VOLUME 26 · NUMBER 19 · JULY 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

Kazuyuki Shimada, Kosei Matsue, Kazuhito Yamamoto, Takuhei Murase, Naoaki Ichikawa, Masataka Okamoto, Nozomi Niitsu, Hiroshi Kosugi, Norifumi Tsukamoto, Hiroshi Miwa, Hideki Asaoku, Ako Kikuchi, Morio Matsumoto, Yoshio Saburi, Yasufumi Masaki, Motoko Yamaguchi, Shigeo Nakamura, Tomoki Naoe, and Tomohiro Kinoshita

From the Department of Hematology and Oncology, Nagoya University Graduate School of Medicine; Department of Hematology and Cell Therapy, Aichi Cancer Center Hospital; Department of Pathology and Clinical Laboratories, Nagoya University Hospital, Nagoya; Division of Hematology/Oncology, Kameda General Hospital, Kamogawa; Department of Internal Medicine, Nishio Municipal Hospital, Nishio; First Department of Internal Medicine, Nagano Red Cross Hospital, Nagano; Department of Medicine, Fujita-Health University School of Medicine, Tokyoake; Department of Hematology, Comprehensive Cancer Center, International Medical Center, Saitama Medical University, Hidaka; Department of Hematology, Ogaki Municipal Hospital, Ogaki; Medicine and Clinical Science, Gunma University Graduate School of Medicine, Maebashi; Department of Internal Medicine, Division of Hematology, Aichi Medical University School of Medicine, Nagakute; Internal Medicine, Hiroshima Red Cross Hospital, Hiroshima; Department of Hematology, Tokai University School of Medicine, Isehara; Department of Hematology, Nishigunma National Hospital, Shibukawa; Department of Hematology, Oita Prefectural Hospital, Oita; Department of Hematology and Immunology, Kanazawa Medical University School of Medicine, Uchinada; and Department of Hematology and Oncology, Mie University Graduate School of Medicine, Tsu, Japan.

Submitted November 22, 2007; accepted March 31, 2008; published online ahead of print at www.jco.org on May 27, 2008.

Supported in part by Grant No. 19-8, a Grant-in-Aid for Cancer Research, from the Ministry of Health, Labour, and Welfare, Tokyo, Japan.

Presented in part at the 49th Annual Meeting of the American Society of Hematology, December 10, 2007, Atlanta, GA.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Tomohiro Kinoshita, MD, Department of Hematology and Oncology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550 Japan; e-mail: kinosita@med.nagoya-u.ac.jp.

0732-183X/08/2619-3189/$20.00

DOI: 10.1200/JCO.2007.15.4278

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.

J Clin Oncol 26:3189-3195. © 2008 by American Society of Clinical Oncology

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

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.

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).

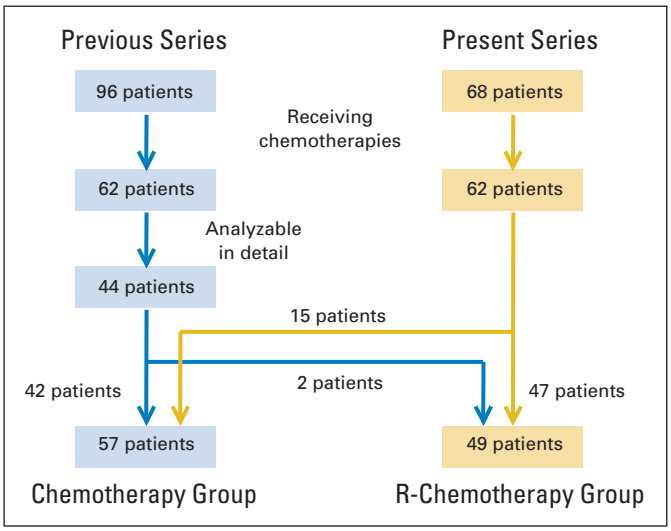

Fig 1. Patient selection. Blue lines represent the number of patients from the previous series. Yellow lines represent the number of patients from the present series. R-Chemotherapy, chemotherapy with rituximab.

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

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.

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.

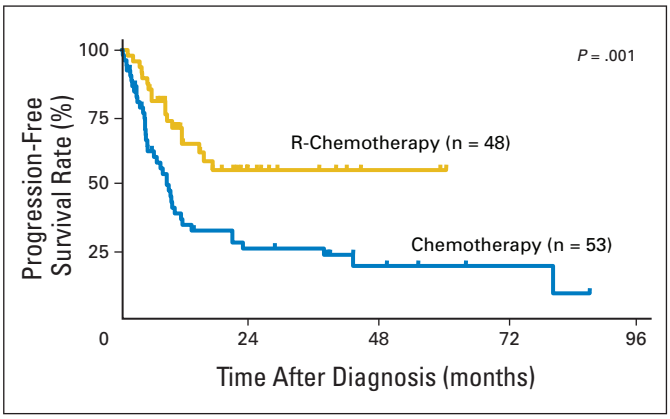

Fig 2. Comparison of progression-free survival for patients who received chemotherapies with (R-Chemotherapy) or without rituximab (Chemotherapy).

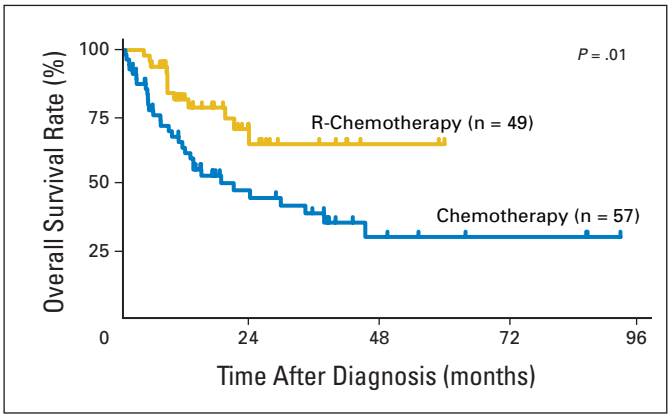

Fig 3. Comparison of overall survival for patients who received chemotherapies with (R-Chemotherapy) or without rituximab (Chemotherapy).

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 < $350 \times 10^4/\mu L$.

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

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** None **Stock Ownership:** None **Honoraria:** Kazuyuki Shimada, Chugai Pharmaceutical Co Ltd; Shigeo Nakamura, Chugai Pharmaceutical Co Ltd; Tomohiro Kinoshita, Chugai Pharmaceutical Co Ltd **Research Funding:** None **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Kazuhito Yamamoto, Takuhei Murase, Motoko Yamaguchi, Shigeo Nakamura, Tomohiro Kinoshita
Financial support: Shigeo Nakamura, Tomoki Naoe, Tomohiro Kinoshita
Administrative support: Shigeo Nakamura, Tomoki Naoe, Tomohiro Kinoshita
Provision of study materials or patients: Kazuyuki Shimada, Kosei Matsue, Kazuhito Yamamoto, Takuhei Murase, Naoaki Ichikawa, Masataka Okamoto, Nozomi Niitsu, Hiroshi Kosugi, Norifumi Tsukamoto, Hiroshi Miwa, Hideki Asaoku, Ako Kikuchi, Morio Matsumoto, Yoshio Saburi, Yasufumi Masaki, Tomohiro Kinoshita
Collection and assembly of data: Kazuyuki Shimada, Kosei Matsue, Takuhei Murase, Motoko Yamaguchi, Shigeo Nakamura, Tomohiro Kinoshita
Data analysis and interpretation: Kazuyuki Shimada, Motoko Yamaguchi, Tomohiro Kinoshita
Manuscript writing: Kazuyuki Shimada, Kazuhito Yamamoto, Motoko Yamaguchi, Shigeo Nakamura, Tomohiro Kinoshita
Final approval of manuscript: Kazuyuki Shimada, Kosei Matsue, Kazuhito Yamamoto, Takuhei Murase, Naoaki Ichikawa, Masataka Okamoto, Nozomi Niitsu, Hiroshi Kosugi, Norifumi Tsukamoto, Hiroshi Miwa, Hideki Asaoku, Ako Kikuchi, Morio Matsumoto, Yoshio Saburi, Yasufumi Masaki, Motoko Yamaguchi, Shigeo Nakamura, Tomoki Naoe, Tomohiro Kinoshita

REFERENCES

1. Gatter KC, Warnke RA: Intravascular large B-cell lymphoma, in Jaffe ES, Harris NL, Stein H, Vardiman JW (eds): World Health Organization: Pathology and Genetics of Tumors of Haematopoietic and Lymphoid Tissues. Lyon, France, IARC Press, 2001, pp 177-178

2. Ponzoni M, Ferreri AJ, Campo E, et al: Definition, diagnosis, and management of intravascular large B-cell lymphoma: Proposals and perspectives from an international consensus meeting. J Clin Oncol 25:3168-3173, 2007

3. Murase T, Nakamura S, Kawauchi K, et al: An Asian variant of intravascular large B-cell lymphoma: Clinical, pathological and cytogenetic approaches to diffuse large B-cell lymphoma associated with haemophagocytic syndrome. Br J Haematol 111:826-834, 2000

4. Ferreri AJ, Campo E, Seymour JF, et al: Intravascular lymphoma: Clinical presentation, natural history, management and prognostic factors in a series of 38 cases, with special emphasis on the 'cutaneous variant'. Br J Haematol 127:173-183, 2004

5. Anghel G, Petrinato G, Severino A, et al: Intravascular B-cell lymphoma: Report of two cases with different clinical presentation but rapid central nervous system involvement. Leuk Lymphoma 44: 1353-1359, 2003

6. Monteiro M, Duarte I, Cabecadas J, et al: Intravascular large B-cell lymphoma of the breast. Breast 14:75-78, 2005

7. Domizio P, Hall PA, Cotter F, et al: Angiotropic large cell lymphoma (ALCL): Morphological, immunohistochemical and genotypic studies with analysis of previous reports. Hematol Oncol 7:195-206, 1989

8. Gill S, Melosky B, Haley L, et al: Use of random skin biopsy to diagnose intravascular lymphoma presenting as fever of unknown origin. Am J Med 114: 56-58, 2003

9. Narimatsu H, Morishita Y, Saito S, et al: Usefulness of bone marrow aspiration for definite diagnosis of Asian variant of intravascular lymphoma: Four autopsied cases. Leuk Lymphoma 45:1611-1616, 2004

10. Estalilla OC, Koo CH, Brynes RK, et al: Intravascular large B-cell lymphoma: A report of five cases initially diagnosed by bone marrow biopsy. Am J Clin Pathol 112:248-255, 1999

11. DiGiuseppe JA, Nelson WG, Seifter EJ, et al: Intravascular lymphomatosis: A clinicopathologic study of 10 cases and assessment of response to chemotherapy. J Clin Oncol 12:2573-2579, 1994

12. Ferreri AJ, Campo E, Ambrosetti A, et al: Anthracycline-based chemotherapy as primary treatment for intravascular lymphoma. Ann Oncol 15: 1215-1221, 2004

13. Sonneveld P, de Ridder M, van der Lelie H, et al: Comparison of doxorubicin and mitoxantrone in the treatment of elderly patients with advanced diffuse non-Hodgkin's lymphoma using CHOP versus CNOP chemotherapy. J Clin Oncol 13:2530-2539, 1995

14. Reff ME, Carner K, Chambers KS, et al: Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. Blood 83:435-445, 1994

15. Maloney DG, Liles TM, Czerwinski DK, et al: Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent B-cell lymphoma. Blood 84:2457-2466, 1994

16. Maloney DG, Grillo-Lopez AJ, Bodkin DJ, et al: IDEC-C2B8: Results of a phase I multiple-dose trial in patients with relapsed non-Hodgkin's lymphoma. J Clin Oncol 15:3266-3274, 1997

17. Coiffier B, Lepage E, Briere J, et al: CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 346:235-242, 2002

18. Pfreundschuh M, Trumper L, Osterborg A, et al: CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: A randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol 7:379-391, 2006

19. Shimizu I, Ichikawa N, Yotsumoto M, et al: Asian variant of intravascular lymphoma: Aspects of diagnosis and the role of rituximab. Intern Med 46:1381-1386, 2007

20. Bouzani M, Karmiris T, Rontogianni D, et al: Disseminated intravascular B-cell lymphoma: Clinicopathological features and outcome of three cases treated with anthracycline-based immunochemotherapy. Oncologist 11:923-928, 2006

21. Bazhenova L, Higginbottom P, Mason J: Intravascular lymphoma: A role for single-agent rituximab. Leuk Lymphoma 47:337-341, 2006

22. Byrd JC, Waselenko JK, Maneatis TJ, et al: Rituximab therapy in hematologic malignancy patients with circulating blood tumor cells: Association with increased infusion-related side effects and rapid blood tumor clearance. J Clin Oncol 17:791-795, 1999

23. Murase T, Yamaguchi M, Suzuki R, et al: Intravascular large B-cell lymphoma (IVLBCL): A clinicopathologic study of 96 cases with special reference to the immunophenotypic heterogeneity of CD5. Blood 109:478-485, 2007

24. Trotti A, Colevas AD, Setser A, et al: CTCAE v3.0: Development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 13:176-181, 2003

25. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med 329:987-994, 1993

26. Nyman H, Adde M, Karjalainen-Lindsberg ML, et al: Prognostic impact of immunohistochemically defined germinal center phenotype in diffuse large B-cell lymphoma patients treated with immunochemotherapy. Blood 109:4930-4935, 2007

27. Wu SJ, Chou WC, Ko BS, et al: Severe pulmonary complications after initial treatment with Rituximab for the Asian-variant of intravascular lymphoma. Haematologica 92:141-142, 2007

28. Martusewicz-Boros M, Wiatr E, Radzikowska E, et al: Pulmonary intravascular large B-cell lymphoma as a cause of severe hypoxemia. J Clin Oncol 25:2137-2139, 2007

29. Matsue K, Takeuchi M, Uryu H, et al: Rapid improvement of hypoxemia by the use of rituximab in patients with pulmonary intravascular lymphoma. Leuk Lymphoma 48:197-200, 2007

30. Sawamoto A, Narimatsu H, Suzuki T, et al: Long-term remission after autologous peripheral blood stem cell transplantation for relapsed intravascular lymphoma. Bone Marrow Transplant 37:233-234, 2006

31. Koizumi M, Nishimura M, Yokota A, et al: Successful treatment of intravascular malignant lymphomatosis with high-dose chemotherapy and autologous peripheral blood stem cell transplantation. Bone Marrow Transplant 27:1101-1103, 2001

32. Yamaguchi M, Kimura M, Watanabe Y, et al: Successful autologous peripheral blood stem cell transplantation for relapsed intravascular lymphomatosis. Bone Marrow Transplant 27:89-91, 2001

Acknowledgment

The Acknowledgment is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

