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ORIGINAL ARTICLE

Bendamustine-120 plus rituximab therapy for relapsed or refractory follicular lymphoma: a multicenter phase II study

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Abstract

The optimal dose, schedule, and other aspects of bendamustine plus rituximab treatment remain unclear for patients with relapsed or refractory follicular lymphoma (FL). Herein, we analyzed the efficacy of bendamustine combined with rituximab (RB-120) treatment for Japanese patients with relapsed or refractory FL. This phase II clinical trial included patients with relapsed or refractory FL who received 375 mg/m^2 rituximab on day 1 and 120 mg/m^2 bendamustine on days 2 and 3 every 28 days for up to 6 cycles. The primary endpoint was the overall response rate (ORR), and the secondary endpoints included the complete response (CR) rate, progression-free survival (PFS), overall survival (OS), and safety. Thirty-seven patients were enrolled in the trial (median age 62 years, range 42–75 years). All patients were previously treated with rituximab-containing chemotherapy, and 83.8% were previously treated with the R-CHOP regimen. A median of 5 cycles (range 1–6) and 48.6% of patients completed 6 cycles. The ORR was 91.9% (95% confidence interval [CI] 78.1–98.3%), with a CR rate of 86.5% (95% CI 71.2–95.5%). The 3-year PFS and OS were 70.9% (95% CI 52.3–83.3%) and 88.9% (95% CI 73.1–95.7%), respectively, with the median 39.5 months follow-up duration. The most-frequently observed grade 3/4 adverse events were hematologic: lymphopenia (95%) and neutropenia (70%). No treatment-related deaths were observed. RB-120 showed a good efficacy with equivalent toxicities, compared with the bendamustine 120 mg/m^2 monotherapy. However, the problem of high drop-out incidences cannot be ignored.

Keywords Follicular lymphoma · Relapsed · Refractory · Bendamustine · Rituximab

Introduction

Bendamustine, a unique cytotoxic agent containing a bi-functional mechlorethamine derivative and benzimidazole heterocyclic ring structure, was designed to confer properties of both alkylators and purine analogs [1]. On the basis of two North American pivotal trials that reported responses in > 70% of enrolled patients, bendamustine monotherapy at a dose of 120 mg/m^2 was approved by the Food and Drug Administration for patients with relapsed/refractory (R/R) indolent B cell non-Hodgkin lymphoma (B-NHL) [2, 3].

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In phase II trials of a combination treatment of bendamustine and rituximab for patients with R/R indolent B-NHL and mantle cell lymphoma (MCL), the overall response rates (ORR) ranged from 90 to 92%, with complete remission (CR) rates of 41–60% and acceptable toxicities [4, 5]. These studies of rituximab-combination treatments were designed to decrease the bendamustine dosage to 90 mg/m^2, which was expected to reduce toxicity. Following the excellent results obtained by those studies, an international consensus panel suggested an optimal bendamustine dosage of 90 mg/m^2 when combined therapeutically with rituximab [6]. However, in a previous Japanese phase I trial of bendamustine at 90 or 120 mg/m^2 in combination with rituximab for patients with R/R aggressive lymphoma, no dose-limiting toxicity was observed at either dose level. Accordingly, a dose of 120 mg/m^2 was recommended for the phase II study [7]. Certain factors regarding the optimal bendamustine plus rituximab treatment for patients with R/R indolent B-NHL remain undetermined, including the optimal dose and schedule of the regimen. This phase II clinical trial of 120 mg/m^2 bendamustine in combination with rituximab (RB-120) for treatment of Japanese patients with R/R follicular lymphoma (FL) aimed to address these uncertainties. To our knowledge, this is the first clinical trial to assess the safety and efficacy of RB-120 for patients with R/R FL.

Patients and methods

Study design and objective

The present multicenter, open-label, single-arm, phase II study was designed to determine the antitumor effect and safety of RB-120 in patients with R/R FL. The primary endpoint was the ORR, defined as the proportion of treated patients who achieved a complete response (CR), CR unconfirmed (CRu), or partial response (PR), in accordance with the international workshop response criteria (IWRC) for NHL [8]. The secondary endpoints were the CR rate, the ORR according to the revised response criteria for malignant lymphoma (revised RC) [9], progression-free survival (PFS), overall survival (OS), and safety. This study was performed in compliance with the ethical principles provided by the declaration of Helsinki and approved by the institutional review board of each participating institution. The clinical trial was registered with university hospital medical information network (reference no. UMIN000005386). Informed consent was obtained from all individual participants included in the study.

Patient eligibility

Patients aged 20–80 years were eligible if they had documented refractory or relapsed CD20-positive FL after rituximab monotherapy, a rituximab-containing regimen, or ibritumomab tiuxetan treatment. There were no maximum number of prior therapies allowed. Patients were required to meet the following inclusion criteria: a measurable lesion > 1.5 cm at the major axis, as assessed by computed tomography (CT); an Eastern Cooperative Oncology Group performance status of 0–2; and a life expectancy of > 3 months. Adequate hematologic (neutrophil count ≥ 1500/μL, hemoglobin level ≥ 8.0 g/dL, and platelet count ≥ 100,000/μL), hepatic (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] < 2.5 times the upper limit of normal [ULN], total bilirubin level ≤ 2.0 mg/dL), renal (serum creatinine level ≤ 2.0 mg/dL), and respiratory and cardiovascular (percutaneous arterial blood oxygen saturation ≥ 95%, no abnormal electrocardiogram findings requiring treatment) function were required. Patients were excluded if they were pregnant or lactating, or if they had any of the following conditions: infiltration of lymphoma to the central nervous system, high lymphoma burden in the peripheral blood (≥ 25,000/μL), active malignancy other than lymphoma, interstitial pneumonia, prior bendamustine treatment, prior allogeneic stem cell transplantation, or another serious medical disorder.

Treatment

Patients received 375 mg/m^2 rituximab on day 1 according to standard procedures at each center, followed by 120 mg/m^2 bendamustine over 60 min via intravenous infusion on days 2 and 3 every 28 days for up to 6 treatment cycles. Before beginning the next treatment cycle, the recovery of neutrophil and platelet counts (≥ 1500/μL and ≥ 75,000/μL, respectively) and the absence of grade ≥ 3 toxicities were required. If recovery was not evident within 2 weeks of a scheduled treatment, the patient was re-evaluated for continued treatment. Dose reductions of bendamustine to 90 mg/m^2 were performed in patients with any of the following: grade 4 neutropenia persisting for > 1 week despite treatment with granulocyte colony-stimulating factor (G-CSF), febrile neutropenia or infection with grade 3–4 neutropenia, a neutrophil recovery time of > 14 days, platelet count < 50,000/μL, or other grade 3–4 non-hematologic toxicities (at the investigator's discretion). If toxicity recurred, the dose was reduced to 60 mg/m^2. If toxicity of similar severity occurred at the reduced dose, the study treatment was discontinued. Antiemetic prophylaxis and opportunistic infection prophylaxis with trimethoprim sulfamethoxazole and acyclovir, respectively, were recommended. The primary prophylactic use of G-CSF was discouraged; however, treatment was allowed for prolonged neutropenia or febrile neutropenia in a prior treatment cycle.

Assessment

CT examinations were performed at enrollment and during the third and last cycles. When available, [^{18}F] fluorodeoxyglucose (FDG)-positron emission tomography (PET) examination was

performed at enrollment and after the last cycle. Responses were assessed after the third and last cycles of treatment according to both the IWRC and revised RC. Patients were classified by their best tumor response, as follows: CR, CRu (IWRC only), PR, stable disease (SD), or progressive disease (PD). PFS was calculated as the time from study enrollment to the first documentation of disease progression or death from any cause. Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events, version 3.0 (http://ctep.cancer.gov/reporting/ctc.html).

Statistical analyses

We hypothesized that RB-120 had a good efficacy with acceptable toxicities, compared with previously available bendamustine monotherapy for R/R indolent lymphoma. Earlier studies of bendamustine-120 monotherapy in the USA and Japan reported ORRs of 75–77% [2, 3] and 90% [10], respectively. Based on these studies, RB-120 was considered to yield the expected and threshold ORRs of 95% and 75%, respectively (α value, 0.05 [one-tailed] and β value, 0.20); in statistical power calculations, these values translated to a minimum sample size of 33 patients and a planned sample size of 36 patients, considering the exclusion rate of 10% from statistical analyses. The ORR was defined as the proportion of treated patients who achieved PR or better outcome and was calculated along with its 95% confidence interval (CI). The CR rate was defined as the proportion of treated patients who achieved a CR or CRu and was calculated with 95% CI. OS and PFS were assessed using the Kaplan–Meier method. Student's *t* test was used for continuous variables, and the log-rank test was used to compare OS and PFS. EZR statistical software (version 1.35; Saitama Medical Center, Jichi Medical University, Saitama, Japan) was used for the statistical analysis [11].

Results

Patients

Between February 2011 and March 2013, 37 patients were enrolled at 8 hospitals. The responses of all patients were evaluated and constituted the full analysis set. Patients' baseline characteristics are summarized in Table 1. The study subjects comprised 13 men and 24 women, with a median age of 62 years (range, 42–75 years). Although the inclusion criteria as per the Eastern Cooperative Oncology Group performance status (PS) was scored from 0 to 2, the status of 36 (97.3%) patients was 0 and one patient had a status of 1 (Table 1). A median of one prior regimen (range 1–4) was administered. Twenty-eight (75.7%) of the 37 patients received < 2 prior chemotherapy regimens. In addition, 32 (90%) patients were previously treated with the R-CHOP/CHOP-like regimen, including one patient who received only one cycle of rituximab treatment because of concerns regarding infusion reactions. Four patients previously received autologous stem cell transplantation. No patient received prior ibritumomab tiuxetan treatment. A median of 31 months (range 1.5–128.8 months) had elapsed since the last treatment.

Table 1 Patient demographics and baseline characteristics

Characteristics	Patients ($N = 37$)	
	No.	%
Age, years		
Median	62	
Range	42–75	
Sex		
Male	13	35.1
Female	24	64.9
ECOG performance status		
0	36	97.3
1	1	0.7
No. of prior chemotherapy regimens		
1	19	51.4
2	9	24.3
3	5	13.5
4	4	10.8
Previous rituximab-containing regimens		
R-CHOP/CHOP-like	32	90.0
R-alone	6	16.2
Other	3	8.1
ASCT	4	10.8
Previous radiotherapy	5	13.5
Clinical stage (Ann Arbor staging)		
I	2	5.4
II	7	18.9
III	11	29.7
IV	17	45.9
FLIPI		
Low risk	18	48.6
Intermediate risk	10	27.0
Poor risk	9	24.3
Time since last treatment, months		
Median	31	
Range	1.5–128.8	

ECOG, Eastern Cooperative Oncology Group; *ASCT*, autologous stem cell transplantation; *FLIPI*, Follicular Lymphoma International Prognostic Index

Disposition

All patients received a median of 5 cycles (range 1–6). Thirty-five (94.5%) patients underwent 3 cycles, 29 patients (78.3%) underwent 4 cycles, 24 patients (64.9%) underwent 5 cycles, and 18 patients (48.6%) completed 6 cycles of RB-120. The number of patients who received bendamustine 120, 90, and 70 mg/m^2 and G-CSF in each cycle were also summarized in Table 2. The number of patients who received bendamustine 90 mg/m^2 in cycles 2, 3, 4, 5, and 6 were 4 (11.1%), 7 (20%), 5 (17.2%), 6 (37.5%), and 5 (27.8%), respectively (Table 2). Four (10.8%) patients discontinued treatment because of AEs (intoxication dermatosis, fatigue, pneumonia, and amebic dysentery), and 15 (40.5%) patients discontinued treatment because they did not meet the criteria for beginning the next cycle of treatment due to complications including neutropenia ($N = 14$, 37.8%), thrombocytopenia ($N = 4$, 10.8%), and liver dysfunction ($N = 1$, 2.7%). Because of delays in neutrophil recovery, one patient received cycle 3 and another patient received cycles 2 and 3 at > 6 weeks after administration of the prior therapy cycles; both patients finished the scheduled treatment after cycle 3. Among a total of 179 cycles, treatment delays and dose reductions occurred in 60 and 26 cycles, respectively (Table 2).

Efficacy

The ORR was 91.9% (95% CI 78.1–98.3%), and the CR rate was 86.5% (95% CI 71.2–95.5%). Of all subjects, 5.4% achieved PR according to the IWRC (Table 3). Two patients (5.4%) who discontinued protocol treatment before 3 cycles were not evaluated. Six out of 37 patients received CT examination alone to evaluate treatment efficacy and all of them achieved CR according to the IWRC. After excluding these 6 patients, the ORR was 93.5% (95% CI 78.6–99.2%) and the CR rate was 80.6% (95% CI 62.5–92.5%); among the remaining 31 patients, 10.0% achieved PR and 6.4% were not evaluated according to the revised RC (Table 3).

The median follow-up duration was 39.5 months (range 20.7–52.0 months) among the surviving patients. The 3-year PFS and OS were 70.9% (95% CI 52.3–83.3%) and 88.9% (95% CI 73.1–95.7%), respectively (Figs. 1 and 2). The median PFS and OS times were not reached.

Four deaths were reported during the study period, of which, three were attributed to disease progression and one was attributed to pemphigoid with primary disease progression.

Safety

The main toxicity observed with RB-120 treatment was reversible myelosuppression, including grade 3–4 leukopenia (59%), neutropenia (70%), lymphocytopenia (95%), and thrombocytopenia (14%) (Table 4). Among the 179 total cycles, 51 cycles (28.5%) were supported by G-CSF (Table 2). One patient received platelet transfusions. Common non-hematologic AEs included nausea (68%), anorexia (49%), and fatigue (38%), the majority of which received severity grades of 1–2 (Table 4). Grade 3 infections were observed in four patients (11%; one patient each with febrile neutropenia, amebic dysentery, bacterial pneumonia, and opportunistic infection associated with lymphopenia grade ≥ 2), and no grade

Table 2 Patient disposition

	No. of patients							
	Cycles completed	Treatment delay or dose reduction	Treatment delay	Dose reduction	Dose of bendamustine (mg/m^2)			G-CSF administration
					120	90	70	
Cycle								
1	37	(−)	(−)	(−)	37	0	0	5
2	36*	13	13	4	32	4	0	10
3	35**	16	15	8	27	7	1	10
4	29	13	11	5	24	5	0	13
5	24	15	13	5	18	6	0	9
6	18	11	8	4	13	5	0	4
Reasons for discontinuation ($N = 19$)			No.	%				
Failure to meet the next cycle onset criteria			15	40.5				
Adverse events			4	9.2				
Progressive disease			0	0				

*One patient received cycle 2 treatment at more than 6 weeks from the prior treatment

**Two patients received cycle 3 treatment at more than 6 weeks from the prior treatment

Table 3 Treatment response to bendamustine plus rituximab

		CR		PR		SD		PD		NE		ORR		CR rate	
	No.	No.	%	No.	%	No.	%	No.	%	No.	%	%	95% CI	%	95% CI
Response by IWRC[a]	37	32	86.5	2	5.4	1	2.7	0	0	2	5.4	91.9	78.1–98.3	86.5	71.2–95.5
Response by revised RC[b]	31	25	80.6	4	10.0	0	0.0	*0*	0	2	6.4	93.5	78.6–99.2	80.6	62.5–92.5

CR, complete response; *PR*, partial response; *SD*, stable disease; *PD*, progressive disease; *NE*, not evaluable; *ORR*, overall response rate; *CI*, confidence interval

[a] According to the International Workshop Response Criteria for Non-Hodgkin Lymphoma

[b] According to the Revised Response Criteria for Malignant Lymphoma

4 infection was observed. No deaths were attributed to RB-120 treatment. Secondary malignancy was observed in two patients: one developed breast cancer 125 days after the final protocol treatment, and one developed lung cancer 455 days after treatment.

Discussion

In this multicenter phase II study of RB-120 for patients with R/R FL, the 92% ORR and 86.5% CR rates reflected better efficacy than those reported in the previous pivotal North American trials of 120 mg/m^2 bendamustine monotherapy (70–75% and 17–34%, respectively) [2, 3].

The present study showed an equivalent efficacy on ORR to previous phase II or III studies of 90 mg/m^2 bendamustine and rituximab treatment (RB-90) for R/R FL (82–96%) [4, 5, 12]. Regarding CR rate, the results of these previous studies were varied (40–71%) and were mainly attributable to differences in prior rituximab treatment [4, 5, 12]. In previous phase II studies of RB-90, Rummel et al. reported an ORR of 96% and CR rate of 71% among patients who had rituximab-naïve R/R FL [4]. Another group reported an ORR of 93% and CR rate of 41% among patients with R/R indolent B-NHL, including those with prior rituximab treatment exposure [5]. In the recent multicenter phase III study of Stil NHL2-2003, Rummel et al. reported that the ORR was 82% and the CR rate was 40%, among 114 patients with R/R indolent B-NHL and MCL who received RB-90 and 39% of them had prior rituximab treatment exposure [12]. In the present study of RB-120, the 86.5% CR rate was observed even though all patients had received prior rituximab treatment.

Trotman et al. reported that PET–CT assessment revealed more predictive value than contrast-enhanced CT in clinical practice [13]. Although RB-120 treatment yielded a higher CR rate according to PET–CT-guided revised RC, it should be considered a reference because we excluded six patients who received CT examination alone for the analysis. After including these 6 patients into the statistical population, 25 out of 37 patients (67.6%) achieved CR according to revised RC. Considering the background of patients that all of them having prior rituximab treatment exposure, the 67.7% CR rate of the RB-120 regimen may still be considered as representing good efficacy.

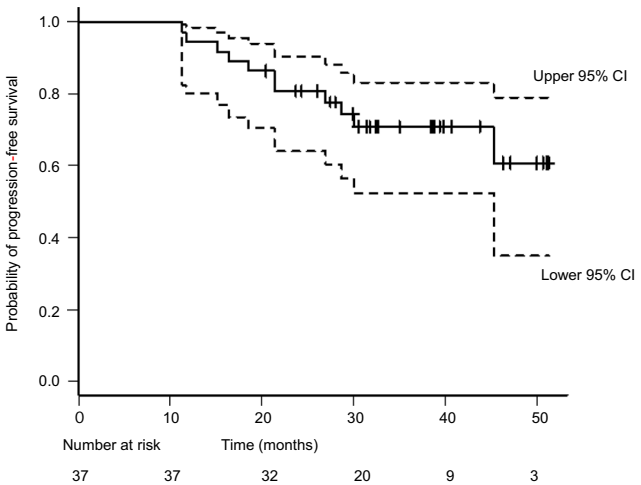

Fig. 1 Kaplan–Meier plot of progression-free survival. Broken lines: lower and upper 95% confidence interval (CI)

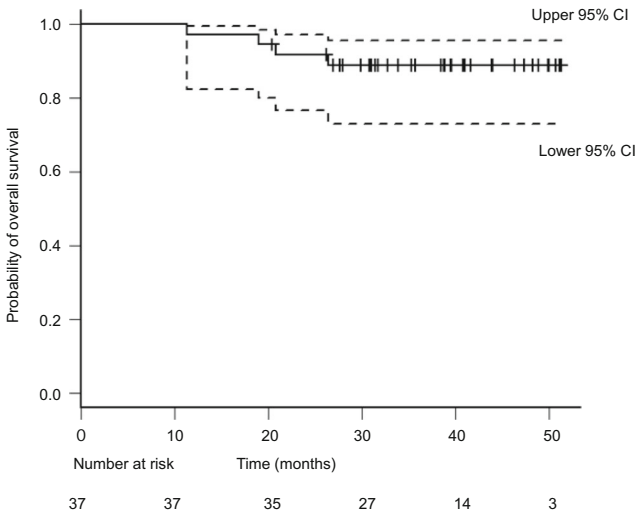

Fig. 2 Kaplan–Meier plot of overall survival. Broken lines: lower and upper 95% confidence interval (CI)

Table 4 Adverse events by severity grade ($N = 37$)

Adverse event	Patients affected, *n*											
	Grade, *n*								All grades		Grades 3/4	
	1		2		3		4					
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Hematologic												
Leukopenia	1	3	12	32	17	46	5	14	35	95	22	59
Neutropenia	2	5	7	19	11	30	15	41	35	95	26	70
Lymphocytopenia			1	3	9	24	26	70	36	97	35	95
Thrombocytopenia	22	59	5	14	3	8	2	5	32	86	5	14
Anemia	14	38	12	32	1	3	0	0	27	73	1	3
Non-hematologic												
Nausea	17	46	6	16	2	5			25	68	2	5
Fatigue	6	16	6	16	2	5			14	38	2	5
Vomiting	7	19	1	3	1	3			9	24	1	3
Anorexia/decreased appetite	10	27	6	16	2	5			18	49	2	5
Diarrhea	1	3			1	3			2	5	1	3
Weight loss	1	3	1	3					2	5		
Dizziness					1	3			1	3	1	3
Dyspnea					1	3			1	3	1	3
Wheezing					1	2			1	2	1	3
Infusion-related reaction	6	16	3	8					9	24		
Hypertension	1	3			1	3			2	5	1	3
Fever[a]	7	19	1	3	1	3			9	24	1	3
Pruritus/itching	7	19	2	5					9	24		
Urticaria	3	8			1	3			4	11	1	3
Intoxication dermatosis					1	3			1	3	1	3
Subepidermal blistering disorder					1	2			1	3	1	3
Mucositis/stomatitis	4	11							4	11		
Neuropathy: sensory	1	3	2	5					3	8		
Phlebitis	4	11	8	22					12	32		
Alopecia	2	5							2	5		
Infectious episodes with grade 3 or 4 neutrophils					1[b]	3			1	3	1	3
Opportunistic infection associated with grade ≥ 2 lymphopenia					1	3			1	3	1	3
Febrile neutropenia					1	3			1	3	1	3
Infection with normal ANC or grade 1 or 2 neutrophils, bacterial pneumonia					1	3			1	3	1	3

As graded by the Common Terminology Criteria for Adverse Events, version 3.0

ANC, absolute neutrophil count

[a] In the absence of neutropenia, where neutropenia is defined as ANC < 1.0×10^9/L

[b] Amoebic dysentery

The phase III study of RB-90 showed the results of patients with R/R FL, including patients receiving rituximab maintenance with a median PFS of 54.5 months (median follow-up 96 months); after excluding patients who received rituximab maintenance from the analysis, the BR group had a median PFS of approximately 2 years [12]. Though the present study showed a 3-year PFS of 70.9%, the median follow-up duration was too short (39.5 months)

and long-term follow-up is needed to confirm whether the effect of RB-120 on PFS will be continued.

Regarding AEs, the observed incidences of grade 3–4 leukopenia (59%), neutropenia (70%), and thrombocytopenia (14%) in the present study were similar to those in previous studies of bendamustine 120 mg/m^2 monotherapy (65%, 54–72%, and 16–25%, respectively) [2, 3, 10]. However, comparing to the previous phase II and III RB-90 studies, the incidences of the hematological toxicities were significantly high (in the RB-90 studies; leukopenia 13–30%, neutropenia 9–37%, and thrombocytopenia 2–9%, respectively) [4, 5, 12]. In the present study, although 94.6% of patients completed treatment by cycle 3, the number of patients dropping out from the study increased with each subsequent cycle during cycles 4–6, mainly due to hematological toxicities. The number of patients who completed 6 cycles (48.6%) was similar to that in the phase II bendamustine 120 mg/m^2 monotherapy (44%) but lower than that in the RB-90 phase II study (62%) [2, 5]. Although there were no deaths attributed to RB-120 treatment, the high drop-out rate in this study could not be ignored. G-CSF prophylaxis might be one possible solution to this problem. On the other hand, only 7% of cycles received G-CSF supporting in the previous RB-90 phase III study [12].

In the present study, four patients reported infections including febrile neutropenia, amebic dysentery, bacterial pneumonia, and opportunistic infection associated with lymphopenia grade ≥ 2. In a phase II study of bendamustine 120 mg/m^2 and rituximab combination treatment for patients with R/R diffuse large B cell lymphoma, Ohmachi et al. [14] reported that 32 infections were observed in 27 patients, including 6 cytomegalovirus (CMV) and 8 herpesvirus infections. The previous study used dexamethasone for antiemetic purposes; in addition, 34 of the 59 patients did not receive acyclovir prophylaxis, despite guideline recommendations [14]. In the protocol for the present study, we recommended avoiding antiemetic prophylaxis with corticosteroid therapy and administering an opportunistic infection prophylaxis instead. Although the incidences of grade 4 neutropenia and lymphocytopenia were similar, no cases of herpesvirus or CMV infection were observed in the present study. Ogura et al. [15] recommended the use of sulfamethoxazole–trimethoprim and acyclovir in their phase II RB-90 study. Consequently, they observed no *Pneumocystis jirovecii* infection and only one herpesvirus infection during the study period. In the present study, most other non-hematologic AEs were resolved and manageable, and the distributions were similar to those reported in previous clinical trials of RB-90 [2, 5].

Our study had some limitations. First, although the 94.5% of patients underwent 3 cycles, less than half of the patients completed 6 cycles. In terms of the risk-benefit balance, the appropriate number of cycles of RB-120 treatment for R/R FL remains unclear after the present study, and further investigation is warranted. Second, because 6 patients received CT examination alone, we could not present accurate information regarding response rates of the study according to the revised RC which has higher predictive value compared to IWRC. Third, the follow-up duration was not sufficiently long to confirm whether therapy remained efficacious for PFS, and therefore, long-term follow-up is needed.

In conclusion, RB-120 showed good efficacy with equivalent toxicities, compared with that of the previous bendamustine 120 mg/m^2 monotherapy for R/R indolent lymphoma. However, compared with the previous RB-90 studies, high drop-out incidences during cycles 4–6 in the present study are a problem that cannot be ignored and the appropriate number of cycles of RB-120 treatment remains unclear with regard to the risk-benefit balance.

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Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments.

Conflict of interest Dr. Sakai has received research funding from Chugai, Kyowa Hakko Kirin, Ono, Yakult, Taiho, and Eisai and honoraria from Takeda, Bayer, Bristol-Meyer-Squibb, Sumitomo Dainippon, Celgene, Mundipharma, Eisai, and Kyowa Hakko Kirin. Dr. Ohmachi has received honoraria from Chugai, Kyowa Hakko Kirin, Eisai, Pfizer, Takeda, Celgene, and Meiji Seika. Dr. Sano has received research funding from Chugai and Kyowa Hakko Kirin and honoraria from Celgene, Janssen, Bristol-Meyer-Squibb, Eisai, Pfizer, Chugai, and Alexion. Dr. Takasaki has received honoraria from Kyowa Hakko Kirin, Eisai, and Janssen. Dr. Miyazaki has received research funding from Astellas. Dr. Yamamot has received honoraria from Celgene, Janssen, Kyowa Hakko Kirin, Bristol-Meyer-Squibb, MSD, Meiji Seika, Novartis, Shaire Japan, Alexion, and Chugai. Dr. Tomita has received research funding from Terumo Foundation for Life Sciences and Arts. Dr. Ando has received research funding from Kyowa Hakko Kirin, Eisai, Bristol-Meyer-Squibb, Novartis, and Takeda. All remaining authors have declared no conflicts of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

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