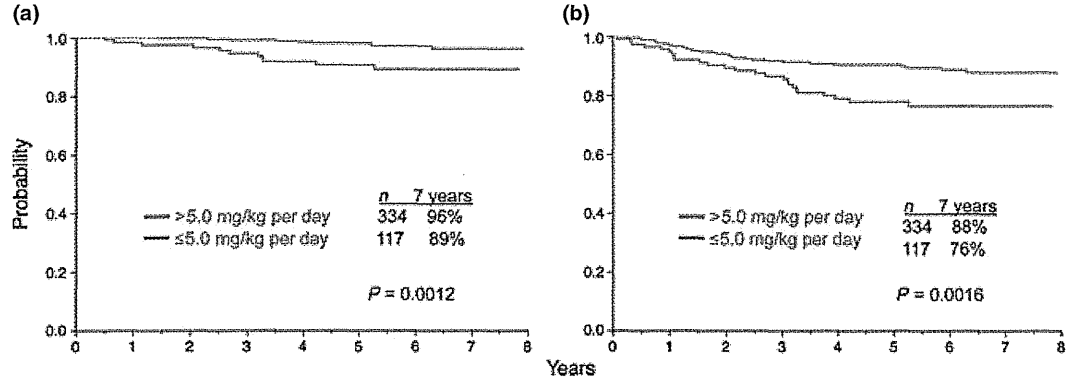

Fig. 4. (a) Overall and (b) event-free survival according to the mean daily dose during the first 24 months per body weight. The cut-off value was set at >5.0 mg/day/kg (e.g. if a patient whose body weight was <60 kg received imatinib at a mean daily dose of 300 mg).

Table 5. Number of patients and survival according to the mean daily dose of imatinib during the first 24 months per body weight

	Mean daily dose/body weight (mg/day/kg)				
	>5.0†		≤5.0		*P*-value
	Actual bodyweight (kg)	No. patients	Actual bodyweight (kg)	No. patients	
Imatinib daily dose group‡					
400 mg	<80	266	≥80	28	
300 mg	<60	63	≥60	27	
200 mg	<40	5	≥40	62	
Estimated 7-year OS	96%		89%		0.0012
Estimated 7-year EFS	88%		76%		0.0016

†The cut-off value was set at >5.0 mg/day/kg (e.g. the mean daily dose of imatinib during the first 24 months (300 mg) divided by body weight [<60 kg]). ‡Mean daily doses in the 400-, 300-, and 200-mg groups were ≥360, 270–359, and <270 mg imatinib, respectively. Patients who discontinued imatinib were not included in the analysis. EFS, event-free survival; OS, overall survival.

to the mean daily dose during the first 6, 12, and 24 months of treatment. The rate of achieving CCyR or MMR differed significantly between the 300- and 400-mg groups during the first 24 months. Even so, there were no significant differences in OS, PFS, and EFS between the 300- and 400-mg groups during the first 6, 12, or 24 months of treatment. Conversely, the 200-mg group showed markedly inferior cytogenetic and/or molecular responses, as well as inferior survival, compared with the 300- and 400-mg groups. We also analyzed outcomes according to the mean daily dosage during the first 24 months per BW, with the results suggesting that patients who had relatively high daily dosage per BW were likely to have better OS and EFS even though the actual daily dose had been lower than 400 mg imatinib. The OS and EFS in the 300-mg group in the present study were not inferior compared with rates reported in the IRIS study (85% at 7 years vs. 83% at 6 years), which suggests that a considerable number of Japanese patients who received doses lower than 400 mg demonstrated an adequate response. A prospective comparative study would be necessary to confirm this observation.

Two recent studies showed a correlation between the plasma trough levels (C_{min}) and response, suggesting that maintaining C_{min} above approximately 1000 ng/mL was associated with improved outcomes.[22,23] In the present study, the mean daily dose was 331 ± 108 mg during the first 24 months and the relatively high dosage of imatinib per BW was associated with better OS and EFS, whereas in the IRIS study the mean daily dose among the patients who continued receiving imatinib was 382 ± 50 mg.[1] On the basis of our results, we assume that the relatively small body size of Japanese patients compared with their Western counterparts may have affected C_{min}, although differences in the metabolism of imatinib because of ethnicity cannot be ruled out either. Therefore, we measured the C_{min} of imatinib in a group of patients who had received imatinib continuously at a daily dose of either 300 or 400 mg. The patients from whom blood samples were collected showed almost similar background characteristics to the entire study population. There was no significant difference in the mean C_{min} between patients receiving 300 or 400 mg imatinib, and there was no significant difference in the ratio of patients whose C_{min} was higher than 1000 ng/mL between the two groups. When pharmacokinetic analyses of patients receiving 400 mg imatinib in the present study are compared with the IRIS study, the C_{min} in the present study was distributed at higher concentrations than in the IRIS study (mean C_{min} 1165 vs. 979 ng/mL, respectively); however, the distribution of C_{min} in patients receiving 300 mg imatinib was similar between the studies.[23] Larson *et al.* reported a weak correlation between C_{min} and age, BW, or BSA in the IRIS study, but also suggested that the effects of body size and age on C_{min} were not likely to be of clinical significance because C_{min} showed large interpatient variability.[23] However, the C_{min} in their female patients was significantly higher than that in male patients, and they speculated that this may be due to the small body size of the female patients. The same tendency was seen in the present study, especially in terms of age and gender. Therefore, a small body size among Japanese old and/or female patients may partly account for the higher C_{min} of imatinib. Regarding

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Table 6. Patient characteristics and plasma trough levels of imatinib according to the daily dose of imatinib

	Imatinib daily dose†		*P*-value
	400 mg	300 mg	
No. patients	26	24	
No. men/women	19/7	12/12	0.092
Age (years)	49 (17–79)	58 (33–76)	0.012
Body weight (kg)	65.2 ± 10.6	59.5 ± 10.7	0.062
BSA (m^2)	1.68 ± 0.17	1.57 ± 0.17	0.034
Sokal risk group (*n*)			
Low	18	13	0.357
Intermediate	6	6	
High	2	5	
C_{min} (ng/mL)			
Mean ± SD	1165 ± 445	1113 ± 426	0.673
Median (range)	1035 (710–2420)	1130 (439–2140)	
% Patients on >1000 ng/mL imatinib	57.7 (15/26)	62.5 (15/24)	0.1
Best response (%)			
MCyR	26 (100)	23 (96)	
CCyR	26 (100)	22 (92)	
MMR	24 (92)	23 (96)	

Unless indicated otherwise, data are given as the mean ± SD, as the median with the range given in parentheses, or as the number of patients in each group with percentages given in parentheses, as appropriate. †Imatinib at a daily dose of 400 or 300 mg without any dose modification. BSA, body surface area; CCyR, complete cytogenetic response; C_{min}, plasma trough level; MCyR, major cytogenetic response; MMR, major molecular response.

the plasma concentration of imatinib in Japanese patients, there are other reports showing sufficient C_{min} in patients receiving imatinib at doses lower than 400 mg,[6,24] but it remains uncertain whether there are any individual or ethnic differences in the metabolism of imatinib.[24,25]

Another possible reason for the satisfactory outcomes seen for patients in the 300-mg group could be that, at this dose, imatinib could be administered continuously to some patients without serious adverse events. A recent study regarding imatinib dosage in Japanese patients reported that, based on multivariate analysis, older age and lower BW are significant risk factors for the discontinuation of imatinib therapy and that patients with these factors were less likely to achieve a CCyR.[18] Continuous and adequate dosage is essential for optimal outcome, and adherence to imatinib therapy is critical.[26,27]

In conclusion, the long-term follow-up of the JALSG CML202 study revealed almost similar excellent outcomes to those of the IRIS study and others. There were no significant differences in OS and EFS between the 300- and 400-mg imatinib groups. However, cumulative rates of cytogenetic or molecular responses in the 300-mg group were inferior to those in the 400-mg group. The results of the present study suggest that imatinib at a dose of 400 mg may be optimal for Japanese patients, but that 400 mg imatinib is not tolerable in a considerable number of patients, and that the measurement of C_{min} is useful in finding the optimal dose, especially in elderly and/or female patients. Nevertheless, excessive dose reductions to <300 mg imatinib should be avoided even in patients who are intolerant to 400 mg imatinib or have a small body size. We hope our findings are useful for the treatment of CML patients in other Asian countries.

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Disclosure Statement

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Correlation between Amp-CMLTM (FUJIREBIO Inc., Tokyo, Japan) and Fusion Quant M-BCRTM (Ipsogen, Marseille, France).

Data S1. Measurement of major *BCR-ABL1* transcript.

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ORIGINAL ARTICLE: CLINICAL

Clinical outcome of non-surgical treatment for primary small intestinal lymphoma diagnosed with double-balloon endoscopy

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Abstract

Primary small intestinal lymphoma (PSIL) is often treated with surgical resection, and therefore response to non-surgical treatment is rarely known. We retrospectively analyzed the clinicopathological features of 19 patients with PSIL, who had been diagnosed by double-balloon endoscopy (DBE) and had not received surgical treatment. The immunohistological phenotypes of 18 patients were B-cell lymphomas. Five patients had tumors within the jejunum, nine within the ileum and five in multiple sites including the duodenum. Most cases were in the low or low-intermediate risk group of the International Prognostic Index score. Seventeen patients received chemotherapy, with an overall response rate of 82.4%. The estimated overall survival at 5 years was 72.2%. Response to initial chemotherapy and levels of hemoglobin (Hb) and albumin (Alb) were identified as favorable prognostic indicators. We conclude that PSIL can be effectively diagnosed by DBE and shows a good prognosis with chemotherapy alone.

Keywords: Primary small intestinal lymphoma, double-balloon endoscopy, chemotherapy

Introduction

Primary gastrointestinal lymphoma is one of the most common extranodal non-Hodgkin lymphomas (NHLs), and recently its incidence has been increasing [1]. The most common primary site is the stomach (50–70%), followed by the small intestine (20–30%). Primary small intestinal lymphoma (PSIL) represents 20% of all malignant tumors in the small intestine and 4–12% of NHLs [2–5].

Compared to primary gastric lymphoma, the clinicopathological features of PSIL are less well documented [6–9]. Surgical resection is often performed to confirm a diagnosis of PSIL or to deal with tumor-associated complications such as bleeding, perforation and stenosis [10,11]. Thus, surgical procedures are mainly selected and performed as initial treatment followed by chemotherapy or radiation therapy if necessary. However the appropriateness for this therapeutic strategy is still controversial [12,13].

Salles *et al.* reported that surgical resection before chemotherapy has no impact on the complete response (CR) rate, overall survival or disease-free survival in patients with aggressive histopathological subtypes of primary gastrointestinal lymphoma [14]. Furthermore, gastrectomy is considered unnecessary as initial therapy for patients with primary gastric lymphoma, including extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) [7,15–19]. In contrast, surgical resection may still be useful to control complications due to a mucosal lesion. In addition, surgical resection followed by chemotherapy was reported to produce significantly longer overall survival than chemotherapy alone in cases of diffuse large B-cell lymphoma (DLBCL) localized in the small intestine [20]. However, there are very few reports for PSIL in which the clinical outcome has been compared between patients receiving chemotherapy with and without surgical resection. Therefore, the optimal therapeutic strategy for PSIL has not yet been established.

Double-balloon endoscopy (DBE) is a novel system of electronic enteroscopy via which many endoscopic procedures such as biopsy, hemostasis, balloon dilatation, stent placement, polypectomy and endoscopic mucosal resection have become possible for small-intestinal tumors. Success rates for total inspection of the small intestine using DBE have been reported to be 40–80% [22]. It now plays an important role in the diagnosis and treatment of small-intestinal diseases [23,24]. Furthermore, pretreatment diagnosis as well as evaluation of tumor distribution in the total intestine has become possible. DBE, thus, allows diagnosis of PSIL without surgical resection.

We retrospectively analyzed the clinicopathological features of PSIL in patients diagnosed by DBE in order to develop a standard therapeutic model.

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Patients and methods

Patients

In our institution, DBE was performed under conscious sedation for 550 cases from June 2002 to May 2007. The procedure of DBE has been described previously [21]. The median duration of the procedures was 70 min. Among patients, 19 diagnosed as having PSIL have been analyzed in this study. In all cases, a tumor biopsy was performed, and PSIL was diagnosed based on histological features of the biopsy specimen. Cases with only duodenal or ileocecal lesions were excluded, because these types of lymphoma can be diagnosed with traditional upper gastrointestinal endoscopy or colonoscopy, and are well documented in previous literature [4,25–28]. We observed no patients diagnosed with PSIL who had surgical resection in the same time period, probably due to our institution's policy of conducting DBE in preference to surgery for diagnosis in patients who are suspected of PSIL unless they suffer from emergent intestinal bleeding or stenosis.

Diagnostic and staging procedures

Each formalin-fixed specimen was reviewed by two pathologists at our institution and categorized by the latest World Health Organization (WHO) "classification of tumours of haematopoietic and lymphoid tissues" [29]. Each biopsy was investigated by immunohistochemical staining for CD20, CD10, CD5, BCL-2 and CD3. Polymerase chain reaction amplifications of genes for the immunoglobulin heavy chain or T-cell receptor gamma chain were added to show monoclonal disease when necessary.

Patients were staged according to criteria of the recent International Workshop (Lugano classification) [13]. Lesions were classified as multifocal when more than one lesion was observed. An International Prognostic Index (IPI) score was calculated for each patient.

Follow-up and statistical analysis

Response to treatment was assessed using clinical and histopathologic findings. A CR was considered to be a full clinical response and histopathologic remission. A partial response (PR) was considered to be a clinical response and improvement of histopathologic findings to those of a preceding stage. Survival curves were calculated according to the Kaplan–Meier method. Survival analysis was performed using the log-rank test. Differences were considered significant if the p-value was < 0.05. Correlations between groups were evaluated by Pearson's correlation coefficient (r).

Results

Clinicopathological features

Clinical, pathological and computed tomography (CT) imaging features of 19 patients are summarized in Table I. The ages of the 19 patients ranged from 37 to 81 years (median 64 years), including nine males and 10 females. Of the 19 patients, five had lymphoma lesions located within the jejunum, and nine within the ileum. Two patients had lesions in multiple sites within the duodenum and jejunum, and three within the jejunum and ileum. These lymphoma lesions showed various macroscopic features including tumor mass, polyposis, diffuse infiltration and ulceration. In 16 patients CT scanning showed abnormal findings, including swellings of the small intestinal wall and abdominal lymph nodes. In three patients, however, no abnormal findings were observed [Figure 1(A)], whereas DBE clearly demonstrated lymphoma lesions macroscopically [Figure 1(B)] and pathologically [Figures 1(C)–1(E)]. Eighteen patients had disease-related symptoms such as abdominal pain, anorexia, anemia, tarry stool, diarrhea, weight loss and ileus. There was no relationship between

Table I. Clinical, pathological and CT imaging features of 19 patients with primary small intestinal lymphoma.

No.	Sex	Age	Histology	Primary site	Stage (Lugano)	IPI	Symptoms at onset	Abdominal lymph node lesion on CT	Mucosal mass lesion on CT	Initial therapy	Response to initial therapy
1	F	69	B cell	I/J	I	HI	Anemia, tarry stool	N	P	Not done	—
2	M	75	DLBCL	J/D	I	LI	Anemia, tarry stool	N	P	R-CHOP	NR
3	F	55	MALT	I	I	L	Abdominal pain	NA	NA	R-CHOP	CR
4	M	67	MALT	J	II	L	Anemia, tarry stool	Mesenterium	N	R-CHOP	CR
5	F	65	DLBCL	I/J	II	L	Abdominal pain, anorexia	Mesenterium	P	R-CHOP	PR
6	F	61	ND	I	IIE	LI	Diarrhea, abdominal pain	Mesenterium, paraaorta	N	CHOP	PD
7	F	64	MALT	I/J	I	L	Nausea, abdominal pain	N	N	R-CHOP	CR
8	M	50	DLBCL	I	I	LI	Diarrhea, abdominal pain	N	P	R-CHOP	CR
9	M	52	FL	J/D	II	L	Epigastralgia	Mesenterium	N	R-CHOP	PR
10	M	50	FL	J	II	L	Epigastralgia	Mesenterium	N	R-CHOP	CR
11	F	72	DLBCL	I	IIE	LI	Anemia, fever abdominal pain	Mesenterium	N	R-CHOP	CR
12	M	56	DLBCL	I	II	L	Ileus	Mesenterium	N	R-CHOP	CR
13	M	67	FL	I	I	LI	No symptoms	N	N	EMR	CR
14	F	67	FL	J	I	LI	Abdominal pain	N	N	R-CHOP	CR
15	F	52	FL	J	II	L	Epigastralgia	Mesenterium	P	R-CHOP	CR
16	M	81	DLBCL	I	II	HI	Anorexia, weight loss	Mesenterium, paraaorta	P	R-CHOP	PR
17	F	56	DLBCL	J	IV	LI	Anemia, bloody stool	Paraaorta	N	R-CHOP	CR
18	F	72	DLBCL	I	II	LI	Abdominal pain, weight loss	Mesenterium	P	R-CHOP	NR
19	M	37	DLBCL	I	I	L	Abdominal pain, anorexia	N	P	R-CHOP	CR

CT, computed tomography; F, female; M, male; DLBCL, diffuse large B-cell lymphoma; MALT, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue; ND, not defined; FL, follicular lymphoma; I, ileum; J, jejunum; D, duodenum; L, low risk; LI, low-intermediate risk; HI, high-intermediate risk; NA, not applicable; EMR, endoscopic mucosal resection; N, negative; P, positive; CR, complete response; PR, partial response; NR, no response; PD, progressive disease.

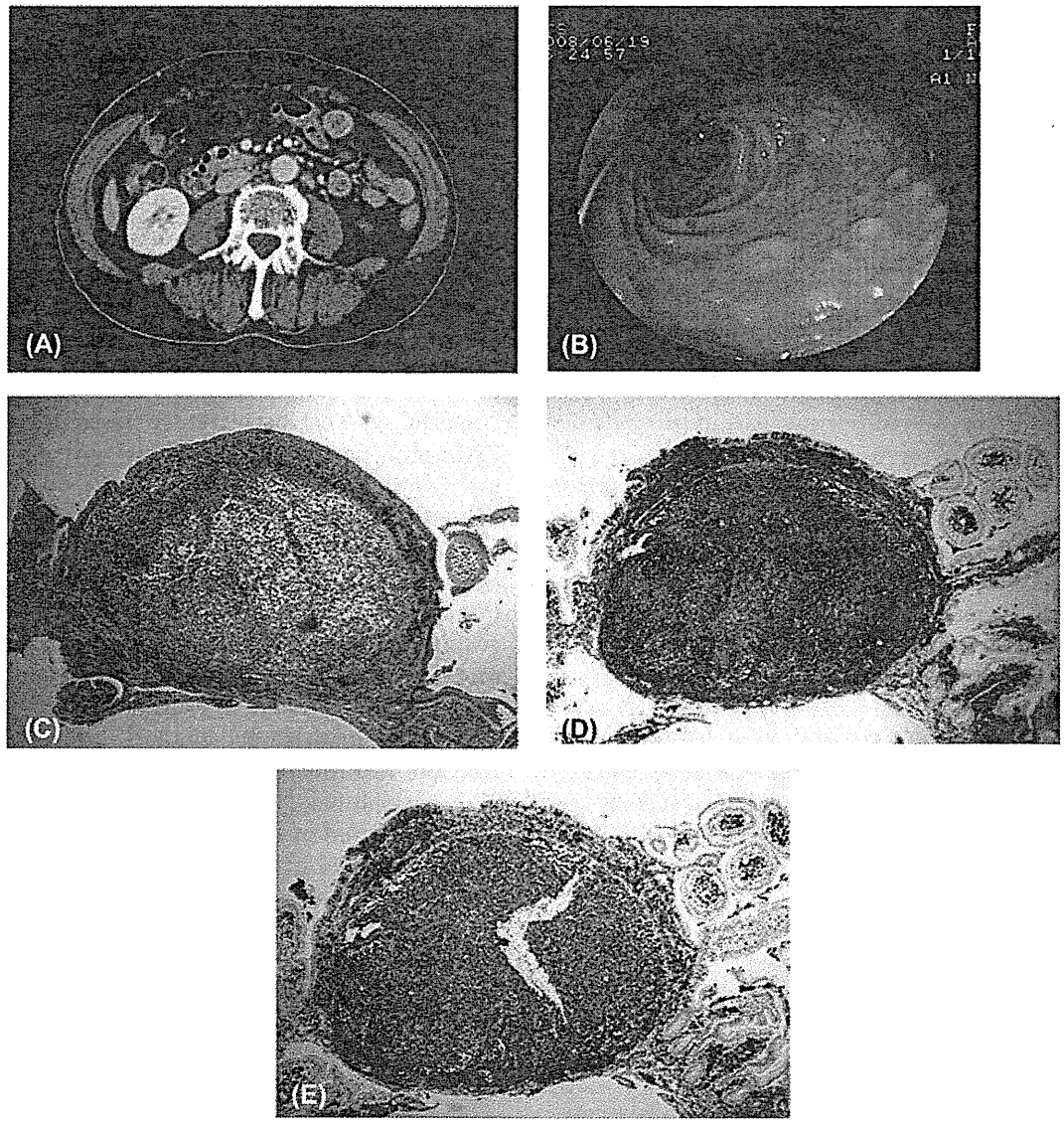

Figure 1. Radiographic, endoscopic and photomicrographic images of 67-year-old female patient admitted to our institution complaining of persistent abdominal pain. (A) Abdominal CT found no lymphadenopathy or mucosal mass lesion. (B) Double-balloon endoscopic view of jejunum revealed multiple ovoid, sessile and papular tumors with whitish granules. (C) Histopathological analysis of the biopsy specimen demonstrated that tumor cells formed a neoplastic follicle in the submucosal region of the jejunum (hematoxylin and eosin, ×100). (D) Immunohistochemical staining of lymphoid lesion was positive for CD20 (×100). (E) Immunohistochemical staining of lymphoid lesion was positive for BCL-2 (×100).

tumor location and these clinical symptoms. Most cases had localized disease (eight stage I, eight stage II, two stage IIE, one stage IV), and 17 patients had low or low-intermediate IPI scores.

Of the 19 cases of PSIL, nine (47.4%) were classified as DLBCL, five (26.3%) as follicular lymphoma (FL) and three (15.8%) as MALT. The remaining two patients could not be defined as having any certain histopathological subtype. One of these two cases was regarded as a B-cell lymphoma, because the tumor cells were positive for CD20 and negative for CD3 on immunostaining. The other case was negative for both CD20 and CD3, but was still regarded as lymphoma because amplifications of immunoglobulin heavy chain were detected on polymerase chain reaction.

Therapeutic response and prognosis

Among the 19 patients, 17 (89.5%) received chemotherapy, and one who was diagnosed with localized follicular lymphoma had curative endoscopic mucosal resection as initial treatment. One patient with B-cell lymphoma, in whom a definite histopathological subtype had not been obtained, died before treatment.

Of the patients treated with chemotherapy, one patient who did not have a definite histopathological diagnosis received cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) chemotherapy. The other 16 patients received R-CHOP (rituximab plus CHOP) chemotherapy. Responses to the initial chemotherapy in each histopathological subtype are summarized in Table II. The overall response rate (CR + PR) to the initial chemotherapy was 82.4% (14 of 17 patients) (95% confidence interval [CI] 56.6–96.2%). During chemotherapy, we experienced no case who needed emergent surgery for perforation or bleeding of mucosal lesions, and there were no patients who received salvage surgery after failure of initial chemotherapy.

Table II. Response to initial treatment ($n = 18$).

Initial treatment	n	Histology	Response	n
R-CHOP	9	DLBCL	CR	5
			PR	2
			SD	2
	4	FL	CR	3
			PR	1
	3	MALT	CR	3
CHOP	1	Not defined	PD	1
EMR	1	FL	CR	1

R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; EMR, endoscopic mucosal resection; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MALT, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Survival analysis was performed for all patients, with a median follow-up time of 41.3 months. The Kaplan–Meier curve for overall survival demonstrated that the estimated 5-year survival rate was 72.2% (95% CI 49.5–81.2%) [Figure 2(A)]. We next performed univariate analysis for survival rate. The analysis revealed that responses to the initial therapy (CR + PR vs. stable disease [SD] + progressive disease [PD]), hemoglobin (Hb) level (≥11.5 g/dL vs. <11.5 g/dL) and albumin (Alb) level (≥3.5 g/dL vs. <3.5 g/dL) were significantly correlated with overall survival by log-rank test [Figures 2(B)–2(D)]. Other clinical factors, such as age, sex, location of the primary site, clinical stage, IPI score and immunohistological phenotype, had no significant relationship to the survival rate.

Discussion

We report here a retrospective study conducted in a single institution involving 19 patients with PSIL who were diagnosed using DBE. The histopathological analyses in our study showed that most patients had B-cell lymphoma, which is consistent with previous findings that B-cell lymphoma such as DLBCL, MALT and follicular lymphoma is dominant, whereas T/natural killer (NK) type lymphoma is less often found in PSIL [4,11,28,30,31]. Importantly, diagnosis of PSIL was made for three patients for whom CT scanning demonstrated no abnormal findings. One of these patients had no symptoms, but he showed repeated positivity in fecal occult blood tests. This suggests that PSIL cannot be ruled out in patients with continuous abdominal symptoms or with fecal occult blood, even if there is no particular finding in CT scanning. Thus, DBE is a useful tool to obtain an accurate diagnosis less invasively in such cases. Moreover, it plays a role in assessment of response to chemotherapy. Indeed, DBE provided an appropriate evaluation of therapeutic effect for all patients, including those in whom pretreatment CT showed no lymphadenopathy and no mucosal mass lesion (cases 3, 7, 13, 14).

Previous reports have demonstrated a variety of macroscopic features observed in primary intestinal malignant lymphoma. These include tumor mass, polyposis, diffuse infiltration and ulceration [32]. Indeed, patients who were analyzed in this study showed a variety of these macroscopic features of lymphoma lesions. However, it

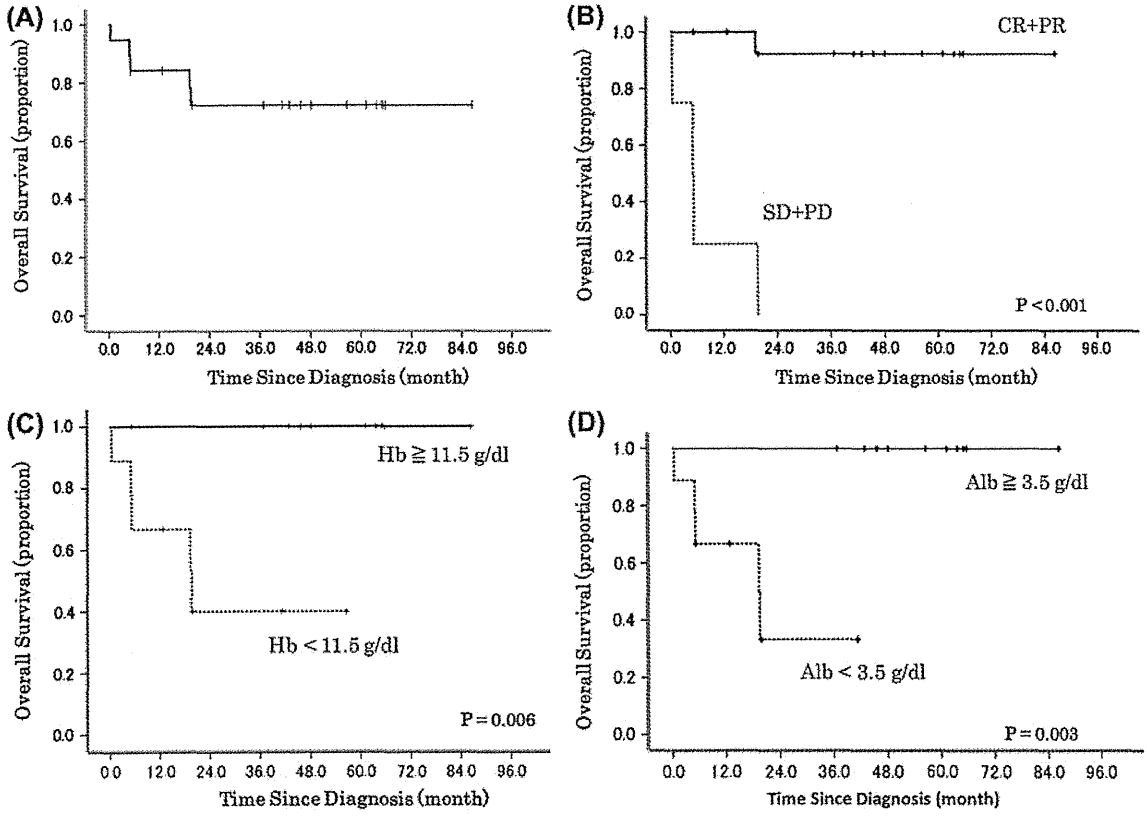

Figure 2. Kaplan–Meier curve analyses of overall survival (median follow-up time: 41.3 months). (A) OS of all 19 patients. Estimated 5-year OS was 72.2%. (B) OS according to response to initial therapy (CR + PR vs. NR + PD). (C) OS according to Hb level (Hb ≥11.5 g/dL vs. Hb <11.5 g/dL). (D) OS according to Alb level (Alb ≥3.5 g/dL vs. Alb <3.5 g/dL). OS, overall survival; CR, complete response; PR, partial response; NR, non-response; PD, progressive disease; Alb, albumin; Hb, hemoglobin.

has been shown that macroscopic features are not correlated with histopathological subtype [33], and our results showed that neither the macroscopic appearance nor the number of lesions was related to the clinical outcome. These results thus suggest that macroscopic features are not prognostic factors for patients with PSIL treated with chemotherapy.

The patients with PSIL in this study showed a favorable outcome, with high response rates to initial chemotherapy. Importantly, the clinical outcome is not inferior to that of a previous study, in which most cases had a surgical resection followed by chemotherapy [1,34]. Our results are consistent with the fact that surgery-based treatment does not have an advantage over chemotherapy alone in primary gastric lymphoma [35,36]. However, there are also some reports showing that the combination of surgical resection and postoperative chemotherapy achieved a favorable outcome for primary intestinal DLBCL [20,37]. The reasons for this discrepancy are unknown; however, it might be because of the different locations and histopathological types of diseases between patients in our study and those in previous studies. Indeed, more than half of the patients analyzed in previous studies had ileocecal-origin lymphoma, which was excluded in our study.

Our study also revealed that the levels of Hb and Alb at the time of diagnosis were strongly correlated with overall survival. Interestingly, there was a tendency toward negative correlation in levels between those factors and C-reactive protein (CRP) ($r = -0.583$, $p = 0.009$ and $r = -0.670$, $p = 0.002$, respectively). This result suggests that the level of inflammation is involved in the clinical outcome of patients with PSIL.

In our study, we showed that PSIL could be diagnosed by DBE and effectively treated with chemotherapy alone. However, surgical resection still has clinical value in the treatment of PSIL. Indeed, there were two patients in whom a definite histopathological subtype could not be determined, probably due to insufficient specimens of mucosal biopsy. In these cases, we performed chemotherapy because a diagnosis of malignant lymphoma was made. However, if a sufficient biopsy sample to diagnose malignant lymphoma could not be obtained by DBE, surgical resection might be required. Furthermore, Kim *et al.* reported that a few cases of patients with PSIL who received chemotherapy as initial treatment underwent later surgery because of chemotherapy-related complications or disease control [20].

Capsule endoscopy is another tool for observing PSIL lesions without physical burden. However, biopsy specimens for histopathological analysis cannot be obtained by this method. Capsule endoscopy is contraindicated in cases where there is a stricture of the small intestine [38], whereas DBE can explore and traverse such a region. In this regard, DBE might have an advantage over capsule endoscopy in diagnosis and treatment of PSIL.

In conclusion, DBE sheds new light on the diagnosis of PSIL. By using this technology, PSIL can be diagnosed less invasively compared with conventional surgical resection. In most cases, DBE can confirm the final diagnosis of PSIL with immunohistopathological studies of a mucosal biopsy. Furthermore, DBE makes it easy to evaluate tumor distribution in the total intestine and response to chemotherapy. The results of our study also suggest that PSIL can achieve a good prognosis with chemotherapy alone. Further prospective investigation with larger sample numbers is warranted to establish the optimal therapeutic approach for PSIL.

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Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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Letter to the Editor

Autologous Hematopoietic Recovery with Aberrant Antigen Expression after Allogeneic Bone Marrow Transplantation

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Keywords: bone marrow transplantation, rejection, antigen expression, myelodysplastic syndrome

TO THE EDITOR

A 50-year-old woman was admitted in December 2006 with progressive petechiae. Bone marrow (BM) aspiration showed massive proliferation of leukemic myeloblasts with myeloperoxidase staining. Three-color flow cytometry (FCM) with a CD45 gate for the BM cells was performed in our laboratory[1]; the blasts were positive for CD7, CD11c, CD13, CD15, CD33, myeloperoxidase and HLA-DR and negative for CD34 and CD117. Karyotypes of the BM cells were normal. A diagnosis of acute myeloblastic leukemia (AML)-M2 was made on the basis of French-American-British classification. The patient needed standard induction chemotherapy twice to achieve complete remission. Refractoriness to platelet transfusions due to anti-HLA antibody developed. She received an allogeneic BM transplant from an ABO-matched and HLA-DR-mismatched unrelated female donor in September 2007. The conditioning regimen consisted of total body irradiation (2 Gy twice daily for 3 days) followed by cyclophosphamide (60 mg/kg/day for 2 days). On day 0, 4.0×10^8 BM cells per recipient body weight were infused. Tacrolimus and short-course methotrexate were used as prophylaxis for graft-versus-host disease. After BM transplantation, severe pancytopenia persisted. BM aspiration on day 22 revealed marked hypocellularity, suggesting graft rejection. Peripheral blood neutrophils gradually increased from day 50. BM aspiration smears on day 75 showed recovery of the BM cells, especially myeloid cells, without significant morphologic abnormalities and proliferation of myeloblasts, indicating that complete remission was maintained. Chromosomal analysis of the BM cells showed various cytogenetic abnormalities (Table 1). A chimerism-based analysis of the BM cells using short tandem repeat-polymerase chain reaction showed that 100% of the cells originated from the recipient. A diagnosis of autologous (recipient) hematopoietic recovery after graft rejection was made. Multiparametric FCM based on a four-color method (ReproCELL, Yokohama, Japan), which had been approved by the Jichi Medical University Institutional Review Board (no. 06-70), did not show the abnormal expression of antigens in the blasts in the BM on days 75 and 183. However, it showed small populations of $CD34^+CD7^+$ cells and $CD34^+CD15^+$ cells in the blasts on day 253 (Fig. 1). The latter cells were characterized by a high intensity of CD34, which indicates abnormal expression of the antigen. BM aspiration was performed every three to six months; various chromosomal abnormalities of BM cells were found in each sample (Table 1). After day 253, routine three-color FCM instead of the multiparametric FCM was conducted to analyze phenotypes of the blasts in the BM. This FCM can detect $CD34^+CD7^+$ cells but not $CD34^+CD15^+$ cells because of antibody combinations. The proportions of $CD34^+CD7^+$ cells among the blasts of the BM were as follows: on day 323, 37.2%; on day 421, 30.9%; on day 603, 35.5%; on day 785, 21.5%; on day 975, 49.2%; on day 1,149, 36.0%; and on day 1,232, 24.5%. Although chromosomal abnormalities were detected on and after day 75, obvious dysplastic features associated with myelodysplastic syndrome (MDS) were not found. The patient is clinically well with normal peripheral blood cell counts.

There are several reports on autologous (recipient) hematopoietic recovery after allogeneic hematopoietic stem cell transplantation.[2-6] All patients received total body irradiation

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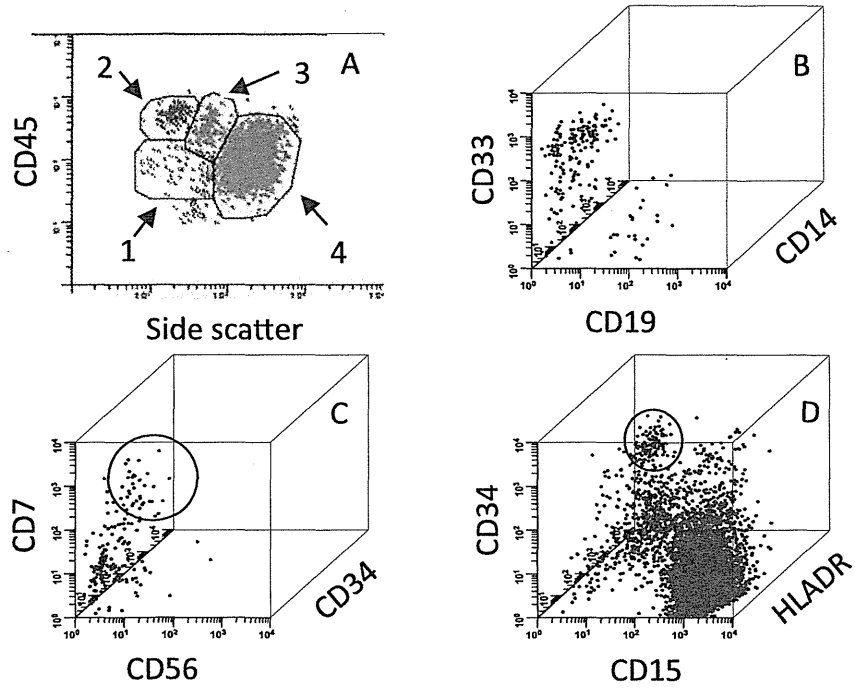

Fig. 1. Flow cytometric analysis of bone marrow cells on day 253 after bone marrow transplantation. 1, blasts ; 2, lymphocytes ; 3, monocytes ; 4, granulocytes. Antigen levels in the blasts are plotted in *1B* (right upper), *1C* (left lower) and *1D* (right lower), while those in granulocytes are plotted in *1D*. The cycle indicates the blasts expressing abnormal antigens.

with a total of 12 Gy or more as conditioning. In these patients, various chromosomal abnormalities in the BM cells were found to be associated with autologous hematopoietic recovery. Because chromosomal abnormalities in these patients were random and not related to the patients' underlying diseases, such aberrations indicate that normal hematopoietic progenitors may have been injured by the irradiation used for conditioning. In our case, various chromosomal abnormalities were found concomitantly with small populations of $CD34^+CD7^+$ cells and $CD34^+CD15^+$ cells in the BM, which have been used as markers for aberrant antigen expression in AML.[7-10] Taking these findings together, the $CD34^+CD7^+$ cells and $CD34^+CD15^+$ cells in the blasts of our patient were derived from injured normal hematopoietic progenitors that have self-renewal activity. Although the reason why neither $CD34^+CD7^+$ cells nor $CD34^+CD15^+$ cells were detected on day 75 or 183 is not known, it may be due to clonal changes to the injured hematopoietic stem cells. To the best of our knowledge, there is no report on progression to MDS or AML in patients who showed autologous hematopoietic recovery.[2-6] It is necessary to follow up the patient carefully for the long term to clarify whether the disappearance of $CD34^+CD7^+$ cells in the BM leads to the normalization of BM karyotypes or an increase in these cells causes hematopoietic diseases including MDS and AML.

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Table 1. Karyotypes of the bone marrow cells before and after bone marrow transplantation

Day	Karyotype
At diagnosis	46, XX (20/20)
Day-14	46, XX (20/20)
Day 22	No metaphases because of insufficient specimen
Day 75	46, X, -X, add(1)(p32), -5, add(6)(q21), add(11)(p15), +mar1 (4/16)
	46, XX, -8, del(15)(q22), +mar2 (2/16)
	46, XX (10/16)
Day 183	45-46, X, X, -2, -6, -10, -16, -22, +1-3mar (8/20)
	46, XX (12/20)
Day 253	46, XX, add(7)(p11) (7/17)
	46, XX, add(7)(q32) (5/17)
	46, XX, t(3;15)(q29;q15) (1/17)
	46, XX(4/17)
Day 323	No metaphases because of insufficient specimen
Day 421	46, XX, -3, add(7)(q32), +1 (3/5)
	46, XX (2/5)
Day 603	46, XX, -3, add(7)(q32), +1-5mar (3/5)
	46, XX (2/5)
Day 785	45, XX, add(11)(p15), -22, +mar (4/9)
	46, XX, del(10)(q24) (3/9)
	44-45, XX, add(7)(q36) (2/9)
Day 975	46, XX, add(3)(q23), add(7)(q32) (2/6)
	46, XX (4/6)
Day 1,149	45-46, XX, -7, -9, +1-8mar (4/7)
	46, XX (3/7)
Day 1,232	46, XX (3/4)
	AK (1/4)

AK, unidentified abnormal karyotypes.
The numerators and denominators in parentheses indicate identified karyotype numbers and total metaphase numbers.

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ORIGINAL ARTICLE: CLINICAL

Rituximab plus 70% cyclophosphamide, doxorubicin, vincristine and prednisone for Japanese patients with diffuse large B-cell lymphoma aged 70 years and older

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Abstract

In the rituximab era, several large studies have suggested that full-dose rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) might be the best treatment for patients with diffuse large B-cell lymphoma (DLBCL) aged 60 years and older. However, it remains unclear whether this is also the case for those aged 70 years and older. Previously untreated patients with DLBCL aged 70 years and older (elderly) were treated with R-70%CHOP, and patients younger than 70 years (younger) were treated with full-dose R-CHOP every 3 weeks, for a total of 6–8 cycles. Complete remission (CR) rates in elderly versus younger patients were 75 vs. 78% ($p = 0.7$), respectively. The 3-year overall survival, event-free survival and progression-free survival of elderly versus younger patients were 58 vs. 78% ($p < 0.05$), 45 vs. 70% ($p < 0.05$) and 64 vs. 72% ($p = 0.43$), respectively. Severe adverse events were more frequent in the elderly, even with the dose reduction in that age group. Three-year PFS with R-70%CHOP for patients aged 70 years and older was not significantly worse than that with full-dose R-CHOP for younger patients, suggesting that R-70% CHOP might be a reasonable choice for patients with DLBCL aged 70 years and older, especially for those with comorbidities.

Keywords: DLBCL, dose reduction, elderly, R-70%CHOP

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive lymphoma worldwide [1]. Applying gene expression profiling to DLBCL enables subclassification of the disease into three groups, activated B-cell type, germinal center B-cell type and primary mediastinal B-cell lymphona [2–4]. The activated B-cell type has a poorer prognosis than the germinal center B-cell type, even after the introduction of rituximab [5]. However, gene profiling is not used in daily clinical practice due to technical and financial limitations. In contrast to gene profiling, the International Prognostic Index (IPI) consists of easily assessable clinical parameters and is widely used [6]. As a part of the IPI, age is an established prognostic factor for patients with aggressive lymphoma, especially for those with DLBCL [7,8]. Even in the rituximab era, age is still a prognostic factor [9]. Although a dose reduction of chemotherapy has been a frequent approach for the treatment of DLBCL in clinical practice, particularly in patients aged 60 years and older [10], two recent large studies have recommended full-dose rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) for elderly patients with DLBCL [11–13].

The present study aimed to investigate whether dose reduction still has a role in the treatment of DLBCL for the specific subgroup of patients aged 70 years and older. The "elderly" age category in previous studies has been defined as 60 years and older. However, recent excellent outcomes with full-dose R-CHOP [11,12] have suggested that an age of 60 years might be too young to benefit from a dose reduction. Thus, in the present study, full-dose R-CHOP was chosen for younger patients up to 69 years old, and R-70%CHOP (70% cyclophosphamide, doxorubicin, vincristine and prednisone) was chosen for patients 70 years and older. It is still unclear whether dose-reduced R-CHOP is able to achieve as good a response as full-dose R-CHOP, and how much of a dose reduction is appropriate in order to achieve the best efficacy and safety. The present

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study retrospectively assessed efficacy and safety of R-70% CHOP for patients with DLBCL aged 70 years and older.

Materials and methods

Patients

This study was a retrospective analysis of patients with DLBCL treated in a single center, Jichi Medical School (Tochigi, Japan). A patient database has been collected by the Division of Hematology from 1997, and it includes all inpatients in the Division with any hematological disease. All ambulatory emergent patients are included in this database. Study inclusion criteria were as follows: patients diagnosed as DLBCL according to the World Health Organization (WHO) 2001 classification [14], treated for the first time between December 2003 and June 2010, aged 70 years and older, and treated with R-70%CHOP at least once. For comparison, younger patients with DLBCL aged 50–69 years treated with full-dose R-CHOP were also included in the study. We classified the two groups only according to age. Patients with DLBCL younger than 50 years old were excluded from the study. As we perform the first cycle of R-CHOP on an inpatient basis, this study theoretically includes all patients with DLBCL who have been treated in our hospital. Unfortunately, we could not determine how many patients were not treated without admission due to poor performance status or any other reason. Patients referred after first-line treatment, transformed from indolent lymphoma, diagnosed as having Burkitt lymphoma, Burkitt-like lymphoma or post-transplant lymphoproliferative disease, treated with radiation therapy alone and treated without doxorubicin (R-CVP, etc.) were excluded from this study. Routine examination included chest and abdominal X-ray, electrocardiogram, complete blood count, laboratory tests for nutrition and renal and hepatic function, bone marrow aspiration/biopsy, and chest and abdominal computed tomography (CT) scans. Echocardiograms were performed in most of the patients. Fluorodeoxyglucose positron emission tomography (FDG-PET) scans were routinely performed after 2004 for initial staging and evaluation of response.

Treatment

A dose of standard R-CHOP (rituximab 375 mg/m^2 at any time point, cyclophosphamide 750 mg/m^2 on day 1, doxorubicin 50 mg/m^2 on day 1, vincristine 1.4 mg/m^2 on day 1, prednisone 50 mg/m^2 on days 1–5) was reduced to 70%, except for the rituximab. Dose reduction was applied to only elderly patients, aged 70 years and older, and all other patients were primarily treated with standard R-CHOP without dose reduction. Further dose reduction might have been selected by a responsible physician in a small proportion of patients likely due to bulky mass or poor performance status. Patients with the disease at a limited stage were free to select either combined modality treatment or 6–8 cycles of chemotherapy alone. A subcutaneous injection of granulocyte-colony stimulating factor (G-CSF) was primarily performed when the neutrophil count was below 1×10^9/L.

Endpoints and assessment of response

Event-free survival (EFS) was calculated from the date of diagnosis to events; events were defined as progressive disease (PD) during treatment, new alternative treatment, PD after stable disease (SD), PD after partial remission (PR), relapse, death during treatment and death after treatment. Progression-free survival (PFS) was calculated from the date of diagnosis to disease progression or death from lymphoma. Death in complete remission (CR) due to disease not related to lymphoma was censored, as described previously [11,12]. This censoring enabled comparison of the

Table I. Characteristics of patients.

	R-70%CHOP ($n=61$)		R-CHOP ($n=69$)		
Characteristic	*n*	%	*n*	%	*p*-Value
Age, years					
70–79	46	75.4			
80–	15	24.6			
50–59			31	44.9	
60–69			38	55.1	
Sex					0.89
Male	37	60.7	41	59.4	
Female	24	39.3	28	40.6	
Performance status*					0.87
0–1	43	70.5	47	68.1	
≥2	18	29.5	21	30.5	
Unknown			1	1.4	
Stage					<0.05
I	9	14.8	24	34.8	
II	25	40.9	12	17.4	
III	7	11.5	7	10.1	
IV	20	32.8	26	37.7	
B symptoms†	16	26.2	18	26.1	
No. of extranodal sites					0.99
0	23	37.7	12	17.4	
1	26	42.6	34	49.3	
≥2	12	19.7	22	31.9	
Unknown			1	1.4	
Bulky tumor	7	11.5	11	15.9	0.46
Bone marrow involvement	3	4.9	9	13	0.11
Elevated LDH	40	65.6	44	63.8	0.83
Age-adjusted IPI score					0.57
0	16	26.2	15	21.7	
1	20	32.8	25	36.3	
2	17	27.9	14	20.3	
3	8	13.1	14	20.3	
Unknown	0		1	1.4	
Standard IPI score					<0.01
0–1	14	22.95	32	46.4	
2	17	27.9	13	18.9	
3	14	22.95	5	7.2	
4–5	16	26.2	18	26.1	
Unknown	0		1	1.4	
Revised IPI score					<0.01
Very good	0		5	7.2	
Good	31	50.8	40	58	
Poor	30	49.2	23	33.4	
Unknown	0		1	1.4	
Auto-PBSCT	0		5	7.25	
Radiation‡	10	16.4	15	21.7	0.44
Combined modality§	6	9.8	9	13	0.57

R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; LDH, lactate dehydrogenase; IPI, International Prognostic Index; PBSCT, peripheral blood stem cell transplant.
*Performance status was defined according to criteria of the Eastern Clinical Oncology Group.
†B symptoms were defined as weight loss, fever and night sweats.
‡Any type of radiation including combined modality.
§R-CHOP × 3-4 + involved field radiation therapy.

Table II. Comorbidity.

	R-70%CHOP		R-CHOP		
	n	%	*n*	%	*p*-Value
Hypertension	25	41	14	20.3	<0.05
Hyperlipidemia	8	13.1	6	8.7	0.42
Diabetes mellitus	9	14.8	5	7.2	0.17
Cerebral vascular disease	3	4.9	4	5.8	0.82
Cardiac disease	8	13.1	5	7.2	0.27
Viral hepatic disease	3	4.9	6	8.7	0.4
Pulmonary disease	3	4.9	0	0	0.06
Renal disease	3	4.9	0	0	0.06
Tuberculosis	1	1.6	2	2.9	0.63
Collagen disease	0	0	2	2.9	0.18
Malignancy	10	16.4	4	5.8	0.05
Others	2	3.3	2	2.9	0.09

R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone.

Table III. Number of R-CHOP courses and G-CSF injections.

	R-70%CHOP ($n=61$)			R-CHOP ($n=69$)		
	Range	Average	Median	Range	Average	Median
Rituximab (inpatient)	1–8	2	1	1–8	1.38	1
Rituximab (outpatient)	0–7	3.44	4	0–7	4.81	5
CHOP (inpatient)	1–8	2	1	1–8	1.4	1
CHOP (outpatient)	0–7	3.44	4	0–7	4.76	5
Total number of G-CSF injections	0–73	10.2	7	0–56	11.27	8
Cycles using G-CSF/total cycles (%)		64			75	
Dose intensity (%)*		85			97	
Less than 90% dose†		26			13	

R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; G-CSF, granulocyte-colony stimulating factor.
*Actual dose/full dose or 70% dose according to patient age × 100 (%).
†More than 10% reduction from planned dose.

PFS of elderly patients with that of younger patients. Overall survival (OS) was calculated from the date of diagnosis until death from any cause or the last date confirmed alive. Response was judged by each physician according to the International Workshop Criteria [15] or revised International Workshop Criteria [16].

Statistics

OS, PFS and EFS curves were obtained by the Kaplan–Meier method and compared with the log-rank test. For variables, Fisher's test or the χ^2 test was used for *p*-value analysis. Cox regression models were prepared for hazard ratios associated with treatment dose in the presence of covariates such as age and IPI. We did not include stage in the regression model because it is already included in the IPI. All statistical calculations were performed with the software Statmate, version 6.0 (Tokyo, Japan).

Results

Patient characteristics

A total of 61 patients who met the inclusion criteria and were aged 70 years and older (elderly group) were treated with R-70%CHOP. A total of 69 patients who met the inclusion criteria and were aged 50–69 years (younger group) were treated with full-dose R-CHOP. The median follow-up for the elderly group was 36 months and for the younger group was 41 months. Median ages at diagnosis in the elderly and younger groups were 76 and 61 years, respectively. Stage, age-adjusted IPI (aaIPI), standard and revised IPI, autotransplant and combined modality with radiation were assessed between the two groups (Table I). Gender, performance status, number of extranodal sites, bulky tumor, bone marrow involvement, elevated lactate dehydrogenase (LDH) and aaIPI in elderly and younger patients were comparable ($p=0.89$, 0.87, 0.99, 0.46, 0.11, 0.83 and 0.57, respectively). The frequency of additional radiotherapy in elderly and younger patients was also comparable (16 vs. 22%, $p=0.44$, Table I). The elderly group contained fewer patients with stage I and more patients with stage II disease than the younger group; however, the proportions of patients with extended stage (III–IV) and limited stage (I–II) were comparable ($p=0.68$). The distribution of standard IPI was significantly different between the two age groups ($p<0.01$); the elderly group contained fewer IPI-low patients than the younger group (23 vs. 46%), and the elderly group contained more high-intermediate patients than the younger group (23 vs. 7%). Distribution of the revised IPI was also significantly different ($p<0.01$). This difference was most likely because no patients in the elderly group could be classified as "very good," simply due to age. The number of patients who received combined modality is indicated in Table I (six patients in the elderly group and nine patients in the younger group). Autotransplant was performed only in the younger group, at a frequency of 7.2%, and could have increased the OS in the younger group. Taken together, there were no differences between the two age groups in prognostic factors when the aaIPI was applied.

The most frequent pre-existing comorbidity in elderly patients was hypertension ($p<0.05$), but pulmonary disease, renal disease and other malignancies tended to be more frequent in elderly patients ($p=0.05$–0.06, Table II).

Table IV. Hematological toxicities*.

	R-70%CHOP		R-CHOP		
	n	%†	*n*	%†	*p*-Value
Leukocytopenia					
Grade 3	18	29.5	13	18.8	0.15
Grade 4	37	60.7	53	76.8	<0.05
Thrombocytopenia					
Grade 3	2	3.3	3	4.3	0.75
Grade 4	5	8.2	3	4.3	0.36
Anemia					
Grade 3	7	11.5	11	15.9	0.46
Grade 4	3	4.9	4	5.8	0.82
Red blood cell transfusions	6	9.8	5	7.2	0.62
Platelet transfusions	3	4.9	2	2.9	0.55

R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone.
*Grade was determined according to National Cancer Institute Common Toxicity Criteria.
†Number of patients/total number of patients in treatment group × 100 (%).

Table V. Non-hematological toxicities*.

Event	Any grade, n (%†)			Grade 3 or 4, n (%†)		
	R-70%CHOP	R-CHOP	p-Value	R-70%CHOP	R-CHOP	p-Value
Fever	18 (29.5)	17 (24.6)	0.53	16 (26.2)	16 (23.2)	0.69
Infection	10 (16.4)	5 (7.2)	0.1	5 (8.2)	3 (4.3)	0.36
Mucositis	1 (1.6)	0	0.29	1 (1.6)	0	0.29
Liver toxicity	0	1 (1.4)	0.35	0	0	
Cardiac toxicity	1 (1.6)	0	0.29	1 (1.6)	0	0.29
Neurologic toxicity	10 (16.4)	10 (14.5)	0.76	3 (4.9)	0	0.06
Renal toxicity	6 (9.8)	0	<0.01	5 (8.2)	0	<0.05
Lung toxicity	1 (1.6)	0	0.29	0	0	
Nausea or vomiting	11 (18)	4 (5.8)	<0.05	2 (3.3)	0	0.13
Constipation	31 (50.8)	34 (49.3)	0.86	8 (13.1)	2 (2.9)	<0.05
Other toxicities	6 (9.8)	2 (2.9)	0.1	4 (6.6)	2 (2.9)	0.32

R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone.
*Grade was determined according to National Cancer Institute Common Toxicity Criteria.
†Number of patients/total number of patients in treatment group × 100 (%).

Treatment

The average number of cycles of R-70%CHOP for elderly patients versus full-dose R-CHOP for younger patients was 5.4 vs. 6.2 courses, respectively (Table III). This difference in number of courses suggests that physicians might have halted treatment sooner in elderly patients. The numbers and frequency of G-CSF injections were comparable between the two groups (Table III). The proportion of the actual dose delivered to patients per planned dose was calculated in each group and was 85% vs. 97%, respectively (Table III). Concerning relative dose intensity, less than 90% of the planned dose was administered in 26% and 13% of elderly and younger patients, respectively. The number of patients treated with only one cycle of R-CHOP was seven in the elderly group. These included a patient whose disease was complicated with cerebral infarction, a patient subjected to salvage chemotherapy due to poor response, a patient complicated by severe paralytic ileus, a patient who was judged intolerant by a responsible physician and three other patients, who discontinued by self-judgement.

Complications

Hematological toxicities are listed in Table IV. Grade 4 leukocytopenia was more frequent in the younger group compared to the elderly group (61 vs. 77%, respectively, $p < 0.05$), suggesting that the dose reduction in the elderly group reduced the frequency of grade 4 leukocytopenia. In contrast, the incidence of grade 3–4 thrombocytopenia and anemia was comparable between the two groups.

Table VI. Response to treatment.

Response	R-70%CHOP ($n = 61$)		R-CHOP ($n = 69$)	
	n	%	n	%
Complete response	46	75.4	54	78.3
Unconfirmed complete response	2	3.3	0	0
Partial response	5	8.2	4	5.8
Stable disease	2	3.3	0	0
Progressive disease	3	4.9	8	11.6
Could not be assesed*	3	4.9	3	4.3

R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone.
*Treatment was discontinued due to side effect, patient's self-judgement, decision or responsible physician's decision, before evaluation.

Non-hematological toxicities are shown in Table V. The frequency of fever and infection was comparable in both groups despite the dose reduction. Renal insufficiency and grade 3–4 constipation, including paralytic ileus most likely due to vincristine, were more frequent in elderly patients (Table V). These results suggest that severe complications tended to be more frequent in the elderly patients despite the dose reduction.

Outcome

Complete remission rates including complete remission unconfirmed (CRu) in elderly and younger patients were 79 vs. 78%, respectively ($p = 0.7$, Table VI). In the elderly and younger patients, overall response rates were 87 vs. 84% ($p = 0.65$) and PD rates were 5 vs. 12% ($p = 0.17$), respectively. These results suggest that the dose reduction in elderly patients did not exacerbate the short-term response.

Long-term response was the endpoint of the present study. According to the Japanese median life span (79 years for males, 86 years for females), for example a 75-year-old male can theoretically expect to live only 4 additional years on average. Reflecting this population-based average, none of the younger patients in CR died during the observation period, but eight of the elderly patients in CR died due to reasons other than lymphoma (Table VII). Therefore, the deaths in CR were censored from PFS analysis, because the frequency of death in CR was quite different between the elderly and younger groups (13 vs. 0%, respectively, $p < 0.01$). In fact, this was the most striking difference in events (Table VIII).

According to Kaplan–Meier analysis, in the elderly and younger groups, 3-year OS was 58 vs. 78% ($p < 0.05$), EFS

Table VII. Causes of death in complete remission.

Patient	Age	Survival (months)	Cause of death
8	73	12	Cerebral infarction
19	77	9	Rupture of an abdominal aortic aneurysm
28	80	24	Colon cancer
47	78	7	Failure of multiple organs
48	80	27	Renal failure
53	71	28	Acute myelocytic leukemia
68	83	28	Uterine cervical cancer
69	85	30	Pulmonary tuberculosis

Table VIII. Events*.

Event	R-70%CHOP n	R-70%CHOP %	R-CHOP n	R-CHOP %	p-Value
PD during treatment	3	4.9	8	11.6	0.17
New alternative treatment	4	6.6	1	1.4	0.13
PD after SD	1	1.6	0		0.29
PD after PR	3	4.9	4	5.8	0.82
Relapse	10	16.4	8	11.6	0.43
Death without progression					
During treatment	3	4.9	1	1.4	0.25
After treatment	7	11.4	0		<0.01
Could not be assessed	0		1	1.4	
All events	31	50.8	23	33.3	<0.05
No event	30	49.2	46	66.7	
Total patients	61		69		

R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; PD, progressive disease; SD, stable disease; PR, partial response.
*All events during observation period are listed.

was 45 vs. 70% ($p < 0.05$) and PFS was 64 vs. 72% ($p = 0.43$), respectively (Figure 1). The difference in PFS did not reach statistical significance at 3 years. In contrast, both OS and EFS in the elderly group were inferior to those in the younger group, most likely due to the eight deaths in CR.

Seven patients were refractory to R-70%CHOP and subjected to salvage chemotherapy in the middle or soon after R-70%CHOP. All of them were IPI-high. Except for one case, all cases died because of the lymphoma.

Finally, we performed multivariate analysis using a Cox regression model for PFS (Table IX). Parameters included chemotherapy, IPI and age but not stage, as IPI *per se* contains stage. Both the hazard ratio and *p*-value of chemotherapy for PFS were very close to 1.0, suggesting that R-70%CHOP in the elderly age group was not inferior

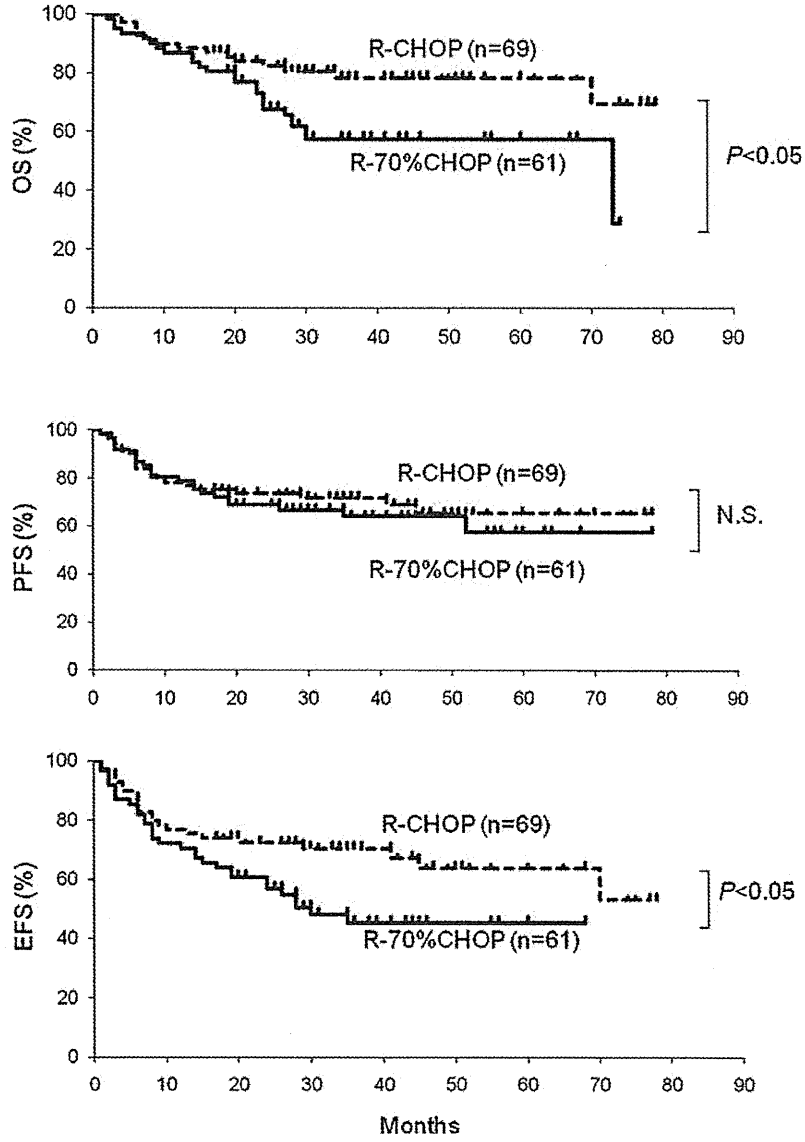

Figure 1. Overall survival (OS), progression-free survival (PFS) and event-free survival (EFS) at 3 years. OS and EFS include all patients, but in PFS, eight deaths in continuous complete remission (CR) due to reasons other than lymphoma were censored.

Table IX. Multivariate analysis for progression.

Parameter	Hazard ratio*	95% CI	*p*-Value
Chemotherapy: R-CHOP vs. R-70%CHOP	1.05	0.43–2.55	0.92
IPI			
2–3 vs. 1	0.86	0.53–1.40	0.53
4 vs. 1	0.98	0.49–1.98	0.95
Age (years)	1.02	0.97–1.06	0.48

R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; IPI, International Prognostic Index; CI, confidence interval.
*Hazard ratios are adjusted for all other variables in the table.

to R-CHOP in the younger age group, even if the sample size was expanded and even though there were differences in IPI and age.

Discussion

We have historically reduced doses of CHOP at random to 70%, 75% and 80%. The 70% dose was chosen for elderly patients in this study, because 70% would mean that patients could come to hospital less frequently for G-CSF injections in most cases. In fact, the average number of G-CSF injections in the elderly group was comparable to that in the younger group (Table III).

In the present study, the 3-year PFS of R-70%CHOP for elderly patients with DLBCL was not significantly worse than that of R-CHOP for younger patients. This is the first report to present evidence that the 70% dose may be feasible for older patients, and it was accompanied by a reasonably fair outcome, although our study has several limitations: age-mismatch comparison, retrospective study and limited number of patients.

The 2-year outcomes in the present study, an OS of 68% and EFS of 57% for patients aged 70 years and older, were comparable to those of the previously published Groupe d'Etude des Lymphomes de l'Adulte (GELA) LNH-98.5 study [11], in which full-dose R-CHOP was applied for patients aged 60–80 years. Their 2-year outcomes were an OS of 70% and EFS of 57%. However, direct comparison is difficult, because only half of the patients in that study were aged 70–80 years. The authors of that report published follow-up data [12] that included 5-year outcomes of an OS of 58% and EFS of 47%. Compared to these results, the present results appear to be slightly inferior, as the outcomes at 3 years in the present study are already close to their 5-year outcomes. One of the reasons for the inferior results at 3 years but not 2 years could be that four patients (7%) in the present study died in CR due to reasons other than lymphoma between 25 and 36 months (Table VII). As expected, the younger group (50–69 years old) in the present study showed better results at 3 years, with an OS of 78% and EFS of 70%. This suggests that 70 years might be an appropriate cut-off age for reduced-dose therapy. Biweekly R-CHOP14 for patients with DLBCL aged 61–80 years (RICOVER-60) showed better results compared to the present study [13]. However, patient characteristics were quite different: that study included 5% of patients with follicular lymphoma, only 80% of patients were diagnosed as having DLBCL and only 36% of patients were aged 70–80 years. Moreover, other studies following this regimen did not show any benefits of biweekly R-CHOP14 over standard R-CHOP21 [17]. To conclude that R-70%CHOP is not inferior to full-dose R-CHOP for patients aged 70 years and older, a randomized, prospective, multicenter study might be required.

In clinical practice, we have historically chosen a dose reduction of CHOP for patients aged 70 years and older, before and after the introduction of rituximab. As the present study suggests, patients aged 70 years and older sometimes have severe complications despite receiving dose-reduced therapy (Table V). However, there are no established data to support dose reduction in the rituximab era, and the appropriate dose and efficacy are unknown. Recent publications have suggested using full-dose R-CHOP for patients aged 60–80 years, but this regimen might not be optimal for all patients, especially those aged 70 years and older. The more severe complications in the elderly group in the present study suggested that the reduced dose was still near the maximum dose for the patients, and most likely was due to slower pharmacokinetics in older patients [18]. Additional dose modification or patient selection according to comorbidities may be needed. Moreover, as there is a 7-year difference in average life span between men and women in Japan, gender-dependent modification may be also needed.

In summary, the present study provides new evidence for physicians and hemato-oncologists considering dose-reduction for elderly patients with DLBCL, especially those with comorbidities.

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