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Original Article

Bendamustine-induced rash is associated with a favorable prognosis in patients with indolent B-cell lymphoma

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Bendamustine is now recognized as a key drug for indolent B-cell lymphoma (iBCL), mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL). Skin toxicity associated with bendamustine is one of the characteristic adverse effects. We retrospectively examined the relationship between bendamustine-associated drug rashes and disease prognosis of iBCL and MCL at our institution. Between January 2011 and August 2019, 65 patients (39 men and 26 women, median age 68, range 41-84 years) were treated with bendamustine alone (n=11, 120 mg/m^2 on days 1 and 2) or a combination of rituximab and bendamustine (n=54, 90 mg/m^2 on days 1 and 2). Of these patients, 47 had follicular lymphoma (FL), 10 had MCL and 8 had other iBCLs. Drug rash occurred in 27 (41.5%). Eight cases (29.6%) were grade 1, 5 (18.5%) were grade 2 and 14 (51.9%) were grade 3. The onset was in the first course in 17 (63.0%), 2nd course in 5 (18.5%), 3rd course in 2 (7.4%), 4th course in 1 (3.7%) and 5th course in 2 (7.4%). No treatment was administered in 1 case (3.7%), topical steroid was applied in 10 (37.0%), antiallergic drug was administered in 2 (7.4%), topical steroid and antiallergic drug were administered in 5 (18.5%), and oral and topical steroid and antiallergic drug were administered in 9 (33.3%). The 3-year progression-free survival (PFS) and overall survival (OS) in patients with rash development were 80.0% and 85.5%, respectively, and those in patients without development were 36.4% and 54.0%, respectively (p=0.009 and 0.02, respectively). By multivariate analysis, the development of rash was associated with a better PFS and a diagnosis of iBCL was associated with a better OS. This study revealed that bendamustine-induced rash is associated with a favorable prognosis among patients with iBCL.

Keywords: Bendamustine-induced rash, Indolent B-cell lymphoma, Mantle cell lymphoma, Favorable prognosis

INTRODUCTION

Bendamustine is a cytotoxic agent with a multifaceted mechanism of action. Structurally, it includes both a mechlorethamine group and a benzimidazole ring, which confer properties of both alkylators and purine analogues.[1] Bendamustine directly damages DNA, and induces apoptosis and mitotic catastrophe.[2] Bendamustine is used to treat indolent B-cell lymphoma (iBCL), mantle cell lymphoma (MCL) and chronic lymphocytic leukaemia.[3,4] Several trials demonstrated high efficacy and manageable toxicity of bendamustine in relapsed/refractory iBCL and MCL patients, both as monotherapy and in combination with rituximab (BR).[5,6] The efficacy and safety of BR as first-line treatment for iBCL and MCL patients were also confirmed in several phase III trials.[4,7]

Skin toxicity is one of the important adverse effects of bendamustine. Rash is characteristic, often severe, and affects the treatment, but few detailed reports are available.[8-10] In this study, we examined the relationship between bendamustine-associated rash and clinical features, including clinical outcome, for iBCL and MCL at our institution.

MATERIALS AND METHODS

We reviewed the medical records of 65 patients with iBCL, consisting of follicular lymphoma (FL), lymphoplasmacytic lymphoma (LPL), marginal zone lymphoma (MZL), mucosa-associated lymphoid tissue (MALT) lymphomas, lymphoplasmacytic lymphoma (LPL) and lymphocytic lym-

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phoma (SLL) or MCL who were treated with bendamustine at our institution as first- or second-line treatment between 2011 and 2019. The diagnosis was made according to the World Health Organization (WHO) 2008 classification. The rashes were graded according to the Common Terminology Criteria for Adverse Events version 4.0. The follow-up period was defined as from the initiation of bendamustine to the last contact. The cut-off date for analysis was August 2020.

Associations between clinical features and skin rashes were analyzed by univariate analysis using the nonparametric Mann–Whitney U test or Fisher's exact test, as appropriate. $p<0.05$ was considered significant. Progression-free survival (PFS) was calculated from the date of diagnosis of lymphoma for the patients with initial treatment and date of relapse/progression for salvage therapy, to the date of relapse, progression or death from any cause, and censored at the last verifiable progression-free date. Overall survival (OS) was defined as the time from diagnosis of lymphoma for the patients with initial treatment and date of relapse/progression for salvage therapy, respectively, to death from any cause, and censored at the last verifiable surviving date. Probabilities of PFS and OS were estimated using the Kaplan-Meier method; time-to-event outcomes were compared among risk groups using the log-rank test. Multivariate analyses were performed with a Cox proportional multiple regression model. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Sixty-five patients (39 men and 26 women; median age 68 years, range 41–84 years) with iBCL or MCL who were treated with bendamustine between January 2011 and August 2019 were analyzed (Table 1). The histological diagnoses were 47 FLs, 10 MCLs, 4 MZLs, 2 MALT lymphomas, one LPL and one SLL. At the time of bendamustine treatment, 20 patients (30.8%) were previously untreated; the others had relapsed or become refractory. Eleven patients received bendamustine monotherapy (120 mg/m^2) on days 1 and 2 every 3 weeks, whereas 54 patients received a combination of bendamustine (90 mg/m^2) on days 1 and 2 and rituximab (375 mg/m^2) on day 1 every 4 weeks.

Twenty-seven patients developed drug rash (41.5%; Table 2). Eight cases (29.6%) were grade 1, 5 (18.5%) were grade 2, and 14 (51.9%) were grade 3. Most were erythema with/without concrescence tendency. Thirteen patients had localized patterns (48.4%) and 14 had generalized patterns (51.9%). No toxic epidermal necrolysis was observed. Seventeen patients (63.0%) experienced symptom onset during the first course, 5 (18.5%) during the second, 2 (7.4%) during the third, 1 (3.7%) during the fourth, and 2 (7.4%) during the fifth. Treatment was based on grade and localization, in addition to observation in 1 (3.7%), steroid topical application in 10 (37.0%), antiallergic drugs in 2 (7.4%), topical steroid application and antiallergic drugs in 5 (18.5%), and oral and topical steroid administration and antiallergic drugs in 9 (33.3%). In 5 of 14 cases of grade 3 rashes, bendamustine was discontinued permanently and changed to rituximab monotherapy (n=3) or watchful waiting (n=2). The median follow-up duration was 24 months (range 1-101)

Table 1. Characteristics of 65 patients with indolent B-cell lymphoma and mantle cell lymphoma treated by bendamustine

Age	Range (Median)	41–84 (68)
Sex	Male/Female	39/26
Diagnosis (WHO classification)		
	Follicular lymphoma	47 (72.3%)
	Mantle cell lymphoma	10 (15.4%)
	Marginal zone B-cell lymphoma	4 (6.2%)
	MALT lymphoma	2 (3.1%)
	Lymphoplasmacytic lymphoma	1 (1.5%)
	Small lymphocytic lymphoma	1 (1.5%)
Disease status		
	Newly diagnosed	20 (30.8%)
	Relapse/Refractory	45 (69.2%)
Chemotherapy		
	Bendamustine	11 (16.9%)
	Bendamustine+Rituximab	54 (83.1%)
Response		
	CR	47 (72.3%)
	PR	9 (13.8%)
	CR+PR	56 (86.2%)
	PD	9 (13.8%)

MALT, mucosa-associated lymphoid tissue; CR, complete response; PR, partial response; PD, progressive disease

Table 2. Characteristics of drug rash after bendamustine treatment

Drug rash development		27
Grade		
	Grade 1	8 (29.6%)
	Grade 2	5 (18.5%)
	Grade 3	14 (51.9%)
Pattern of rash		
	Generalized	14 (51.9%)
	Localized	13 (48.1%)
Onset time		
	course 1	17 (63.0%)
	course 2	5 (18.5%)
	course 3	2 (7.4%)
	course 4	1 (3.7%)
	course 5	2 (7.4%)
Treatment		
Steroid topical application		10 (37.0%)
Antiallergic drug		2 (7.4%)
Steroid topical application and antiallergic drug		5 (18.5%)
Steroid oral and topical application and antiallergic drug		9 (33.3%)
Observation		1 (3.7%)

in all patients. The 3-year PFS was 80.0% in 27 patients who developed drug rashes and 36.4% in 38 patients without rashes (p=0.009; Fig. 1A). The 3-year OS was 85.5% in patients who developed drug rashes and 54.0% in those without rashes (p=0.02; Fig. 1B). Among iBCL only, excluding MCL, the 3-year PFS and OS were 83.2% and 95.7% in 24 patients with drug rashes, and 46.9% and 56.2% in 31 patients without rashes, respectively (p=0.0166 and 0.0238, respectively; Fig. 2A and 2B). The graphs for FL-only and MCL-only patients are shown in Fig. 3 and 4, respectively. FL patients with rashes had a significantly better PFS and OS rates than those without rashes (82.5% vs. 56.9%, p=0.0413, Fig. 3A, 95.2% vs. 59.8%, p=0.0487, Fig. 3B).

The relationship between the time of appearance of eruption in BR (course 1 vs. course 2 or later) and treatment response and prognosis was as follows: overall response rate 88.2% vs. 100%, 3-year OS 78.1% vs. 66.6% (p=0.818) and 3-year PFS was 78% vs. 85.7% (p=0.405), and no significant difference was observed.

Patients who developed rashes after bendamustine typically had a history of allergy (p=0.0259), no previous lymphoma treatment (p=0.0147), localized stage (p=0.0398) or combined rituximab treatment (p=0.0197) compared with those without rashes (Table 3). Age, sex, pathological diagnosis of lymphoma, leukocyte counts, eosinophil counts, lymphocyte counts and cycles of therapy did not significantly differ (Table 3). The relationships between the clinical features and prognosis are shown in Table 4. In univariate analysis, iBCL (p=0.02), extranodal involvement (p=0.02), use of rituximab (p=0.01) and rash after bendamustine (p=0.009) were significant factors for PFS. In multivariate analysis, iBCL (p=0.02) and rash after bendamustine (p=0.03) were significant factors for PFS. In univariate and multivariate analysis, rash after bendamustine (p=0.02) was the only sig-

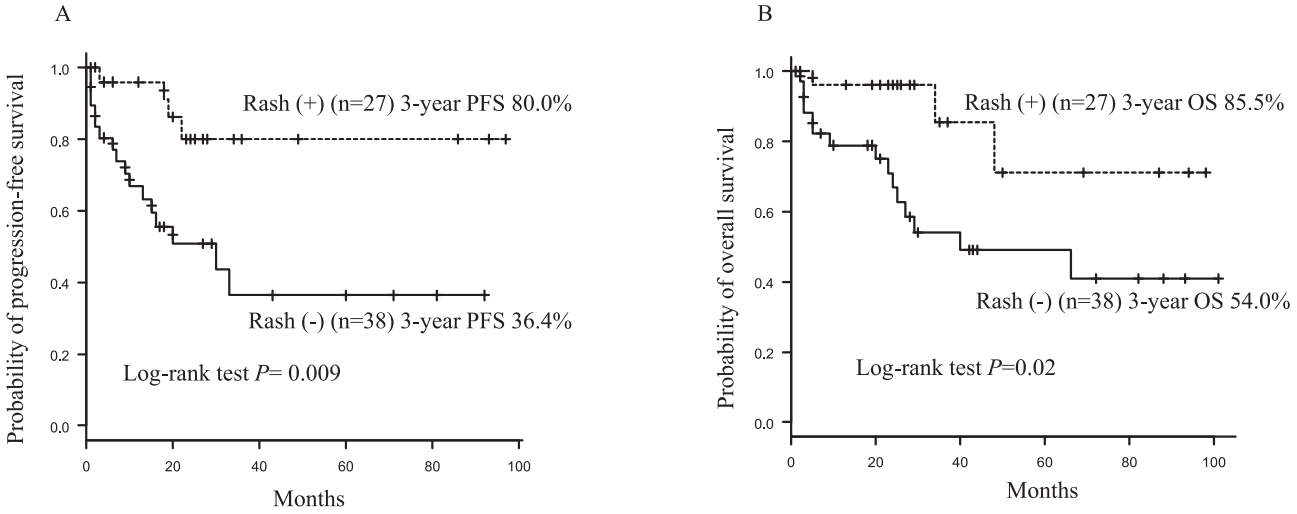

Fig. 1. Outcomes of patients with indolent B-cell lymphoma and mantle cell lymphoma relative to bendamustine-induced rash (***A***: progression-free survival, ***B***: overall survival)

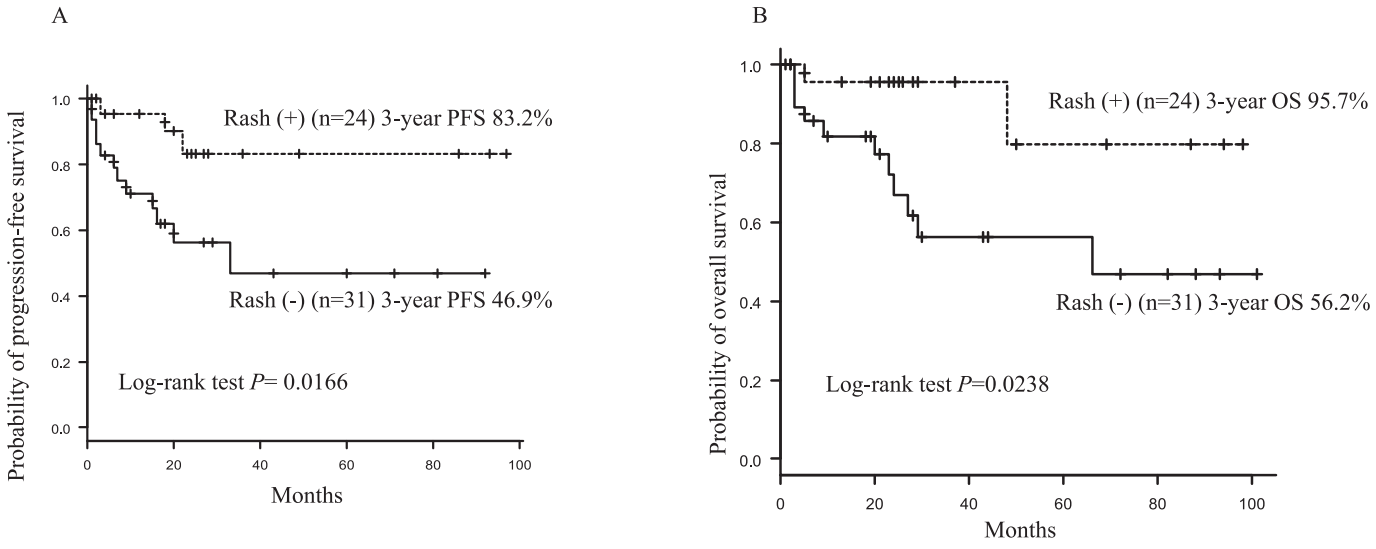

Fig. 2. Outcomes of patients with indolent B-cell lymphoma relative to bendamustine-induced rash (***A***: progression-free survival, ***B***: overall survival)

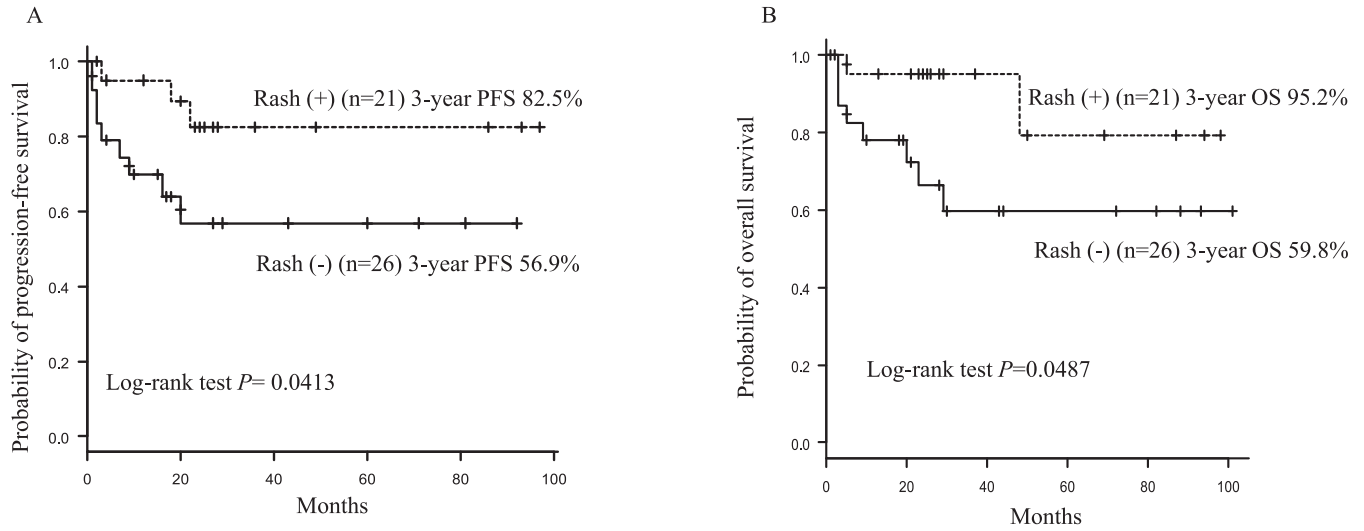

Fig. 3. Outcomes of patients with follicular lymphoma relative to bendamustine-induced rash (***A***: progression-free survival, ***B***: overall survival)

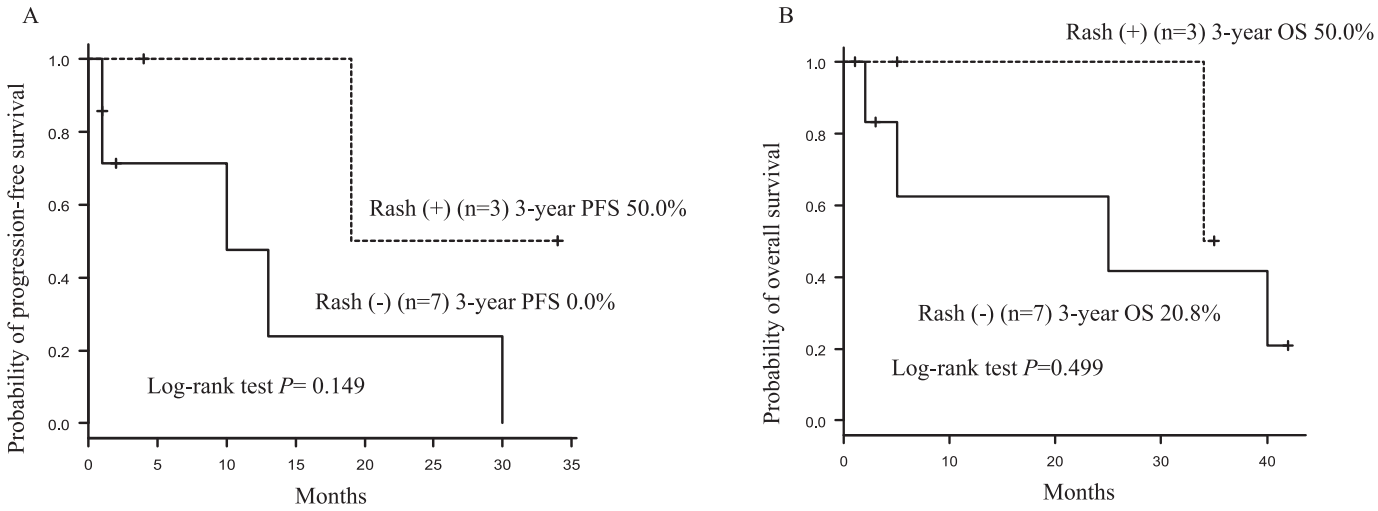

Fig. 4. Outcomes of patients with mantle cell lymphoma relative to bendamustine-induced rash (***A***: progression-free survival, ***B***: overall survival)

nificant factor for OS. Patients with 4 or more courses of bendamustine + rituximab therapy and with rash had a 3-year OS of 84.7% vs. 70.6% (p=0.149) and a 3-year PFS of 77.0% vs. 45.3% compared with those without rash (p=0.116).

DISCUSSION

This study revealed that after bendamustine treatment for iBCL and MCL, rash development was relatively frequent, and was a better prognostic factor for PFS and OS by multivariate analysis.

The incidence rate of skin and subcutaneous tissue injury was 46% in a pivotal phase 2 clinical trial of bendamustine monotherapy in Japan, and 1% of cases were grade 3 or higher.[3] The onset rate by course was highest (36.2%) after 1 course but occurred at multiple times over 2–6 courses. This is consistent with our study, excluding the high frequency of grade 3 toxicity. Fourteen patients (51.9%) presented with grade 3 toxicity and generalized rash, and were administered prednisolone prophylactically after the rash developed from days 1–7 of bendamustine retreatment. Although rashes relapsed in 7 patients (50.0%), no exacerbation occurred and the bendamustine retreatment was completed. Two patients were followed by watchful waiting after rash development because their lymphomas were in partial remission; they have remained in remission for more than 1 year.

Hypersensitivity reactions associated with cancer chemotherapy include infusion reactions and immediate allergic reactions. Most infusion reactions and anaphylaxis with rituximab are thought to occur at the time of initial infusion and within 24 hours of initiation.[11] Bendamustine-induced rash is considered to be a late-onset hypersensitivity and not due to an acute hypersensitivity reaction such as infusion

Table 3. Characteristics of patients who developed rash after bendamustine and those who did not

		Rash+ (n=27)	Rash- (n=38)	*P*-value
Age Median (range)		67 (41-84)	66 (47-84)	0.547
Sex Male		16	15	0.949
Female		11	23	
History of allergy				
Yes		4	0	0.0259
No		23	38	
Diagnosis (WHO classification)				
Follicular lymphoma		21	16	0.574
Mantle cell lymphoma		3	7	
Marginal zone B-cell lymphoma		2	2	
MALT lymphoma		0	2	
Lymphoplasmacytic lymphoma		0	1	
Small lymphocytic lymphoma		1	0	
Disease status				
Newly diagnosed		13	7	0.0147
Relapse/Refractory		14	31	
Stage 1-2		8	2	0.0398
3-4		19	36	
WBC ($x10^3/\mu l$)				
Median (range)		5.12 (2.72-22.9)	5.06 (3.03-79.8)	0.8
Lymphocytes ($x10^3/\mu l$)				
Median (range)		1.26 (0.368-19.8)	1.19 (0.33-70.3)	0.599
Eosinophils ($x10^3/\mu l$)				
Median (range)		0.23 (0.03-0.58)	0.12 (0.02-0.48)	0.806
Extranodal involvement				
Yes		10	24	0.0468
No		17	14	
Cycles of therapy				
Bendamustine	1~3	1	1	0.182
	4~6	0	9	
Bendamustine+Rituximab	1~3	4	4	0.918
	4~6	22	24	

WHO, World Health Organization; MALT, mucosa-associated lymphoid tissue; WBC, white blood cell

reaction or anaphylaxis.[12] Delayed hypersensitivity reactions were noted in 6 patients in this study. Bellón proposed T cell-mediated drug-specific immune response due to delayed type IV hypersensitivity reaction.[13] Delayed hypersensitivity reactions have also been reported in patients who received brentuximab-vedotin plus bendamustine.[14]

In our series, more rashes occurred with B-R therapy (26/54) than with bendamustine alone (1/11) (48.1% vs. 9.1%, p=0.0197). However, in the case of B-R therapy, the rash developed on days 3 to 27, which was different from the time of the infusion reaction of rituximab, and rash due to bendamustine was considered.

The rashes were generally not severe, and post-treatment recurrence was frequent but manageable with steroids. In our series, patients with drug rashes typically had a history of allergy, no previous lymphoma treatment, localized stages, extranodal involvement or combined rituximab treatment (Table 3). The ratio and the change in absolute value of absolute lymphocyte counts (ALC) at initial bendamustine administration and the onset of rash in rash-positive patients was not significantly different from those at initial bendamustine administration and final bendamustine administration in rash-negative patients (data not shown).

Cencini E *et al*. reported the association between a single nucleotide polymorphism of *IL2* and skin rash in lymphoma patients treated with bendamustine and rituximab.[15] The TT example reported more skin rashes after bendamustine + rituximab treatment than with GT/GG. However, they reported that they were not associated with the treatment response.

Uchida *et al*. analyzed 95 patients with non-Hodgkin's lymphoma who received bendamustine alone or BR therapy and reported that no prior treatment was a significant factor in skin toxicity.[16] In our study, 13/20 (65%) newly diagnosed patients developed rash and 14/45 (31%) relapsed/refractory patients developed rash, demonstrating a signifi-

Table 4. Clinical features and outcomes of 65 patients with indolent B-cell lymphoma and mantle cell lymphoma treated by bendamustine

Variable		n	PFS				OS			
			Univariate		Multivariate		Univariate		Multivariate	
			HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	≥ 70 years	26	1.4 (0.60-3.3)	0.43			1.5 (0.58-3.8)	0.40		
	< 70 years	39								
Sex	Male	31	1.1 (0.44-2.5)	0.91			0.93 (0.36-2.4)	0.89		
	Female	34								
Disease	iBCL	55	3.1 (1.20-8.1)	0.02	3.1 (1.2-8.0)	0.02	2.8 (0.96-8.0)	0.06	2.6 (0.89-7.5)	0.08
	MCL	10								
Status	Newly	20	3.8 (0.88-17)	0.07			2.1 (0.45-9.7)	0.35		
	R/R	45								
Stage	1-2	10	5.3 (0.71-40)	0.10			3.9 (0.52-29)	0.19		
	3-4	55								
ExtraN	Yes	34	3.2 (1.17-8.7)	0.02	1.9 (0.65-5.5)	0.23	3.1 (1.02-9.5)	0.05	2.3 (0.71-7.1)	0.17
	No	31								
Allergy	Yes	4		0.99				0.99		
	No	61								
Therapy	Bendamustine	11	0.3 (0.12-0.75)	0.01	0.48 (0.18-1.27)	0.14	0.41 (0.16-1.11)	0.08		
	BR	54								
Rash	Present	27	0.23 (0.08-0.69)	0.009	0.29 (0.09-0.90)	0.03	0.24 (0.07-0.83)	0.02	0.24 (0.07-0.83)	0.02
	Absent	38								

R/R; relapse/refractory, iBCL; indolent B-cell lymphoma; MCL, mantle cell lymphoma, ExtraN; extranodal involvement, BR; bendamustine+rituximab

cant difference (p=0.0147). The newly diagnosed patients were chemotherapy-naive and the lack of immunosuppression was considered to be related to the development of rash.

Although this study comprised only 65 patients, patients with iBCL and MCL treated with bendamustine who developed rashes had a better 3-year OS and PFS than those without rashes. Several patients experienced continuous remission with watchful waiting after rash developed. To our knowledge, no studies have reported rashes after bendamustine administration in relation to the prognosis of lymphoma. Nishikori *et al*. found increased CD8+ lymphocytes in the peripheral blood of patients with delayed skin reactions after bendamustine administration.[17] They suggested that inappropriate activation of CD8+ lymphocytes by latently infected pathogens may be one of the triggers of late-onset skin reactions caused by bendamustine. The activated CD8+ lymphocytes may suppress tumor cell growth, which requires further investigation. In addition, the high frequency of grade 3 skin rash may have been associated with better outcomes for iBCL in the current study.

Patients with grade 2 or higher rashes had a 62% response rate, and those without rashes had a 23% response rate in a phase II trial of lenalidomide, an immunomodulatory agent, for adult T-cell leukaemia-lymphoma.[18] Lenalidomide reportedly exerts direct antitumoral effects, and improves T-cell-mediated and NK-cell-mediated anti-tumor immune responses.[19,20] In solid tumors, epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer patients with grade 2 or higher skin rashes within 1 week after afatinib treatment alone had higher maximum tumor reduction effects than those without rashes (80% vs. 39%; p=0.077), suggesting that skin rash development is related to the therapeutic response to afatinib monotherapy.[21]

This study has several limitations. It was a retrospective study and limited to single-center patient data. It is difficult to make a firm conclusion in a mixed group of histology and treatment phases. A study consisting of a homogenous group treated with bendamustine as first-line treatment is more suitable for this purpose.

In conclusion, this study suggested that bendamustine-induced skin toxicity is associated with a better prognosis among patients with iBCL.

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AUTHOR CONTRIBUTIONS

NT, KuT, MK and KeT collected and analyzed the data; NT, KuT and NA contributed to the concept of the manuscript and interpretation of the results; all authors gave final approval of the manuscript.

COMPLIANCE WITH ETHICAL STANDARDS

The study was approved by the institutional review board of the Saitama Medical University International Medical Center in Saitama, Japan.

CONFLICT OF INTEREST

NT received honoraria from Eisai Pharma. KuT has consultancies with Daiichi-Sankyo, Ono Pharma and HUYA, and received research funding from Bayer and Celgene, and honoraria from Chugai Pharma, Celgene, Mundy and Kyowa Kirin. MI received honoraria from Bristol-Myers Squibb and Pfizer. TM received honoraria from Nippon Shinyaku and sits on advisory boards for Janssen. AM received honoraria from GlaxoSmithKline, Kyowa Kirin, Nippon Shinyaku, Celgene, Alexion, Sanofi, Beckman Coulter, Siemens Healthineers and Shire Japan. NA received scholarships from Chugai Pharma, Astellas, Sumitomo Dainippon and Eisai, and research funding from Novartis and Otsuka Pharma; consulted for SRL, Nippon Shinyaku and Novartis; and received honoraria from Kyowa Kirin, Sumitomo Dainippon, Asahi Kasei and Fuji Pharma. MB received honoraria from Chugai Pharma and GlaxoSmithKline. These sponsors had no control over the interpretation, writing or publication of this study. The other authors have no conflicts of interest to declare in relation to this manuscript.

REFERENCES

1 Hirschberg E, Gellhorn A, Gump WS. Laboratory evaluation of a new nitrogen mustard, 2-[di-(2-chloroethyl)amino-methyl] benzimidazole, and of other 2-chloroethyl compounds. Cancer Res. 1957; 17: 904-910.

2 Leoni LM, Bailey B, Reifert J, *et al*. Bendamustine (Treanda) displays a distinct pattern of cytotoxicity and unique mechanistic features compared with other alkylating agents. Clin Cancer Res. 2008; 14: 309-317.

3 Ohmachi K, Ando K, Ogura M, *et al*. Japanese Bendamustine Lymphoma Study Group. Multicenter phase II study of bendamustine for relapsed or refractory indolent B-cell non-Hodgkin lymphoma and mantle cell lymphoma. Cancer Sci. 2010; 101: 2059-2064.

4 Rummel MJ, Niederle N, Maschmeyer G, *et al*. Study group indolent Lymphomas (StiL). Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet. 2013; 381: 1203-1210.

5 Rummel M, Kaiser U, Balser C, *et al*. Study Group Indolent Lymphomas. Bendamustine plus rituximab versus fludarabine plus rituximab for patients with relapsed indolent and mantle-cell lymphomas: a multicentre, randomised, open-label, non-inferiority phase 3 trial. Lancet Oncol. 2016; 17: 57-66.

6 Czuczman MS, Goy A, Lamonica D, *et al*. Phase II study of bendamustine combined with rituximab in relapsed/refractory mantle cell lymphoma: efficacy, tolerability, and safety findings. Ann Hematol. 2015; 94: 2025-2032.

7 Flinn IW, van der Jagt R, Kahl BS, *et al*. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood. 2014; 123: 2944-2952.

8 Barbarroja-Escudero J, Sanchez-Gonzalez MJ, Antolin-Amerigo D, Rodriguez-Rodriguez M, Alvarez-Mon M. Hypersensitivity reactions and drug fever by bendamustine: a case report of three patients. Allergol Int. 2015; 64: 109-111.

9 Carilli A, Favis G, Sundharkrishnan L, Hajdenberg J. Severe dermatologic reactions with bendamustine: a case series. Case Rep Oncol. 2014; 7: 465-470.

10 Kusano Y, Terui Y, Yokoyama M, Hatake K. Lichenoid drug eruption associated with Bendamustine. Blood Cancer J. 2016; 6: e438.

11 Chung CH. Managing premedications and the risk for reactions to infusional monoclonal antibody therapy. Oncologist. 2008; 13: 725-732.

12 Shikdar S, Totton D, Turco T, Rachshtut M. Presentation and management of the delayed type of hypersensitivity reaction with bendamustine. Anticancer Drugs. 2018; 29: 814-816.

13 Bellón T. Mechanisms of severe cutaneous adverse reactions: recent advances. Drug Saf. 2019; 42: 973-992.

14 LaCasce AS, Bociek RG, Sawas A, *et al*. Brentuximab vedotin plus bendamustine: a highly active first salvage regimen for relapsed or refractory Hodgkin lymphoma. Blood. 2018; 132: 40-48.

15 Cencini E, Sicuranza A, Fabbri A, *et al*. Study of gene polymorphisms as predictors of treatment efficacy and toxicity in patients with indolent non-hodgkin lymphomas and mantle cell lymphoma receiving bendamustine and rituximab. Br J Haematol. 2019; 184: 223-231.

16 Uchida M, Mori Y, Akiba K, *et al*. Risk factors for skin toxicities associated with bendamustine-based chemotherapy in patients with non-Hodgkin lymphoma. Biol Pharm Bull. 2020; 43: 1577-1582.

17 Nishikori M, Kitano T, Kobayashi M, *et al*. Increased number of peripheral CD8+ T cells but not eosinophils is associated with late-onset skin reactions caused by bendamustine. Int J Hematol. 2015; 102: 53-58.

18 Ishida T, Fujiwara H, Nosaka K, *et al*. Multicenter phase II study of lenalidomide in relapsed or recurrent adult T-cell leukemia/lymphoma: ATLL-002. J Clin Oncol. 2016; 34: 4086-4093.

19 Bartlett JB, Dredge K, Dalgleish AG. The evolution of thalidomide and its IMiD derivatives as anticancer agents. Nat Rev Cancer. 2004; 4: 314-322.

20 Reddy N, Hernandez-Ilizaliturri FJ, Deeb G, *et al*. Immunomodulatory drugs stimulate natural killer-cell function, alter cytokine production by dendritic cells, and inhibit angiogenesis enhancing the anti-tumour activity of rituximab in vivo. Br J Haematol. 2008; 140: 36-45.

21 Kudo K, Hotta K, Bessho A, *et al*. Development of a skin rash within the first week and the therapeutic effect in afatinib monotherapy for EGFR-mutant non-small cell lung cancer (NSCLC): Okayama Lung Cancer Study Group experience. Cancer Chemother Pharmacol. 2016; 77: 1005-1009.