma (n = 37). In this prospective study, the median number of cycles of B-R therapy was 5 (range 1 to 6), and approximately half of the patients completed 6 cycles. The ORR was 91.9% (95% CI, 78.1 to 98.3), with a CR rate of 86.5% (95% CI, 71.2 to 95.5). The 3-year PFS and OS rates were 70.9% (95% CI, 52.3 to 83.3) and 88.9% (95% CI, 73.1 to 95.7). The dose of bendamustine was 240 mg/m^2 per cycle in their study [12]. Although our study was retrospective, the ORR, CR/CRu rate, and median PFS were 93%, 62%, and 39 months, respectively; these results were better than those of other retrospective studies and consistent with those of prospective studies. Furthermore, the median PFS and OS of several factors were "not reached" in subgroup analyses, and B-R therapy demonstrated durable clinical responses in patients with these factors. Two reasons why our study had a favorable outcome despite its retrospective nature may have been that the patients in our study were more likely to be using B-R as a second-line therapy and fewer patients were refractory.

The FLIPI is an index widely used to predict the outcomes of patients with FL. The risk factors in this equation include age, clinical stage, number of nodal lesions, low hemoglobin level, and high LDH [8]. In our study, high LDH and the presence of extranodal lesions were identified as significant factors for predicting poor PFS and OS. A cumulative bendamustine dose of 720 mg/m^2 or more seemed to contribute to favorable PFS and OS. It is notable that the cumulative dose of bendamustine has been identified as a prognostic factor for PFS and OS in B-R therapy. Ohmachi *et al.* reported that bendamustine monotherapy was less effective in patients with < 3 cycles than in those with ≥ 3 cycles [13]. The dose of bendamustine was 240 mg/m^2 per cycle in their study, and such that the cumulative dose of three cycles was 720 mg/m^2. In another study, Matsumoto reported the efficacy of RBD (rituximab, bendamustine, dexamethasone) therapy for LGBCL (n = 27) and MCL (n = 6). The ORR was 88% (29/33) with 58% (19/33) of patients showing CR/CRu. The 3-year PFS and OS rates were 75.5% and 88% respectively. The dose of bendamustine was 180 mg/m^2 per cycle, and the OS of the group treated with 5 (= 900 mg/m^2) or 6 cycles was significantly prolonged compared with that of the group treated with 4 (= 720 mg/m^2) or fewer cycles ($p = 0.033$, univariate analysis) [14]. These results are consistent with ours. Furthermore, we investigated the RDI of bendamustine in patients with LGBCL and MCL treated with B-R therapy. To the best of our knowledge, this is the first report to evaluate the RDI and clinical outcomes in patients with r/r LGBCL and MCL treated with B-R therapy. There was no significant relationship between the clinical outcomes and the RDI of bendamustine. It has been reported that a high RDI is a favorable factor for PFS and OS in patients with diffuse large B-cell lymphoma treated with R-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone, and rituximab) [15,16]. However, increasing the RDI is not related to improvements in PFS, OS, and ORR in patients with LGBCLs, such as follicular lymphoma, treated with R-CHOP [17]. LGBCLs progress slowly because of the slow growth rate of lymphoma cells. Therefore, administering the target dose may be more important than continuing dosing schedule.

A retrospective study of 9395 LGBCL patients registered between 2006 and 2013 through the SEER-

Medicare-linked database analyzed differences in infectious disease profiles of case treated with (n = 1,239) and without bendamustine (n = 8,156) [18]. In that report, the hazard ratios for bacterial pneumonia, cytomegalovirus reactivation, herpes virus infection, and pneumocystis pneumonia were significantly higher in the bendamustine combination regimen than in the non-bendamustine combination regimen [18]. It has been reported that bendamustine causes sustained lymphopenia, especially for CD4+ T cells [19]. In our analysis, the incidence of grade 3/4 lymphopenia was high. Based on the abovementioned data, antibiotic and antiviral drug prophylaxis was performed in all our patients; thus, development of these severe infections was rare. Our study confirmed the importance of prophylaxis with antibiotic and antiviral drugs during B-R therapy.

The incidence of FN in our study was 9%, which is higher than that reported previously. In our study, FN tended to increase after 4 cycles of B-R therapy (1 patient in the 3rd cycle, 3 patients each in the 4th through 6th cycles), with a high relative incidence in outpatients. However, after the onset of FN, broad-spectrum antibiotics and G-CSF were administered immediately in all patients, resulting in early improvement. FN could be adequately managed by such a supportive care. The incidence of severe anemia and thrombocytopenia was low, and similar to that in other phase II clinical trials. Grade 3 nausea, fatigue, and rash were observed, but were improved by supportive care in almost all patients. There was no discontinuation of B-R therapy due to these AEs.

The major reason for administering a low cumulative bendamustine dose (< 720 mg/m^2) was prolonged neutropenia (n = 5, 42%). Thus, the use of G-CSF to ameliorate prolonged neutropenia could enable a cumulative dose of bendamustine ≥ 720 mg/m^2. This is expected to lead to an improved prognosis, a better ORR, and a deeper response. The inability to administer a cumulative dose of bendamustine up to 720 mg/m^2 reflected diseases exacerbation and, not surprisingly, correlated with a poor prognosis.

In conclusion, we investigated the efficacy and safety of B-R therapy for r/r LGBCL and MCL in clinical practice. B-R therapy was highly effective and well tolerated. A cumulative dose of bendamustine ≥ 720 mg/m^2 appeared to contributed to improved PFS and OS. However, our study had the following limitations: (i) we did not reconfirm the histology of each lymphoma, (ii) the study was retrospective, and (iii) the number of patients was limited. Therefore, further studies are needed.

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