Table 1. Patient characteristics

Characteristics	No. of cases		Characteristics	No. of cases	
	Enrolled	Eligible		Enrolled	Eligible
No. of patients	68	57	No. of extranodal diseases		
Median years of age (range)	63 (20–74)	63 (34–74)	0	31	24
Gender, male/female	47/21	40/17	1	21	18
Performance status (ECOG)			≥2	16	15
0	38	30	Bone marrow involvement		
1	23	21	Positive	15	14
2	7	6	Negative	53	43
Histology (REAL)			Tumor size, cm		
Diffuse large B-cell lymphoma	52	50	≥5	30	25
Mantle cell lymphoma	7	5	<5	38	32
Other aggressive B-cell lymphoma	2	2	LDH		
Follicular center lymphoma	5	0	Normal	26	22
Low-grade B-NHL not specified	1	0	Elevated	42	35
Specimen not available	1	0	No. of prior chemo-Tx		
Clinical stage at entry (Ann Arbor)			1	22	18
I	2	2	2	26	22
II	8	7	3	19	17
III	14	11	4	1	0
IV	44	37	Prior AHSCT		
B-symptoms			No	58	48
Present	16	15	Yes	10	9
Absent	52	42	International prognostic index		
No. of relapses			Low	15	12
0 (primary refractory)	26	19	Low-intermediate	22	18
1	33	30	High-intermediate	21	18
2	9	8	High	10	9
Response to prior chemo-Tx					
Responder	41	36			
Non-responder	27	21			

AHSCT, autologous hematopoietic stem cell transplantation; Chemo-Tx, chemotherapy; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; NHL, non-Hodgkin's lymphoma.

criteria during rituximab treatment was withdrawn early from the study. No patient developed grade ≥3 non-hematological toxicity requiring the discontinuation of rituximab treatment. Thus 44 of 67 patients (66%) completed the planned rituximab treatment.

ORR, PFS and TTP

Fifty-seven eligible patients were evaluated for response to rituximab on a protocol-compatible (PC) basis, whereas 68 patients were evaluated on an intention-to-treat (ITT) basis. As shown in Table 2, the ORRs on the basis of PC and ITT were 37% (21/57; 95% CI 25–51%) and 35% (24/68; 95% CI 24–48%), respectively.

Among 57 eligible patients, 11 patients had a washout period <4 weeks (21–26 days, eight cases; 18 days, one case; 17 days, one case; 15 days, one case). None of the 11 patients responded to the last prior salvage chemotherapy (three SD and eight PD), and they all had massive tumor lesions immediately before rituximab treatment. Only one patient responded to rituximab (one CR, one SD, eight PD, and one not evaluable).

Median PFS and the 95% CI were estimated by the Kaplan–Meier method for all eligible patients on the basis of PC and for all enrolled patients on the basis of ITT. However, unevaluable patients (use of steroid or anti-cancer agents, four patients; early withdrawal from the study, two patients; and inadequate measurement of tumor lesion, two patients) were excluded from the estimation of PFS. Median PFSs for all eligible and evaluable patients ($n = 53$) and for all enrolled and evaluable patients ($n = 60$) were 52 days (95% CI 33–111 days) and 61 days (95% CI 41–156 days), respectively, as shown in Figure 1. The median TTP of 21 eligible responders was 245 days (95% CI 176–435 days; Figure 1).

Table 2. Responses

	n	No. of patients						ORR, % (95% CI)
		CR	PR	CR+PR	SD	PD	NE	
Intention to treat	68	15	9	24	9	27	8	35 (24–48)
Protocol compatible	57	15	6	21	5	27	4	37 (25–51)

Responses to rituximab were evaluated according to the International Workshop NHL response criteria. No patient showed CR/unconfirmed.

CI, confidence interval; CR, complete response; NE, not evaluable due to insufficient follow-up; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

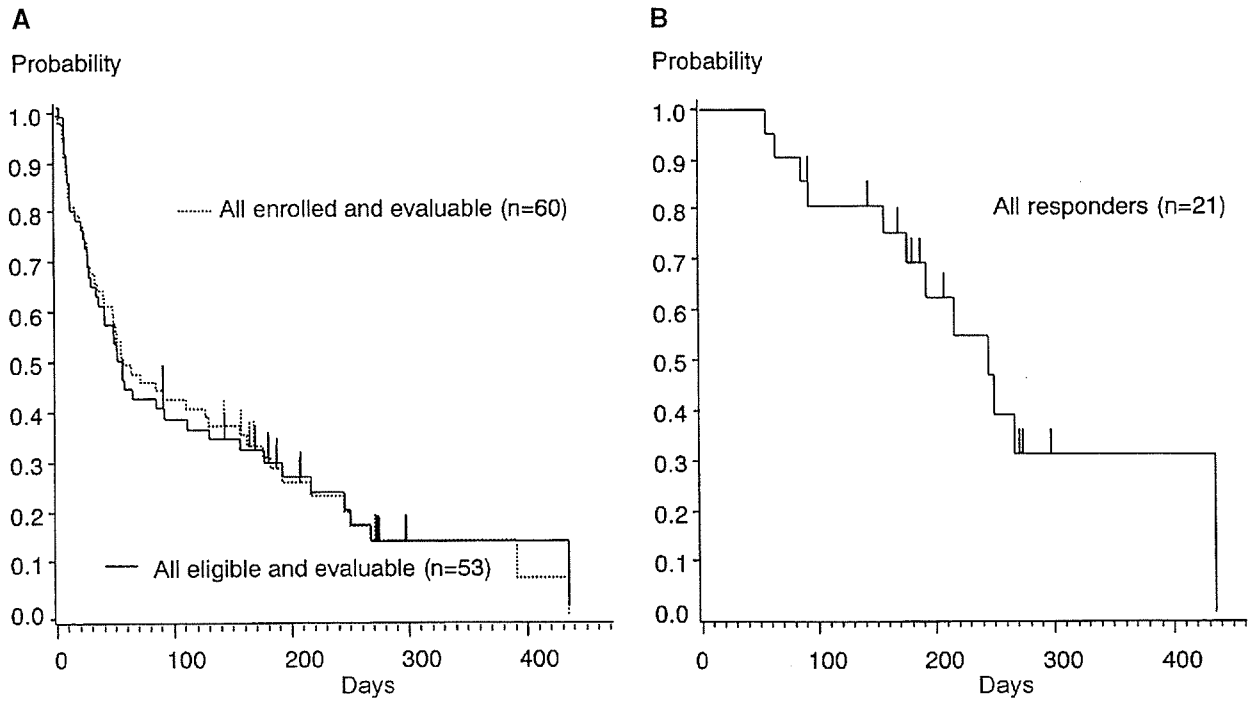

Figure 1. (**A**) Progression-free survival (PFS) and (**B**) time to progression (TTP). The median PFS values for all eligible and evaluable patients (n = 53) and for all enrolled and evaluable patients (n = 60) were 52 days [95% confidence interval (CI) 33–111] and 61 days (95% CI 41–156), respectively. The median TTP for all 21 eligible responders was 245 days (95% CI 176–435).

Non-hematological toxicities

Non-hematological toxicities were evaluated for all 67 patients who received at least one infusion of rituximab. Fifty-nine patients (88%) developed non-hematological toxicities. Commonly observed toxicities were infusion-related symptoms including fever, chills, burning sensation, headache, asthenia, pain, throat discomfort, perspiration and pruritus, most of which did not exceed grade 2, as shown in Table 3. These symptoms generally occurred during the first infusion. They were effectively managed with prophylactic or supportive antihistamines and antipyretics, and generally resolved within 24 h. Infusion-related ADRs decreased at subsequent infusions.

One patient developed a grade 3 upper-respiratory infection 3 months after completion of the planned rituximab treatment. Hematological testing indicated that the patient had also developed grade 4 neutropenia. Supportive care with antibiotics, G-CSF and immunoglobulin preparations was performed under hospitalization, and he recovered 9 days after the onset of infection.

Hematological toxicities

Twenty-nine patients (43%) developed hematological toxicities, as shown in Table 3. Grade 4 toxicities were observed in four patients (6%), including one case of leukopenia (2%) and four of neutropenia (6%). Out of the four patients, three had a history of receiving autologous peripheral blood stem cell transplantation. While one patient required G-CSF, the remaining three recovered without any medical intervention.

Abnormal laboratory findings

As also shown in Table 3, 20 patients (30%) had abnormal laboratory values for which a relationship to rituximab was not clearly ruled out. Elevation of hepatic enzymes (AST, ALT or ALP) and/

Table 3. Adverse drug reactions ($n = 67$)

JCOG toxicity grading	No. of patients				Total, n (%)
	Grade 1	Grade 2	Grade 3	Grade 4	
Non-hematological toxicity	31	27	1	0	59 (88)
General					
Fever	18	23	0	0	41 (61)
Chills	17	3	0	0	20 (30)
Burning sensation	16	0	0	0	16 (24)
Headache	14	2	0	0	16 (24)
Asthenia	13	1	0	0	14 (21)
Pain	9	2	0	0	11 (16)
Thirst	5	0	0	0	5 (8)
Numbness	2	1	0	0	3 (5)
Flu-like reaction	3	0	0	0	3 (5)
Facial flushing	3	0	0	0	3 (5)
Back pain	3	0	0	0	3 (5)
Infection	0	0	1	0	1 (2)
Cardiovascular					
Hypotension	7	0	0	0	7 (10)
Tachycardia	4	0	0	0	4 (6)
Respiratory					
Throat discomfort	10	0	0	0	10 (15)
Cough	4	0	0	0	4 (6)
Rhinorrhea	3	0	0	0	3 (5)
Digestive					
Nausea	8	0	0	0	8 (12)
Vomiting	0	3	0	0	3 (5)
Nervous system					
Dizziness	3	0	0	0	3 (5)
Skin/appendages					
Sweating	8	2	0	0	10 (15)
Pruritus	9	0	0	0	9 (13)
Rash	5	1	0	0	6 (9)
Hematological toxicity	9	9	7	4	29 (43)
Leukopenia	11	9	4	1	25 (37)
Neutropenia	6	5	7	4	22 (33)
Anemia	0	0	0	0	0 (0)
Thrombocytopenia	2	0	0	0	2 (3)
Abnormal laboratory findings	12	7	0	1	20 (30)
ALT (s-GPT)	5	0	0	1	6 (9)
AST (s-GOT)	6	0	0	1	7 (10)
Total bilirubin	–	1	1	0	2 (3)
ALP	4	0	0	0	4 (6)
Hyponatremia	2	1	0	0	3 (4)
Hyperglycemia ($n = 61$)	0	2	0	0	2 (3)
Proteinuria ($n = 58$)	2	2	0	0	4 (7)
Hematuria ($n = 58$)	1	2	0	0	3 (5)

An adverse drug reaction was defined as any adverse event which was related to rituximab or whose relationship to rituximab was unknown. Grading was made according to the Japan Clinical Oncology Group Toxicity Criteria, an expanded version of the National Cancer Institute–common toxicity criteria, version 1.0. Frequent (>3%) or grade 3 non-hematological toxicities and abnormal laboratory findings, and all hematological toxicities observed during treatment and during the follow-up period (for 6 months after the first rituximab infusion) are listed.

or total bilirubin was observed in 10 patients (15%). Out of the 10, one patient, who had developed a flu-like syndrome, asthenia and jaundice 5 days after the final rituximab infusion, demonstrated grade 4 AST and ALT elevations along with grade 3 total bilirubin elevation. He was diagnosed as having developed acute hepatitis and was hospitalized. The patient had a history of TT virus infection and the TT virus-DNA [28, 29] was detected at the time of the event, while hepatitis B virus surface, core and envelope antigens were all negative; antibodies to hepatitis A and C virus were also negative. The patient recovered 32 days after the onset of the syndrome with conservative management. In addition to routine laboratory testing, examination of serum C-reactive protein (CRP) was performed for all 67 patients. Elevation (≥1.0 mg/dl) of CRP values was observed in 14 patients (21%). All non-hematological toxicities, including abnormal laboratory findings, were reversible.

Infection

Within 6 months after the initiation of rituximab administration, 37 episodes of infection or suspected infection (events for which antibiotic, anti-fungal and/or anti-viral agents were prescribed) were reported in 28 patients, including one patient who developed a grade 3 upper-respiratory tract infection and the patient described above who developed acute TT virus-positive hepatitis.

Early death

Two patients died within 30 days following the last rituximab infusion. They showed rapid lymphoma progression during rituximab treatment and were withdrawn early from the study. They both received salvage chemotherapy 5 or 7 days after withdrawal and developed grade 4 neutropenia and septic shock leading to death 14 days and 15 days after the initiation of the chemotherapy, respectively.

PB T- and B-cell counts, and serum immunoglobulins

All 67 patients receiving rituximab exhibited a marked decrease in CD19- and CD20-positive cells after the first rituximab infusion (data not shown). On the other hand, no change was observed in CD3-positive cells. Changes in the mean percentage ± standard deviation (SD) of CD19- and CD20-positive cells in the PB from immediately before the first rituximab infusion until 2 days thereafter were 8.5 ± 9.4% to 0.5 ± 0.3% and 9.4 ± 10% to 0.4 ± 0.7%, respectively. There was little change in serum immunoglobulin levels (IgG, IgA and IgM) for 12 months (data not shown).

HACA development

The number of patients whose sera were tested for HACA at 3 and 6 months or thereafter were 40 and 25, respectively. HACA was not detected in these patients.

Factors affecting ORR and PFS

Univariate and multivariate analyses of pretreatment factors affecting ORR and PFS were performed in 53 patients who were eligible and evaluable. As shown in Table 4, elevated LDH and primary chemorefractoriness were found to be unfavorable factors significantly affecting ORR and PFS in the univariate and multivariate analyses. In the univariate analysis, PFS in patients in the low/low-intermediate risk group according to IPI was longer than that in patients in the high-intermediate/high risk group ($P = 0.034$). PFS in patients with a history of AHSCT was also longer than that in patients without it ($P = 0.045$).

Pharmacokinetic parameters and correlation with responses

Serum rituximab levels were determined in seven responders and five non-responders whose planned rituximab treatments were completed. As shown in Table 5, the mean ± SD values of trough levels and AUCs of the responders and the non-responders were 59.7 ± 11.4 and 43.0 ± 6.4 μg/ml and 608 585 ± 147 373 and 383 053 ± 176 903 μg.h/ml, respectively, and there were significant differences between the two groups ($P = 0.021$; $P = 0.037$). In addition, pre-treatment tumor size measured as the sum of the products of the perpendicular diameters (SPD) was inversely correlated with AUC by Spearman's rank order correlation analysis (coefficient: $r = -0.566$, $P < 0.05$) (data not shown). There were no significant differences between the two groups regarding maximum concentration (C_{max}) or serum half-life of rituximab.

Discussion

We report here the findings of a multicenter phase II study in Japan to evaluate the efficacy and feasibility of eight consecutive weekly administrations of rituximab for relapsed or refractory patients with aggressive B-cell lymphoma. The first clinical study of rituximab for aggressive B-cell lymphoma was conducted in Europe by Coiffier et al. [10]. The study evaluated rituximab monotherapy in 54 relapsed or elderly untreated patients with aggressive B-cell lymphoma that mainly consisted of DLBCL. Rituximab was given as two dosing schedules: eight consecutive weekly infusions at 375 mg/m^2 (arm A; $n = 28$), or one infusion at 375 mg/m^2 followed by seven consecutive weekly infusions at 500 mg/m^2 (arm B; $n = 26$). The ORR over the two arms was 31% (17/57) including 9% CR (5/54) on the basis of ITT, and there was little difference between the two arms. The most commonly observed AEs were mild to moderate infusion-related reactions such as fever, rigors, hypotension and dyspnea. Slightly more patients experienced serious AEs related to rituximab at 500 mg/m^2 than at 375 mg/m^2 (three versus six cases).

The schedule of administration of rituximab in our study was similar to that of arm A of the European study. The ORR obtained in the present study was 35% on the basis of ITT. The seemingly higher ORR in the present study may be ascribed to the difference in the patient pathological demography. The ORR in DLBCL in the present study was 34% (17/50), which was similar to that of the European study (37%, 11/30). The median TTP of responders in the present study was 245 days, which was also comparable with that observed in the European study (246 days+; $n = 17$). There was little difference in the toxicity profiles between the two studies, while the incidence of non-hematological toxicity was higher in the present study. The high incidence of toxicities in the

Table 4. Pretreatment factors affecting response and progression-free survival (PFS) by univariate and multivariate analyses

Factors affecting overall response rate (ORR)				
	ORR, % (95% CI)	Univariate P^a	Multivariate P^b	Odds ratio (95% CI)
LDH				
Normal	65 (41–85)	0.004**	0.003**	0.12 (0.03–0.49)
Elevated	24 (11–42)			
No. of relapses				
0 (Primary refractory)	22 (6–48)	0.081	0.030*	5.81 (1.18–28.5)
Relapsed one or two times	49 (31–66)			
Factors affecting progression-free survival (PFS)				
	Median PFS, days (95% CI)	Univariate P^c	Multivariate P^d	Risk ratio (95% CI)
LDH				
Normal	156 (85–267)	0.002**	0.0002**	4.47 (2.04–9.81)
Elevated	27 (21–48)			
No. of relapses				
0 (primary refractory)	27 (10–52)	0.005**	0.0004**	0.25 (0.12–0.54)
Relapsed one or two times	85 (40–216)			

[a]P value by Fisher's exact test.
[b]P value by logistic regression model (stepwise procedure).
[c]P value by log-rank test.
[d]P value by Cox's proportional hazard model (stepwise procedure).
Statistically significant difference at *P <0.05 and **P <0.01.
CI, confidence interval; LDH, lactate dehydrogenase; ORR, overall response rate.

Table 5. Pharmacokinetic parameters of responders and non-responders

	Responders, mean ± SD (n = 7)	Non-responders, mean ± SD (n = 5)	P^a
Trough (μg/ml)	59.7 ± 11.4	43.0 ± 6.4	0.015[b]
C_{max} (μg/ml)	502.9 ± 123.4	398.8 ± 52.2	0.109
$t_{1/2}$ (h)	517.1 ± 165.9	314.5 ± 153.8	0.057
AUC (μg·h/ml)	608 585 ± 147 373	383 053 ± 176 903	0.037[b]

[a]Student's t-test.
[b]Significant difference at P <0.05.
AUC, area under the concentration–time curve; C_{max}, maximum concentration; SD, standard deviation; $t_{1/2}$, serum half-life.

present study may partially have resulted from the relatively frequent performance of examinations.

One patient developed grade 4 elevations of AST (2564 IU/l) and ALT (3176 IU/l) concomitantly with grade 3 elevation of total bilirubin after completion of the planned infusion, and was diagnosed with acute hepatitis in the present study. Virus testing revealed that hepatitis viruses A, B and C were negative, but TT virus-DNA was present in his serum. TT virus has been reported to be a novel virus associated with elevation of hepatic transaminase in patients with post-transfusion as well as acute and chronic non-A to G hepatitis [28, 29]. Neither hepatomegaly nor space-occupying lesion was observed on CT films in this patient. Pretreatment transaminase levels were all within normal ranges. Moreover, the acute hepatitis resolved without particular treatment, suggesting that TT virus might have been causative for the hepatitis.

The incidence of grade 4 hematological toxicity was 6%, which was very similar to that in the European study (arm A, 6%; arm B, 8%) [10]. Out of four patients who developed grade 4 neutropenia, three had a history of receiving AHSCT. The remaining patient had a history of three regimens of prior chemotherapy. One of the four patients developed a grade 3 respiratory infection 12 weeks after completion of the final rituximab infusion. The neutrophil count at that time was 10/μl. He was effectively treated with G-CSF and antibiotics. This patient also developed grade 2 herpes zoster concomitantly with grade 4 neutropenia 20 weeks after completion of the final rituximab infusion.

According to the International Non-Hodgkin's Lymphoma Prognostic Factors Project, age >60 years, ECOG PS of 2–4, clinical stage III–IV, elevated LDH and extranodal involvement of two or more organs were significant factors unfavorably affecting OS [27]. In the present study, elevated LDH and primary refractoriness to prior chemotherapy were unfavorable factors

affecting both ORR and PFS, while other factors as listed in IPI were not unfavorable. However, when we compared the median PFS of the low/low-intermediate subgroup with that of the high-intermediate/high subgroup, there was a significant difference, suggesting that IPI is an important predictor of efficacy of rituximab monotherapy. Tsai et al. reported that rituximab has significant activity in intermediate-grade B-cell lymphoma that has relapsed after AHSCT [30]. Similar results were obtained in the present study.

The trough levels and AUCs of rituximab were significantly higher in the responders than in the non-responders. Berinstein et al. reported, based on their analyses of the pivotal study in the USA, that there was a correlation between response and serum rituximab level [31]. In our previous study of indolent B-cell lymphoma, patients with higher serum rituximab levels had longer PFS [9]. These results suggest that PK-guided treatment may be worthy of future investigations to further improve the efficacy of rituximab.

In conclusion, rituximab monotherapy is effective in relapsed or refractory patients with aggressive B-cell lymphoma with acceptable toxicity. Several pretreatment variables, including refractoriness to prior chemotherapy, elevated LDH and higher IPI score, and serum rituximab level are useful for predicting the efficacy of rituximab. Further investigations on rituximab-incorporating combination chemotherapy are warranted for improving the outcome in untreated and relapsed or refractory patients with B-cell lymphoma.

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