Table 1. Demographics and baseline characteristics of 40 patients with relapsed or refractory indolent B-cell non-Hodgkin lymphoma (B-NHL) who received ^{90}Y-ibritumomab tiuxetan

Characteristic		Baseline platelet count (/L)		Total
		≥100 × 10^9, <150 × 10^9	≥150 × 10^9	
		n (%)	*n* (%)	*n* (%)
All		18 (100)	22 (100)	40 (100)
Sex	Male	11 (61)	5 (23)	16 (40)
	Female	7 (39)	17 (78)	24 (60)
Disease stage at study entry	I/II	3 (17)	10 (45)	13 (33)
	III/IV	14 (78)	12 (55)	26 (65)
	Unknown	1 (6)	0 (0)	1 (3)
World Health Organization histopathology classification	SLL	1 (6)	0 (0)	1 (3)
	MALT	0 (0)	2 (9)	2 (5)
	FL	15 (83)	18 (82)	33 (83)
	MCL	1 (6)	1 (5)	2 (5)
	LG-B-NHL-NOS	1 (6)	0 (0)	1 (3)
	Transformed	0 (0)	1 (5)	1 (3)
Bone marrow involvement (%)	0	9 (50)	19 (86)	28 (70)
	>0–≤5	4 (22)	1 (5)	5 (13)
	>5–≤20	5 (28)	1 (5)	6 (15)
	>20–<25	0 (0)	1 (5)	1 (3)
FLIP	Low risk	9 (50)	12 (55)	21 (53)
	Intermediate risk	5 (28)	5 (23)	10 (25)
	Poor risk	4 (22)	5 (23)	9 (23)
Prior therapy including rituximab	No	3 (17)	2 (9)	5 (13)
	Yes	15 (83)	20 (91)	35 (88)
Prior therapy with rituximab plus chemotherapy†	No	8 (44)	9 (41)	17 (43)
	Yes	10 (56)	13 (59)	23 (58)
Number of prior regimens	1	3 (17)	10 (45)	13 (33)
	2–3	9 (50)	5 (23)	14 (35)
	≥4	6 (33)	7 (32)	13 (33)

FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; LG-B-NHL-NOS, low-grade B-NHL, not otherwise specified; MALT, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; SLL, small lymphocytic lymphoma.

†Eighteen patients with R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone), two with R-C-MOPP (cyclophosphamide, vincristine, procarbazine, and prednisone), two with CHASER (cyclophosphamide, cytarabine, etoposide, dexamethasone, and rituximab), one with R-fludarabine, one with R-FND (fludarabine, mitoxantrone, and dexamethasone), and one with R-EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin).

14.8 MBq/kg (0.4 mCi/kg) according to the number of platelets. No patients received Y2B8 exceeding the maximum dose of 1184 MBq/kg (32 mCi/kg).

The baseline characteristics of the 40 patients who received Y2B8 are summarized in Table 1. The median age was 57 years (range 32–72 years). All 40 patients had relapsed or refractory disease. According to the central pathology review, 33 (83%) had follicular lymphoma. Twelve patients (30%) had a tumor mass of ≥5 cm, and 30% had bone marrow involvement. Patients had received a median of three prior regimens (range 1–11). Twenty-three patients (58%) were treated previously with R-chemo, and 12 (30%) had been pretreated with rituximab monotherapy. Nineteen patients (48%) had intermediate or poor risk of disease according to the Follicular Lymphoma International Prognostic Index (FLIPI).[22]

Efficacy. Among the 40 patients who received Y2B8, the ORR was 83% (33/40; 95% CI, 67–93%), and the %CR was 68% (27/40; 95% CI, 51–81%). The ORR and %CR were 83% (19/23) and 70% (16/23) for the patients pretreated with R-chemo, and 94% (17/18) and 78% (14/18) for those treated with R-CHOP, respectively (Table 2). In follicular lymphoma, the ORR and %CR were 85% (28/33) and 70% (23/33), respectively. Of two patients with mantle cell lymphoma, one achieved partial remission. One patient with transformed B-NHL achieved complete remission. In the remaining histopathological types, three of four patients responded. Patients with the largest tumor mass of <5 cm responded better compared to patients with tumor mass of ≥5 cm.

Responses according to the FLIPI are shown in Table 2. The ORR and %CR appeared to decline as the FLIPI score increased. In patients with only one prior therapy, the ORR and %CR were 92 and 85%, respectively, compared to 69 and 46%, respectively, in patients with four or more prior regimens.

The median PFS of the 40 patients who received Y2B8 was 9.6 months with a median follow-up time of 6.5 months (range 1.2–12.7 months) (Fig. 1a). In the 23 patients pretreated with R-chemo, the median PFS was 9.6 months with a median follow-up time of 6.0 months (range 1.2–12.7 months) (Fig. 1b).

Safety. External radioactivity for each patient was less than 10 μSv/h (range 0–5 μSv/h) at 1 m within 1 h of the Y2B8 injection.

Hematological toxicities were seen commonly. Among the 40 patients who received Y2B8, grade 4 neutropenia was observed in 43%, whereas grade 4 thrombocytopenia and anemia were each seen in 5% (Table 3). Critical toxicity as defined with the primary safety variable was observed in two patients (grade 4 thrombocytopenia), both in the group with baseline platelet counts of 150 × 10^9/L or more. Neutrophil and platelet counts declined to the nadirs in a median of 54.5 and 42.0 days after the first rituximab infusion, respectively, and recovered to grade 2 or less in a median of 10 and 14 days after the nadirs, respectively (Table 4).

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Table 2. Responses assessed by the Central Computed Tomography Review Committee

Background factor		*n*	Overall response rate (%)	Complete response rate (%)	No. patients with clinical response		
					CR	CRu	PR
Any		40	83	68	25	2	6
Baseline platelet count (/L)	$\geq 100 \times 10^9$, $< 150 \times 10^9$	18	78	61	11	0	3
	$\geq 150 \times 10^9$	22	86	73	14	2	3
World Health Organization	SLL	1	100	100	1	0	0
histopathology classification	MALT	2	50	50	0	1	0
	FL	33	85	70	22	1	5
	MCL	2	50	0	0	0	1
	LG-B-NHL-NOS	1	100	100	1	0	0
	Transformed	1	100	100	1	0	0
FLIPI	Low	21	90	76	14	2	3
	Intermediate	10	90	70	7	0	2
	Poor	9	56	44	4	0	1
Prior R-Chemo	Yes	23	83	70	15	1	3
	No	17	82	65	10	1	3
Prior R-CHOP	Yes	18	94	78	13	1	3
	No	22	73	59	12	1	3
1 prior regimen		13	92	85	10	1	1
2 or 3 prior regimens		14	86	71	9	1	2
≥4 prior regimens		13	69	46	6	0	3

CR, complete remission; CRu, complete remission unconfirmed; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; LG-B-NHL-NOS, low-grade B-NHL, not otherwise specified; MALT, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; PR, partial remission; R-chemo, rituximab-containing chemotherapy; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; SLL, small lymphocytic lymphoma.

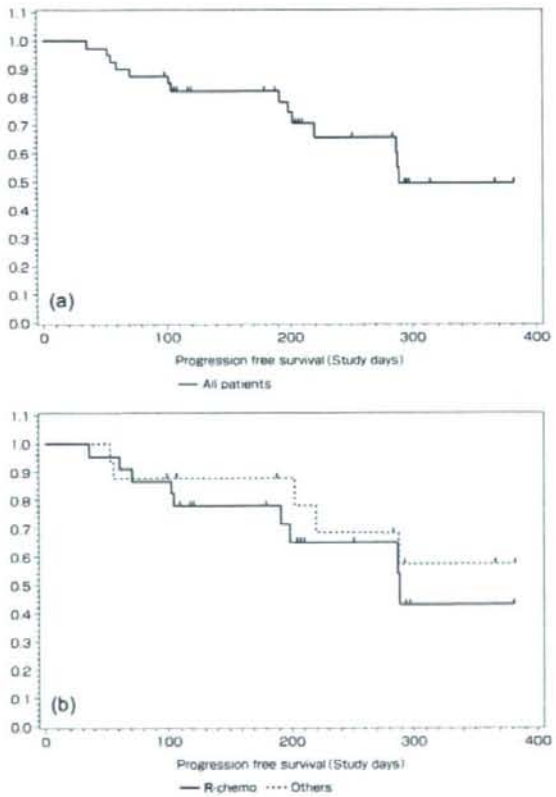

Fig. 1. Kaplan–Meier curve of progression-free survival. (a) All treated patients ($n = 40$); (b) patients with ($n = 23$) or without prior treatment with rituximab plus chemotherapy (R-chemo) ($n = 17$).

Table 3. Incidence of grade 3 or 4 hematological toxicities in 40 patients treated with ^{90}Y-ibritumomab tiuxetan ($n = 40$)[1]

Hematological toxicity		Baseline platelet count (/L)		
		$\geq 100 \times 10^9$, $< 150 \times 10^9$ ($n = 18$)	$\geq 150 \times 10^9$ ($n = 22$)	Total ($n = 40$)
		n (%)	*n* (%)	*n* (%)
Leukopenia	Grade 3	9 (50)	10 (45)	19 (48)
	Grade 4	5 (28)	7 (32)	12 (30)
Neutropenia	Grade 3	5 (28)	8 (36)	13 (33)
	Grade 4	7 (39)	10 (45)	17 (43)
Thrombocytopenia	Grade 3	13 (72)	14 (64)	27 (68)
	Grade 4	0 (0)	2 (9)	2 (5)
Anemia	Grade 3	2 (11)	7 (32)	9 (23)
	Grade 4	1 (6)	1 (5)	2 (5)

[1]In the five patients who received In2B8 alone, there was one with neutropenia.

Non-hematological toxicities were very mild (Table 5). No grade 4 non-hematological toxicities were observed during the study. The most frequent grade 3 non-hematological toxicities were febrile neutropenia, cystitis, and pneumonia, each in two patients (5%).

Twenty-two AE requiring hospitalization were observed in 11 patients (28%) during the study period: five patients with baseline platelet counts between 100×10^9/L and 150×10^9/L, and six with counts of 150×10^9/L or more. In 10 patients, a causal relationship with the study drug was suspected: seven neutropenia, seven thrombocytopenia, four leukopenia, one pancytopenia, one febrile neutropenia, and one pneumonia. Of the 10 patients who developed serious hematological AE requiring hospitalization, seven had received purine analogs (six with fludarabine and one with cladribine), and one had received interferon-α. All patients recovered from these AE.

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Table 4. Nadir analysis of hematological toxicities

Parameter	Baseline	Nadir	[1]Median days from baseline to nadir (range)	[2]Median days from nadir to recovery[1] (range)
Baseline platelet counts ≥ 100 × 10⁹/L, <150 × 10⁹/L (*n* = 18)				
ANC (×10⁹/L)	3.2	0.6	55 (36–102)	7 (4–49)
Platelet count (×10⁹/L)	140	32	41.5 (32–60)	15 (2–42)
Hemoglobin (g/dL)	14.0	10.9	67 (3–107)	12.5 (4–112)
Baseline platelet counts = 150 × 10⁹/L (*n* = 22)				
ANC (×10⁹/L)	2.8	0.5	52.5 (41–174)	10.5 (2–35)
Platelet count (×10⁹/L)	215	31	42.5 (35–51)	11 (2–30)
Hemoglobin (g/dL)	13.1	9.8	57.5 (1–115)	25 (7–35)
Overall (*n* = 40)				
ANC (×10⁹/L)	3.0	0.6	54.5 (36–174)	10 (2–49)
Platelet count (×10⁹/L)	184	31	42 (32–60)	14 (2–42)
Hemoglobin (g/dL)	13.5	10.2	63 (1–115)	21 (4–112)

[1]ANC ≥ 1 × 10⁹/L, platelet counts ≥ 50 × 10⁹/L, hemoglobin ≥ 10.0 g/dL.
[2]Days from the first rituximab infusion.
ANC, absolute neutrophil counts.

Table 5. Incidence of common[1] and all grade 3 or 4 non-hematological adverse events (*n* = 40)

Non-hematological event	Baseline platelet count (/L)						Overall (*n* = 40)		
	≥100 × 10⁹, <150 × 10⁹ (*n* = 18)			≥150 × 10⁹ (*n* = 22)					
	Grade 3 *n*	Grade 4 *n*	Any grade *n* (%)	Grade 3 *n*	Grade 4 *n*	Any grade *n* (%)	Grade 3 *n*	Grade 4 *n*	Any grade *n* (%)
LDH elevation	0	0	11 (61)	0	0	8 (36)	0	0	19 (48)
Headache	0	0	5 (28)	0	0	9 (41)	0	0	14 (35)
Stomatitis	0	0	4 (22)	0	0	8 (36)	0	0	12 (30)
Bilirubin elevation	1	0	7 (39)	0	0	4 (18)	1	0	11 (28)
Malaise	0	0	7 (39)	0	0	4 (18)	0	0	11 (28)
Pyrexia	0	0	5 (28)	0	0	5 (23)	0	0	10 (25)
Constipation	0	0	2 (11)	0	0	8 (36)	0	0	10 (25)
Hemorrhage subcutaneous	0	0	4 (22)	0	0	5 (23)	0	0	9 (23)
ALT elevation	0	0	4 (22)	0	0	5 (23)	0	0	9 (23)
AST elevation	0	0	4 (22)	0	0	4 (18)	0	0	8 (20)
Urticaria	1	0	3 (17)	0	0	5 (23)	1	0	8 (20)
Diarrhea	0	0	2 (11)	0	0	6 (27)	0	0	8 (20)
Nausea	0	0	4 (22)	0	0	4 (18)	0	0	8 (20)
Fatigue	0	0	3 (17)	0	0	4 (18)	0	0	7 (18)
Anorexia	0	0	3 (17)	0	0	4 (18)	0	0	7 (18)
Blood urine present	0	0	1 (6)	0	0	6 (27)	0	0	7 (18)
Cough	0	0	3 (17)	0	0	4 (18)	0	0	7 (18)
Nasopharyngitis	0	0	2 (11)	0	0	5 (23)	0	0	7 (18)
Dizziness	0	0	2 (11)	0	0	4 (18)	0	0	6 (15)
Total protein decreased	0	0	3 (17)	0	0	3 (14)	0	0	6 (15)
Upper respiratory tract inflammation	1	0	2 (11)	0	0	4 (18)	1	0	6 (15)
Hypersensitivity	0	0	1 (6)	1	0	4 (18)	1	0	5 (13)
Febrile neutropenia	1	0	1 (6)	1	0	1 (5)	2	0	2 (5)
Cystitis	1	0	1 (6)	1	0	1 (5)	2	0	2 (5)
Pneumonia	1	0	1 (6)	1	0	1 (5)	2	0	2 (5)
Infection, NOS	0	0	0 (0)	1	0	1 (5)	1	0	1 (3)

[1]≥15% incidence of adverse events in total.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; NOS, not otherwise specified.

Granulocyte colony-stimulating factors (G-CSF) and transfusions were given frequently (Table 6). In total, 21 patients (53%) received G-CSF. Platelet transfusion was required in 16 patients (40%). The G-CSF use and transfusion requirement were similar in the two cohorts.

Six patients showed prolonged cytopenia of over 100 days from initial grade 3 to final grade 3. Leukopenia occurred in six, neutropenia in four, thrombocytopenia in two, and anemia in one. One patient showed prolonged pancytopenia requiring approximately 1 year for recovery to grade 2 or less after receiving Y2B8 (14.8 MBq/kg [0.4 mCi/kg]). This patient had follicular lymphoma without bone marrow involvement and had been treated with five regimens including fludarabine.

Discussion

The present study provided additional evidence that ^{90}Y-ibritumomab tiuxetan RIT is highly effective and safe for

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Table 6. Treatment with granulocyte colony-stimulating factors (G-CSF) and transfusion

Treatment	Baseline platelet count (/L)		
	≥100 × 10⁹, <150 × 10⁹ (*n* = 18)	≥150 × 10⁹ (*n* = 22)	Total (*n* = 40)
	n (%)	*n* (%)	*n* (%)
G-CSF and/or transfusion	11 (61)	12 (55)	23 (58)
G-CSF	10 (56)	11 (50)	21 (53)
Platelet transfusion	7 (39)	9 (41)	16 (40)
Red blood cell transfusion	1 (6)	3 (14)	4 (10)

patients with relapsed or refractory indolent B-NHL. It achieved a high %CR for patients treated previously with R-chemo including R-CHOP. The ORR and %CR were 83 and 68%, respectively, in patients pretreated with R-chemo. These results justify the use of ^{90}Y-ibritumomab tiuxetan RIT in patients with relapsed or refractory indolent B-NHL who have undergone R-chemo.

The efficacy of ^{90}Y-ibritumomab tiuxetan RIT for relapsed or refractory diffuse large B-cell lymphoma (DLBCL) was reported recently.[23] In this phase II study,[23] the ORR for relapsed or refractory DLBCL pretreated with R-chemo was only 19% compared with 53% in patients pretreated with chemotherapy alone, and the median PFS in the former was only 1.6 months. These results and those of the present study suggest that the role of ^{90}Y-ibritumomab tiuxetan RIT in patients pretreated with R-chemo might be different between DLBCL and indolent B-NHL.

Compared with previous US studies for relapsed or refractory indolent B-NHL, including a randomized controlled study with rituximab (34% [25/73])[24] and a phase II study for rituximab-refractory patients (15% [8/54]),[10] the %CR in the present phase II study (68% [27/40]) was higher, probably due to the differences in eligibility criteria and the response criteria.[10,19,24]

In the current study patients with only one prior therapy fared better than patients with four or more prior regimens, as shown in Table 2. In ^{131}I-tositumomab RIT, first-line use was associated with higher rates of ORR (95%) and %CR (75%).[25] In addition, promising results of abbreviated fludarabine followed by ^{131}I-tositumomab RIT[26] and CHOP followed by ^{131}I-tositumomab RIT[27] were reported. Thus, RIT might be a treatment option early in the course of this difficult-to-cure disease, although further studies are needed.

The principal toxicities of ^{90}Y-ibritumomab tiuxetan RIT were hematological, similar to in the preceding US studies.[10,24,28] They were mostly transient and reversible, with hematological values reaching their nadirs in 6–9 weeks and recovering to grade 2 or less in 2 or 3 weeks after that; however, prolonged cytopenia was observed in six patients (15%) in the present study. These toxicities need to be followed carefully and be treated appropriately, with transfusions or cytokines if necessary. In contrast, non-hematological toxicities of ^{90}Y-ibritumomab tiuxetan RIT were mild, with no grade 4 toxicities.

In conclusion, ^{90}Y-ibritumomab tiuxetan RIT is safe and highly effective in the treatment of patients with relapsed or refractory indolent B-NHL, including those pretreated with R-chemo.

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Appendix

The participating institutions and principal investigators of the ^{90}Y-Ibritumomab Tiuxetan Study Group included the following: Tohoku University Hospital (K. Ishizawa, J. Kameoka, H. Harigae, T. Kaneda), National Cancer Center Hospital East (H. Minami, K. Itoh, M. Nakata, S. Nawano), National Cancer Center Hospital (K. Tobinai [study chair], Y. Kobayashi, T. Watanabe, D. Maruyama, S. Terui), Keio University (S. Okamoto, A. Kubo, T. Nakahara), Tokai University Hospital (T. Hotta, Y. Ogawa, A. Kikuchi, Y. Imai), Aichi Cancer Center Hospital (Y. Morishima, M. Ogura, Y. Kagami, H. Yamaura), Kyoto Prefectural University of Medicine (M. Taniwaki, K. Nomura, Y. Matsumoto, T. Nishimura, Y. Ushijima), Gunma University (N. Tsukamoto, K. Endo, N. Oriuchi), and Kanazawa University (H. Okumura, S. Kinuya, K. Yokoyama).

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Lecture

解　説

限局期びまん性大細胞型B細胞リンパ腫の治療：現在の標準治療と今後の課題*

木下朝博**

Key Words：diffuse large B-cell lymphoma, CHOP, rituximab, radiotherapy

はじめに

Diffuse large B-cell lymphoma（DLBCL）はいわゆる中高悪性度リンパ腫の主要な部分を占める，わが国ではもっとも頻度が高い悪性リンパ腫病型である．モノクローナル抗体治療が開発されるまではB細胞リンパ腫やT細胞リンパ腫は基本的に同じ治療方法が用いられてきた．DLBCLを含むaggressive lymphomaに対しては，シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロン（CHOP）療法が標準的化学療法として位置づけられてきた．しかし近年，抗CD20モノクローナル抗体薬剤リツキシマブが開発されて，B細胞リンパ腫とT細胞リンパ腫は異なる治療法が行われるようになった．現在DLBCLに対してはリツキシマブ併用CHOP（R-CHOP）療法が標準的治療である．また放射線治療も有効であり，化学療法との併用療法も広く行われている．

本稿では限局期DLBCLに対する治療研究を概観し，現在の標準的治療と今後の課題について考察したい．

限局期DLBCLについて

限局期とはAnn Arbor分類での臨床病期IおよびII期に該当する．ただし一般的には巨大腫瘤病変を有するII期は進行期に準じた治療が行われる．巨大腫瘤病変を有するI期の取り扱いは研究グループによって異なる．放射線治療においては，臨床病期II期の中でも病変が連続性に存在して1照射野として治療可能であることがポイントとなる．

進行期中高悪性度リンパ腫における代表的な予後予測モデルはInternational Prognostic Index（IPI）である[1]．しかし限局期については，IおよびII期のみとなるためIPIでの臨床病期区分（I/II vs. III/IV）は意味をもたない．同様に節外病変数2個以上は臨床病期IV期となるため無意味である．これらを考慮して，SWOGからstage-modified IPIが提唱されている[2]．すなわち，臨床病期II期，年齢61歳以上，performance status（PS）2以上，血清LDH高値の4つの予後不良因子に基づいて層別化するものである．

限局期中高悪性度リンパ腫に対する治療研究

限局期中高悪性度リンパ腫に対するもっとも重要な臨床試験の1つはSWOGのS8736である[2]．臨床病期I期，および巨大腫瘤病変を有しないII期の症例を対象として，標準的なCHOP8コース（CHOP×8）と，CHOP3コースに引き続いてinvolved field radiation（IF-RT），40～55Gyを行うcombined modality treatment（CMT）（CHOP×3＋IF-RT）がランダム化試験によって比較検討された．5年無増悪生存割合はCHOP×3＋IF-RTで77%に対してCHOP×8で64%，5年全生存割合

* Treatment for localized diffuse large B-cell lymphoma.

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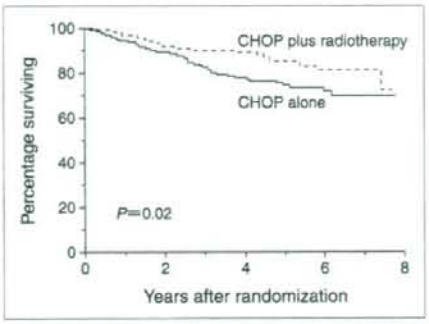

図1　限局期中高悪性度リンパ腫に対するCHOP×8とCHOP×3＋IF-RTの無作為化比較試験（S8736）における生存曲線
5年生存割合はCHOP×3＋IF-RTで82％に対してCHOP×8で72％であり，CHOP×3＋IF-RTがCHOP×8より有意に良好だった．（文献[2]より引用改変）

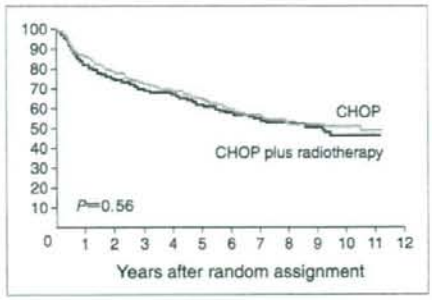

図2　高齢者限局期中等悪性度リンパ腫に対するCHOP×4＋IF-RTとCHOP×4の無作為化比較試験の無事故生存曲線
両群の無事故生存割合には有意差を認めない．（文献[3]より引用改変）

はCHOP×3＋IF-RTで82％に対してCHOP×8で72％であり，有意にCHOP×3＋IF-RTが勝っていた（図1）．

一方GELAでは高齢者限局期aggressive lymphomaを対象としたCHOP×4＋IF-RTとCHOP×4のランダム化試験が行われた[3]．対象は61歳以上の高齢者限局期aggressive lymphomaで，age-adjusted IPIでの予後不良因子を有しない患者である．5年無事故生存割合はCHOP×4＋IF-RTで64％に対してCHOP×4で61％，5年全生存割合はCHOP×4＋IF-RTで68％に対してCHOP×4で72％であり，両群に有意差を認めなかった（図2）．この試験結果からCHOP×4＋IF-RTはCHOP×4に勝らないとされた．これは前述のS8736とは一致しない結果である．

GELAでは若年限局期aggressive lymphomaを対象としたCHOP×3＋IF-RTと治療強度を高めた併用化学療法であるACVBP療法とのランダム化試験が行われ，ACVBP療法が勝ることが報告された[4]．しかし，ACBVP療法はCHOP療法に比べて治療強度が高く高毒性であることなどから，限局期に対する治療としては一般化していない．

進行期DLBCLに対するリツキシマブを用いた治療研究

マウス・ヒトキメラ型抗CD20モノクローナル抗体であるリツキシマブはB細胞表面抗原であるCD20を標的とする薬剤であり，B細胞リンパ腫に対して高い治療効果を示す．リツキシマブは主にcomplement-dependent cytotoxicity（CDC；補体依存細胞傷害反応）やantibody-dependent cellular cytotoxicity（ADCC；抗体依存性細胞傷害反応）といった機序によってCD20陽性細胞を傷害する．このほかに免疫反応を介さずアポトーシスを誘導することもその作用機序とされる．リツキシマブは通常の化学療法剤と薬物有害反応が重複しないために化学療法への併用が可能である．

R-CHOP療法はもっとも代表的なリツキシマブ併用化学療法である．DLBCLに対するR-CHOPの有用性を検証する複数の大規模臨床試験が施行された．GELAでは未治療高齢者DLBCLを対象としたR-CHOPとCHOPのランダム化試験が実施され，event free survival（EFS），overall survival（OS），完全奏効（complete response；CR）割合すべてでR-CHOPがCHOPに勝った（図3）[5][6]．米国でも未治療高齢者DLBCLを対象としたR-CHOPとCHOPの比較試験（E4494）が施行された．E4494はR-CHOPまたはCHOPでCRまたはpartial response（PR）が得られた場合にさらにリツキシマブ維持療法を施行する群としない群に割り付ける複雑な試験デザインである[7]．3年failure free survival（FFS）はR-CHOPがCHOPに勝った．また維持療法割り付け後2年でのFFSでは維持療法施行群が維持療法を施行しない群に勝った．た

だしOSではR-CHOPとCHOP，および維持療法の有無によって有意差を認めなかった．その理由はCHOP群では維持療法が有効だったのにR-CHOP群では有効性が乏しかったためとされた．維持療法を施行しなかった例に限ればR-CHOPはCHOPに対してFFS，OSともに有意に勝っていた．

MInT studyでは予後不因子が少ない若年者DLBCLを対象として，CHOP-like chemotherapyとリツキシマブを併用したCHOP-like chemotherapyが比較された[8]．対象は18歳から60歳，臨床病期はbulky diseaseを有するⅠ期，およびⅡ～Ⅳ期，age-adjusted IPIでlow riskおよびlow intermediate risk groupに属する予後良好なDLBCLである．リツキシマブ併用化学療法施行群は化学療法群に対してEFS，OSともに勝っていた（図4）．

さらにドイツではリツキシマブ併用CHOP-14（R-CHOP-14）とリツキシマブを併用しないCHOP-14の比較試験（RICOVER-60）が行われた[9]．61歳から80歳の高齢者DLBCLを対象として，CHOP-14が6または8コース，およびリツキシマブ併用ありまたはなしの合計4群にランダム割り付けを行って比較検討した．評価可能1,222例の解析で，6コースのCHOP-14と比べた場合3年EFSはR-CHOP-14 6コース，8コースともに有意に優れていた．3年OSについてはR-CHOP-14はR-CHOP-14に有意に勝ったが，R-CHOP-14 8コースについてはCHOP-14 6コースと有意差を認めなかった．この結果から高齢者DLBCLに対しては6コースのR-CHOP-14が標準的治療であるとされた．

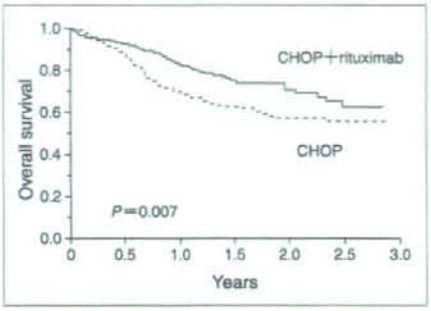

図3　高齢者DLBCLに対するR-CHOPとCHOPの無作為化比較試験
R-CHOPではCHOPよりも有意に生存期間が改善していた．（文献[7]より引用改変）

以上に示したような大規模試験の結果から，R-CHOPは進行期DLBCLに対する標準的治療法として確立したといえる．

限局期DLBCLに対するリツキシマブを用いた治療研究

以上のように進行期DLBCLに対してはいくつ

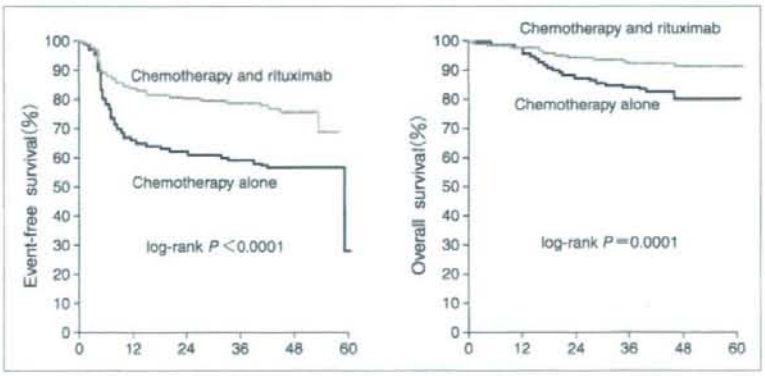

図4　予後不良因子が少ない若年者DLBCLを対象としたリツキシマブ併用CHOP-like chemotherapyとCHOP-like chemotherapyのランダム化試験（MinT試験）
対象はBulky diseaseを有するⅠ期およびⅡ～Ⅳ期．リツキシマブ併用CHOP-like chemotherapyがCHOP-like chemotherapyに比べて無事故生存期間，全生存期間ともに勝っていた．
（文献[8]より引用改変）

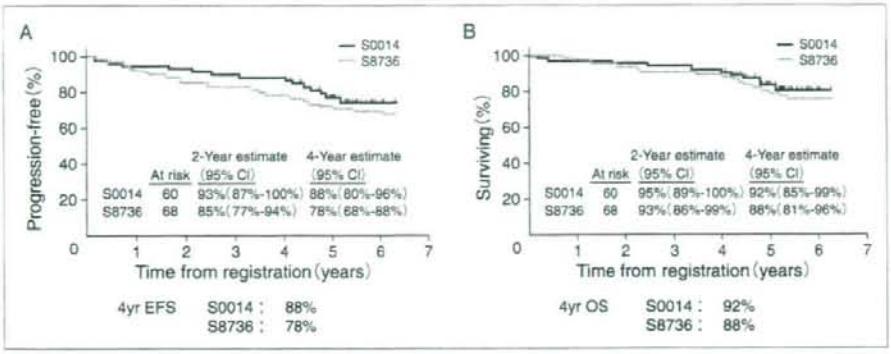

図5　限局期DLBCLに対するR-CHOP×3＋IF-RT（S0014）とCHOP×3＋IF-RT（S8736）の後方視的な比較検討での生存曲線

SWOG8706については組織型とstage-modified IPIがS0014と一致する症例を抽出した．A：無事故生存曲線，B：全生存曲線．4年無事故生存割合はS8736の78％に対して，S0014では88％，4年生存割合はS8736の88％に対して，S0014では92％だった．（文献[10]より引用改変）

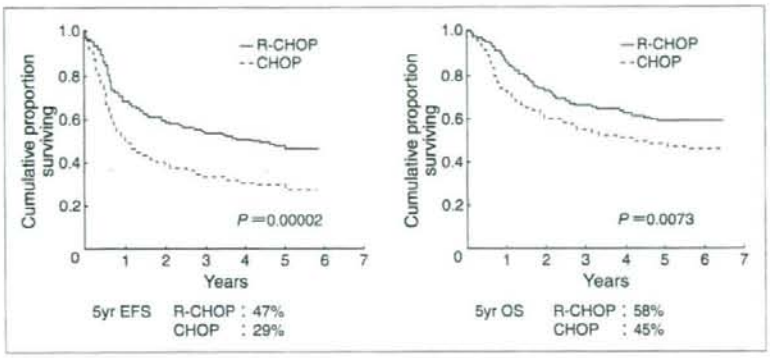

図6　高齢者DLBCLに対するR-CHOPとCHOPの無作為化比較試験の長期観察結果

5年無増悪生存割合はCHOPの29％に対して，R-CHOPでは47％，5年全生存割合はCHOPの45％に対して，R-CHOPでは58％だった．（文献[6]より引用改変）

もの大規模ランダム化試験が行われた結果R-CHOP療法が標準的治療として確立した．一方リツキシマブを用いた限局期DLBCLに対する大規模試験は乏しい．SWOGはstage-modified IPIで1つ以上のrisk factorを有する限局期DLBCL 62例を対象にして，R-CHOP×3＋IFRT（リツキシマブは4回投与）の臨床第II相試験（S0014）を施行した[10]．4年全生存割合は92％，4年無増悪生存割合も88％とその治療成績は良好だった（図5）．ただしこの試験においてはR-CHOPで治療された進行期DLBCLにおいて認められるような無増悪生存曲線や生存曲線の平坦化が認められず，再発が持続する問題が指摘されている．また，S8736とS0014で背景因子を一致させて後方視的に比較すると，R-CHOP×3＋IF-RTとCHOP×3＋IF-RTの生存期間の差は比較的小さい．この結果は進行期DLBCLに対してCHOPにリツキシマブを追加した場合の生存期間の著しい改善に比べた場合，CHOP×3＋IF-RTへのリツキシマブの追加効果は比較的限定的である可能性を示唆している（図5，6）．

MinTは若年者で低リスクのDLBCLを対象とした臨床試験で，R-CHOPなどのリツキシマブ併用化学療法を6コース施行した群が化学療法のみ

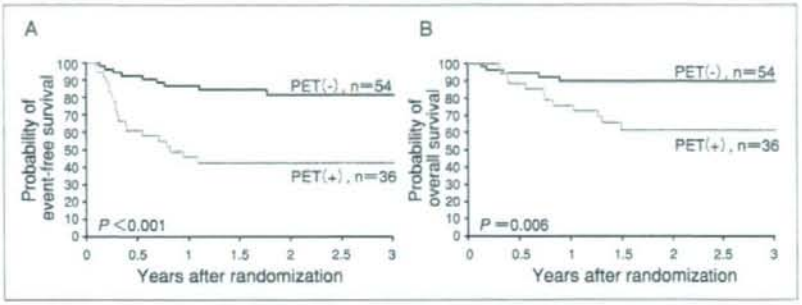

図7　Aggressive lymphomaにおける治療途中のPET評価と予後
94％の症例はDLBCLだった．A：無事故生存期間，B：全生存期間．2コースの化学療法終了時にPETを施行．PET陰性群ではPET陽性群に比べて無事故生存期間，全生存期間ともに有意に良好だった．
（文献[12]より引用改変）

の群に対して生存期間で勝ることを明らかにした試験である[8]．この試験は限局期DLBCLに対する研究としても注目される．すなわちMinTには臨床病期I/II期の限局期症例が72％含まれていた．MinTの結果ではリツキシマブ併用化学療法と化学療法の3年無事故生存割合がそれぞれ79％と59％，3年全生存割合が93％と84％であり，リツキシマブ併用化学療法で優れていた．本試験では巨大腫瘤病変や節外病変部位に対して補助的な放射線治療が施行されたが，その試験結果からは若年低リスクの限局期DLBCLに対して，リツキシマブ併用化学療法と巨大腫瘤病変や節外病変部位への補助的な放射線治療の併用療法が高い治療効果を示すことが明らかとなった．

FDG-PETは現在では悪性リンパ腫の診断と治療効果判定に広く用いられている．また，Hodgkin lymphomaやDLBCLでは治療途中のPET評価が予後因子となることが報告されており（図7）[11][12]，治療途中のPET評価を治療変更の重要な指標とする研究も活発化している．British Columbia Cancer Agency（BCCA）では巨大腫瘤病変を伴わない臨床病期I/II期のDLBCLに対して，R-CHOPの治療途中にFDG-PET評価を行いその結果による治療法の選択が行われている．すなわちR-CHOPを3コース施行したのちFDG-PETを行い，FDG-PET陰性の場合はR-CHOPを1コース追加して治療を完了し，FDG-PET陽性の場合はIF-RTを30Gy施行するというものである．2007年の米国血液学会では初期50例の治療成績が報告された[13]．観察期間の中央値は17か月（4～26か月）で，37例（74％）はFDG-PETが陰性となったが，1例が再発したのみだった．一方FDG-PETが陽性だった13例（26％）中3例が再発して2例がリンパ腫によって死亡した．2年PFSはFDG-PET陰性群で97％，陽性群で75％，2年OSはそれぞれ97％と69％だった（図8）．この結果からは，限局期DLBCLではR-CHOPの途中でFDG-PET評価を行うことで放射線治療を行わないで良好な治療効果が得られる群が同定しうる可能性が示唆される．ただし本成績についてはいまだ観察期間が短いため，さらに長期の観察が必要である．

限局期中高悪性度リンパ腫に対する標準的治療

DLBCLについては後述する．リツキシマブの適応がない限局期中高悪性度リンパ腫に対する標準的治療はCHOP×3コース＋IF-RTのCMTである．標準的CHOP療法を3週間隔で3コース施行し，引き続いて病巣に対する40GyのIF-RTを施行する．放射線治療の効果が不十分な場合は合計55Gyまでの増量を検討する．

CMTにおいては放射線治療の有害事象が問題となる場合がある．たとえば頭部やWaldeyer病変では口腔乾燥症によるQOL低下が問題となる．このような場合には，CMTに変えてCHOP×8コースを行うことも考慮すべきである．逆に合併症などのために化学療法の耐用性が低いと考えられる場合にはCHOP×8コースを選択せずにCMT

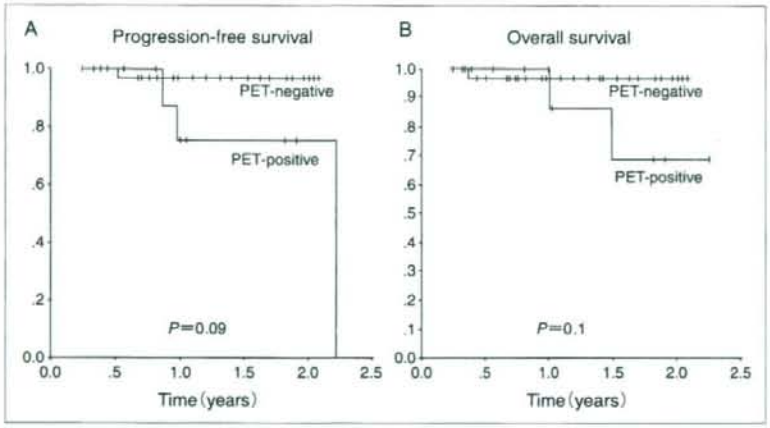

図8　限局期DLBCLに対する治療途中でのPET評価に基づく治療成績
A：無増悪生存期間，B：全生存期間．3コースのR-CHOP後にPETを行い，PET陰性ではR-CHOPを1コース追加して合計4コースで治療完了，PET陽性では放射線治療を追加する．観察期間中央値17か月（4～26か月）でPET陰性化37例中再発は1例のみだったのに対して，PET陽性では13例中3例が再発した．（文献[13]より引用改変）

を選択することが合理的である．

限局期DLBCLに対する標準的治療

リツキシマブ導入後に報告された限局期DLBCLを対象とした大規模臨床試験の成績は乏しく，標準的治療は未確立である．一般的には，進行期DLBCLに対するR-CHOPの成績を踏まえ，限局期DLBCLに対する化学療法としてもR-CHOPが行われている．SWOGから報告されたR-CHOP×3（リツキシマブは4回投与）＋IF-RTのCMT（S0014）や，MinTで行われたR-CHOP×6コースが標準的治療の候補と考えられる．リツキシマブの適応がない中高悪性度リンパ腫の項に記載したように，放射線治療の有害事象が問題となる場合にはCMTではなくR-CHOP×6～8を行うことも十分に考慮すべきである．

限局期DLBCLのうち特定の節外性リンパ腫では通常の限局期DLBCLとは異なる治療法が行われる場合がある．たとえば中枢神経原発DLBCLではメトトレキサート大量療法と全脳照射などからなる治療法が行われる．また精巣原発DLBCLでは高率に中枢神経や対側精巣に再発を認めるため，R-CHOPに加えて中枢神経浸潤予防としての抗がん剤の髄腔内投与と対側精巣への予防的な放射線治療が行われている．このように，節外性DLBCLは原発臓器によって異なる臨床像や治療への反応性を示すため，その病態を考慮した治療法が必要となる場合がある．

今後の課題

限局期DLBCLについてはR-CHOP×3＋IF-RTのCMT，R-CHOP×6コースなどが行われているが，前述のように標準的治療は未確立である．今後放射線治療の位置づけ，R-CHOPのコース数，リツキシマブの投与回数などに関する検討が必要である．

欧米では放射同位元素で標識された抗CD20モノクローナル抗体薬剤，イブリツモマブ（ibritumomab tiuxetan，Zevalin®）やトシツモマブ（Bexxar®）を用いた治療研究が行われている．わが国においてはZevalin®が認可されたが，適応疾患はCD20陽性の再発または難治性の低悪性度B細胞性非ホジキンリンパ腫およびマントル細胞リンパ腫であり，初発DLBCLに対する保険適用はない．米国ではZevalin®を組み込んだ限局期DLBCLに対する治療研究が行われており，その結果が注目される．

前述のように，現在FDG-PETは悪性リンパ腫

の診断と治療効果判定に広く用いられつつある．しかし治療途中のPET評価に基づいて治療法を変更することによって予後が改善するかどうかは証明されていないため，いまだ研究段階にあることに留意が必要である．したがって限局期DLBCLについても，BCCAから報告されたような治療途中のFDG-PET結果に基づく治療変更は実地診療における診療方針とすべきではない．

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ORIGINAL REPORT

Retrospective Analysis of Intravascular Large B-Cell Lymphoma Treated With Rituximab-Containing Chemotherapy As Reported by the IVL Study Group in Japan

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ABSTRACT

Purpose
To evaluate the safety and efficacy of rituximab-containing chemotherapies for intravascular large B-cell lymphoma (IVLBCL).

Patients and Methods
We retrospectively analyzed 106 patients (59 men, 47 women) with IVLBCL who received chemotherapy either with rituximab (R-chemotherapy, n = 49) or without rituximab (chemotherapy, n = 57) between 1994 and 2007 in Japan. The median patient age was 67 years (range, 34 to 84 years). The International Prognostic Index was high-intermediate/high in 97% of patients.

Results
The complete response rate was higher for patients in the R-chemotherapy group (82%) than for those in the chemotherapy group (51%; $P = .001$). The median duration of follow-up for surviving patients was 18 months (range, 1 to 95 months). Progression-free survival (PFS) and overall survival (OS) rates at 2 years after diagnosis were significantly higher for patients in the R-chemotherapy group (PFS, 56%; OS, 66%) than for patients in the chemotherapy group (PFS, 27% with $P = .001$; OS, 46% with $P = 0.01$). Multivariate analysis revealed that the use of rituximab was favorably associated with PFS (hazard ratio [HR], 0.45; 95% CI, 0.25 to 0.80; $P = .006$) and OS (HR, 0.42; 95% CI, 0.21 to 0.85; $P = .016$). Treatment-related death was observed in three patients (6%) who received R-chemotherapy and in five patients (9%) who received chemotherapy.

Conclusion
Our data suggest improved clinical outcomes for patients with IVLBCL in the rituximab era. Future prospective studies of rituximab-containing chemotherapies are warranted.

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INTRODUCTION

Intravascular large B-cell lymphoma (IVLBCL) is a rare subtype of extranodal diffuse large B-cell lymphoma (DLBCL), as classified by WHO.[1] IVLBCL is a rapidly progressive and often disseminated tumor that is characterized by selective growth of lymphoma cells only in the lumina of small vessels of various organs.[2-6] The absence of marked lymphadenopathy makes accurate and timely diagnosis difficult. In previous reports, approximately half of patients were diagnosed postmortem.[7] Accuracy of diagnosis for this type of lymphoma has improved recently with the development of diagnostic procedures, such as random skin biopsies and repetitive bone marrow biopsies.[8-10]

Anthracycline-containing chemotherapies have been reported to improve clinical outcomes for patients with IVLBCL.[11] A recent study demonstrated a 3-year overall survival (OS) rate of 33% for patients with IVLBCL who received anthracycline-based chemotherapies.[12] This was comparable to that for common DLBCL patients,[13] but it remained unsatisfactory without application of rituximab.

Rituximab is a chimeric monoclonal antibody against CD20[14] that is highly effective against various types of CD20-positive B-cell lymphomas.[15,16] Addition of rituximab to cyclophosphamide, vincristine, doxorubicin, and prednisolone (CHOP) and CHOP-like regimens has been found to improve the outcome of DLBCL.[17,18] Improvement of clinical outcomes in IVLBCL, thus, has been

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expected with the use of rituximab. However, although several recent reports have suggested efficacy of rituximab,[19-21] no large-scale study has been reported previously. The safety of rituximab for patients with IVLBCL has remained unclear regarding the presence of tumor cells in the lumina of vessels.[22] To elucidate the efficacy and safety of rituximab added to chemotherapy treatments for IVLBCL, we retrospectively analyzed patients who received chemotherapy either with rituximab (R-chemotherapy) or without rituximab (chemotherapy).

PATIENTS AND METHODS

Patient Selection

Sixty-eight patients who were diagnosed with IVLBCL between 1999 and 2007 were retrospectively registered from 17 participating centers. We registered consecutive patients who were diagnosed with IVLBCL regardless of ante- or postmortem diagnosis and administration of chemotherapy or not. Of these 68 patients, 62 patients (91%) received chemotherapy (ie, present series). IVLBCL was diagnosed by expert hematopathologists in each institute in accordance with the WHO classification.[1] Patients were diagnosed with IVLBCL only when tumor cells filled the small vessels in organ biopsy specimens and/or were present in intrasinusoidal patterns in bone marrow specimens. Patients were excluded from the study if extravascular components were suggestive of DLBCL with intravascular patterns in diagnostic tissue specimens. CD20 and/or CD79a positivity on tumor cells was confirmed by immunohistochemical staining or by flow cytometry. The study protocols were approved by the institutional review board at each participating hospital and complied with all provisions of the Declaration of Helsinki.

We previously have reported in detail about 96 patients with IVLBCL from a pathologic perspective.[23] We selected 44 of the 62 patients from this previous series who received chemotherapy and could be analyzed in detail. The remaining 18 patients were eliminated, because we could not identify the treatment regimen, the first day of treatment, or the day of disease progression. The final analysis in the present study, therefore, included 106 patients with IVLBCL who received chemotherapy (Fig 1).

Treatment

Patients received treatment for IVLBCL according to the respective institutional protocols. Patients were eligible for this retrospective analysis if they received tentative steroid therapy for disease progression before definite diagnosis. Patients who received any cycles of rituximab (median, 8 cycles; range, 2 to 8 cycles) were analyzed as the R-chemotherapy group. The dose of rituximab was 375 mg/m^2 for all patients in the R-chemotherapy group. Patients who underwent autologous or allogeneic stem-cell transplantation after initial therapy or for the treatment of relapsed disease (RD) were eligible for analysis.

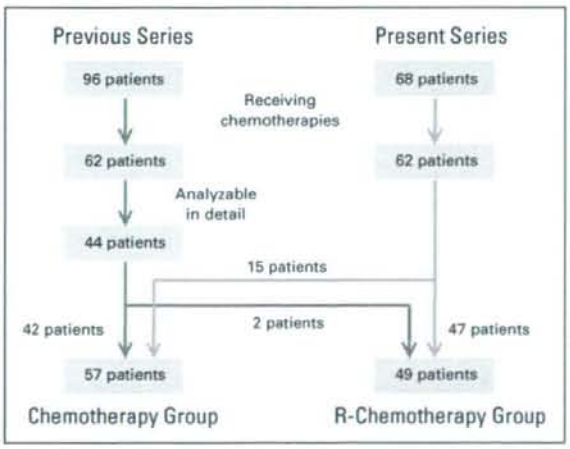

Fig 1. Patient selection. Blue lines represent the number of patients from the previous series. Yellow lines represent the number of patients from the present series. R-Chemotherapy, chemotherapy with rituximab.

Response to Treatment and Adverse Events

Antitumor responses were assessed after initial chemotherapy or at the end of treatment and were classified as complete response (CR), progressive disease (PD), no change, or RD. CR was defined as the disappearance of all clinical symptoms and of radiographic or clinical laboratory abnormalities (including in bone marrow) observed at diagnosis and the absence of any new abnormalities. PD was defined as the appearance of new abnormalities associated with the disease or evident deterioration of the initial abnormalities associated with the disease. No change was defined as no status that corresponded to complete response or progressive disease. RD was defined as the progression of disease after achievement of CR.

Grade 3 or 4 hematologic and nonhematologic adverse events observed by the physician were collected from the case report form. Each event was graded according to Common Toxicity Criteria for Adverse Events (version 3).[24] All adverse events related to the infusion of rituximab were collected. Grade 3 or 4 adverse events related to the infusion of rituximab were investigated in detail retrospectively.

Statistical Analysis

Distributions of variables between the R-chemoteherapy and chemotherapy groups were assessed by using Fisher's exact test. Progression-free survival (PFS) was calculated from the date of diagnosis to the first day of disease progression, relapse, death as a result of any cause, or last date of follow-up, whereas OS was calculated from the date of diagnosis to death or the last date of follow-up. PFS and OS were analyzed by using the log-rank test, and results were expressed by using Kaplan-Meier methods. Univariate and multivariate Cox regression analyses were performed to assess the effects of prognostic factors, including age, sex, "B" symptoms, clinical stage, performance status, number of extranodal sites, results of clinical laboratory tests (ie, lactate dehydrogenase, hemoglobin, platelet count, WBC, creatinine, albumin, and soluble interleukin-2 receptor level), Asian-variant of IVLBCL, hemophagocytic syndrome, use of rituximab, and clinical symptoms (ie, respiratory, neurologic) on PFS and OS. Multivariate analysis was built with a forward/backward, stepwise method by using threshold values for removal from and addition to the model of $P = .20$ and $P = .10$, respectively. All probability values were two-sided and had an overall significance level of .05. Statistical analyses were performed with Stata SE 9 software (StataCorp, LP, College Station, TX).

RESULTS

Patient Characteristics

Patient characteristics are listed in Table 1. The R-chemotherapy group comprised 49 patients, and the chemotherapy group comprised 57 patients (Fig 1). The median age of all patients in both groups was 67 years, and 76 patients (72%) were older than 60 years. All eligible patients displayed stage IV disease. According to the International Prognostic Index,[25] 90 patients (85%) were categorized as high risk. The numbers of patients with skin lesions, anemia, and elevated serum bilirubin levels differed significantly between the chemotherapy and R-chemotherapy groups ($P = .020$, $P = .037$, and $P = .026$, respectively).

Treatment

All patients, except one elderly patient, in the two series received anthracycline-containing chemotherapy. The CHOP regimen was used for initial treatment in 37 (65%) of 57 patients in the chemotherapy group and in 35 (71%) of 49 patients in the R-chemotherapy

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Table 1. Comparison of Patients Who Received Chemotherapy With or Without Rituximab

Characteristic	Treatment Group				
	Chemotherapy		R-Chemotherapy*		
	No.	%	No.	%	*P*
No. of patients	57		49		
Age at diagnosis, years					
Median	68		66		
Range	41-84		34-84		
> 60	37	65	39	80	.130
Sex, male	28	49	31	63	.172
PS > 1	46	81	36	73	.490
Serum LDH level > ULN	55	96	49	100	.498
Stage IV	57	100	49	100	—
Extranodal involvement > 1	38	67	36	73	.527
IPI					
Low or low-intermediate	2	4	1	2	.99
High-intermediate or high	55	96	48	98	.99
High	49	86	41	84	.790
Presence of "B" symptoms	47	82	42	86	.792
Hepatomegaly	31	54	20	41	.178
Splenomegaly	38	67	31	63	.838
Respiratory symptoms	21	37	14	31	.412
Neurologic symptoms	15	26	11	22	.659
Skin lesions	5	9	13	27	.020
Hemophagocytosis in BM	34	60	29	59	.99
Tumor cells in PB	15 of 55	27	20	41	.153
Anemia†	44	77	28	57	.037
Thrombocytopenia‡	35	61	27	55	.557
Leukocytopenia§	13	23	16	33	.282
Albumin level < 3.0 g/dL	31 of 54	57	31 of 48	65	.544
Bilirubin level ≥ 1.5 mg/dL	6 of 54	11	14 of 48	29	.026
Creatinine level ≥ 1.5 mg/dL	5 of 56	9	8 of 46	17	.242
CRP level ≥ 5.0 mg/dL	31 of 56	55	30 of 48	63	.550
sIL-2R level ≥ 5,000 U/L	28 of 48	58	35 of 48	73	.197
AIVL¶	34	60	25	51	.435
Date of diagnosis					
Pre–rituximab approval era					
December 1994 to August 2001‖	33	58	1	2	—
September 2001 to September 2003#	23	40	10	20	—
Post–rituximab approval era					
October 2003 to March 2007	1	2	38	78	—
Initial treatment					
CHOP or CHOP-like regimen	49	86	39	80	.443
Triweekly CHOP	32	56	32	65	.426
Biweekly CHOP	5	9	3	6	.722
CHOP-like	12	21	4	8	.101
Other	8	14	10	20	.443
Antitumor response					
CR	29	51	40	82	.001
NC	4	7	3	6	.99
PD	19	33	6	12	.012
NA	5	9	—	—	.060

Abbreviations: R-chemotherapy, chemotherapy with rituximab; PS, performance status; LDH, lactate dehydrogenase; ULN, upper limit of normal; IPI, international prognostic index; BM, bone marrow; PB, peripheral blood; CRP, C-reactive protein; sIL-2R, soluble interleukin-2 receptor; AIVL, Asian variant of intravascular large B-cell lymphoma; CHOP, cyclophosphamide, vincristine, doxorubicin, and prednisolone; CR, complete response; NC, no change; PD, progressive disease; NA, not assessable.

*Received rituximab in addition to chemotherapy.

†Hemoglobin < 11 g/dL or red blood cell count < $350 \times 10^4/\mu L$.

‡Platelet count < $10 \times 10^4/\mu L$.

§WBC count < 4,000/μL.

¶Diagnostic criteria of variant of intravascular large B-cell lymphoma[3]: (1) At least two of three of the following clinical and laboratory criteria: cytopenia (hemoglobin < 11 g/dL, or RBC < $350 \times 10^4/\mu L$, and/or platelet count < $10 \times 10^4/\mu L$); hepatomegaly and/or splenomegaly; absence of overt lymphadenopathy and tumor formation; and (2) all three of the following histopathologic criteria: erythrocyte-hemophagocytis; immunophenotypic evidence of proliferating neoplastic B cells with large-cell morphology; pathologic findings of intravascular proliferation and/or sinusoidal involvement of lymphoma cells.

‖Use of rituximab for indolent CD20-positive B-cell lymphoma was approved under the National Health Insurance system in August 2001.

#Use of rituximab for diffuse large B-cell lymphoma was approved under the National Health Insurance system in September 2003.

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group. A CHOP-like regimen was administered to 12 patients (21%) in the chemotherapy group and to four patients (8%) in the R-chemotherapy group. In all patients who received the CHOP regimen, 32 patients in each group (56% and 65% in chemotherapy and R-chemotherapy groups, respectively) received a CHOP regimen every 3 weeks (Table 1). Of the 49 patients in the R-chemotherapy group, 38 patients (81%) received greater than five courses of rituximab. In this group, 12 (24%) of the 49 patients received rituximab on the first day of treatment. Twenty-five patients (51%) received rituximab with or after the second course of chemotherapy. The median duration between start chemotherapy or prephase therapy and first rituximab dose was 17 days (range, 0 to 145 days; Table 2). Rituximab was administered by concurrent combination for 46 (94%) of the 49 patients, and sequential combination with administration of rituximab after a series of chemotherapy was only performed for three patients. No patients received rituximab as maintenance therapy until relapse. A total of seven patients (14%) in the R-chemotherapy and seven patients (12%) in the chemotherapy group received high-dose chemotherapy and underwent autologous stem-cell transplantation (ASCT). In this series, no patients received allogeneic stem-cell transplantation.

Efficacy

CR was achieved after initial treatment by 40 (82%) of 49 patients in the R-chemotherapy group and 29 (51%) of 57 patients in the chemotherapy group. Thus, the CR rate was higher for the R-chemotherapy group than for the chemotherapy group ($P = .001$; Table 1). PD during treatment was observed in six patients (12%) in the R-chemotherapy group and in 19 patients (33%) in the chemotherapy group. Four of six patients in the R-chemotherapy group and four of 19 patients in the chemotherapy group developed disease progression to the CNS. Five patients in the chemotherapy group were not assessed for treatment response because of early death and the resultant short observation period.

During a median follow-up of surviving patients in the R-chemotherapy group of 17 months (range, 5 to 62 months), RD developed in nine patients (23% of patients who achieved CR). Conversely, during a median follow-up for surviving patients in the chemotherapy group of 24 months (range, 1 to 95 months), RD developed in 19 patients (66% of patients who achieved CR). Three patients (6%) in the R-chemotherapy group died within 180 days after diagnosis, whereas 13 patients (23%) in the chemotherapy group died within 180 days after diagnosis (Wilcoxon test, $P = .007$). Two-year PFS and OS rates were 56% and 66%, respectively, in the R-chemotherapy group and 27% and 46%, respectively, in the chemotherapy group (log-rank test, $P = .001$ and $P = .01$, respectively; Figs 2 and 3).

The significant difference in early death within 180 days after diagnosis between groups might suggest that conditions for patients in the R-chemotherapy group were superior to conditions for those in the chemotherapy group, thus representing a guaranteed-time bias for patients in the R-chemotherapy group who could survive between the start of chemotherapy and the start of rituximab. To compensate for this potential bias, we excluded those three patients who received rituximab as sequential combination and matched the entry point into each cohort; that is, the entry point of the chemotherapy group was on day 1 of their chemotherapy, and that of the R-chemotherapy group was the commencement of rituximab. In this analysis, PFS and OS (the date of entry of each group) in the R-chemotherapy group were significantly superior to those in the chemotherapy group (log-rank test, $P < .001$ and $P = .003$, respectively).

In Japan, use of rituximab for DLBCL, including IVLBCL, was approved under the National Health Insurance system in September 2003. We classified all patients into groups, according to the time period of diagnosis, of pre – and post–rituximab approval. In the pre–rituximab approval era group, 11 (16%) of 67 patients received rituximab-containing chemotherapy. In the post–rituximab approval era group, one (3%) of 39 patients received chemotherapy without rituximab. In our analysis, PFS and OS were significantly superior in the post–rituximab approval era group than in the preapproval era group (log-rank test, $P = .008$ and $P = .011$, respectively).

Of the 14 patients who received ASCT, five patients in each group received ASCT during first complete remission. The other two patients in each group received ASCT during second remission. Of the 10 patients who received ASCT in the first remission, two of five patients in the chemotherapy group and all five patients in the R-chemotherapy group were alive without relapse as of last follow-up (median PFS, 18 and 23 months, respectively; range, 7 to 57 months and 8 to 43 months, respectively).

Table 2. Adverse Events Related to Infusion of Rituximab

Treatment-to-Rituximab Period*	Patients Who Received Rituximab		Infusion Reaction	
	No.	%	No.	%
Overall	49		14	29
With first cycle of chemotherapy				
0	12	24	7	58
1-6	10	20	2	20
7-16	1	2	1	100
With or after second course of chemotherapy				
17+	25	51	4	16
Unknown	1	2	0	0

*Treatment-to-rituximab period is the duration between the day treatment begins and the day of the first dose of rituximab.

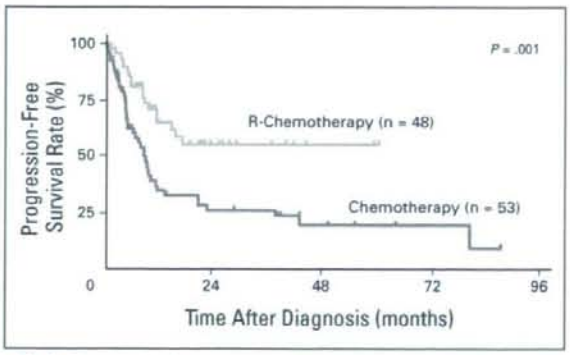

Fig 2. Comparison of progression-free survival for patients who received chemotherapies with (R-Chemotherapy) or without rituximab (Chemotherapy).

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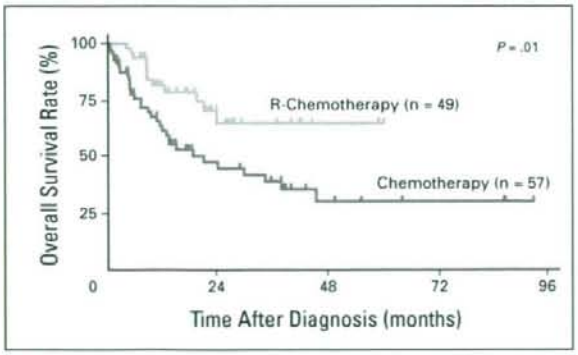

Fig 3. Comparison of overall survival for patients who received chemotherapies with (R-Chemotherapy) or without rituximab (Chemotherapy).

Prognostic Factors

Use of rituximab was identified as a favorable prognostic factor for both PFS (hazard ratio, 0.45; 95% CI, 0.25 to 0.80; $P = .006$) and OS (hazard ratio, 0.42; 95% CI, 0.21 to 0.85; $P = .016$) after adjustment of other prognostic factors by multivariate analysis (Table 3).

Adverse Events

Adverse events related to rituximab infusion are listed in Table 2. Twenty-eight (57%) of 49 patients received steroid therapy and/or chemotherapy before the first dose of rituximab. Adverse events related to rituximab infusion were observed in 14 (29%) of 49 patients. Seven of 12 patients who received rituximab on the first day of treatment developed infusion reaction. Of these seven patients, three patients developed hypoxia related to rituximab infusion. Grade 3 severe hypoxia was observed in one of these three patients. All three patients recovered without complications. Patients who received no prephase therapies (steroid therapy and/or chemotherapy) before the first dose of rituximab tended to develop adverse events related to infusion of rituximab compared with patients who received prephase therapies ($P = .062$).

Grade 3 or 4 nonhematologic adverse events were observed in six (12%) of 49 patients in the R-chemotherapy group. Treatment-related death was observed in three patients (6%) in the R-chemotherapy group (one each as a result of hepatitis B virus reactivation, tuberculosis, and *Pneumocystis* pneumonia) and in five patients (9%) in the chemotherapy group (one each as a result of cerebral hemorrhage, septic shock, pneumonia, acute pyelonephritis, and acute abdominal complication of unknown cause).

Twelve (24%) 49 patients in the R-chemotherapy group and 31 (54%) of 57 patients in the chemotherapy group had died as of the final follow-up. In the R-chemotherapy group, four patients each died as a result of PD and RD. One patient died as a result of esophageal cancer after treatment. In the chemotherapy group, 15 patients and 11 patients died of PD and RD, respectively.

DISCUSSION

The present study estimated the efficacy and safety of rituximab added to chemotherapy for IVLBCL. We found that the CR rate and survival rates in the R-chemotherapy group were superior to those in the chemotherapy group, whereas adverse events were equivalent in the two groups. These findings demonstrate the potential efficacy of rituximab-containing chemotherapy in IVLBCL. Although these results may have been influenced by the substantial biases associated

Table 3. Prognostic Factors for PFS or OS

	PFS						OS					
	Univariate			Multivariate			Univariate			Multivariate		
Variable	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age > 60 years	1.20	0.65 to 2.19	.561	—	—	—	1.34	0.67 to 2.67	.402	—	—	—
Sex, male	1.15	0.68 to 1.95	.606	—	—	—	1.08	0.59 to 1.97	.803	—	—	—
"B" symptoms	1.55	0.70 to 3.44	.277	—	—	—	1.10	0.49 to 2.48	.813	—	—	—
AIVL	1.13	0.66 to 1.94	.662	—	—	—	0.79	0.43 to 1.45	.453	—	—	—
HPS	1.26	0.72 to 2.20	.426	—	—	—	0.83	0.45 to 1.53	.560	—	—	—
Leukocytopenia*	0.88	0.48 to 1.62	.684	—	—	—	0.82	0.40 to 1.67	.590	—	—	—
Anemia†	2.01	1.08 to 3.74	.027	1.74	0.93 to 3.25	.083	1.70	0.91 to 3.75	.090	1.72	0.82 to 3.59	.149
Platelet count < $10 \times 10^4/\mu L$	0.94	0.56 to 1.59	.821	—	—	—	1.01	0.55 to 1.86	.967	—	—	—
Albumin < 3.0 g/dL	1.49	0.84 to 2.67	.176	—	—	—	1.10	0.59 to 2.09	.753	—	—	—
Bilirubin ≥ 1.5 mg/dL	0.77	0.35 to 1.71	.517	—	—	—	1.11	0.49 to 2.51	.807	—	—	—
Creatinine ≥ 1.5 mg/dL	1.81	0.88 to 3.72	.107	—	—	—	2.36	1.07 to 5.19	.033	3.38	1.50 to 7.67	.003
sIL-2R ≥ 5,000 U/L	0.96	0.53 to 1.73	.891	—	—	—	0.79	0.42 to 1.51	.480	—	—	—
PS > 1	1.11	0.58 to 2.17	.745	—	—	—	0.86	0.42 to 1.75	.678	—	—	—
Extranodal involvement at > 1 site	0.58	0.34 to 1.00	.052	0.58	0.34 to 1.01	.055	0.66	0.35 to 1.23	.189	—	—	—
LDH > 2 × ULN	1.27	0.64 to 2.51	.494	—	—	—	1.39	0.62 to 3.12	.428	—	—	—
Respiratory symptoms	0.64	0.36 to 1.15	.139	—	—	—	0.57	0.28 to 1.13	.106	—	—	—
Neurologic symptoms	1.30	0.72 to 2.35	.388	—	—	—	0.92	0.44 to 1.93	.835	—	—	—
Treatment with rituximab	0.41	0.23 to 0.72	.002	0.45	0.25 to 0.80	.006	0.42	0.22 to 0.83	.012	0.42	0.21 to 0.85	.016

Abbreviations: PFS, progression-free survival; OS, overall survival; HR, hazard ratio; AIVL, Asian variant of intravascular large B-cell lymphoma; HPS, hemophagocytic syndrome; sIL-2R, soluble interleukin-2 receptor; PS, performance status; LDH, lactate dehydrogenase; ULN, upper limit of normal.
*Leukocytopenia was defined as WBC < 4,000/μL.
†Anemia was defined as Hb < 11 g/dL or RBC < $350 \times 10^4/\mu L$.

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with retrospective analysis, we believe that our data provide a basis for future prospective studies of rituximab-containing chemotherapy for IVLBCL.

Our data revealed that 2-year OS and PFS rates in the R-chemotherapy group were 66% and 56%, respectively, compared with 46% and 27% in the chemotherapy group. A recent report revealed that the OS rate of patients who received immunochemotherapy in the high-risk group of DLBCL was 63%, and failure-free survival rate of patients with non–germinal center B-cell (non-GCB)-type DLBCL improved from 30% to 63% with the addition of rituximab to chemotherapy.[26] Most patients with IVLBCL are categorized as high-risk according to the International Prognostic Index, and as with non–GCB-type DLBCL,[23] survival of IVLBCL patients in this study was probably comparable to that of patients with DLBCL. Furthermore, improvement of PFS in our analysis might demonstrate that the efficacy of rituximab in IVLBCL is comparable to that of rituximab in non–GCB-type DLBCL.[26]

In our study, 14 (29%) of 49 patients developed adverse events related to rituximab infusion. Grade 3 hypoxia was observed in only one patient (2%). This result was comparable to that of a previous report in DLBCL.[17] However, three of five patients who developed hypoxia related to rituximab infusion had received no prior steroid therapy and/or chemotherapy before administration of rituximab. A recent report revealed severe pulmonary complications related to rituximab infusion as an initial treatment.[27] Although no significant relationship was observed between prior treatment and infusion reaction in our analysis, further studies are required to establish optimal timing of rituximab administration while taking into consideration the risk of pulmonary complications in patients with IVLBCL.[28,29]

Several previous reports have revealed the efficacy of high-dose chemotherapy with stem-cell support in IVLBCL.[30-32] In our study, 11 of 14 patients survived without relapse after undergoing transplantation. This result suggests that ASCT for IVLBCL might be promising for suitable patients. Further studies are warranted to evaluate the role and optimal timing of high-dose chemotherapy for patients with IVLBCL.

This investigation identified a significant difference in early death within 180 days after diagnosis between groups. There remained the potential bias against the superiority of condition of the R-chemotherapy group compared with the chemotherapy group. Our analysis, which compensated for this potential bias by entry point of study, demonstrated that PFS and OS in the R-chemotherapy group were significantly superior to those in the chemotherapy group. Furthermore, in our analysis, outcome by time period of diagnosis differed significantly between pre– and post–rituximab approval groups. These results might also confirm the efficacy of rituximab added to chemotherapy.

Although this study provides novel information on IVLBCL, some limitations should be discussed. First, this retrospective study included enrollments from many institutions and might have been influenced by unrecognized biases. Second, the percentage of patients who received chemotherapy differed between our previous (65%) and present series (91%). This difference between groups might be attributable to recent improvements in diagnostic procedures, including random skin biopsies. Although Kaplan-Meier survival rates for the previous (n = 42) and present (n = 15) patients in the chemotherapy group were coincident (data not shown), a substantial bias in the condition of patients between groups might have influenced favorable outcomes in the R-chemotherapy group. Third, patients received various regimens of chemotherapy according to individual institutional protocols, so we could not simply evaluate CR rates for rituximab-containing chemotherapies. Fourth, between the approval of rituximab for use in indolent B-cell lymphoma in August 2001 and the approval for use in DLBCL in September 2003, 10 (33%) of 33 patients received rituximab-containing chemotherapy according to the policy of physicians (Table 1). This might have been a cause of case-selection bias. Finally, patients received rituximab at various times during treatment and with various precautions against infusion reaction in this study. Toxicities related to infusion of rituximab, therefore, might have been underestimated.

In conclusion, addition of rituximab to chemotherapy in patients with IVLBCL is safe and effective, as with DLBCL. With recent developments in the understanding of IVLBCL, diagnosis can be more timely and accurate. Further prospective studies are required to establish optimal clinical strategies for IVLBCL, including therapy and diagnosis.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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ORIGINAL ARTICLE

Evaluation of organ involvement in intravascular large B-cell lymphoma by ^{18}F-fluorodeoxyglucose positron emission tomography

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Abstract To evaluate the role of ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) in intravascular large B-cell lymphoma (IVLBCL), we retrospectively analyzed four consecutive IVLBCL patients receiving FDG-PET before treatment between May 2006 and November 2007. Patients were two men and two women (median age 62 years, range 54–76 years). All patients received bone marrow biopsies and random skin biopsies and two of the four patients underwent renal biopsy for diagnosis. Accuracy of FDG-PET for the detection of organ involvements was analyzed by comparing results of pathological findings. Concordant results with respect to bone marrow involvement were accurately obtained for two patients. Skin and renal involvements were undetectable by FDG-PET regardless of positive pathological findings. One patient with a false-negative FDG-PET result showed fewer lymphoma cells in the bone marrow specimen than patients with concordant FDG-PET results. These results suggest false-negative results for some types of organ involvement. Careful interpretation of the results of FDG-PET in IVLBCL is thus required.

Keywords Intravascular large B-cell lymphoma · FDG-PET · Diagnostic accuracy

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1 Introduction

In the assessment of patients with Hodgkin lymphoma (HL) or non-Hodgkin's lymphoma (NHL), ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) has recently emerged as a powerful functional imaging tool [1]. The advantages of FDG-PET over conventional imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) lie in the ability to distinguish between viable tumor and necrosis or fibrosis in the residual masses that are often present after treatment [2]. This ability is thus expected to allow accurate assessment of pre-treatment staging and post-treatment effect. The recent revised response criteria for malignant lymphoma reveals that FDG-PET is highly recommended for initial and post-treatment assessment of diffuse large B-cell lymphoma (DLBCL) and HL [2].

Intravascular large B-cell lymphoma (IVLBCL) is a rare subtype of extranodal DLBCL as classified by the World Health Organization (WHO) [3]. IVLBCL is a rapidly progressive and often fatal disease, characterized by the selective growth of tumor cells in the lumina of small vessels in various organs [4]. If the efficacy of FDG-PET in IVLBCL is similar to that in nodal DLBCL, the technique will be useful for early diagnosis and prediction of organ