Risk factors for skin toxicities associated with bendamustine-based chemotherapy in patients with non-Hodgkin lymphoma

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Summary

Bendamustine plays an especially important role as a treatment for non-Hodgkin lymphoma (NHL). However, patients administered bendamustine alone or in combination with rituximab (BR) may experience drug-associated skin toxicities that can profoundly impact their health-related quality of life through both physical discomfort and psychological distress. Moreover, worsening skin symptoms may lead to dose reduction or termination in the management of cancer chemotherapy. We retrospectively investigated patient backgrounds and pretreatment characteristics from medical records of NHL patients treated with bendamustine alone or BR therapy and identified predictive factors for skin toxicities at the start of chemotherapy.

Patients were eligible for the study if they were 20 years older, diagnosed with NHL, and received bendamustine alone or BR therapy at the Department of Hematology, Kobe City Medical Center General Hospital, between April 1, 2011, and March 31, 2018.

This study included 95 patients with newly diagnosed or refractory or relapsed NHL. Multivariate stepwise logistic regression analysis with backward selection revealed that baseline non-prior chemotherapy (odds ratio [OR], 15.72; 95% confidence interval [CI], 4.24–83.13, p<0.001) was a significant factor influencing the occurrence of skin toxicity.

Our results demonstrated that non-prior chemotherapy was a significant risk factor for skin toxicities in patients with NHL receiving bendamustine alone or BR therapy. No patient experience serious side effects of grade 3 or higher and that bendamustine is very useful as a first-line treatment.

Key words: Bendamustine; non-Hodgkin lymphoma; Prior chemotherapy; Skin toxicities; Risk factor
Introduction

Malignant lymphoma (ML) is one of the most common types of cancer; with 29,400 new cases diagnosed annually in Japan, the number has increased in recent decades. 1 Of the two major types of ML, non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL), approximately 90% to 95% of ML patients are diagnosed with NHL. Indolent lymphomas such as follicular lymphoma, the most frequent, comprise 40% of all NHL subtypes. 2,3 Indolent lymphomas can follow a chronic relapse-remission disease course; thus, patients may receive several different treatments over successive courses. Meanwhile, Mantle-cell lymphoma (MCL), another type of NHL, comprises about 3–10% of all NHL cases and has a worse prognosis than those of other types of NHL. 2

A standard rituximab-chemotherapy regimen including cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is used for treatment-naive patients with indolent NHL. Bendamustine, a unique cytotoxic agent containing a benzimidazole heterocyclic ring, is also used to treat NHL by multifaceted mechanisms of action. Clinical studies have demonstrated the efficacy of bendamustine-based chemotherapy in malignant lymphoma, including refractory and/or relapsed indolent NHL 8-10 and MCL. 2,9-11 Bendamustine is mostly used in combination with rituximab, a chimeric anti-CD20 monoclonal antibody. Phase II clinical trials of a combination therapy comprising bendamustine and rituximab (BR) in patients with refractory and/or relapsed indolent NHL or MCL 5,6,12 have shown an overall response rate above 90%. A phase III clinical trial conducted overseas showed that bendamustine in combination with rituximab was more effective than fludarabine for the treatment of patients with relapsed indolent NHL or MCL. 7

In a phase II clinical trial in Japan of patients with indolent NHL and MCL administered bendamustine alone as a second-line treatment, the major nonhematologic side effects—nausea, fatigue, anorexia, constipation, and rash—occurred in 86%, 62%, 61%, 46%, and 46% of patients, respectively. 4 In particular, bendamustine-associated skin toxicities appear to occur with higher frequency in Asia. Both physical discomfort and psychological distress due to these skin toxicities can profoundly affect patient health-related quality of life. 13-15 Moreover, worsening skin symptoms may lead to dose reduction or treatment termination in the management of cancer chemotherapy. 13,14 Discontinuation or dose reduction of bendamustine alone or in BR therapy suggests that treatment intensity is reduced, which directly impacts survival. 16 Therefore, clarifying the risk factors for skin toxicities associated with bendamustine treatment may be useful for patient management.
The present study retrospectively investigated patient background and pretreatment characteristics from medical records and identified the predictive factors of skin toxicities in NHL patients treated with bendamustine alone or in BR therapy.

Materials and methods

Study design, setting, and patient population

This study was conducted in accordance with the principles of the Declaration of Helsinki and the Ethical Guidelines for Epidemiological Research by the Ministry of Education, Culture, Sports, Science and Technology, and the Ministry of Health, Labour and Welfare of Japan. The protocol was approved by the Ethics Committee of Kobe City Medical Center General Hospital (approval no. zn 180626). The requirement for informed consent was waived due to the retrospective study design. Patients were eligible for the study if they were 20 years or older, diagnosed with NHL, and received bendamustine alone or in BR therapy at the Department of Hematology, Kobe City Medical Center General Hospital, between April 1, 2011, and March 31, 2018.

Treatment schedules

The bendamustine-based chemotherapy regimens are shown in Table 1. Bendamustine was administered alone at a dose of 120 mg/m² on days 1 and 2 or at a dose of 90 mg/m² in combination with rituximab (375 mg/m²) (BR therapy) of a 21-day cycle, up to 6 cycles. Adequate topical agents and anti-allergic oral medicine were administered when skin toxicities occurred. Specifically, hydrocortisone butyrate and/or alclometasone dipropionate, betamethasone butyrate propionate, betamethasone valerate, clobetasol propionate, prednisolone valerate, and gentamicin sulfate was used as topical treatments, while ebastine, olopatadine hydrochloride, and fexofenadine hydrochloride were administered orally as rescue medications.

Clinical parameter data collection and assessment

All data from April 1, 2011 to May 31, 2019, were collected retrospectively from the electronic medical record system. We evaluated information on patients’ sex, age, Eastern Cooperative Oncology Group performance status (ECOG-PS), absence or presence of prior chemotherapy, absence or presence of B symptoms (i.e., systemic symptoms of fever, night
sweats, and weight loss), absence or presence of hepatitis B core antibody (anti-HBc), skin
toxicities, serum creatinine (Scr) level, aspartate aminotransferase (AST) level, alanine
aminotransferase (ALT) level, lactate dehydrogenase (LDH) level, C-reactive protein (CRP)
level, leukocyte count, neutrophil count, lymphocyte count, albumin level, hemoglobin level,
and platelet count. These variables were monitored from the beginning of the first course of
therapy at the Department of Hematology, Kobe City Medical Center General Hospital. In the
present study, the frequency of laboratory tests was determined at the physician’s discretion.
The severity of toxicities was classified according to the Common Terminology Criteria for
Adverse Events (CTCAE) version 4.0. CTCAE grade 1 or higher was considered to indicate
skin toxicities.

Statistical analysis
Fisher’s exact tests were used to compare categorical data. Continuous data are presented
as medians and minimum and maximum values. Wilcoxon rank-sum tests were used to
compare nonnormally distributed variables between groups.

To identify the factors associated with skin toxicities, univariate logistic regression
analyses were performed including patient sex; age; ECOG-PS; prior chemotherapy; B
symptom status; anti-HBc status; Scr, AST, ALT, LDH, and CRP levels; leukocyte,
neutrophil, and lymphocyte counts; albumin level; hemoglobin level; and platelet counts as
independent variables. Factors with p<0.05 in univariate analyses were evaluated as potential
covariates in multivariate stepwise logistic regression analysis with backward selection. The
classification performances (specificity and sensitivity) of the candidate factors were also
tested by area under the curve (AUC) of the receiver operator characteristic (ROC) curve. We
also investigated the relationship between the predictive factors and time to the first
occurrence of skin toxicities, using the Kaplan–Meier method with log-rank test. Data were
analyzed using JMP 13.2.1 (SAS Institute Inc., Cary, NC, U.S.A.), with p<0.05 considered to
indicate statistical significance.

Results
Patient baseline clinical characteristics
The patients’ demographic data and baseline clinical characteristics are shown in Table 2.
This study included a total of 95 patients (48.4% male and 51.6% female) with new diagnoses
or refractory and/or relapsed indolent NHL. Seventy-four patients had the history of chemotherapy before the initiation of bendamustine-based chemotherapy. There were 55 prior chemotherapy regimens including differences in types of drugs, duration of the cycle, frequency of the cycle, and how many cycles (Table 2).

**Incidence of skin toxicities**

Forty-two (44.2%) of the 95 patients experienced skin toxicities after the initiation of bendamustine-based chemotherapy. The occurrence frequencies of skin toxicities were 47.8% (22 of 46) and 40.8% (20 of 49) in male and female patients, respectively. During the observation period, 73.8%, and 26.2% of patients experienced grade 1, and 2 skin toxicities, respectively, whereas no patients had severe skin toxicities of grade 3 or higher. Eight out of the 42 patients with grade 1 and 2 toxicities required symptomatic relief with topical corticosteroid ointments, and oral antihistamines.

Table 3 shows total number of patients experiencing skin toxicities after the initiation of bendamustine-based chemotherapy. During the observation period, 27, 17, 14, 15, 6 and 3 patients experienced skin toxicities in the 1st, 2nd, 3rd, 4th, 5th, and 6th cycles of bendamustine-based chemotherapy, respectively. The number of the patients tended to decrease as the treatment progressed, although some patients experienced a recurrence of one or more of skin toxicities during the observation period. Similar tendency was also observed in a total of 19 patients who completed 6 courses of bendamustine-based chemotherapy. Of these 19 patients, 11 patients experienced skin toxicities with a median time to onset of 12.0 days (ranging from 1 to 168 days), whereas 8 patients did not experience the toxicities and all of whom had received previous chemotherapy.

**Risk factors for skin toxicities**

Univariate and multivariate logistic regression analyses were performed to calculate the odds ratios (ORs) of factors influencing the occurrence frequency of skin toxicities. Univariate analysis revealed that baseline non-prior chemotherapy (odds ratio [OR], 12.49; 95% confidence interval [CI], 3.78–57.13; p<0.001), non-anti-HBe (OR, 2.79; 95% CI, 1.11–7.53; p=0.028), CRP (OR, 0.72; 95% CI, 0.49–0.95; p=0.015), and hemoglobin (OR, 1.24; 95% CI, 1.02–1.54; p=0.027) were significantly associated with the incidence rate of skin toxicities during bendamustine-based chemotherapy (Table 3). A baseline CRP cut-off of 1.33 (AUC: 0.61, sensitivity: 90.5%, specificity: 34.0%) showed a significant difference in the
occurrence frequency of skin toxicities between the patients with baseline CRP ≥1.33 and <1.33 (5.3% and 39.0%, p=0.009). A baseline hemoglobin cut-off of 10.5 (AUC: 0.62, sensitivity: 85.7%, specificity: 35.9%) showed significant differences in the occurrence frequencies of skin toxicities between patients with baseline hemoglobin ≥10.5 and <10.5 (37.9% and 6.3%, p=0.020). Variables with p<0.05 were included in the subsequent multivariate logistic regression analysis with backward selection, which revealed baseline non-prior chemotherapy (OR, 15.72; 95% CI, 4.24–83.13, p<0.001) as a significant factor influencing the occurrence rate of skin toxicities (Table 3). To further explore the relationship between prior chemotherapy and the occurrence of skin toxicities, we performed Kaplan–Meier analysis of the time to the first occurrence of skin toxicities (Figure 1). The cumulative incidence of skin toxicities differed significantly between the patients with and without prior history of chemotherapy (p <0.001).

**Discussion**

Bendamustine alone or BR therapy are widely used as first-line therapy for untreated therapy or relapsed/refractory in NHL patients.\(^{18}\) Additionally, bendamustine is also used as first-line therapy for patients with chronic lymphocytic leukemia (CLL) \(^{18,19}\) and is a highly effective therapy in patients for relapsed/refractory or elderly patients with multiple myeloma (MM) \(^{20,21}\). Bendamustine therapy is expected to be increasingly used in a wide variety of hematologic malignancies such as NHL and CLL, MM. Therefore, it is important to identify the risk factors for skin toxicities associated with the use of bendamustine alone or in BR therapy.

Skin toxicities are common in patients receiving bendamustine-based chemotherapy, and several studies have reported the occurrence frequencies in patients with hematologic malignancy. When bendamustine was used as a monotherapy, the occurrence frequency of skin toxicities was 9.2% in NHL patients in a phase II study in the United States \(^{22}\) and at frequencies of 15.0% to 24.0% in NHL patients receiving bendamustine alone or BR therapy in clinical trials. \(^{2,10}\) Meanwhile, in a phase II study in Japan, the occurrence frequency of skin toxicities was 46.0% in NHL and MCL patients treated with bendamustine alone. \(^{12}\) Malipatil *et al.* reported an occurrence frequency of skin toxicities attributed to bendamustine alone or in combination with rituximab or with vincristine and prednisolone of 56.3% in Indian patients with NHL or CLL. \(^{23}\) In the present study, the occurrence frequency of skin toxicities...
toxicities was 44.2% in NHL patients receiving bendamustine-based chemotherapy. The influence of the combination drugs could not be thoroughly ruled out, although there was no significant difference in the occurrence frequencies of skin toxicities between bendamustine monotherapy and BR therapy. Further studies in large populations are necessary to investigate the possibilities of high occurrence in Asia.

The univariate and multivariate logistic regression analyses performed in the present study of data from the NHL patients receiving bendamustine alone or BR therapy showed that non-prior chemotherapy was a significant risk factor for skin toxicities during treatment (Table 4). To our knowledge, this is the first report to demonstrate the association between a history of previous chemotherapy and bendamustine-associated skin toxicities. Our findings are supported by the results of previous reports which have focused on patients with either primary or recurrent NHL. In their multicenter phase III study of treatment-naive patients with indolent NHL and MCL, Rummel and coinvestigators demonstrated that at least one dose of BR treatment was associated erythematous skin reaction including urticaria and rash, as well as skin irritations assessed as allergic reactions, in 16% and 15% of patients, respectively. 2) In another phase III study of relapsed indolent NHL and MCL patients, the authors reporting that 3% and 1% of patients administered BR therapy as second-line treatment experienced grade 3 and higher allergic reaction and grade 3 skin reactions, respectively. 7) Differences in the occurrence frequencies of skin toxicities between these two studies were observed.

The details of the mechanisms underlying skin toxicities during bendamustine-based chemotherapy are not fully understood. Nishikori et al. reported that the increase in CD8-positive T cells and the ratio of CD4- and CD8-positive cell numbers were related to late-onset skin toxicities at the end of BR therapy in patients with relapsed or refractory indolent B cell lymphomas and MCL and that the suppression of CD8-positive T cells by steroids contributed to the prevention of skin reactions. 15) Bellón also proposed T cell-mediated drug-specific immune response due to delayed type IV hypersensitivity reaction. 24, 25) Typically the maximal reaction time for skin toxicities is 48–72 hours. 25) The occurrence of skin toxicities was not limited to a few days after the initiation of bendamustine-based chemotherapy. Concerning continuous treatment with bendamustine, meanwhile, two bendamustine desensitization protocols have been proposed for patients who develop hypersensitivity reactions, including rash, after BR therapy. 26, 27) These treatments were successfully completed without developing a rash, and the symptoms were well-managed by antihistamines and corticosteroids. Bendamustine-based chemotherapy is an
outpatient chemotherapy regimen, and so the administration of premedication with antihistamines such as diphenhydramine may be acceptable choice for prophylaxis. In contrast, routine use of prophylactic use of corticosteroid is not recommended because the bendamustine-associated skin toxicities are unlikely to be so serious even if bendamustine is used as a first-line treatment. Collectively, it is considered that the skin toxicities observed during the bendamustine-based chemotherapy are not due to an acute hypersensitivity reaction such as infusion reaction or anaphylaxis but to delayed-onset hypersensitivity. As data are lacking regarding the numbers of CD4- and CD8-positive cells during the bendamustine desensitization procedure, monitoring of the number of these cells might provide new insights to elucidate the molecular mechanisms underlying the onset and suppression of skin toxicities during bendamustine-based chemotherapy.

In conclusion, the results of the present study demonstrated that no history of chemotherapy was a significant risk factor for skin toxicities in patients with NHL receiving bendamustine-based chemotherapy. Thus, oncologists and clinical pharmacists should be more cautious about the occurrence of skin toxicities for chemotherapy-naive patients receiving bendamustine-based chemotherapy. Despite the limitations of this study, including its retrospective design, outpatient chemotherapy regimen, single-center site, and small sample size, the results showed that baseline non-prior chemotherapy may be an important indicator before the administration of bendamustine alone or as BR therapy.

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Conflict of interest

The authors declare no conflict of interest.
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**Table 1.** Bendamustine-based chemotherapy regimens

| Regimen          | Drugs         | Daily dosage | Timing of administration                                      |
|------------------|---------------|--------------|---------------------------------------------------------------|
| Bendamustine alone | Bendamustine | 120 mg/m²   | once daily on days 1 and 2 of a 21-day cycle, up to 6 cycles |
| BR therapy       | Bendamustine  | 90 mg/m²    | once daily on days 1 and 2 of a 21-day cycle, up to 6 cycles |
|                  | Rituximab     | 375 mg/m²   | once daily on day 1                                           |
Table 2. Baseline patient characteristics at the beginning of bendamustine-based chemotherapy

| Variable                                      | Value   |
|-----------------------------------------------|---------|
| Number of patients                            | 95      |
| Sex                                           |         |
| Male                                          | 46      |
| Female                                        | 49      |
| Age\(^a\), years                             | 69 (44-91) |
| ECOG-PS\(^b\) score                          |         |
| 0                                             | 86      |
| 1                                             | 9       |
| Diagnosis                                     |         |
| Follicular lymphoma                           | 49      |
| Mucosa associated lymphoid tissue             | 15      |
| Diffuse large B-cell lymphoma                 | 9       |
| Others                                        | 22      |
| Number of prior chemotherapy regimen(s)       |         |
| 0                                             | 21      |
| 1                                             |         |
| R-CHOP\(^c\)                                  | 23      |
| R-CVP\(^d\)                                   | 3       |
| Rituximab alone\(^e\)                        | 9       |
| Others\(^f\)                                 | 7       |
| 2 and more                                    | 32      |
| Regimen                                       |         |
| Bendamustine alone                            | 6       |
| BR\(^g\) therapy                             | 89      |
| B symptoms                                    |         |
| Yes                                           | 22      |
| No                                            | 73      |
| Anti-HBe\(^h\)                                |         |
| Test          | Value                        |
|--------------|------------------------------|
| Positive     | 29                           |
| Negative     | 66                           |
| Scr<sup>a<i></sup>, mg/dL | 0.77 (0.33-2.10)             |
| AST<sup>a<j></sup>, U/L       | 21 (10-75)                   |
| ALT<sup>a<k></sup>, U/L       | 16 (5-51)                    |
| LDH<sup>a<l></sup>, U/L       | 197 (111-1347)               |
| CRP<sup>m</sup>             | 0.29 (0.01-15.02)            |
| Leukocyte count<sup>a</sup>, 10<sup>3</sup>/μL | 5.40 (1.60-21.10)            |
| Neutrophil count<sup>a</sup>, 10<sup>3</sup>/μL | 3.72 (0.51-12.69)            |
| Lymphocyte count<sup>a</sup>, 10<sup>3</sup>/μL | 1.06 (0.21-6.14)             |
| Albumin<sup>a</sup>, g/dL     | 3.9 (2.3-4.8)                |
| Hemoglobin<sup>a</sup>, g/dL   | 12.4 (6.2-16.2)              |
| Platelet count<sup>a</sup>, 10<sup>3</sup>/μL | 17.5 (2.2-35.7)              |

<sup>a</sup> Median and minimum value, maximum value.  
<sup>b</sup> ECOG-PS, Eastern Cooperative Oncology Group performance status.  
<sup>c</sup> R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone.  
<sup>d</sup> R-CVP, rituximab, cyclophosphamide, vincristine and prednisolone.  
<sup>e</sup> Rituximab alone, or in combination with radiation.  
<sup>f</sup> Others, monotherapy or combination therapy of rituximab, cyclophosphamide, pirarubicin, vincristine, prednisone, dexamethasone, mitoxantrone, cladribine, fludarabine, methylprednisolone, etoposide, cytarabine, cisplatin, gemcitabine, carboplatin, ifosfamide, mitoxantrone, methotrexate, and irinotecan.  
<sup>g</sup> BR, bendamustine and rituximab.  
<sup>h</sup> Anti-HBc, hepatitis B core antibody.  
<sup>i</sup> Scr, serum creatinine.  
<sup>j</sup> AST, aspartate aminotransferase.  
<sup>k</sup> ALT, alanine aminotransferase.  
<sup>l</sup> LDH, lactate dehydrogenase.  
<sup>m</sup> CRP, C-reactive protein.
Table 3. Total number of patients experiencing skin toxicities after the initiation of bendamustine-based chemotherapy

| Chemotherapy cycles | Total number of patients*,** |
|---------------------|-----------------------------|
| 1st.                | 27                          |
| 2nd.                | 17                          |
| 3rd.                | 14                          |
| 4th.                | 15                          |
| 5th.                | 6                           |
| 6th.                | 3                           |

* A total of 42 patients experienced skin toxicies.
** Some patients experienced a recurrence of one or more of skin toxicities during the observation period.
Table 4. Univariate and multivariate analyses to evaluate bendamustine-associated skin toxicities.

| Variables                        | Univariate analyses | Multivariate analysis<sup>Δ</sup> |
|---------------------------------|---------------------|-----------------------------------|
|                                 | OR<sup>a</sup> (95% CI) | p-value<sup>b</sup> | OR<sup>a</sup> (95% CI) | p-value<sup>b</sup> |
| non-Prior chemotherapy          | 12.49 (3.78-47.13)   | <0.001 | non-Prior chemotherapy | 15.72 (4.24-83.13) | <0.001 |
| non-Anti-HBe<sup>a</sup>         | 2.79 (1.11-7.53)     | 0.028 | non-Anti-HBe<sup>a</sup> | 2.68 (0.88-9.20)   | 0.085 |
| CRP<sup>b</sup>                  | 0.72 (0.49-0.95)     | 0.015 | CRP <1.33              | 3.46 (0.93-15.9)   | 0.064 |
| Hemoglobin (g/dL)               | 1.24 (1.02-1.54)     | 0.027 | Hemoglobin ≥10.5 g/dL  | 3.04 (0.85-12.9)   | 0.087 |
| Male Sex                        | 1.33 (0.59-3.01)     | 0.492 | Male Sex               | —                  | —     |
| Age (years)                     | 0.96 (0.92-1.00)     | 0.057 | Age (years)            | —                  | —     |
| ECOG-PS<sup>c</sup> 1           | 1.01 (0.24-4.07)     | 0.988 | ECOG-PS<sup>c</sup> 1  | —                  | —     |
| BR<sup>d</sup> therapy          | 1.03 (0.30-12.21)    | 0.575 | BR<sup>d</sup> therapy | —                  | —     |
| non-B symptoms                  | 2.59 (0.95-7.91)     | 0.063 | non-B symptoms         | —                  | —     |
| Scr<sup>e</sup>, mg/dL          | 1.44 (0.38-5.54)     | 0.586 | Scr<sup>e</sup>, mg/dL | —                  | —     |
| AST<sup>f</sup>, U/L            | 0.98 (0.94-1.02)     | 0.390 | AST<sup>f</sup>, U/L   | —                  | —     |
| ALT<sup>g</sup>, U/L            | 0.99 (0.95-1.04)     | 0.882 | ALT<sup>g</sup>, U/L   | —                  | —     |
| LDH<sup>h</sup>, U/L            | 0.99 (0.99-1.00)     | 0.234 | LDH<sup>h</sup>, U/L   | —                  | —     |
| Leukocyte count (10<sup>3</sup>/µL) | 0.93 (0.80-1.09)   | 0.363 | Leukocyte count (10<sup>3</sup>/µL) | —       | —     |
| Neutrophil count (10<sup>3</sup>/µL) | 0.93 (0.73-1.18)   | 0.522 | Neutrophil count (10<sup>3</sup>/µL) | —       | —     |
| Lymphocyte count (10<sup>3</sup>/µL) | 1.06 (0.68-1.65)   | 0.792 | Lymphocyte count (10<sup>3</sup>/µL) | —       | —     |
| Albumin (g/dL)                  | 1.74 (0.84-3.77)     | 0.158 | Albumin (g/dL)         | —                  | —     |
| Platelet count (10<sup>3</sup>/µL) | 1.02 (0.96-1.08)   | 0.433 | Platelet count (10<sup>3</sup>/µL) | —       | —     |

<sup>a</sup> Anti-HBc, hepatitis B core antibody.
<sup>b</sup> CRP, C-reactive protein.
<sup>c</sup> ECOG-PS, Eastern Cooperative Oncology Group performance status.
<sup>d</sup> BR, bendamustine and rituximab.
<sup>e</sup> Scr, serum creatinine.
<sup>f</sup> AST, aspartate aminotransferase.
<sup>g</sup> ALT, alanine aminotransferase.
<sup>h</sup> LDH, lactate dehydrogenase.
<sup>i</sup> OR, odds ratio.
<sup>j</sup> 95% CI, 95% confidence interval.
<sup>k</sup> Values presented in italics indicate statistical significance.
<sup>Δ</sup> Potential factors in univariate analyses were calculated according to the cut-off value by receiver operating characteristic (ROC) analysis and analyzed as categorical variates in multivariate analysis.
Fig. 1. The Kaplan-Meier curve of cumulative incidence of skin toxicities
The Kaplan-Meier curve of cumulative incidence of skin toxicities in 95 patients with (dotted line) and without (solid line) prior history of chemotherapy. The data were processed individually for each patient as days when skin toxicities were first occurred after the initiation of bendamustine-based chemotherapy. The difference was statistically significant (P<0.05, log-rank test).