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CD5-positive diffuse large B-cell lymphoma: a retrospective study in 337 patients treated by chemotherapy with or without rituximab

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Background: CD5-positive (CD5+) diffuse large B-cell lymphoma (DLBCL) shows poor prognosis and frequent central nervous system (CNS) relapses under anthracycline-containing chemotherapy. The aim of this study was to determine the prognosis and CNS relapse incidence of CD5+ DLBCL in the rituximab era.

Patients and methods: We analyzed 337 patients with CD5+ DLBCL who received chemotherapy with (R-chemotherapy group; $n = 184$) or without (chemotherapy group; $n = 153$) rituximab.

Results: No significant difference was found in clinical background comparisons between the two groups. In the R-chemotherapy group, 60% of the patients were older than 65 years at diagnosis. Both the complete response rate and overall survival (OS) were significantly better in the R-chemotherapy group ($P = 0.0003$ and $P = 0.002$, respectively). Multivariate analysis confirmed that chemotherapy without rituximab was associated with unfavorable OS. However, the probability of CNS relapse did not differ between the two groups ($P = 0.89$). The CNS relapse was strongly associated with short OS ($P < 0.0001$). In the R-chemotherapy group, 83% of patients who experienced CNS relapse had parenchymal disease.

Conclusions: Our results indicate that rituximab improves the OS of patients with CD5+ DLBCL but does not decrease the CNS relapse rate. More effective treatments with CNS prophylaxis are needed for CD5+ DLBCL patients.

Key words: CD5, central nervous system, diffuse large B-cell lymphoma, prognosis, rituximab

introduction

Diffuse large B-cell lymphoma (DLBCL) is the largest lymphoma subcategory and has heterogeneous biological properties [1]. DLBCL cases (5%–10%) are CD5 positive (CD5+) [2–5]. CD5+ DLBCL has been included as an immunohistochemical subgroup in the fourth edition of the World Health Organization (WHO) classification [1]. Our two nationwide retrospective studies in Japan [6, 7] revealed that CD5+ DLBCL was associated with female predominance, higher age at diagnosis, higher serum lactate dehydrogenase (LDH) level, and higher risk groups in the international prognostic index (IPI) [8]. In the pre-rituximab era, CD5+ DLBCL showed a significantly poorer survival outcome than CD5-negative DLBCL under conventional anthracycline-containing chemotherapy [6, 9, 10]. CD5+ DLBCL is also characterized by a high central nervous system (CNS) relapse rate [7].

The current standard therapy for DLBCL incorporates rituximab, but three independent groups have reported that CD5+ DLBCL is associated with a poorer overall survival (OS) rate than CD5-negative DLBCL, regardless of the use of

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rituximab [3, 10, 11]. To explore a more effective therapeutic strategy for CD5+ DLBCL, it is important to examine the response and failure rate of chemotherapy with rituximab in a large number of CD5+ DLBCL cases.

Hence, we conducted the third nationwide retrospective study of >300 Japanese patients with CD5+ DLBCL who received chemotherapy with (R-chemotherapy group) or without (chemotherapy group) rituximab.

patients and methods

patients and treatment

Two hundred and eighty-one patients who were diagnosed with CD5+ DLBCL between 2002 and 2007 were retrospectively registered in this study from 31 participating centers. CD5+ DLBCL was diagnosed by expert hematopathologists (listed in the Appendix) in accordance with the WHO classification [1]. CD20 and/or CD79a positivity on the tumor cells was confirmed by immunohistochemical staining or flow cytometry. Based on our experience that CD5 expression in DLBCL was less visible when tissue sections were examined using paraffinized materials [7], we primarily used flow cytometry and/or immunohistochemical analysis of frozen sections to examine the expression of CD5. We used paraffin-embedded sections only if fresh or frozen material was unavailable. We registered consecutive patients who were diagnosed with CD5+ DLBCL, regardless of the availability of follow-up data. Intravascular large B-cell lymphoma [12], primary DLBCL of the CNS, secondary CD5+ DLBCL [4], cyclin D1+ cases, and cases with insufficient follow-up data were excluded from the study population (Figure 1). Patients who had not received any chemotherapy were also excluded. As a result, 230 patients were included in the present series (Figure 1). The study protocols used were approved by the institutional review board at each participating hospital and complied with all provisions of the Declaration of Helsinki.

We previously reported an analysis of 120 patients with CD5+ DLBCL from a pathological perspective [7]. Our current cohort also included 107 of these 120 patients from our previous series. The remaining 13 patients were excluded as they had not received chemotherapy. The final total of the patient cohort in the present analysis was thus 337 patients with CD5+ DLBCL who had received chemotherapy (Figure 1). In 95 of these patients (28%), CD5 expression could only be examined by immunohistochemistry using paraffin sections.

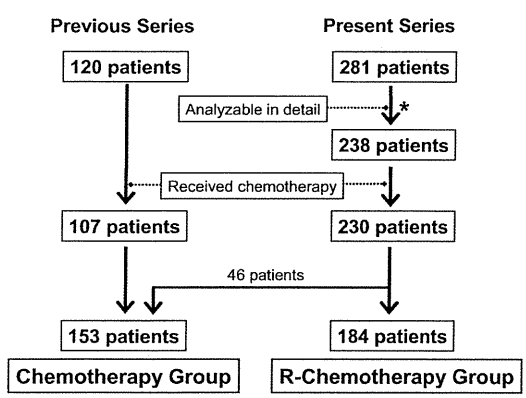

Figure 1. Patient selection. *Forty-three patients were excluded due to the following reasons: lack of clinical data (n = 25), intravascular large B-cell lymphoma (n = 2), primary diffuse large B-cell lymphoma (DLBCL) of the central nervous system (n = 7), secondary CD5-positive DLBCL (n = 6), cyclin D1+ cases (n = 2), and non-DLBCL status (n = 1).

Patients received treatment for CD5+ DLBCL according to the respective institutional protocols. Patients who had received any rituximab treatment cycles (median, seven cycles; range one to eight cycles) were assigned to the R-chemotherapy group, and the dose of rituximab was 375 mg/m^2 for all patients in this group. A pretreatment evaluation of the cerebrospinal fluid (CSF) was not required. CNS prophylaxis was carried out on a patient-by-patient basis in accordance with the clinical decisions made within each institute.

definition of CNS relapse

The definition of CNS relapse used in the current study was previously reported by Bernstein et al. [13] and defined as leptomeningeal, brain parenchymal, or intradural involvement with lymphoma, as documented by pathological, radiological, and/or clinical criteria. Patients with epidural or vertebral body involvement were not classified as having CNS relapse. Based on the criteria of a study from Germany [14], patients with the first recurrence of lymphoma to the CNS after achieving complete response (CR), uncertain CR, or partial response and those with spread of disease to the CNS during first-line therapy were included in this study.

statistical analysis

Distributions of variables between the two groups were assessed using Fisher's exact test. OS and time to CNS relapse were calculated according to the Kaplan–Meier method. Two-year CNS relapse rate was estimated by Cox regression. Multivariate analysis was carried out using Cox regression. The impact of CNS relapse on survival was assessed as a time-dependent covariate. All P values were two-sided and had an overall significance level of 0.05. Statistical analyses were carried out with Stata SE 11 software (StataCorp, LP, College Station, TX).

results

patient characteristics

Patient characteristics are listed in Table 1. The chemotherapy group composed of 153 patients, whereas the R-chemotherapy group contained 184 patients (Figure 1). The median age of all patients in both groups was 65 and 67 years, respectively. In the R-chemotherapy group, 103 patients (60%) were older than 65 years. No statistically significant differences in baseline patient characteristics were found between the two groups.

treatments

Treatment details are summarized in Table 2. A total of 147 patients (97%) in the chemotherapy group and 180 patients (98%) in the R-chemotherapy group received anthracycline-containing chemotherapy. The most popular chemotherapeutic regimen was a standard CHOP (combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone) (-like) regimen, which was selected as an initial treatment for 111 patients (73%) in the chemotherapy group and for 168 patients (91%) in the R-chemotherapy group. In the chemotherapy group, 24% of the patients received chemotherapies that were more intensive than the standard CHOP (-like) regimen.

CNS prophylaxis was carried out in five patients in the chemotherapy group. Among them, four patients received intrathecal administration of methotrexate and the remaining

Table 1. Baseline patient characteristics

	All patients (n = 337)	Chemotherapy group (n = 153)		R-chemotherapy group (n = 184)		P
	N	n	%	n	%	
Age, years						
Median	67	65		67		
Range	15–93	22–93		15–91		
≤60 years	103	48	31	55	30	0.81
>60 years	234	105	69	129	70	
Sex						
Male	176	78	51	98	53	0.74
Female	161	75	49	86	47	
Stage						
I–II	128	56	37	72	39	0.65
III–IV	209	97	63	112	61	
Performance status						
0 or 1	235	104	68	131	74	0.33
>1	95	48	32	47	26	
Extranodal sites						
0 or 1	249	114	75	135	73	0.90
>1	88	39	25	49	27	
Serum LDH						
Normal	97	40	26	57	31	0.34
Elevated	239	113	74	126	69	
IPI risk categories						
Low	164	75	49	89	48	0.91
High	173	78	51	95	52	
B symptoms						
Absent	214	91	61	123	69	0.19
Present	113	57	39	56	31	
BM and/or PB involvement						
Absent	248	112	73	136	77	0.44
Present	81	41	27	40	23	
CNS involvement						
Absent	326	147	96	179	97	0.56
Present	11	6	4	5	3	

LDH, lactate dehydrogenase; IPI, international prognostic index; BM, bone marrow; PB, peripheral blood; CNS, central nervous system.

patient received whole-brain radiation. CNS prophylactic therapy was conducted more frequently in the R-chemotherapy group than in the chemotherapy group ($P < 0.001$; Table 2). Of these individuals, 25 patients received an intrathecal administration of methotrexate with or without cytarabine. Two patients received whole-brain radiotherapy because they had CNS involvement as well as systemic involvement at diagnosis.

Five patients (3%) in the chemotherapy group and 21 patients (11%) in the R-chemotherapy underwent stem-cell transplantation (SCT), with two of these patients in the R-chemotherapy group receiving allogeneic SCT.

response to initial therapy and survival

CR was achieved after initial treatment in 101 (66%) patients in the chemotherapy group and 148 (80%) patients in the R-chemotherapy group. The CR rate was significantly higher in the R-chemotherapy group ($P = 0.003$). The median follow-up of surviving patients was 68 months (range 6–190 months) in the chemotherapy group and 30 months (range 7–82 months) in the R-chemotherapy group. The OS in the R-chemotherapy group was also significantly higher than that in the chemotherapy group (log-rank test, $P = 0.002$; Figure 2). The 2-year OS rate was 54% in the chemotherapy group and 70% in the R-chemotherapy group.

The results of our univariate and multivariate analyses of the OS rates to assess the impact of clinical features in the entire cohort of 337 $CD5^+$ DLBCL patients are shown in Table 3. By univariate analysis, we identified chemotherapy without rituximab, male sex, the presence of B symptoms, and all five risk factors of the IPI as important prognostic factors for the OS. Intensive chemotherapy was not associated with a reduced OS. By multivariate analysis, chemotherapy without rituximab [hazard ratio (HR) 1.72; 95% confidence interval (CI) 1.23–2.43; $P = 0.002$], male sex, and all the risk factors of the IPI except for extranodal sites were each identified as independent prognostic factors affecting the OS. In addition, when multivariate analysis was carried out for chemotherapy without rituximab, male sex and all IPI categories were found to be significant and independent prognostic factors.

Table 3. Multivariate analyses affecting overall survival (n = 337)

Variables (risk factor)	Univariate		Multivariate (final model)	
	HR (95% CI)	P	HR (95% CI)	P
Comparison with risk factors				
Rituximab (−)	1.69 (1.21–2.36)	0.002	1.72 (1.23–2.43)	0.002
Age (>60 years)	2.14 (1.47–3.12)	<0.001	2.40 (1.62–3.57)	<0.001
Sex (male)	1.63 (1.18–2.25)	0.003	1.61 (1.16–2.23)	0.004
B symptoms (present)	2.06 (1.30–2.83)	<0.001	–	–
PS (2–4)	2.83 (2.05–3.91)	<0.001	1.89 (1.33–2.68)	<0.001
Serum LDH (above normal)	3.24 (2.08–5.04)	<0.001	1.86 (1.14–3.02)	0.013
Stage (III or IV)	2.18 (1.53–3.11)	<0.001	1.68 (1.12–2.53)	0.013
Extranodal (more than one site)	1.56 (1.11–2.17)	0.010	–	–
Intensive chemotherapy	1.00 (0.66–1.54)	0.97	–	–
Comparison with IPI categories				
Rituximab (−)	1.69 (1.21–2.36)	0.002	1.85 (1.33–2.59)	<0.001
Sex (male)	1.63 (1.18–2.25)	0.003	1.52 (1.10–2.09)	0.011
IPI (high or high-intermediate)	3.28 (2.33–4.63)	<0.001	3.33 (2.36–4.70)	<0.001

HR, hazard ratio; CI, confidence interval; LDH, lactate dehydrogenase; IPI, international prognostic index.

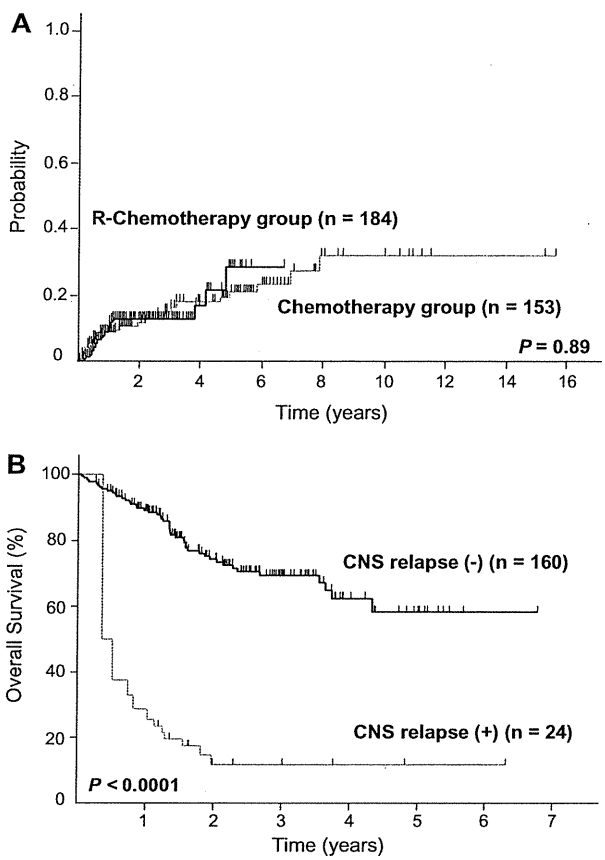

Figure 3. Central nervous system (CNS) relapse in CD5-positive diffuse large B-cell lymphoma patients. (A) Probabilities of CNS relapse of patients in the chemotherapy group (n = 153) and the R-chemotherapy group (n = 184) assessed using the Kaplan–Meier method. (B) Impact of CNS relapse on overall survival of patients in the R-chemotherapy group (n = 184) assessed using time-dependent analysis.

and one received whole-brain radiotherapy. For the remaining patient, there was no available data concerning CNS prophylaxis.

discussion

Our current retrospective study confirms that the OS of CD5+ DLBCL is improved by addition of rituximab to conventional chemotherapies. We also demonstrate that the 2-year CNS relapse rate in CD5+ DLBCL remains high (12.7%) despite the use of rituximab and that CNS relapse is significantly associated with shortened survival of these patients.

We previously reported a high CNS relapse rate (13%) in 120 patients with CD5+ DLBCL at a median follow-up of 6.8 years [7]. The incidence of CNS relapse in aggressive non-Hodgkin's lymphomas, except in lymphoblastic lymphoma and Burkitt's lymphoma, has been reported to be ≤5% [15–17]. In the present study, the 2-year CNS relapse rate of CD5+ DLBCL was 11.6% in the chemotherapy group and 12.7% in the R-chemotherapy group. These two rates were not significantly different, which indicates not only that CD5+ DLBCL has a high CNS relapse rate but also that the addition of rituximab did not reduce the CNS relapse rate in patients with CD5+ DLBCL. Although the observation period in the R-chemotherapy group was shorter than that of our previous study (30 versus 81 months), the incidence of CNS relapse was still >30%. Moreover, our results show that CNS relapse affected the reduced OS rate of CD5+ DLBCL in the R-chemotherapy group. These findings suggest that CNS prophylaxis is required to further improve the OS of CD5+ DLBCL in the rituximab era.

A large retrospective study from Germany identified risk factors for CNS relapse in elderly patients with DLBCL [14]. The presence of more than one site of extranodal involvement and B symptoms were identified as independent risk factors for CNS relapse by multivariate analysis. In contrast, poor performance status was the only independent risk factor for 2-year CNS relapse in our CD5+ DLBCL cohort. We considered that this discrepancy in the results between the German study and ours may be due to difference in the disease status of the subjects analyzed; our cohort was composed of CD5+ DLBCL patients only and, therefore, not representative of all types of DLBCL.

Table 2. Treatment details and patterns of CNS relapse

	Chemotherapy group		R-chemotherapy group		*P*
	n	%	*n*	%	
Treatment details	*n* = 153		*n* = 184		
Cx without anthracycline	6	4	4	2	0.52
Standard CHOP or CHOP-like	111	73	168	91	<0.001
Intensive Cx[a]	36	24	12	7	<0.001
Biweekly CHOP	10	7	2	1	0.014
Third-generation regimen	22	14	6	3	<0.001
HD cytarabine-containing Cx	4	3	4	2	1.00
CNS prophylaxis	5	3	27	15	<0.001
Median number of rituximab (range)	–	–	7 (1–8)	–	–
Patterns of CNS relapse	*n* = 25		*n* = 24		
Brain parenchymal	15[b]	60	16	66	0.77
Leptomeningeal	5	20	3	13	0.70
Both parenchymal and leptomeningeal	1	4	4[c]	17	0.19
Intraocular	2	8	1	4	0.58
Intradural	2	8	0	0	0.49

[a]Biweekly CHOP, third-generation regimen, and HD cytarabine-containing chemotherapy.
[b]One patient who had both brain parenchymal and intraocular relapse.
[c]One patient who had both intradural and leptomeningeal relapses.
Cx, chemotherapy; CHOP, combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone; HD, high dose; CNS, central nervous system.

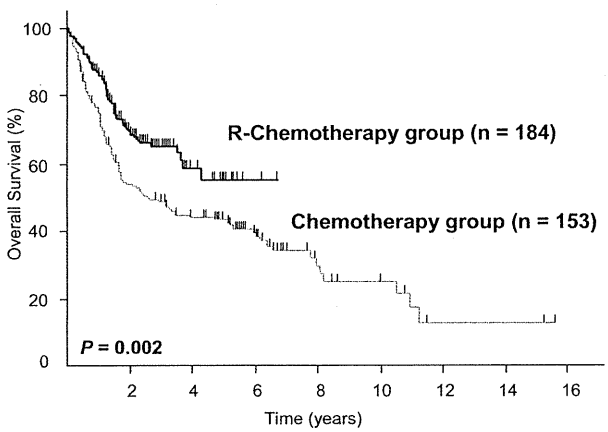

Figure 2. Overall survival of patients in the chemotherapy group (*n* = 153) and in the R-chemotherapy group (*n* = 184).

In the R-chemotherapy group, 19 patients received autologous SCT. Among them, all eight patients who received autologous SCT during the first CR had survived without relapse as of the last follow-up (median progression-free survival of 43 months).

CNS relapse in CD5+ DLBCL

Among our 337 patient subjects, 25 in the chemotherapy group and 24 in the R-chemotherapy group experienced CNS relapse during the follow-up period (Table 2). There was no significant difference in the probability of CNS relapse between these two groups ($P = 0.89$, Figure 3A). The 2-year CNS relapse rate was found to be 11.6% (95% CI 7.1% to 18.6%) in the chemotherapy group and 12.7% (95% CI 8.5% to 18.8%) in the R-chemotherapy group. A time-dependent covariate analysis of the R-chemotherapy group further revealed that CNS relapse strongly affected the OS of CD5+ DLBCL ($P < 0.0001$, Figure 3B).

Twenty of 24 patients in the R-chemotherapy group and 19 of 25 patients in the chemotherapy group experienced an isolated CNS relapse. Patterns of CNS relapse in both groups are shown in Table 2. In both groups, brain parenchymal relapse was the most frequent pattern of CNS relapse (60% in the chemotherapy group and 66% in the R-chemotherapy group). The incidence of each pattern of CNS relapse did not significantly differ between these two groups. In the R-chemotherapy group, 83% (20/24) of patients who experienced CNS relapse had parenchymal disease.

To identify risk factors of CNS relapse in CD5+ DLBCL, we carried out univariate analyses of all the risk factors that had been analyzed in the largest cohort of DLBCL in the report from Boehme et al. [14]. Advanced stage, poor performance status, high serum LDH level, the presence of B symptoms, and bone marrow and/or peripheral blood involvement were found to be significant risk factors by univariate analyses (supplemental Table S1, available at *Annals of Oncology* online). The multivariate analysis showed that poor performance status was the only independent risk factor for 2-year CNS relapse (HR 2.81, 95% CI 1.54–5.13; $P = 0.001$). Among the 24 patients who experienced CNS relapse in the R-chemotherapy group, 11 patients (46%) had bone marrow involvement at diagnosis. In addition, seven patients (29%) received CNS prophylaxis during first-line therapy. Of those patients, five received an intrathecal administration of methotrexate with or without cytarabine

In primary DLBCL of the CNS, the most common site of involvement is the brain parenchyma [1]. Chemotherapy with high-dose methotrexate followed by whole-brain radiotherapy is the most commonly used approach for this disease [18]. As 75% of patients who experienced CNS relapse had brain parenchymal disease (18 of 24) in the current study of CD5+ DLBCL, high-dose methotrexate may be more efficacious than intrathecal administration of methotrexate or cytarabine to prevent CNS relapse in CD5+ DLBCL patients. High-dose chemotherapy with autologous SCT also appears to be an effective approach in patients with CD5+ DLBCL because some clinical trials have indicated efficacy for CNS lymphoma [19, 20]. However, it should be noted that 60% of our patients with CD5+ DLBCL were older than 65 years at diagnosis and would therefore not be eligible for high-dose chemotherapy.

Several clinical parameters such as elevated serum LDH levels and extranodal or bone marrow involvement have been established as risk factors for CNS relapse in DLBCL [13, 21, 22]. Based on the recent results of a study of aggressive lymphoma, which mainly comprises DLBCL [13], bone marrow involvement seems to be less significant. To date, CD5 antigen expression is the only well-known molecular marker that is closely associated with frequent CNS relapse in DLBCL. Quijano et al. [23] developed a sensitive immunophenotyping method for lymphoma cells in the CSF that turned out to be useful in detecting unexplained CNS involvement upon the diagnosis of DLBCL. To investigate the significance of CD5 expression in CNS relapse of DLBCL, further studies using such a procedure may be useful. The relationship between CD5+ DLBCL and primary DLBCL of the CNS should be clarified because the latter frequently shows expression of CD5 (30%) [24]. Such approaches would be expected to contribute to the establishment of both early diagnosis of CNS involvement and optimal treatment in CD5+ DLBCL patients.

In conclusion, we herein report detailed therapeutic and prognostic results for a fairly large number of CD5+ DLBCL cases. Despite the use of rituximab, the 2-year OS of CD5+ DLBCL remains poor (70%). As CD5+ DLBCL is complicated by a high incidence of CNS relapse, a more effective therapeutic strategy with CNS prophylaxis is needed.

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disclosure

The authors declare no conflicts of interest.

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appendix

The following institutions participated in this study: Tohoku University, Gunma University, International Medical Center, Saitama Medical University, Saitama Medical Center, Matsudo City Hospital, National Cancer Center Hospital East, National Cancer Center Hospital, Cancer Institute Hospital, Yokohama City University Hospital, Fujisawa City Hospital, Kanagawa Cancer Center, Yokohama City University Medical Center, Tokai University, Shinshu University, Kanazawa Medical University, Nagoya University, Aichi Cancer Center, East Medical Center Higashi Municipal Hospital City of Nagoya, Ogaki Municipal Hospital, Mie University, Kyoto University, Okayama University, Chugoku Central Hospital, Okayama Medical Center, Himeji St Mary's Hospital, Sumitomo Besshi Hospital, Okayama Rosai Hospital, Hiroshima University, Yamaguchi University, Ehime University, and Ehime Prefectural Central Hospital.

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ORIGINAL ARTICLE

Bulky disease has an impact on outcomes in primary diffuse large B-cell lymphoma of the breast: a retrospective analysis at a single institution

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Abstract

Objectives: Primary breast lymphoma (PBL) is rare, and its clinical behavior and standard initial treatment are not yet established. *Methods:* We retrospectively analyzed the clinicopathological features and treatment outcomes of 14 patients with primary breast diffuse large B-cell lymphoma. *Results:* There were nine patients with stage IE and five with stage IIE disease. The median largest tumor diameter was 4.5 cm, and five patients had bulky disease >5 cm. The complete response rate was 94%. However, the 5-year progression-free survival rate was 52% with a median follow-up of 5.2 years. Patients with bulky disease had an unfavorable prognosis. All five patients with bulky disease progressed or relapsed. Of the four patients that recurred in the central nervous system (CNS), three had bulky disease although some received rituximab. There were no CNS recurrences in the three patients who received CNS prophylaxis. All eight patients who responded to radiotherapy (RT) did not have recurrences in the ipsilateral breast, although one patient with bulky disease relapsed in the adjacent regional lymph nodes within the RT field despite immunochemotherapy. *Conclusions:* Patients with bulky disease had a poorer prognosis and recurred frequently in the CNS. CNS prophylaxis might yield better outcomes, but a larger, prospective trial is needed to elucidate the optimal initial treatment of PBL in the rituximab era.

Key words diffuse large B-cell lymphoma; primary breast lymphoma; CNS prophylaxis

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Primary breast lymphoma (PBL) is a rare subtype of non-Hodgkin' lymphoma (NHL), comprising <1% of all NHLs (1–3) and approximately 2% of extranodal presentations (1, 3–6). In addition, <1% of all breast malignancies are lymphomas (2–4, 7). Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of PBL, accounting for 40–80% of cases (4, 6). Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy are considered the standard regimen for DLBCL. Recently, the addition of the anti-CD20 antibody rituximab to the CHOP regimen has improved the outcome of patients with B-cell lymphoma (8–10).

There are many retrospective series (2, 3, 5, 11–18) but only two small prospective clinical trials (19, 20) which have reported the clinicopathological features of PBL. Most studies recommend a chemotherapy regimen containing anthracycline followed by radiotherapy (RT) (12–14). The 5-year survival rate in the recent larger series ranges from 61% (11) to 73% (12) with anthracycline-containing regimens with or without RT. Some series have suggested that PBL has a poorer prognosis than

aggressive NHLs with mainly nodal involvement; moreover, PBL tends to recur predominantly in extranodal sites, with especially significant risk in both the ipsilateral and contralateral breast and in the central nervous system (CNS) with a recurrence rate ranging from 7% to 29% (5, 11, 13, 16, 17, 19, 21, 22). However, other series have reported that the prognosis and incidence of CNS involvement of PBL were similar to those of aggressive nodal NHLs of the same stage (12, 18, 20). Thus, the clinical course and pathological features of PBL, and what constitutes the optimal initial treatment, remain to be elucidated. Therefore, we conducted a retrospective, single-institution study to analyze the clinicopathological features, treatment efficacy, and prognostic factors in patients with PBL.

Patients and methods

Patients

Data on 20 patients with PBL who were treated at the National Cancer Center Hospital from January 1999 to December 2008 were analyzed retrospectively. Patients with recurrent lymphoma in the breast and those initially presenting with systemic disease including breast involvement were excluded according to the definition previously reported (1). Patients were considered to have bulky disease if the largest tumor was >5 cm in diameter. The study protocol was approved by the institutional review board of the National Cancer Center Hospital, Tokyo, Japan.

Staging

The initial staging in all patients included history and physical examination, blood tests, computed tomography (CT) of the neck, chest, abdomen, and pelvis, bone marrow aspiration, and upper gastrointestinal endoscopy. Patients were staged according to the Ann Arbor classification system (23). Staging of extranodal NHLs within bilateral paired organs remains controversial, but in this study, patients with bilateral presentation were categorized as stage IE. Evaluation of the CNS at diagnosis by CT, magnetic resonance imaging (MRI), or lumbar puncture with cerebrospinal fluid analysis was performed only if clinically indicated. The International Prognostic Index (IPI) (24) was used to assess prognosis.

Treatment

Patients received 3 or 4 courses of CHOP with or without RT, whereas patients with bulky disease received 6 or more courses of CHOP. RT was scheduled before the commencement of chemotherapy because the disease was local, and the radiation field included the involved breast and the regional lymph nodes (the axillary and the supraclavicular region). Rituximab has been available for DLBCL through the Japanese National Health Insurance system since September 2003, and patients also received rituximab since then. CNS prophylaxis, consisting of intrathecal methotrexate (IT-MTX, four doses of 15 mg each), was administered at the treating physician's discretion.

Statistical analysis

Response was assessed after completion of the initial therapy according to the response criteria for NHLs (25). Overall survival (OS) was calculated from the date of diagnosis to the date of last follow-up or death from any cause. Progression-free survival (PFS) was calculated from the date of diagnosis to the date of disease progression, death from any cause, or last follow-up. OS and PFS were estimated by the Kaplan–Meier method (26). The following variables were analyzed for prognostic significance for OS and PFS: Ann Arbor clinical stage (stage IE vs. stage IIE), the largest tumor size (≤ 5 cm vs. >5 cm), and age (<60 vs. ≥ 60). Because the proportion of patients with elevated lactate dehydrogenase (LDH) levels (2 of 14 patients) or the patients classified as the low-intermediate or high-risk group according to the IPI (1 each of 14 patients) was very low (Table 1), these variables were not analyzed. The log-rank test was used to compare survival curves. A P value <0.05 for a two-sided test was considered statistically significant. All statistical analyses were performed using Dr SPSS II software, release 11.0.1J (SPSS Japan, Tokyo, Japan).

Results

Patient characteristics

Using the World Health Organization (WHO) classification, 4th edition (27), there were 17 patients with DLBCL, two patients with follicular lymphoma, one patient with mucosa-associated lymphoid tissue (MALT) lymphoma, and no patients with T/NK-cell lymphoma. Because the proportion of the patients with primary breast low-grade B-cell NHLs was very low (15%, 3/20), the patient population in this study was limited to the DLBCL patients. As three patients were excluded because of Stage IV disease, 14 DLBCL patients were analyzed in this study.

The diagnosis of PBL was established with a core needle biopsy in eight patients, excisional biopsy in four patients, and mastectomy with regional lymph node resection in two patients. Patient characteristics are summarized in Table 1. There were nine patients with stage

Table 1 Patient characteristics

	No. (%)
Age	
Median 57.5 years	
Range 24–69 years	
<60 years	10 (71)
≥60 years	4 (29)
Gender	
Male	0 (0)
Female	14 (100)
Primary site of lymphoma	
Unilateral breast	12 (86)
Bilateral breast	2 (14)
Tumor size[1]	
<5cm	9 (64)
>5 cm	5 (36)
Nodal involvement	
None	9 (64)
Axillary only	4 (29)
Supraclavicular + axillary	1 (7)
ECOG Performance Status	
0	13 (93)
1	1 (7)
LDH	
Normal	12 (86)
Elevated	2 (12)
Ann Arbor stage	
IE	9 (64)
IIE	5 (36)
B symptoms	
Absent	13 (93)
Present	1 (7)
IPI	
Low	12 (86)
Low-intermediate	1 (7)
High	1 (7)

ECOG PS, Eastern Cooperative Oncology Group Performance status; LDH, lactate dehydrogenase; IPI, International Prognostic Index.
[1]For bilateral cases, the diameter of the larger tumor is indicated.

IE and five with stage IIE disease. The median age of all 14 female patients was 57.5 years (range 24–69 years). There were two patients who presented with bilateral breast involvement at diagnosis. The median diameter of the largest tumor was 4.5 cm, with five patients exhibiting bulky disease. Regional nodal involvement was observed in 36% of the patients.

Treatment

Table 2 shows the initial treatment regimens. There was one patient who had undergone mastectomy and a regimen of cyclophosphamide, methotrexate, and fluorouracil under the clinical diagnosis of breast cancer but was later histopathologically diagnosed as having DLBCL. The remaining 13 patients received CHOP with or without RT. Rituximab was administered in seven patients.

Table 2 Initial treatment

			No. (%)
Treatment	Chemotherapy only		3 (21)
	Surgery + Chemotherapy		2 (14)
	Chemotherapy + RT		9 (64)
Surgery	Mastectomy + axillary dissection		2
Chemotherapy	CMF regimen		1
	CHOP regimen		13
	No. of cycles	2–4	3
		6	6
		8	4
	With Rituximab	3–8	7 (50)
	With IT-MTX	4	3 (21)
RT			
Field	Involved breast + regional LNs		9 (64)
Dose (breast)	Median (Range)		40 (40–46)
Dose (regional)			30 (30–32)

CMF, cyclophosphamide, methotrexate, and fluorouracil; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; RT, radiotherapy; IT-MTX, intrathecal administration of methotrexate; LNs, lymph nodes.

RT to the involved breast was administered in nine patients (8 of 9 patients with stage IE disease and 1 of 4 with stage IIE disease) with total doses ranging between 40 and 46 Gray (Gy) and to the regional lymph nodes (the axillary and the supraclavicular regions) with total doses ranging between 30 and 32 Gy. Intrathecal CNS prophylaxis was given in three patients.

Outcomes

After the initial treatment, 13 patients (93%) showed a complete response (CR) and one patient (7%) showed a partial response (PR). With a median follow-up period of 5.2 years, the estimated OS and PFS rates at 5 years were 76% and 52%, respectively (Fig. 1). The median PFS and OS were not reached at the time of analysis.

Prognostic factors

The presence of bulky disease adversely affected both rates of OS and PFS (Fig. 2A and B, respectively). The Ann Arbor stage and age were not predictive of either OS or PFS (data not shown).

Relapse or progression

The details of patients with relapse or progression are shown in Table 3. Among the 13 patients who achieved CR after the initial treatment, six patients (43%) relapsed. Patient 3 achieved PR but progressed within 3 months of completion of initial therapy. In total, 7 of the 14 patients relapsed or progressed.

All five patients with bulky disease relapsed or progressed, whereas only 2 of 9 patients with tumors ≤5 cm experienced relapse. Of the two patients with bilateral breast involvement, one patient relapsed. The median interval between the completion of the initial therapy and relapse was 12 months. Relapse occurred more than 2 years after the completion of the initial therapy in two patients, occurring in the axillary lymph nodes and the CNS, respectively (Patients 5 and 6).

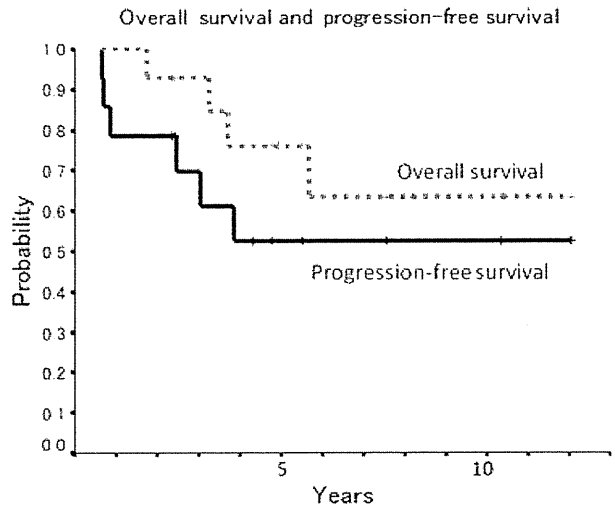

Figure 1 Overall and progression-free survival for all 14 patients.

CNS involvement and CNS prophylaxis

There were four patients (29%) who had recurrence in the CNS, including three mortalities because of progressive disease. The CNS was the first site of relapse or progression in three patients (21%); it was the third relapse site in the remaining patient. Two patients had CNS relapse within 3 months after the initial therapy, and the other two patients had CNS relapse more than 3 years after the initial therapy. Half of the patients had parenchymal brain metastases, and half had leptomeningeal involvement. In the five patients with bulky disease, 3 (60%) had CNS relapses. In patients with disease ≤ 5 cm, one patient had (11%) progression into the CNS as the third relapse site (Patient 1 in Table 3). There were

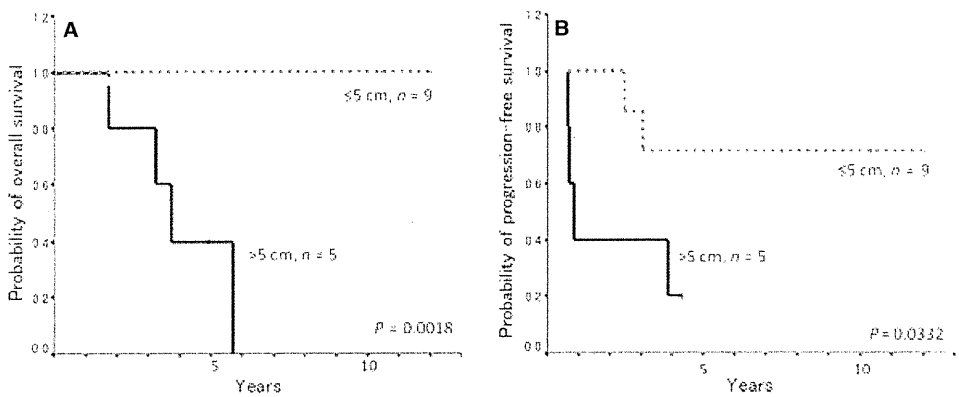

Figure 2 Overall (A) and progression-free survival (B) by tumor size.

Table 3 Details of relapse or progression

Patient No.	Stage	Tumor size (cm)	Initial treatment	Response to initial treatment	Interval to relapse or progression (months)[2]	First site of relapse or progression	Subsequent site(s) of relapse or progression	Outcome
1	I	≤5	CHOP → RT	CR	12	Hypodermis	Hypodermis, CNS (parenchyma)	Alive
2	I	≤5	CHOP → RT	CR	18	Cervical LNs, BM	Multiple LNs	Alive
3	I	>5	CHOP → RT	PR	3	Initial breast	–	Dead
4	I	>5	R-CHOP → RT	CR	3	CNS (parenchyma)	–	Dead
5	I	>5	R-CHOP → RT	CR	44	Axillary LNs	–	Alive
6	II	>5	CHOP → RT	CR	40	CNS (leptomeninges)	–	Dead
7	II[1]	>5	R-CHOP	CR	2	CNS (leptomeninges)	Rectum, adrenal grand	Dead

CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; R, rituximab; RT, radiotherapy; CR, complete response; PR, partial response; PD, progressive disease; CNS, central nervous system; LNs, lymph nodes; BM, bone marrow.

[1]Bilateral breast.

[2]Interval to relapse or progression after the completion of therapy.

no CNS recurrences in the three patients who received CNS prophylaxis. However, 4 of 11 patients (36%) who had not received CNS prophylaxis had CNS involvement.

Relapse/Progression in the breast site and IF-RT

There was one progression in the ipsilateral breast. The progression occurred in the initial breast site after PR induced by the initial treatment. Radiotherapy was administered after chemotherapy in nine patients. Within the RT field, there was 1 progression after PR in the initially involved breast and 1 recurrence after CR in the axillary lymph nodes in 30 Gy irradiated region 3.7 years after the completion of RT (Patients 3 and 5 in Table 3); both patients had bulky disease. In the remaining seven patients who received RT, no relapses occurred within the RT field or in the contralateral breast. On the other hand, none of the eight patients who had not received RT relapsed in the ipsilateral breast.

Immunochemotherapy

All the seven patients who received rituximab showed CR, among them three relapses occurred: 2 in the CNS and 1 in the axillary lymph nodes within the RT field. All three patients with bulky disease who received rituximab relapsed. On the other hand, all four patients with ≤5 cm bulk who received rituximab maintained a CR. Addition of rituximab to chemotherapy did not have any prognostic significance on either OS or PFS (data not shown).

Discussion

Some studies have suggested that PBL portends a poorer prognosis than aggressive nodal NHL, with a 5-year survival rate ranging from 61% to 73% in recent larger series (11, 12). In the present study, the estimated 5-year OS and PFS rates were 69% and 36%, respectively. Our results were similar to those previously reported (11, 12). Furthermore, most patients (13/14 patients, 93%) had a CR, although seven patients (50%) relapsed. The median interval between the completion of the initial therapy and relapse was 12 months, with two patients relapsing more than 2 years later. A high proportion of relapses despite the high CR rate might contribute to poor prognosis in PBL patients. Therefore, improvement in risk stratification of patients and tailoring initial treatment regimens to such may lead to better outcomes in PBL by reducing the rate of relapse.

We found that if the maximum tumor diameter at diagnosis was above 5 cm, there was a negative prognostic impact on OS and PFS. It is noteworthy that all of the patients with bulky disease relapsed or progressed. Patients with bulky disease comprised 3 of the 4 patients with CNS involvement and one patient with ipsilateral breast progression. Prognostic factors such as age (7, 28), IPI (2, 18, 21), PS (11, 21, 29), stage (2, 7, 13, 21), LDH (21, 29), tumor size (2, 18, 30), and the number of extranodal sites (11) have been shown to predict outcomes in patients with PBL.

We observed four CNS relapses in 14 patients. The higher incidence of CNS involvement (4/14 patients, 29%) in our study when compared to previous studies (5, 11–13, 16–22) may reflect bias because of the small sample size. Some retrospective studies have reported a high incidence (ranging from 12% to 39%) of CNS relapse in patients with DLBCL of the breast (5, 13, 17, 19, 21, 22). In contrast, The International Extranodal Lymphoma Study Group (IELSG) and Stanford University reported only 5% and 3% rates of CNS relapse, respectively (12, 29); however, 38% of the patients in the latter study were diagnosed as having low-grade B-cell lymphomas. Therefore, they suggested that CNS prophylaxis did not appear to be routinely indicated (12, 29). However, the risk of CNS relapse and the efficacy of CNS prophylaxis have not yet been clearly defined. Although the eligibility criteria of our study was limited to patients with localized disease, our study showed a relatively high incidence of CNS relapse (4/14 patients, 29%), which was similar to as that in the previous report; that is 30% of patients with early stage PBL (22). In DLBCL patients, the high levels of LDH and the high-risk group according to the IPI were the predictors for CNS involvement (31). However, these populations were very small in our study. On the other hand, when viewed in the tumor diameter, there was a higher risk of CNS relapse in patients with bulky disease (> 5 cm) (3/5 patients, 60%), whereas only 1 of the 9 patients with ≤5 cm disease had CNS involvement, and as the third site of relapse. Therefore, this may imply that tumor size is an important risk factor for CNS involvement. Additionally, the higher rate of CNS relapse (4/11 patients, 36%) in patients who did not receive CNS prophylaxis, in contrast to no CNS relapses in patients who did receive CNS prophylaxis, suggests that CNS prophylaxis is beneficial although the number of patients was small.

In our study, two patients had CNS relapse within 3 months after the initial therapy. We cannot deny the possibility of initial CNS involvement at the time of diagnosis because the patients who were analyzed in the current study had not undergone the examination of the cerebrospinal fluid before the treatment was instituted. On the contrary, the other two patients had CNS relapse more than 3 years after the initial therapy. There is another possibility that CNS relapse after durable CR resulted from a secondary CNS lymphoma because the

recent analysis of the complementarity-determining region 3 of the immunoglobulin heavy chain revealed that the lymphoma clone in CNS was different from that of the original breast lymphoma in one patient (32).

Although a high relapse rate in the ipsilateral breast has been reported in a number of retrospective studies (13, 21), the IELSG study showed that the rate of ipsilateral progression was substantially reduced by the use of RT, which might have contributed to an improvement in outcomes in patients with localized high-grade PBL (12). In our study, among the nine patients who received RT, there was one progression and one relapse observed within the RT field. The patient who progressed had only a PR after the initial course of chemotherapy followed by radiotherapy, and the tumor that relapsed in the axilla was in 30 Gy irradiated region. The remaining seven patients had no relapses within the RT field. In addition, patients who either progressed or relapsed within the RT field had bulky disease. Although a high rate of relapse in the contralateral breast has been previously reported (5, 12, 17, 22), there were no instances of contralateral breast relapse in this study.

Finally, rituximab plus CHOP (R-CHOP) has become the standard chemotherapy regimen for DLBCL. The studies that analyzed outcomes in PBL showed that there was no improvement even when rituximab was added to CHOP (18, 20). In the present study, we administered R-CHOP to seven patients. All the patients with bulky disease treated with rituximab relapsed, but their counterparts with tumors ≤5 cm did not. This might suggest that the patients with bulky disease have a poorer prognosis even in the rituximab era. Additionally, 2 of the 7 patients (29%) treated with rituximab experienced CNS relapse. These results may indicate that CNS prophylaxis reduces the probability of relapse and improves outcomes in the rituximab era.

In conclusion, our study delineated the clinicopathologic features of primary DLBCL of the breast. Most patients achieved a CR, although they relapsed at a high rate with some patients experiencing late relapses. Patients with bulky disease demonstrated a poor prognosis. A high rate of CNS relapses in patients with PBL suggests that CNS prophylaxis might yield better outcomes, especially in patients with bulky tumors > 5 cm. However, given the small number of patients in this study, a larger scale, prospective trial is needed to elucidate the optimal treatment strategy for PBL, especially in the rituximab era.

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Conflicts of interest

None declared.

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悪性リンパ腫－最近の診断と治療の進展

Recent advances in diagnosis and treatment of malignant lymphoma

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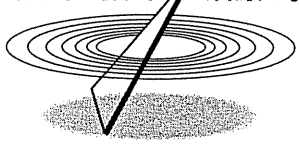
診断の指針 / 治療の指針



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悪性リンパ腫とは，リンパ系細胞を起源とする悪性腫瘍である．現在その分類としては，2008年に改訂第4版が刊行されたWHO分類が用いられる．WHO分類は，悪性リンパ腫を含むリンパ系腫瘍を網羅する分類として策定されている．悪性リンパ腫は，ホジキンリンパ腫(Hodgkin lymphoma；HL)と非ホジキンリンパ腫(non-Hodgkin lymphoma；NHL)に大別される．

1. 診　　断

1)リンパ節生検

リンパ節など腫瘍組織を生検し，免疫組織染色を含む病理組織検査，細胞表面マーカー，染色体分析を行って病型を確定する．後述するように，B細胞リンパ腫の治療においてはCD20を標的とするモノクローナル抗体治療薬，リツキシマブが広く用いられているため，免疫組織染色や細胞表面マーカー検査によってCD20発現を確認する．

ステージング

病気の進展範囲を決定するために，頸部・胸腹部・骨盤部CT，FDG-PET，上部消化管内視鏡検査，骨髄穿刺・生検などを行う．FDG-PETは病期診断のみならず治療効果判定にも用いられており，現在では悪性リンパ腫の診療には欠かせない重要な検査である．国際的なリンパ腫治療の効果判定規準として用いられているInternational Workshop Criteriaの改訂版では，FDGをよく取り込むホジキンリンパ腫(Hodgkin lymphoma；HL)やびまん性大細胞型B細胞リンパ腫(Diffuse largeB-cell llymphoma；DLBCL)では，治療後にPETが陰性化することが完全寛解の条件として規定されている．

2)予後因子

NHLに対して最も広く用いられる予後因子・予後予測モデルとしてはinternational prognostic index(IPI)がある．濾胞性リンパ腫(follicular lymphoma；FL)では，follicular lymphoma IPI(FLIPI)やFLIPI-2，進行期HLではinternational prognostic score(IPS)が用いられる．

3)検体検査

血液像を含む末梢血検査，血液生化学検査，ウイルス検査などを行う．血液生化学検査では血清LDH，CRP，カルシウムなどが重要である．LDHは腫瘍量を反映する．成人T細胞白血病・リンパ腫(Adult T-cell leukemia/lymphoma；ATLL)などでは時に高カルシウム血症を合併する．可溶性IL-2受容体(sIL-2R)はNHLの腫瘍マーカーとして有用である．

ウイルス・感染症検査としてはB型，C型肝炎ウイルス，HTLV-1，HIVなどを検査する．B型肝炎ウイルス(HBV)キャリアでは，全身化学療法後にHBVの再活性化により肝炎の増悪や劇症肝炎を発症する場合があるため，投与前にHBs抗原，HBc抗体，HBs抗体を検査する．HBs抗原陽性者では抗ウイルス薬(エンテカビルなど核酸アナログ)を投与する．HBs抗原陰性でも，HBc抗体またはHBs抗体陽性例はHBV再活性化ハイリスクとされるため，HBV-DNAなど肝炎ウイルスマーカーをモニターし，再活性化を認めた場合には抗ウイルス薬を投与する．

2. 主なリンパ腫に対する治療

1)HL

HLは化学療法や放射線治療の効果が高く，高率に治癒が期待できる．標準的な化学療法はABVD療法である．限局期に対しては，ABVD療法4コースと病変部位への放射線治療併用療法で，90％程度に長期生存が期待できる．最近，予後不良因子を有しない限局期HLでは，ABVD 2コースと減量した放射線治療(20Gy)で良好な治療成績が得られることが報告された．一方，進行期に対してはABVD療法を6～8コース施行する．70％以上に長期生存が期待できる．

2)DLBCL

治療は，大きく限局期と進行期に分けられる．B細

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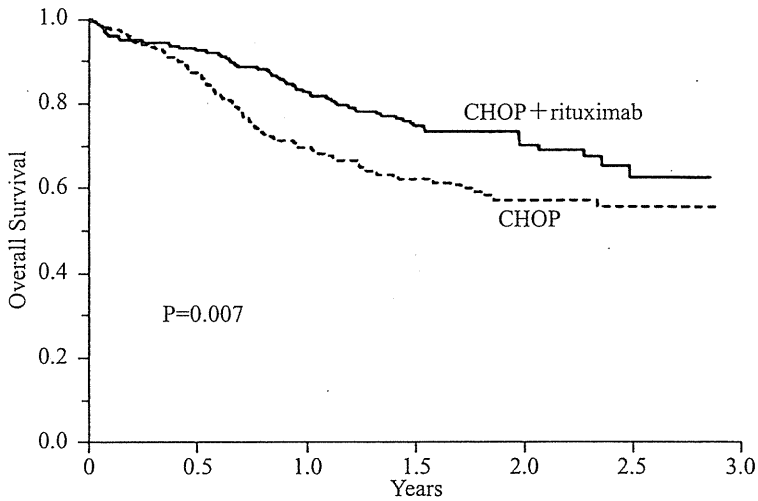

図1 高齢者進行期DLBCLに対するR-CHOPとCHOPのランダム化比較試験(Coiffier, et al：NEJM 2002より改変して引用)

胞の表面抗原であるCD20に対するマウス・ヒトキメラ型モノクローナル抗体であるリツキシマブによって，DLBCLの治療は大きく進歩した．リツキシマブは通常の化学療法剤と有害事象が異なるため，化学療法への追加投与が可能である．限局期DLBCLに対してはリツキシマブとシクロフォスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロン(CHOP)の併用療法，R-CHOPを3コースと放射線治療の併用療法，あるいはR-CHOP 6コースを行う．80～90%に長期生存が得られる．

進行期DLBCLに対しては，R-CHOP療法とCHOP療法の比較試験の結果，R-CHOPがCHOPに勝ったためR-CHOP療法が標準的治療法とされる(図1)．R-CHOP 8コースによって60%程度に長期生存が期待できる．

予後不良因子を有する初発進行期DLBCLの通常化学療法による治療成績はまだ不十分であり，若年例に対しては自己末梢血幹細胞移植を併用した大量化学療法の研究が盛んに行われている．

3)FL

限局期に対しては，病変部位に対する放射線治療が標準的治療である．進行期FLに対しては無治療での経過観察，化学療法，リツキシマブ，リツキシマブと化学療法の併用療法，造血幹細胞移植，などさまざまな治療方法が行われている．これらの方法のなかで最も重要な薬物療法はリツキシマブである．リツキシマブ併用化学療法によって通常化学療法よりも生存期間が改善することが報告されており，進行期FLに対する標準的治療法と考えられている．わが国ではR-CHOP療法が行われることが多い．また，R-CHOPなどに引き続いて2年程度リツキシマブを間欠的に投与するリツキシマブ維持療法による治療成績の向上が報告されており，わが国においても保険適用を目指した治験が行われている．

FLに対しては近年有効な新薬の開発が活発化している．現在わが国で承認されている主な薬剤しては，フルダラビン，クラドリビン，ベンダムスチン，yttrium-90 (^{90}Y) ibritumomab tiuxetan(ゼヴァリン)などがある．

4)MALTリンパ腫

節外臓器において，多くの場合は限局性病変として発症する．最も頻度が高い臓器は胃であり，その大部分にヘリコバクター感染が認められる．胃MALTリンパ腫は*H. pylori*感染との関連が深く，*H. pylori*除菌療法が有効であり，寛解率は60～80%である．わが国においても2010年にMALTリンパ腫に対する*H. pylori*除菌療法の保険適用が承認された．

5)ATLL

HTLV-1感染と密接に関連する，きわめて予後不良な疾患である．ATLに対しては，JCOGリンパ腫グループの研究によって，CHOP療法に比べて治療強度が高い多剤併用療法であるmLSG15療法の治療効果が勝ることが示されて標準的治療として位置づけられた．注目される新薬として，CCR4に対するモノクローナル抗体がある．わが国で基礎開発から臨床開発までが進められている薬剤であり，臨床第II相試験でCR 27%を含む奏功割合54%という高い治療効果が報告された．現在，同抗体とmLSG15併用療法の臨床試験が行われている．

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白血病 リンパ腫 骨髄腫

今日の診断と治療

第4版

中外医学社

D 血管内大細胞型B細胞リンパ腫の治療

血管内大細胞型B細胞リンパ腫（IVLBCL）は，1959年にPflegerとTappeinerにより初めて報告されたまれなnon-Hodgkin lymphomaの一型である[1]．当初上皮由来と考えられていたIVLBCLは，1980年代に本邦の森らによってリンパ系腫瘍であることが示され，以後の臨床および病理学的な研究により徐々に病態が明らかにされてきた[2]．2008年に改訂されたWorld Health Organization（WHO）分類では，B細胞リンパ腫の一型として独立した疾患概念に分類され，疾患認知度はますます向上している[3]．従前より一般的にリンパ節腫脹を伴わない特徴が診断を困難にしてきたが，本邦では多くの研究者および医家の努力により適切な診断がなされるようになってきている．最新の動向として疾患認知度の向上の反映からか欧米からの報告例が目立つようになり，さらなる生前診断率の向上，病態の解明が期待される．

a 診 断

腫瘍細胞の存在を生検臓器の血管内腔に病理像で確認することが診断のすべてである（図6-27）．発熱，LDH上昇，進行性の病態などがキーワードであるが，血球減少も6～7割程度の症例で認められる[4, 5]．臨床症状および検査値異常から疾患の存在を疑い生検を考慮することが必要である．可溶性IL-2レセプター値も上昇することが多く，疾患の存在を疑った場合は測定することが大切である．しかし上記の病態は何ら特異的な所見ではないため，疾患の診断には鑑別を要し，最終的に病理像で確認するまでは常に他の疾患の存在を念頭におかなければならない．

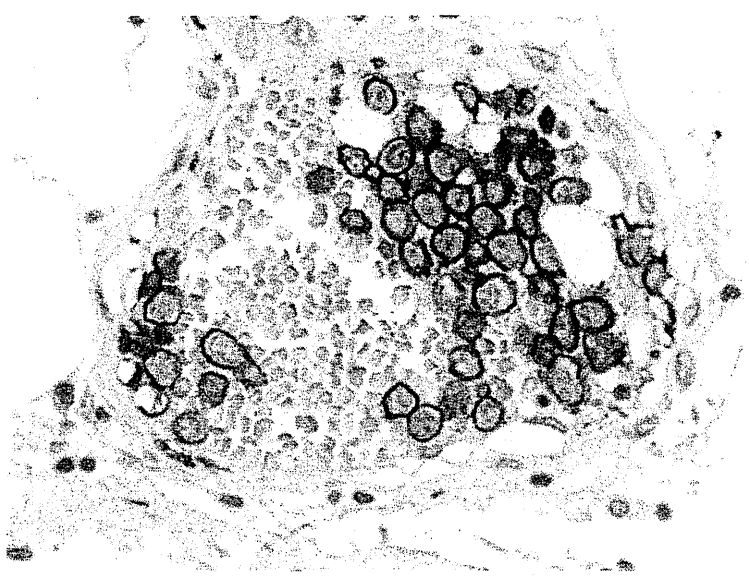

図6-27 IVLBCLの組織像
脾門部組織血管内に腫瘍細胞を認める（L26染色　x200）．