Phase II study of a salvage regimen using cyclophosphamide, high-dose cytarabine, dexamethasone, etoposide, and rituximab in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma

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The management of relapsed or refractory B-cell non-Hodgkin's lymphoma (B-NHL) remains challenging. We investigated the efficacy and safety of salvage chemoimmunotherapy (CHASER) in patients with relapsed or refractory B-NHL who had radiographically measurable disease and adequate major organ function. The CHASER treatment consisted of: rituximab 375 mg/m^2, day 1; cyclophosphamide 1200 mg/m^2, day 3; cytarabine·2 g/m^2, days 4 and 5; etoposide 100 mg/m^2, days 3–5; and dexamethasone 40 mg, days 3–5. The treatment was repeated every 3 weeks up to a total of four courses in the absence of disease progression. Thirty-two patients were enrolled and received a median of four courses of treatment (range 1–4 courses) per patient. Twenty patients (63%) were previously treated with rituximab-containing regimens. The median age was 54 years (range 28–67 years). The treatment was generally well tolerated, with major toxicities being grade 4 neutropenia (n = 32), thrombocytopenia requiring transfusion (n = 28), and grade 3 transaminase elevation (n = 2). Overall response rates in the entire group, and in patients with indolent (n = 17) and aggressive (n = 15) diseases were 84%, 100% and 67%, respectively. Responses were observed similarly in patients with (n = 20) and without (n = 12) previous rituximab exposure (85% and 83%, respectively). Stem cell harvest was successful in 19 of 22 patients. The median time to treatment failure for the entire group was 24.5 months. This promising result of high activity and favorable toxicity profile warrants further investigation in large-scale multicenter trials. (*Cancer Sci* 2008; 99: 179–184)

Although a certain proportion of patients with NHL have an excellent prognosis after initial treatment, many patients with NHL develop relapsed or refractory disease. Management of such conditions remains challenging, and salvage regimens to better control the disease are needed. We previously reported the safety and efficacy of combination salvage chemotherapy called CHASE[1] that consists of cyclophosphamide, high-dose cytarabine, steroid (dexamethasone), and etoposide. CR was observed in 10 of 14 patients (71%) with relapsed or refractory NHL. This regimen was well tolerated, and was associated with no renal toxicities, in contrast to other commonly used cisplatin containing salvage regimens such as DHAP[2] and ESHAP[3] which are associated with irreversible increase in serum creatinine in 4–8% of patients. Although the original report of CHASE included only a small number of patients, CHASE has been widely used as a salvage therapy in Japan given the significant efficacy and tolerability.

Anti-CD20 monoclonal antibody, rituximab, has recently revolutionized the management of B-NHL. Rituximab can contribute to improved disease control and survival when added to initial standard combination chemotherapy[4,5] and the use of rituximab in the salvage setting has also shown significant activity with minimal toxicity.[6,7] However, it remains to be shown whether rituximab containing salvage chemotherapy is still as effective in patients with previous exposure to rituximab. Based on the encouraging clinical data of CHASE chemotherapy as well as rituximab in salvage settings, we carried out an open-label, phase II clinical trial to evaluate the efficacy and safety of combination chemoimmunotherapy using CHASE and rituximab (CHASER) in patients with relapsed or refractory B-NHL.

Materials and Methods

Patient selection. The protocol for the current study was approved by the institutional review board of Aichi Cancer Center Hospital (Aichi, Japan). To be eligible for the study, patients were required to have histologically confirmed relapsed or refractory NHL, with CD20 positivity on tumor cells by immunohistochemistry and bidimensionally measurable disease by computed tomography scan. Patients were also required to: be aged between 15 and 69 years; have an Eastern Cooperative Oncology Group performance status 0–2; have received ≥1 previous treatment regimens; and have adequate bone marrow function (ANC ≥1.5 × 10^9/L, and platelet count ≥100 × 10^9/L), liver function (total bilirubin level ≤2 mg/dL, and aspartate aminotransaminase and alanine aminotransaminase levels ≤2.5 times the upper limit of normal), and kidney function (serum creatinine level ≤2 mg/dL).

Patients were ineligible if they had lymphoma involvement in the central nervous system; had serum hepatitis B surface antigen; had serum HIV antibody; had uncontrolled intercurrent illnesses such as active infection, cardiac diseases, active second malignancy, or psychiatric disease. Those who were pregnant or lactating were ineligible. Written informed consent was obtained from all patients before study entry, consistent with national and local requirements. All patients gave written informed consent indicating that they were aware of the investigational nature of the study, in keeping with the policies of Aichi Cancer Center Hospital.

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Abbreviations: ANC, absolute neutrophil count; B-NHL, B-cell non-Hodgkin's lymphoma; CHASE, cyclophosphamide, high-dose cytarabine, dexamethasone, and etoposide; CHASER, cyclophosphamide, cytarabine, etoposide, dexamethasone, and rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CI, confidence interval; CR, complete response; CRu, complete response unconfirmed; DHAP, dexamethasone, high-dose cytarabine, and cisplatin; ESHA, etoposide, methylprednisone, and high-dose cytarabine; ESHAP, ESHA plus cisplatin; NHL, non-Hodgkin's lymphoma; ORR, overall response rate; OS, overall survival; R-CHOP, rituximab with CHOP; R-DHAP, rituximab with DHAP; R-ESHAP, rituximab with ESHAP; SCT, stem cell transplantation; TTF, time to treatment failure.

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Treatment schedule. The regimen consisted of rituximab 375 mg/m^2 intravenously on day 1; cyclophosphamide 1200 mg/m^2 intravenously over 3 h on day 3; cytarabine 2 g/m^2 intravenously over 3 h on days 4 and 5; etoposide 100 mg/m^2 intravenously on days 3–5; dexamethasone 40 mg intravenously on days 3–5 and G-CSF (filgrastim, lenograstim, or nartograstim at the primary physician's choice) 2 μg/kg subcutaneously from day 6 till neutrophil recovery. The treatment was to be repeated every 3 weeks up to a total of four courses unless there is disease progression, persistent grade 3/4 toxicity, or delayed recovery of neutrophils ($<1.0 \times 10^9$/L) or platelets ($<75 \times 10^9$/L). Peripheral blood stem cell harvest was carried out after the second and/or third cycle if the patient was a suitable candidate for future SCT, targeting a total CD34 count of 2.0×10^6/kg body weight or higher.

Supportive care during chemotherapy. Patients were to be premedicated with antihistamine and antipyretics prior to rituximab infusion. Effective antiemetics such as 5-HT3 receptor antagonist were given intravenously prior to chemotherapy and as needed. To prevent hemorrhagic cystitis from cyclophosphamide, at least 3000 mL of hydration with bicarbonate-containing fluid was required on day 1. Mesna was not given in this study.

Response and toxicity assessments. To assess response, patients were required to be re-evaluated with a thoracic, abdominal, and pelvic computed tomography scan every two cycles. The International Workshop Response Criteria for NHL were used for evaluating responses[8] except that clearance of tumor cells from bone marrow needed to be confirmed by morphologic as well as flow cytometric assessment in patients who had bone marrow involvement on study entry.

Toxic effects were originally graded according to the National Cancer Center Institute Common Toxicity Criteria (version 2.0), and regarded after data collection and analyses based on version 3.0. Patients were evaluated daily with a complete history and physical examination. The laboratory assessment was carried out at least twice weekly to monitor organ toxicity and electrolyte abnormalities.

Dose modifications. If a patient's ANC was $>1.0 \times 10^9$/L and platelet count was between 75×10^9/L and 100×10^9/L (condition A) at the due date for initiation of the next treatment, doses of cyclophosphamide, cytarabine, and etoposide were reduced by 25% for the next cycle. If a patient's ANC was $<1.0 \times 10^9$/L or platelet count was $<75 \times 10^9$/L, the treatment needed to be postponed until condition A was achieved, and the doses were reduced as in condition A. If this improvement did not occur in a week, that is, at four weeks after the previous cycle, the patient was removed from the study. If persistent arrhythmia, cardiac ischemia, pericarditis, or grade 3/4 heart failure were observed, the patient was removed from the study. If grade 3/4 hepatotoxicity was present at initiation of the next cycle, the treatment was postponed till the toxicity was grade 2 or less. If grade 3 hepatotoxicity was persistent at 4 weeks after initiation of previous treatment, the patient was removed from the study. If serum creatinine was between 1.6 and 1.9 mg/dL, or increased from baseline by 0.5–1.2 mg/dL (condition B), the dose of cytarabine was reduced by 50% (1 g/m^2) because of the risk of severe neurological toxicity. The doses of other agents were not changed, as they were not expected to significantly increase the risks of severe non-hematologic toxicities from this degree of mild renal impairment. If serum creatinine was ≥2 mg/dL, or increased from baseline by 1.3 mg/dL (condition C), the treatment needed to be postponed till condition B was achieved, and the dose of cytarabine was reduced by 50% when initiating treatment. If condition C was persistent at 4 weeks after previous treatment, the patient was removed from the study. If grade 4 non-hematologic toxicity or performance status of 4 without improvement during the treatment course was observed, the patient was removed from the study.

Statistical methods. The primary endpoint of this study was an ORR and the secondary endpoints were TTF, OS, successful stem cell mobilization (in patients planned for SCT, as described earlier), and toxicities. The study used a two-stage design, where 11 patients were recruited in the first stage and if eight or more responses were observed, an additional 21 patients were recruited for the second stage. The two-stage design was based on alpha = 0.05, power = 90%, undesirable response rate = 60%, and desirable response rate = 85%. Statistical analysis for patients' characteristics, response rates, and adverse events was descriptive. Analysis on response rate, TTF, and OS was carried out on an intent-to-treat basis, using the Kaplan–Meier method. The TTF was calculated from the time of registration to the time of disease progression, change of treatment, or disease- or treatment-related death. Those who eventually underwent SCT were censored for TTF at the initiation of conditioning treatment. OS duration was calculated from the time of registration to the time of death of any cause.

Results

Patient characteristics. Thirty-two eligible patients were enrolled between November 2002 and November 2006. All received at least one course of CHASER chemotherapy. Baseline patient and disease characteristics are shown in Table 1. The median age was 54 years (range 28–67 years), and most (n = 30, 94%) of the patients had an Eastern Cooperative Oncology Group performance status of 0 or 1. Seventeen had indolent NHL (all follicular grade 1 or 2), and 15 had aggressive NHL (11 diffuse large B-cell lymphoma, two mantle cell lymphoma, one large cell transformation of marginal zone lymphoma, and one large cell transformation of follicular lymphoma grade 2). The majority of patients (n = 22, 69%) had stage III or IV disease.

All patients were previously treated with CHOP-based chemotherapy at the time of initial diagnoses, and the majority of patients (n = 22, 69%) entered the current study for the first salvage treatment. Twenty patients (63%) were previously treated with rituximab-containing therapy. Four patients (13%) previously received radiation therapy for local disease control. Overall, 10 patients (31%) had diseases refractory to last treatment, and the remaining 22 patients (69%) had relapsed diseases.

Toxicity. A total of 113 courses of CHASER were given, with a median of four courses (range 1–4 courses) per patient. All patients were assessable for adverse events associated with CHASER (Table 2). There was no treatment-related death or toxicity leading to discontinuation of the treatment. All experienced grade 4 neutropenia, but the duration of neutropenia (<500) was short (median 4 days per course, range 0–8). The median time to neutrophil nadir was 13 days (range 10–19 days). Twenty-five patients (78%) experienced neutropenic fever and all but one were managed successfully with a short course of broad-spectrum antibiotics. One patient experienced a prolonged febrile episode and required 10-day intravenous antibiotic treatment. The majority of patients (n = 28, 88%) required at least one platelet transfusion during the therapy, with a median of one transfusion per course (range 1–3 transfusions). The median time to platelet nadir was 14 days (range 10–19 days). Most common non-hematologic toxicity was gastrointestinal (nausea/vomiting, diarrhea, and elevated liver enzymes). Transient elevation of serum transaminases (grade 3) was observed in two patients. One patient experienced an episode of syncope (grade 3), which was most likely to be a vasovagal syncope and the association with the study drugs was unclear. There were no grade 4 or other grade 3 toxicities observed.

Three patients (9%) required delay in the treatment schedule due to slow recovery of the platelet count. One experienced a non-life-threatening but prolonged febrile neutropenia after the third cycle as described earlier, and doses of cyclophosphamide, cytarabine, and etoposide for the fourth course were reduced by

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Table 1. Characteristics of patients ($n = 32$) with relapsed or refractory B-cell non-Hodgkin's lymphoma who participated in this study

Characteristic	No.	%
Total	32	100
Median age in years (range)	54 (28–67)	
Male/female	17/15	53/47
Histology		
Indolent	17	53
Follicular grade 1/2	17	53
Aggressive	15	47
DLBCL	11	34
MCL	2	6
Large cell transformation of indolent lymphoma	2	6
ECOG performance status at entry		
0/1	30	94
2	2	6
Stage at entry		
1	5	16
2	5	16
3	5	16
4	17	53
LDH at entry		
Normal	18	56
High	14	44
No. of sites of extranodal involvement		
0	13	41
1	14	44
2 or more	5	16
IPI score at study entry		
1	12	38
2	10	31
3	10	31
No. of prior treatment regimens		
1	22	69
2	4	16
3	3	6
4 or more	3	9
Prior platinum-containing therapy	1	3
Prior rituximab-containing therapy	20	63
Prior radiation therapy	4	13
Prior radioimmunotherapy (^{90}Yttrium-ibritumomab)	1	3
Prior autologous stem cell transplant	2	6
Refractory to last chemotherapy	10	31
Relapsed disease		
Previous remission duration ≤1 year	8	25
Previous remission duration >1 year	14	44

DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; LDH, lactate dehydrogenase; MCL, mantle cell lymphoma.

25%. One patient who experienced hyperglycemia, which was difficult to control with insulin after the third cycle, received only 12 mg of dexamethasone for the fourth cycle at the discretion of the responsible physician.

Response. The objective response of all 32 evaluable patients is summarized in Table 3. ORR was 84% (95% CI [67–95%]), including CR or CRu in 24 patients (75% [57–89%]), and partial response in three patients (9%). The ORR and CR rates in indolent lymphoma were 100% (84–100%; 17 of 17) and 94% (71–99%; 16 of 17), respectively, and those in aggressive lymphoma were 67% (38–88%; 10 of 15) and 53% (27–79%; 8 of 15), respectively. Response was observed both in patients who previously received rituximab (17 of 20, 85%) and those who did not (10 of 12, 83%) ($P = 0.37$). In patients with aggressive B-NHL with ($n = 8$) or without ($n = 7$) prior rituximab exposure, ORR was 63% and 71%, respectively ($P = 0.39$), and CR rate was 57% and 50%, respectively ($P = 0.38$). The CR rate was higher in patients with longer than 1 year of response duration after last treatment (93%, 13 of 14) than in patients with 1 year or shorter of response duration or refractory disease after last treatment (61%, 11 of 18) ($P = 0.047$). Other factors such as International Prognostic Index (IPI) score at study entry, response to the first treatment were not significantly associated with overall or complete response to CHASER (data not shown). Two patients who had previously undergone autologous SCT also experienced responses (CR and partial response, respectively). Three patients achieved only stable disease and proceeded to different salvage regimens after two, two and four cycles, respectively. Two patients had rapidly progressive disease after one and two cycles, respectively, and eventually received different salvage regimens.

Stem cell collection and SCT. Although not required to enter the study, all patients aged 65 years ($n = 30$) were offered at study entry an option of peripheral blood stem cell harvesting, to be carried out after the second (and third, if necessary) course of CHASER for future SCT. Out of 30 patients, stem cell collection was not attempted in eight patients: three patients with follicular

Table 2. Toxicity observed in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma during salvage chemoimmunotherapy incorporating cyclophosphamide, cytarabine, etoposide, dexamethasone, and rituximab (n = 32)

	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic				
Neutropenia (%)	0 (0)	0 (0)	0 (0)	32 (100)
Thrombocytopenia (%)	0 (0)	0 (0)	4 (13)	28 (88)
Febrile neutropenia (%)	0 (0)	0 (0)	25 (78)	0 (0)
Gastrointestinal				
Nausea/vomiting (%)	9 (28)	4 (13)	0 (0)	0 (0)
Diarrhea (%)	6 (19)	1 (3)	0 (0)	0 (0)
Elevated liver enzymes (%)	14 (44)	4 (13)	2 (6)	0 (0)
Neurological				
Peripheral neuropathy (%)	2 (6)	0 (0)	0 (0)	0 (0)
Syncope (%)	0 (0)	0 (0)	1 (3)	0 (0)
Pain (%)	1 (3)	4 (13)	0 (0)	0 (0)
Edema (%)	4 (13)	0 (0)	0 (0)	0 (0)

Table 3. Responses observed in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma (B-NHL) after treatment with salvage chemoimmunotherapy incorporating cyclophosphamide, cytarabine, etoposide, dexamethasone, and rituximab

Type of B-NHL	Prior treatment	Total no.	CR or Cru	Overall response
Indolent B-NHL	All	n = 17	n = 16	n = 17
			94% (71–99%)	100% (84–100%)
	Previous rituximab	n = 12	n = 11	n = 12
			92% (62–99%)	100% (78–100%)
	Rituximab-naive	n = 5	n = 5	n = 5
			100% (55–100%)	100% (55–100%)
Aggressive B-NHL	All	n = 15	n = 8	n = 10
			53% (27–79%)	67% (38–88%)
	Previous rituximab	n = 8	n = 4	n = 5
			50% (16–84%)	63% (24–91%)
	Rituximab-naive	n = 7	n = 4	n = 5
			57% (18–90%)	71% (29–96%)
Total	All	n = 32	n = 24	n = 27
			75% (57–89%)	84% (67–95%)
	Previous rituximab	n = 20	n = 15	n = 17
			75% (51–91%)	85% (62–97%)
	Rituximab-naive	n = 12	n = 9	n = 10
			75% (43–95%)	83% (52–98%)

Ranges in parentheses indicate 95% confidence interval. CR, complete response; CRu, complete response unconfirmed.

lymphoma declined this option; two patients had undergone autologous SCT prior to CHASER; and three patients had poor control of disease during CHASER (two progressive disease and one stable disease). As a result, stem cell collection was attempted in 22 patients. Three had insufficient mobilization of CD34 positive cells in peripheral blood; one of these patients had had three prior regimens including one cladribine-containing regimen. The remaining 19 patients successfully completed stem cell collection, with a median CD34 count of 4.0×10^6/kg body weight (range 1.9–23.4×10^6) by a median of two rounds of apheresis (range 1–3 rounds). All collected stem cell sources were free of malignant B cells, determined by flow cytometric analyses. In six patients with follicular lymphoma with MBR/JH rearrangement detected by seminested polymerase chain reaction (using primer sets LJH-P, TGAGGAGACGGTGACC and MBR-P, CCAAGTCATGTGCATTTCCACGTC for the first step, and VLJH-P, GTGACCAGGGTNCCTTGGCCCCAG and MBR-P for the second step). Negativity of tumor cell contamination in the stem cell sources was confirmed by the same method (data not shown). Two of 19 patients with aggressive NHL had suboptimal response (stable disease) on imaging studies after CHASER, thus proceeded to other salvage regimens. One patient who had adequate stem cell collection refused to undergo SCT. As a result, a total of 16 patients (50%) underwent autologous SCT as an immediate next treatment after CHASER treatment. One patient who had undergone autologous SCT prior to CHASER underwent allogeneic SCT as an immediate next treatment after CHASER.

TTF and OS. The Kaplan–Meier estimates of TTF and OS are shown in Fig. 1. The median TTF and OS durations for the entire group were 24.5 months and not reached, respectively. The median TTF in patients with indolent and aggressive lymphoma was 24.5 months and not reached, respectively. The median OS duration in patients with indolent and aggressive lymphoma was not reached and 39.3 months, respectively. Neither TTF nor OS duration was significantly different by IPI score at study entry, response duration after last chemotherapy (refractory or ≤1 year *vs* >1 year), previous rituximab exposure, or response to the first treatment (log–rank test, data not shown).

Discussion

Patients with relapsed or refractory NHL have limited options and poor prognosis. Even in patients who might be candidates for autologous SCT, it is critical to reduce the tumor size with

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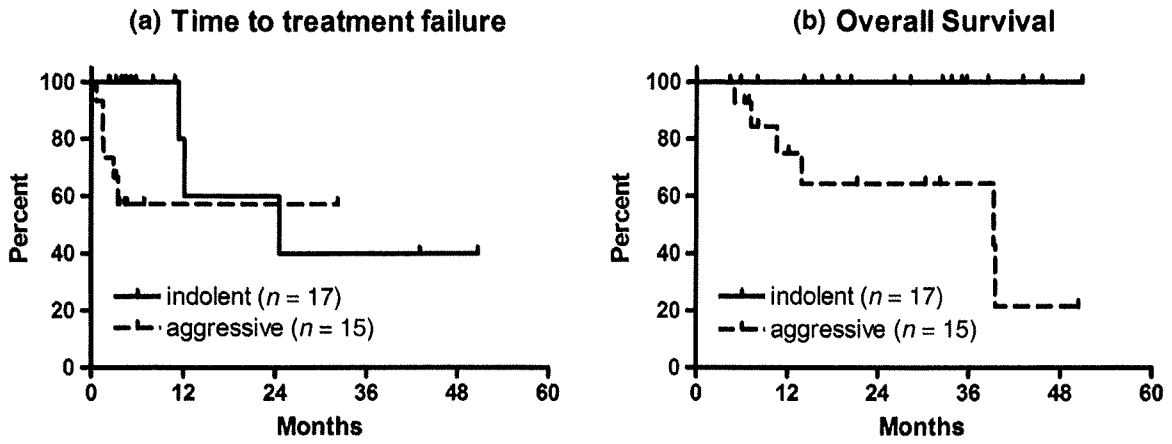

Fig. 1. Overall survival (OS) and time to treatment failure (TTF) in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma undergoing salvage chemoimmunotherapy incorporating cyclophosphamide, cytarabine, etoposide, dexamethasone, and rituximab. Solid lines indicate survival curves of patients with indolent lymphoma (n = 17). Dashed lines indicate those of patients with aggressive lymphoma (n = 15). (a) The median TTF in patients with indolent and aggressive lymphoma was 24.5 months and not reached, respectively. Those who had stem cell transplant were censored for TTF at the initiation of conditioning regimen. (b) The median OS duration in patients with indolent and aggressive lymphoma was not reached and 39.3 months, respectively.

Table 4. Comparison of CHASER, R-DHAP, R-ESHAP and R-ICE in relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma (doses are per course)

	CHASER	R-DHAP[9]	R-ESHAP[7]	R-ICE[6]
Rituximab	375 mg/m^2 × 1	375 mg/m^2 × 1	375 mg/m^2 weekly × 8	375 mg/m^2 × 1
Cytarabine	2 g/m^2 × 2	2 g/m^2 × 2	2 g/m^2 × 1	–
Etoposide	100 mg/m^2 × 3	–	40 mg/m^2 × 4	100 mg/m^2 × 3
Steroid	Dexamethasone 40 mg × 3	Dexamethasone 40 mg × 4	Methylprednisolone 500 mg × 5	–
Platinum agent	–	Cisplatin 25 mg/m^2 × 4	Cisplatin 25 mg/m^2 × 4	Carboplatin AUC 5 × 1
Non-platinum alkylator	Cyclophosphamide 1200 mg/m^2 × 1	–	–	Ifosfamide 5 g/m^2 × 1
No. of patients	15	53	26	36
Prior rituximab exposure (%)	53	4	19†	0
CR rate % (95% CI)	53 (27–79)	32 (20–46)	46 (27–65)	53 (36–69)
OR rate % (95% CI)	67 (38–88)	62 (48–75)	92 (82–100)	78 (61–90)

†L. Hicks *et al.*, 2007, personal communication; –, not included in treatment; AUC, area under the curve; CI, confidence interval; CR, complete response; OR, overall survival.

an effective salvage regimen prior to SCT. For those who are not candidates for transplant, a treatment regimen to induce a durable response is the sole key for long-term survival. The present study showed the significant activity of the new combination salvage regimen CHASER in patients with relapsed or refractory B-NHL who may or may not have undergone prior rituximab-containing treatment such as R-CHOP.

Although rituximab has been studied in salvage settings as an additional drug to commonly used combination chemotherapy, such as ESHAP[7] DHAP[9,10], and ICE (ifosfamide, carboplatin and etoposide)[6,10], currently available data are from studies recruiting mostly rituximab-naive patients (Table 4). Therefore, it remains to be shown whether R-ICE (rituximab with ICE) or R-DHAP is still as effective in patients who were previously treated with a rituximab-containing regimen.[10] It is noteworthy in our study that CHASER produced high CR rates in relapsed or refractory B-NHL after rituximab-containing chemotherapy, and that the activity seems comparable to those of other platinum-containing regimens in patients with aggressive B-NHL (Table 4). Randomized trials would be needed to further compare the efficacy of CHASER with other regimens. Also, careful long-term follow-up is needed to assess the potential late effect of rituximab, such as delayed neutropenia as has recently been recognized.[11–14]

Both CHASER and R-ESHAP contain high-dose cytarabine, etoposide, steroid, and rituximab in common. In the original study of ESHAP, Velasquez *et al.* initially compared ESHA with ESHAP[3], revealing that the addition of cisplatin significantly improved the response rate (33% *vs* 75% at initial phase of the study, but the response rate of ESHAP at the end of the study was 64%), despite only moderate activity of single agent cisplatin against NHL (response rate 26%[15]). Further addition of rituximab to ESHAP seems even more active, and in a phase II study of R-ESHAP in patients with aggressive B-NHL (n = 26, 21 were rituximab-naive), a response rate of 92% (95% [CI 84–100%]) including a CR rate of 46% (95% [27–65%]) was observed. CHASER contains 1200 mg/m^2 of cyclophosphamide instead of cisplatin, producing comparable response rates to R-ESHAP. Virtually all patients with relapsed or refractory B-NHL were exposed to cyclophosphamide at 750 mg/m^2 as a part of CHOP therapy, however, a higher dose of cyclophosphamide seems to play a significant role in overcoming resistance in this setting. Furthermore, one major benefit of using cyclophosphamide instead of cisplatin is absence of renal toxicity.

One important aspect of salvage regimens for relapsed or refractory NHL is their stem cell mobilizing effect. In our study, 19 of 22 attempts at stem cell collection were successful, but it should be noted that one of three who experienced poor stem cell mobilization had been heavily pretreated. Furthermore, addition of rituximab to the CHASE regimen might add an *in vivo* purging effect and allow tumor-free stem cell collection. Further studies are necessary to determine whether *in vivo* purged autologous SCT will improve outcomes compared to non-purged SCT.

In conclusion, CHASER showed favorable tolerability, significant antitumor activity, and stem cell mobilizing effects in patients with relapsed or refractory B-NHL with or without prior rituximab-containing treatment such as R-CHOP. This promising result warrants the further investigation of CHASER in large-scale multicenter trials and comparison to other salvage regimens.

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The International Prognostic Index predicts outcome in aggressive adult T-cell leukemia/lymphoma: analysis of 126 patients from the International Peripheral T-cell Lymphoma Project

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Background: The International Peripheral T-cell Lymphoma Project was organized to better understand the T-cell and natural killer (NK) cell lymphomas, and our task is to present the clinicopathologic correlations and therapeutic results for adult T-cell leukemia/lymphoma (ATL).

Patients and methods: Among 1153 patients with T-cell or NK cell lymphomas, 126 patients (9.6%) with ATL were represented in this project. All were categorized as aggressive ATL, i.e. acute or lymphoma type, and 87% fell into the lymphoma type.

Results: The median age was 62 years and the male to female ratio was 1.2 : 1. Significant prognostic factors for overall survival (OS) by univariate analysis were the presence of B symptoms ($P = 0.018$), platelet count $<150 \times 10^9$/l ($P = 0.065$), and the International Prognostic Index (IPI; $P = 0.019$). However, multivariate analysis indicated that only the IPI was an independent predictor of OS. Combination chemotherapy including anthracyclines was given as the initial therapy in 109 of the 116 patients (94%) who received treatment, and the overall and complete response rates were 70% and 34%, respectively. However, there was no survival benefit for those receiving an anthracycline-containing regimen.

Conclusion: Patients with aggressive ATL have a poor clinical outcome and the IPI is a useful model for predicting outcome in ATL of the lymphoma type.

Key words: ATL, leukemia, lymphoma, T-cell, prognostic index, international

introduction

Adult T-cell leukemia/lymphoma (ATL) is a peripheral T-cell malignancy caused by a retrovirus, human T-cell lymphotropic virus type I (HTLV-1) [1, 2], and is now regarded as a tumor derived from regulatory T cells which express FoxP3 [3, 4]. ATL is diagnosed based on its characteristic clinicopathologic features and the presence of integrated HTLV-1 provirus in the DNA of the tumor cells. ATL has characteristic cytological features with atypical 'flower cells' in the peripheral blood and pleomorphic lymphoma cells in tissue sections [1, 2, 5] and can be divided into four clinical subtypes, i.e. smoldering, chronic, acute, and lymphoma types. The acute type is the most common variant, presenting with disseminated disease and having a highly aggressive clinical course. In contrast, the smoldering type has an indolent clinical course with only a small percentage of leukemic cells and occasional skin involvement. The chronic type also has an indolent clinical course, but with a higher percentage of leukemic cells, slowly progressive skin disease, mild lymphadenopathy, and hepatosplenomegaly. The lymphoma type usually presents with disseminated disease including prominent lymph node enlargement, but with few leukemic cells [1, 2, 5]. The aggressive forms of ATL, including the acute and lymphoma types, are usually treated with combination chemotherapy, but the prognosis is poor with a median survival of <1 year

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compared with other forms of peripheral T-cell lymphoma (PTCL) [6–9].

In the past decade, there have been significant advances in our understanding of the biology of malignant lymphoma and some progress in treatment as well. However, our understanding of PTCL in general is far behind that of the B-cell lymphomas. Therefore, the International Peripheral T-cell Lymphoma Project was organized to assess the clinical applicability and reproducibility of the World Health Organization classification of peripheral T-cell and natural killer (NK) cell lymphomas, as well as to evaluate therapeutic outcomes and identify prognostic factors [10]. This report describes the clinicopathologic correlations and therapeutic results for patients with ATL from the International Peripheral T-cell Lymphoma Project.

patients and methods

We collected previously untreated patients with *de novo* peripheral T-cell or NK/T-cell lymphoma, excluding mycosis fungoides and Sézary syndrome, who were diagnosed from 1 January 1990 to 31 December 2002, in 22 centers in 13 countries around the world (Appendix 1) [10]. The diagnosis of ATL was based on histologic features and the presence of either positive HTLV-1 serology or monoclonal integration of HTLV-1 provirus [2, 9]. All cases were reviewed by four expert hematopathologists, and a consensus diagnosis was made by the agreement of three or four experts. We collected clinical data and laboratory findings including HTLV-1 serology, leukocyte count, and absolute lymphocyte count, as well as initial treatment and subsequent therapy. Treatment outcome was determined by overall survival (OS) and failure-free survival (FFS). OS was defined as the time from diagnosis to death from any cause, with surviving patient follow-up being censored at the last contact date. FFS was defined as the time from diagnosis to first progression, relapse after response, or death from any cause. Follow-up of patients not experiencing any of these events was censored at the date of last contact. OS and FFS were calculated by the method of Kaplan and Meier, and time to event distributions were compared using the log-rank test. Comparisons of clinical and prognostic factors were carried out using the chi-square or Fisher's exact test. Multivariate analysis was carried out with a Cox hazards regression model using stepwise selection.

results

In this project, 1314 cases were collected from North America, Europe, and Asia, and a diagnosis of PTCL or NK/T-cell lymphoma was confirmed in 1153 cases. ATL was diagnosed in 126 patients (9.6%) and was rare in North America (2.0%) and Europe (1.0%), but frequent in Asia (25%) among all PTCL patients. All the Asian cases were from Japan.

There are four clinical subtypes of ATL, i.e. smoldering, chronic, acute, and lymphoma types, in Shimoyama's classification [5]. In this study, smoldering and chronic ATL were excluded. The lymphoma type of ATL is defined by a lymphocyte count of <4000/μl in Shimoyama's classification [5]. Thus, 104 patients (87%) were classified as the lymphoma type and the rest as acute type (13%).

The clinical characteristics of the 126 ATL patients are shown in Table 1. There were 69 males and 57 females, with a median age of 62 years. Major signs and symptoms included lymphadenopathy (77%), fatigue (32%), anorexia (26%), skin eruption (23%), abdominal pain (23%), splenomegaly (13%), and hepatomegaly (10%). Overall, 90% of the patients had advanced stage disease by the Ann Arbor classification, 31% had B symptoms, and 23% were nonambulatory. Bone marrow infiltration and two or more sites of extranodal involvement were seen in 28% and 34% of the cases, respectively. In addition, 20 patients (17%) had a platelet count of $<150 \times 10^9$/l. We were able to evaluate 124 patients according to the International Prognostic Index (IPI) [11] and only 18.5% were in the good prognosis category (IPI = 0/1).

Chemotherapy was given to 116 patients, and combination chemotherapy including an anthracycline was given as an initial therapy to 109 patients (94.0%). Autologous or allogeneic hematopoietic stem-cell transplantation (HSCT) was carried out in 17 patients, including 10 patients as initial therapy and

Table 1. Clinical characteristics of 126 patients with aggressive ATL

Age (years)		
Median (range)	62	(20–92)
Sex		
Male/female	69/57	1.2 : 1
Stage		
I/II	12	9.6%
III	22	17.6%
IV	91	72.8%
B symptoms		
No	87	69.0%
Yes	39	31.0%
Performance status		
Ambulatory	97	77.0%
Nonambulatory	29	23.0%
Largest mass		
<5 cm	74	65.5%
≥5 cm	39	34.5%
Bone marrow involvement		
No	87	71.9%
Yes	34	28.1%
Nodal/extranodal disease		
Nodal only	37	31.4%
Nodal and extranodal	72	61.0%
Extranodal only	9	7.6%
Extranodal sites		
0–1	83	65.9%
≥2	43	34.1%
Serum LDH		
≤Normal	74	59.7%
>Normal	50	40.3%
Absolute lymphocyte count		
<4000/μl	104	86.7%
≥4000/μl	16	13.3%
IPI scores		
0/1	23	18.5%
2	41	33.1%
3	40	32.3%
4/5	20	16.1%

ATL, adult T-cell leukemia/lymphoma; LDH, lactate dehydrogenase; IPI, International Prognostic Index.

seven in first relapse. The response to initial therapy is shown in Table 2. The overall and complete response rates were 70% and 34%, respectively. However, majority of the patients (82%) have died, mostly from lymphoma or the complications of therapy. Only 5% of the patients were in complete remission at the time of death, and the median FFS and OS were only 0.6 and 0.8 years, respectively (Figure 1).

Table 3 shows the significant prognostic factors by the univariate analysis. Adverse prognostic factors for OS were the presence of B symptoms ($P = 0.018$), a platelet count $<150 \times 10^9$/l ($P = 0.065$), and a high (≥3) IPI score ($P = 0.019$; Figure 2A). Unexpectedly, bone marrow involvement, an elevated absolute lymphocyte count (≥4000/μl; Figure 3), elevated serum lactate dehydrogenase (LDH), hypercalcemia, and combination chemotherapy without an anthracycline (Figure 4) had no influence on OS. The IPI score was the only significant predictor of survival in multivariate analysis. Figure 5 shows OS according to the IPI in the lymphoma type of ATL (lymphocytes < 4000/μl). The IPI predicted for OS in the lymphoma type of ATL ($P = 0.04$), but not in the acute type (not shown; $P = 0.24$). Based on these results, the IPI is a useful model for predicting outcome in ATL of the lymphoma type.

Table 2. Response to initial therapy and clinical course in aggressive ATL

Treatment response	CR	32 (28%)		
	CRu	7 (6%)	CR + PR	81 (70%)
	PR	42 (36%)		
	NR	35 (30%)		
Recurrence of disease				71 (88%)
Alive 23 (18%)/dead 103 (82%)				
Causes of death	Lymphoma			74 (75%)
	Toxicity			10 (10%)
	Infection			2 (2%)
	Myelodysplasia			1 (1%)
	Other			8 (8%)
	Unknown			8 (8%)
Remission at death				5 (5%)

ATL, adult T-cell leukemia/lymphoma; CR, complete response; CRu, complete response unconfirmed; PR, partial response; NR, no response.

discussion

The International Peripheral T-cell Lymphoma Project was organized to better understand the T-cell and NK cell lymphomas [10]. ATL is endemic in southwest Japan, the Caribbean Islands, countries surrounding the Caribbean Basin, and parts of Central Africa and South America [12]. In the present study, one half of the patients were registered from Fukuoka, located in southwest Japan, and 30% from the rest of Japan, but none from the rest of Asia. Also, 20% of the patients were registered from Europe or North America including two patients from the Vancouver site and highlighting a previously unknown HTLV-1 endemic region. Both of these patients were indigenous American Indians [13].

The present study reveals that the IPI has predictive value for patients with aggressive ATL, particularly those with the lymphoma type. A previous nationwide study in Japan revealed five adverse prognostic factors for ATL by multivariate analysis: (i) age over 40 years; (ii) low performance score; (iii) hypercalcemia; (iv) elevated serum LDH level; and (v) the number of lesions [14]. These prognostic factors are similar to those in the IPI. This previous study in Japan reported on 818 ATL patients diagnosed from 1984 to 1987 [5, 14], with 56.5% having the acute type, 19.1% the lymphoma type, 18.6% the chronic type, and 5.5% with the smoldering type of ATL. Thus, the acute type is the most common subtype of ATL in Japan [5, 7, 8, 14]. However, in the present study, 87% of the patients had the lymphoma type and the rest had the acute type. The IPI has been shown to predict outcome in patients with PTCL [15], but cases of ATL were not included in that study. Although the IPI was developed for patients with aggressive B-cell lymphoma treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like regimens [11], our study shows that the IPI is also useful for predicting outcome in aggressive ATL, especially the lymphoma type.

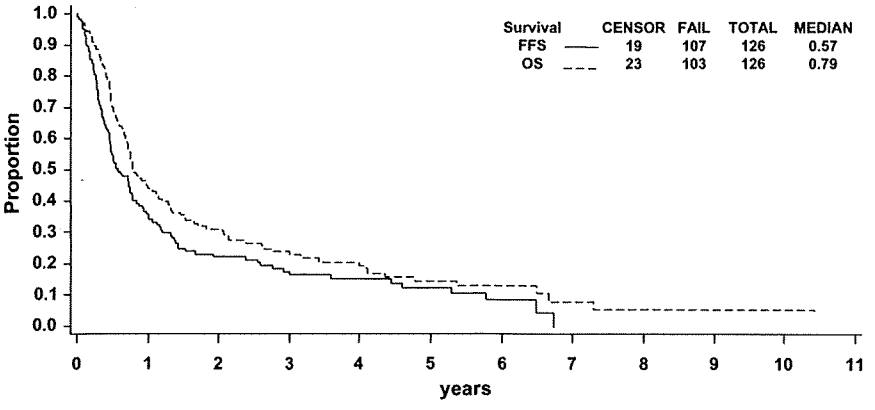

Figure 1. Overall survival (OS) and failure-free survival (FFS) of 124 patients with the aggressive adult T-cell leukemia/lymphoma.

The frequency of bone marrow involvement was only 28% in the present study, but was 85% in the previous Japanese report [14]. This difference is most likely due to the differences in ATL subtypes in the two studies. Although few reports have described the frequency of bone marrow involvement in the various subtypes of ATL, Kinoshita [16] reported that 60 of 65 patients (92.3%) with the acute type, but only 7 of 40 patients (17.5%) with the lymphoma type, had bone marrow involvement. Recently, Takasaki et al. [17] reported that visceral organ involvement, including the bone marrow, was a prognostic factor in ATL. Thrombocytopenia ($<100 \times 10^9$/l) and monocytosis ($\geq 0.8 \times 10^9$/l) were also found to be significant adverse prognostic factors by multivariate analysis. In contrast, we could identify no significant prognostic factors other than the IPI by multivariate analysis. However, Takasaki et al. [17] analyzed 168 ATL patients consisting of 75% with the acute type, 9% with the lymphoma type, 15% with the chronic type, and 4% with the smoldering type. Therefore, the proportions of the various subtypes in that paper were quite different from those in the present study, making meaningful comparisons difficult. Furthermore, in a recent report, the acute and the lymphoma types of ATL were found to be genomically different [18]. Thus, future studies of ATL should include separate analyses of prognostic factors for each of the ATL subtypes.

Table 3. Prognostic factors in aggressive ATL by univariate analysis

Factors	*n*	Median OS (years)	
B symptoms			
No	87	1.12	$P = 0.018$
Yes	39	0.66	
Platelet count ($\times 10^9$/l)			
≥150	101	0.85	$P = 0.065$
<150	20	0.67	
IPI score			
0/1	23	2.07	$P = 0.019$
2	41	1.32	
3	40	0.71	
4/5	20	0.73	

ATL, adult T-cell leukemia/lymphoma; OS, overall survival; IPI, International Prognostic Index

The clinical outcome in our series of aggressive ATL was extremely poor, with a median OS of only 0.8 years. Combination chemotherapy including an anthracycline was given to most of our patients, but did not improve the survival significantly. These data confirm that CHOP and CHOP-like regimens are not effective in aggressive ATL [19, 20]. Tsukasaki et al. [21] recently reported the results of a phase III trial (JCOG 9801) comparing the safety and efficacy of vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP); doxorubicin, ranimustine, and prednisone (AMP); and vindesine, etoposide, carboplatin, and prednisone (VECP) (VCAP–AMP–VECP) versus biweekly CHOP in the aggressive types of ATL. The 3-year OS of those receiving VCAP–AMP–VECP therapy was only 24%, which was similar to our study. Allogeneic HSCT for ATL appears to be effective in some patients [22, 23], but there are inherent problems including

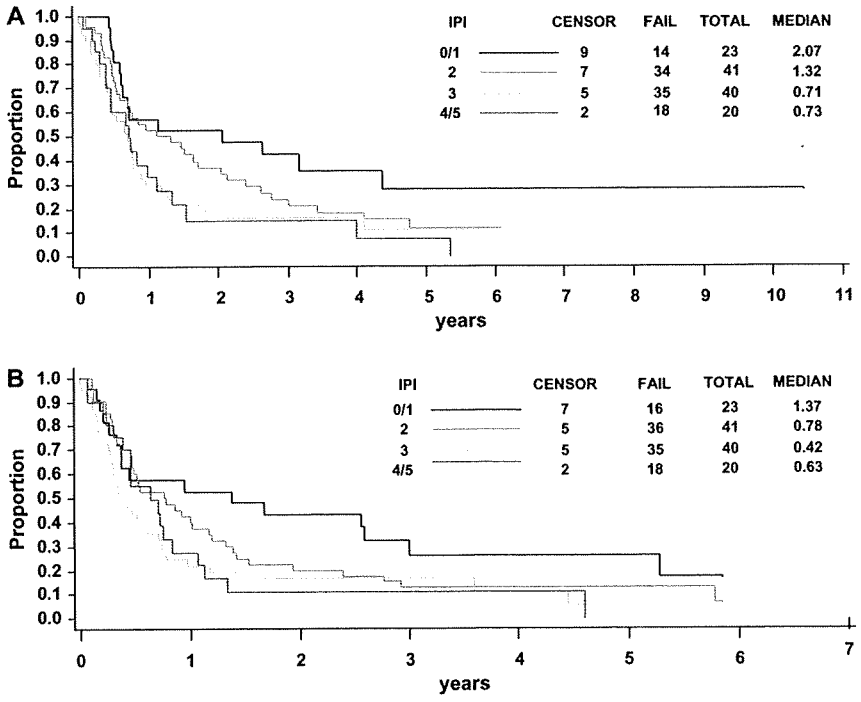

Figure 2. Overall survival (A) and failure-free survival (B) of patients with aggressive adult T-cell leukemia/lymphoma according to the International Prognostic Index (A, $P = 0.019$; B, $P = 0.14$).

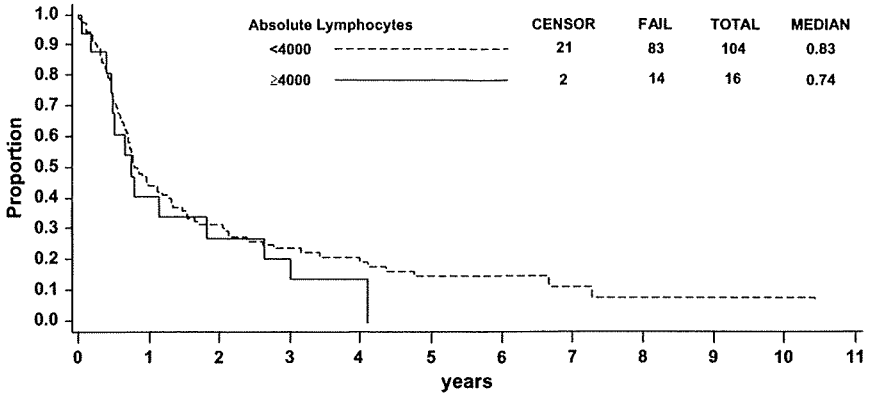

Figure 3. Overall survival of patients with aggressive adult T-cell leukemia/lymphoma according to the absolute lymphocyte count ($P = 0.44$).

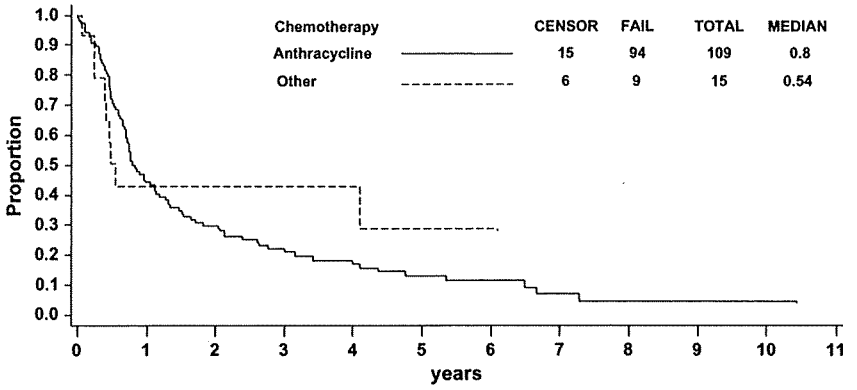

Figure 4. Overall survival of patients with aggressive adult T-cell leukemia/lymphoma according to treatment with or without an anthracycline ($P = 0.63$).

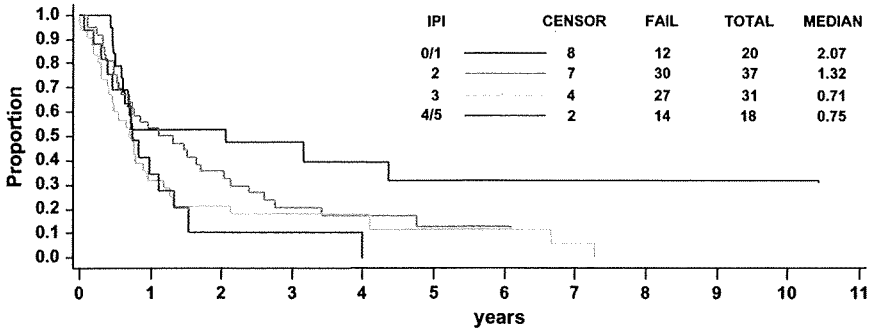

Figure 5. Overall survival of patients with the lymphoma type of adult T-cell leukemia/lymphoma according to the International Prognostic Index ($P = 0.04$).

high transplantation-related mortality, the use of HTLV-1-seropositive donors, and, most importantly, the proper selection of patients who will benefit from this therapy.

Unfortunately, we found no clues that might improve the treatment of ATL from this study. Nonetheless, further international collaboration using novel strategies is necessary to develop better therapies for this difficult disease. This study from the International Peripheral T-cell Lymphoma Project is the first report describing the results of an international cooperative study of ATL and thus represents an important first step in the international effort to improve the treatment and outcome of patients with ATL and other forms of PTCL.

Appendix 1 Participating sites and physicians

British Columbia Cancer Agency	Vancouver, Canada	Kerry Savage, MD; Joseph Connors, MD; Randy Gascoyne, MD; Mukesh Chhanabhai, MD
National Cancer Institute	Bethesda, MD	Wyndham Wilson, MD; Elaine Jaffe, MD
University of Nebraska Medical Center	Omaha, NE	James Armitage, MD; Julie Vose, MD; Dennis Weisenburger, MD; James Anderson, PhD; Fred Ullrich, MS; Martin Bast, BS
Massachusetts General Hospital	Boston, MA	Ephraim Hochberg, MD; Nancy Harris, MD
Los Angeles County Hospital, University of Southern California	Los Angeles, CA	Alexandra Levine, MD; Bharat Nathwani, MD
Arizona Cancer Center	Tucson, AZ	Thomas Miller, MD; Lisa Rimsza, MD
University of Barcelona Hospital	Barcelona, Spain	Emili Montserrat, MD; Armando Lopez-Guillermo, MD; Elias Campo, MD
Spanish National Cancer Center	Madrid, Spain	Marta Cuadros, MD; Javier Alvarez Ferreira, MD; Beatriz Martinez Delgado, MD
Norwegian Radium Hospital	Oslo, Norway	Harold Holte, MD; Jan Delabie, MD
University of Würzburg Hospital	Würzburg, Germany	Thomas Rüdiger, MD; Konrad Müller-Hermelink, MD; Peter Reimer, MD; Patrick Adam, MD
	Nurnberg, Germany	Martin Wilhelm, MD
	Hamburg, Germany	Norbert Schmitz, MD
	Munich, Germany	Christoph Nerl, MD
St James Hospital	Leeds, UK	Kenneth A. MacLennan, MD
University of Bologna Hospital	Bologna, Italy	Pier Luigi Zinzani, MD; Stefano Pileri, MD
Intergruppo Italiano Linfomi and the University of Modena Hospital	Modena, Italy	Massimo Federico, MD; Monica Bellei, PhD
Centre Hospitalier Lyon-Sud	Lyon, France	Bertrand Coiffier, MD; Francoise Berger, MD
King Chulalongkorn Hospital	Bangkok, Thailand	Intragumtornchai Tanin, MD; Pongsak Wannakrairot, MD
Queen Mary Hospital	Hong Kong, China	Wing Au, MD; Raymond Liang, MD; Florence Loong, MD
Singapore General Hospital	Singapore	Sandeep Rajan, MD; Ivy Sng, MD
National Cancer Center Hospital of Japan	Tokyo, Japan	Kensei Tobinai, MD; Yoshihiro Matsuno, MD
Aichi Cancer Center	Nagoya, Japan	Yasuo Morishima, MD; Shigeo Nakamura, MD; Masao Seto, MD, PhD
Okayama University Hospital	Okayama, Japan	Mitsune Tanimoto, MD; Tadashi Yoshino, MD
Fukuoka University Hospital	Fukuoka, Japan	Junji Suzumiya, MD; Koichi Ohshima, MD
Samsung Medical Center	Seoul, Korea	Won-Seog Kim, MD; Young-Hyeh Ko, MD

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bjh research paper

Remission induction therapy containing rituximab markedly improved the outcome of untreated mature B cell lymphoma

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Summary

Many controlled clinical trials have proven that rituximab improves the clinical outcome of patients with mature B cell lymphoma. This study was conducted to assess the contribution of rituximab in the actual clinical practice. Patients with newly diagnosed mature B cell lymphoma treated at 20 National Hospital Organization hospitals from January 2000 to December 2004 were consecutively registered. Rituximab was approved in September 2002 for indolent B cell lymphoma and in September 2003 for aggressive B cell lymphoma in Japan. The patients were divided into two groups depending on whether they received induction therapy containing rituximab. The endpoint was to evaluate the rituximab benefit based on 2-year progression-free survival (PFS) and 2-year overall survival (OS). A total 1126 patients received chemotherapies. Of these, 762 were diagnosed as diffuse large B cell lymphoma (DLBCL) and 215 as follicular lymphoma (FL). PFS and OS were markedly improved in the rituximab group compared with the non-rituximab group in patients with DLBCL (both $P < 0{\cdot}001$) and in patients with FL ($P < 0{\cdot}001$ and $P = 0{\cdot}003$ respectively). Rituximab, when used for remission induction therapy, significantly improved the clinical outcome of the mature B cell lymphoma patient in actual clinical practice.

Keywords: rituximab follicular lymphoma, diffuse large B cell lymphoma, clinical practice.

Non-Hodgkin lymphoma (NHL) is one of the leading causes of cancer death, and its incidence is increasing. The majority of NHL has a B cell phenotype. Almost all B cell lymphomas express CD 20 antigen on the cell surface. Rituximab, a chimeric anti-CD20 monoclonal antibody, was developed and is now widely used to treat B cell lymphoma. Many clinical

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studies have established the effect of rituximab against B cell lymphoma (MacLaughlin *et al*, 1998; Czuczman *et al*, 1999, 2004; Coiffier *et al*, 2002; Forstpointner *et al*, 2004; Hiddemann *et al*, 2005; Lenz *et al*, 2005; Marcus *et al*, 2005; Rivas-Vera *et al*, 2005; Habermann *et al*, 2006; van Oers *et al*, 2006; Pfreundschuh *et al*, 2006, 2008; Herold *et al*, 2007). The toxicity of rituximab has been generally graded as 1 or 2, and it occurs with the first infusion (MacLaughlin *et al*, 1998); the safety of rituximab when combined with chemotherapy has been shown to be similar to that of chemotherapy alone. Randomized phase III studies have proven the survival benefits of the addition of rituximab to multi-agent chemotherapy for patients with untreated follicular lymphoma (FL) (Hiddemann *et al*, 2005; Herold *et al*, 2007) and those with untreated diffuse large B cell lymphoma (DLBCL) (Coiffier *et al*, 2002; Pfreundschuh *et al*, 2006, 2008;). A systematic review also showed the clinical impact of rituximab for low-grade B cell lymphoma (Schulz *et al*, 2007). These data demonstrated that rituximab has an indisputable benefit for patients with untreated and relapsed/refractory B cell lymphoma who were enrolled in well controlled clinical studies. One population-based retrospective analysis by the British Columbia Cancer Registry assessed the effect of rituximab in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) for DLBCL and demonstrated improvement in treatment outcome (Sehn *et al*, 2005). This survey revealed that rituximab contributed to the management of DLBCL in clinical practice. However, the cases studied were restricted to those with DLBCL who received CHOP (with/without rituximab) with curative intent. Therefore, no study has reported the clinical benefit of rituximab in patients with B cell lymphoma in actual clinical practice. To address this point, a retrospective survey comparing patients with B cell lymphoma treated with and without rituximab was conducted. The results showed remarkable improvement in the survival of patients with FL and those with DLBCL, which account for the majority of mature B cell lymphoma patients, by the addition of rituximab in actual clinical practice.

Patients and methods

This was a retrospective cohort study that examined the clinical outcome of all untreated patients with B cell lymphoma who visited the haematological department of 20 hospitals belonging to the National Hospital Organization (NHO), a major, nationwide hospital group in Japan, from January 2000 to December 2004. This research group was founded for the purpose of creating and generalizing clinical evidence in the haematological field by NHO and is called the Clinical Hematology Group of NHO (CHG–NHO). In Japan, rituximab was approved by the Ministry of Health and Labour for the treatment of low-grade B cell lymphoma in September 2002 and for the treatment of aggressive B cell lymphoma in September 2003. The patients with B cell lymphomas were divided into two groups (the rituximab group and the non-rituximab group) based on whether they had received induction therapy containing rituximab in order to determine the benefit of rituximab as part of first remission induction therapy. This study received approval by the responsible ethics committee.

Patients

The patients included in this study were older than 15 years and were newly diagnosed as having mature B cell lymphoma with CD 20 expression by pathological or cytological examination during the period of the study. The pathological diagnosis of each institution was used. Both limited and advanced stage patients based on the Ann-Arbor classification were included (Carbone *et al*, 1971). Patients were excluded if they were human immunodeficiency virus (HIV)-positive or had central nervous system involvement at the time of presentation. All patients fitting the above criteria were serially enrolled. Final statistical analysis was performed for patients who received systemic chemotherapy, whether or not the intention was curative.

Clinical characteristics of the patients included in this survey

All patients' pathological diagnoses were done based on the WHO classification. Age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), lactate dehydrogenase (LDH) levels, clinical staging (Ann-Arbor classification), number of extra-nodal lesions (0, 1 vs. ≥2) were also collected and used to calculate the International Prognostic Index (IPI) (The International Non-Hodgkin's Lymphoma Prognostic Factors Project, 1993) and the revised IPI (R-IPI; Sehn *et al*, 2007). The primary remission induction therapy regimen of all enrolled patents was determined. Usage of rituximab was the focus of this investigation. The kinds of chemotherapy were divided into two groups: those containing anthracyclin and those not containing anthracyclin.

A complete response to treatment was defined as the disappearance of all clinical evidence of disease. Progression-free survival (PFS) was defined as the interval from the diagnosis to the first recurrence of disease (progression or relapse), death from any cause, or the date of the last follow-up in patients who had no relapse. Overall survival (OS) was defined as the interval from diagnosis to death from any cause. Systemic therapy was initiated promptly after diagnosis for almost all of the patients (usually within 1 month).

Statistical analysis

The patients' clinical characteristics and treatment outcomes were compared between patient groups who received systemic chemotherapy with and without rituximab for first induction therapy. The primary endpoint of this study was to confirm the benefit of rituximab for patients with B cell lymphoma when used in remission induction by evaluating the 2-year PFS and

2-year OS. PFS and OS were assessed using the Kaplan–Meier method, and the groups were compared using the log-rank test. A multivariate Cox regression analysis was performed to assess the effects of treatment and the various baseline prognostic factors on PFS and OS. The heterogeneity of treatment effect on the survival outcomes was also examined across the different risk groups based on the R-IPI. The patients with B cell lymphoma were analysed according to pathological diagnosis; therefore, the variables for patients with DLBCL and those with FL were also assessed separately. The analysis is based on follow-up until January 2007. The prognostic variables were compared between the groups using the Mann–Whitney *U*-test for continuous variables and the chi-squared test for categorical variables. All *P* values are two-tailed. Statistical analysis was performed using STATA 8.1 (StataCorp. LP, College Station, TX, USA) and Review Manager (REVMAN; version 5.0. Copenhagen Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). *P* values < 0·05 were considered significant.

Results

All B cell lymphoma patients

A total of 1229 patients with newly diagnosed mature B cell lymphoma were enrolled in the study. Of these, 1126 patients (91·6%) received systemic chemotherapies. Patients given rituximab alone for induction were also included. Patients who received systemic therapies were the subject of this analysis, so that patients given radiation alone or eradication of *Helicobacter pylori* alone for induction were excluded. The pathological classifications are listed in Table I. The breakdown of the pathological classification was significantly different between the groups with and without rituximab for induction therapy (Table I). The ratio of patients with FL was higher in the rituximab group. This was caused by the different approval dates of rituximab for indolent B cell lymphoma and aggressive B cell lymphoma. Therefore, direct comparison of the clinical outcomes between these two groups was not considered appropriate, and the analyses were performed separately for each pathological group. Overall, 762 (67·7%) of these patients were diagnosed as having DLBCL, and 215 (19·1%) were diagnosed with FL. Thus, 86·8% (977/1126) of the patients were classified as having DLBCL or FL, so that these two diseases represented the majority of mature B cell lymphoma.

Table I. Pathological subtype of patients (n = 1126).

Histology at diagnosis	Rituximab group (n = 348)	Non-rituximab group (n = 778)	Total (n = 1126) %
DLBCL	184	578	762 (67·7)
Burkitt lymphoma	1	17	18 (1·6)
Follicular lymphoma	111	104	215 (19·1)
Small lymphocytic lymphoma	1	9	10 (0·9)
Lymphoplasmacytic lymphoma	5	8	13 (1·2)
Splenic marginal zone lymhoma	0	3	3 (0·3)
MALT-lymphoma	14	20	34 (3·0)
Nodal marginal zone B cell lymphoma	9	0	9 (0·8)
Mantle cell lymphoma	18	26	44 (3·9)
Others	5	13	18 (0·7)

DLBCL, diffuse large B-cell lymphoma; MALT-lymphoma, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue.

DLBCL

A total of 762 DLBCL patients were enrolled. Of these, 184 patients received rituximab as part of the first-line treatment in combination with chemotherapy (rituximab group), and 578 patients were treated by chemotherapy alone (non-rituximab group). This difference in patient number was caused by the date of rituximab approval (September 2003 for aggressive B cell lymphoma) and the time period of the study (from January 2000 to December 2004). After approval, almost all DLBCL patients were treated with rituximab, but rituximab was available for only 1 year and 4 months of the 5-year study period. The patients' characteristics are listed in Table II. The ratio of cases receiving anthracyclin containing regimens in each group was not significantly different (rituximab group, 183/184; non-rituximab group, 560/578; P = 0·057). The prognostic variables (IPI and IPI subgroup) were not different between the rituximab group and the non-rituximab group (Table II). The median follow-up time for living patients was 22 months for the non-rituximab group (range, 1–50 months) and 22 months for the rituximab group (range, 1–84 months). PFS was markedly improved in the rituximab group compared with the non-rituximab group [hazard ratio (HR), 0·58; 95% confidence interval (CI), 0·44–0·77; P < 0·001, Fig 1]. The 2-year estimated PFS was 64·4% (95% CI, 56·41–71·3%) in the rituximab group and 48·7% (95% CI, 44·4–52·9%) in the non-rituximab group. OS was also improved in the rituximab group compared with the non-rituximab group (HR, 0·52; 95% CI, 0·37–0·73; P < 0·001, Fig 1). The 2-year estimated OS was 78·0% (95% CI, 70·5–83·7%) in the rituximab group and 61·7% (95% CI, 57·42–65·7%) in the non-rituximab group. Looking only at the patients who received an anthracyclin-containing regimen (CHOP or a CHOP-like regimen), the PFS and OS were compared between the rituximab group and the non-rituximab group in each R-IPI risk group. R-IPI is the revised prognostic model for DLBCL in patients receiving R-CHOP; it identifies three distinct prognostic groups (very good, good and poor). Among DLBCL patients receiving an anthracyclin-containing regimen, the ratio of these risk groups in the rituximab group and the non-rituximab group was not significantly different (Table II). For the R-IPI very good risk

Table II. Characteristics of DLBCL patients (n = 762).

Characteristic	Rituximab group (n = 184)	Non-rituximab group (n = 578)	P
Age (years), median (range)	67 (20–96)	68 (16–95)	0·947*
Gender male/female	100/84	300/278	0·563†
PS at diagnosis			
0	58	182	0·309*
1	74	195	
2	26	100	
3	22	75	
4	4	26	
LDH > normal	101	346	0·233†
Extranodal site > 1	42	130	0·925†
Clinical stage			
I	30	92	0·797*
II	60	176	
III	32	118	
IV	62	192	
IPI			
L	66	174	0·141*
LI	41	138	
HI	37	115	
H	40	151	
Receiving anthracyclin-containing regimen	183	560	0·057†
R-IPI			
Very good	26	60	0·251*
Good	80	244	
Poor	77	256	

PS, ECOG performance status; LDH, lactate dehydrogenase; IPI, International Prognostic Index (L, low; LI, low-intermediate; HI, high-intermediate; H, high); R-IPI, Revised International Prognostic Index.
*Mann–Whitney U-test.
†Chi-squared test.

group, the PFS and OS of the rituximab group were not statistically different from those of the non-rituximab group (HR, 1·38; 95% CI, 0·40–4·72; P = 0·61, HR, 1·89; 95% CI, 0·42–8·49; P = 0·40 respectively) (Fig 2). However, for the R-IPI higher risk groups (good and poor), PFS was significantly improved by the addition of rituximab (HR, 0·58; 95% CI, 0·35–0·96; P = 0·035, HR, 0·54; 95% CI, 0·38–0·76; P < 0·001 respectively) (Figs 3 and 4). OS was also improved in the R-IPI poor risk group (HR, 0·48; 95% CI, 0·32–0·72; P < 0·001), and an improvement in the R-IPI good risk group was also noted, but it was not statistically significant (HR, 0·52; 95% CI, 0·26–1·05; P = 0·069). We also performed a forest plot to explore the heterogeneity between these subgroups. There was no evidence of substantial heterogeneity in the relative treatment effect on PFS and OS between different risk groups based on the R-IPI (The P value for heterogeneity was 0·35 and 0·23 respectively) (Fig 5). These results suggest that rituximab improved the clinical outcome of all DLBCL patients.

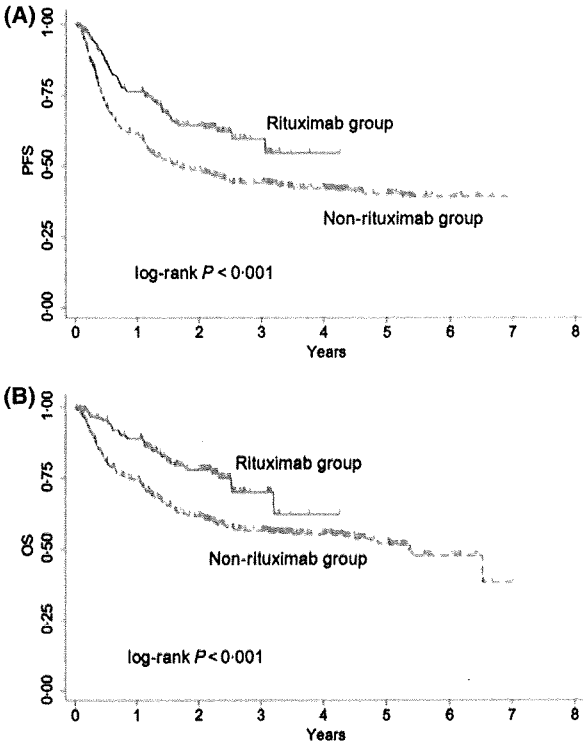

Fig 1. Progression-free survival (A) and overall survival (B) of 762 DLBCL patients. The rituximab group received rituximab in addition to systemic chemotherapy as first remission induction. The non-rituximab group received systemic chemotherapy alone as first remission induction.

Follicular lymphoma

A total of 215 FL patients were enrolled. Of these, 111 patients were in the rituximab group, and the other 104 were in the non-rituximab group. The patient number in each group was almost equal because of the date of rituximab approval (September 2002 for indolent B cell lymphoma) and the time period of the study (from January 2000 to December 2004). After approval, almost all FL cases were treated with rituximab, so that rituximab was available for 2 years and 4 months of the 5-year study period. The patients' characteristics are listed in Table III. The ratio of cases receiving an anthracyclin-containing regimen in each group was not significantly different (rituximab group, 104/111; non-rituximab group, 91/104; P = 0·159). Only three (age, LDH level, Ann-Arbor clinical stage) of the five prognostic variables that make up the FLIPI could be evaluated. These variables were not different between the rituximab group and the non-rituximab group (Table III). The median follow-up time for living patients was 37 months for the non-rituximab group (range, 1–72 month) and 41 months for the rituximab group (range, 1–80 months). PFS was markedly improved in the rituximab group compared with the non-rituximab group (HR, 0·45; 95% CI, 0·30–0·69; P < 0·001, Fig 6). The 2-year estimated PFS was 77·6% (95% CI, 68·1–84·5%) in the rituximab group and 56·3% (95% CI,

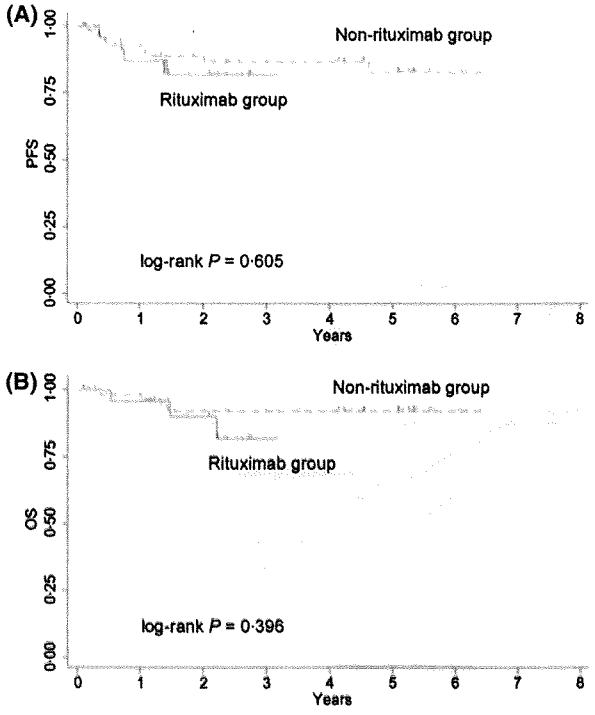

Fig 2. Progression-free survival (A) and overall survival (B) of 86 DLBCL patients (R-IPI very good risk). The rituximab group received rituximab in addition to systemic chemotherapy as first remission induction. The non-rituximab group received systemic chemotherapy alone as first remission induction.

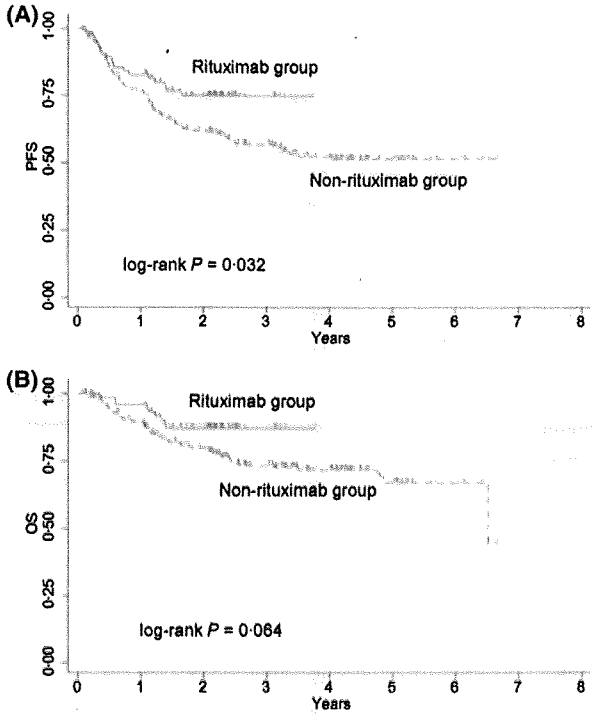

Fig 3. Progression-free survival (A) and overall survival (B) of 324 DLBCL patients (R-IPI good risk). The rituximab group received rituximab in addition to systemic chemotherapy as first remission induction. The non-rituximab group received systemic chemotherapy alone as first remission induction.

45·9–65·5%) in the non-rituximab group. OS was also improved in the rituximab group compared with the non-rituximab group (HR, 0·35; 95% CI, 0·17–0·72; $P = 0·003$, Fig 5). The 2-year estimated OS was 94·3% (95% CI, 87·8–97·4%) in the rituximab group and 81·7% (95% CI, 72·5–88·0%) in the non-rituximab group.

A multivariate analysis was performed to assess the effect of rituximab on clinical outcome after controlling for prognostic variables. After controlling for the prognostic variables included in R-IPI and IPI itself, rituximab remained an independent prognostic predictor of both PFS (risk ratio, 0·56; 95% CI, 0·43–0·74; $P < 0·001$) and OS (risk ratio, 0·50; 95% CI, 0·36–0·70; $P < 0·001$) in DLBCL. In FL, rituximab was also an independent prognostic predictor of both PFS (risk ratio, 0·49; 95% CI, 0·32–0·74; $P = 0·001$) and OS (risk ratio, 0·44; 95% CI, 0·21–0·92; $P = 0·028$) after adjustment for prognostic variables (age, LDH level and clinical stage).

Discussion

This retrospective survey showed that the addition of rituximab significantly improved PFS and OS in patients with FL and DLBCL when used as part of first remission induction therapy. This survey was carried out among 20 hospitals belonging to CHG–NHO. The clinical data of all patients diagnosed with NHL during this study were accumulated, and the PFS and OS of B cell lymphoma patients receiving systemic chemotherapies with and without rituximab were analysed. Rituximab was approved in September 2002 for indolent B cell lymphoma and in September 2003 for aggressive B cell lymphoma in Japan. The period of this survey was from January 2000 to December 2004 (5 years); therefore, differences in clinical outcomes could be compared between the rituximab group and the non-rituximab group. NHL patients were enrolled without regard to the chemotherapeutic regimen. During the study period, 1229 mature B cell lymphoma patients were newly diagnosed, and 1126 (92%) received systemic chemotherapy. Of the 1126 patients, 977 were diagnosed with DLBCL or FL, so that these cases accounted for 86·8% of the 1126 cases of mature B cell lymphoma receiving systemic chemotherapy. Thus, the clinical outcomes of these subjects reflect those of almost the entire mature B cell lymphoma population in clinical practice.

So far, many clinical studies have shown the benefits of rituximab in the treatment of B cell lymphoma. In 1999, a single arm phase II study of a combination of rituximab and CHOP for untreated indolent B cell lymphoma was reported (Czuczman *et al*, 1999). The response rate was 95% (38 of 40), and long-term remissions were observed (Czuczman *et al*, 2004). Several randomized phase III studies have demonstrated

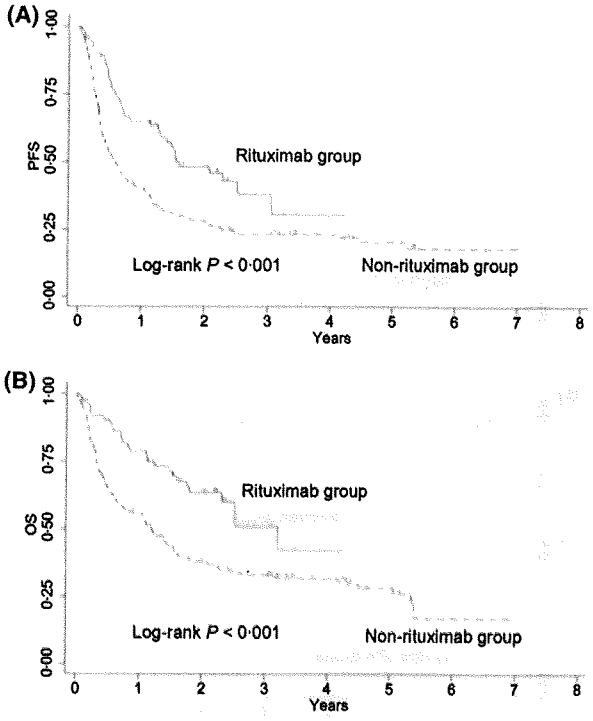

Fig 4. Progression-free survival (A) and overall survival (B) of 333 DLBCL patients (R-IPI poor risk). The rituximab group received rituximab in addition to systemic chemotherapy as first remission induction. The non-rituximab group received systemic chemotherapy alone as first remission induction.

the advantages of the addition of rituximab to chemotherapy, both in previously untreated patients, as well as in relapsed/refractory indolent B cell lymphoma patients (Forstpointner *et al*, 2004; Hiddemann *et al*, 2005; Lenz *et al*, 2005; Marcus *et al*, 2005; Rivas-Vera *et al*, 2005; van Oers *et al*, 2006; Herold *et al*, 2007; Schulz *et al*, 2007). The German Low-Grade Lymphoma Study Group (GLSG) conducted a phase III study comparing CHOP combined with rituximab to CHOP alone, and they showed significant improvements in remission rates, PFS and OS in the combination group (Hiddemann *et al*, 2005). Other studies also showed that chemotherapy with rituximab provided a better PFS than chemotherapy alone. Recently, the Cochrane Hematological Malignancies Group performed a comprehensive systematic review and meta-analysis to compare the efficacy of chemotherapy with rituximab to the identical chemotherapy alone in patients with indolent B cell lymphoma or mantle cell lymphoma (Schulz *et al*, 2007). This analysis included seven well-controlled, randomized studies comparing rituximab–chemotherapy combination therapy with chemotherapy alone, and indicated that the rituximab–chemotherapy combination provided superior OS to chemotherapy alone.

For DLBCL, many phase III studies have proven the benefits of the addition of rituximab to chemotherapy. The Groupe d'Etude des Lymphomes de l'Adulte study showed superiority of CHOP and rituximab to CHOP alone in elderly, advanced, previously untreated, DLBCL patients with respect to PFS and OS (Coiffier *et al*, 2002). The advantage of rituximab in

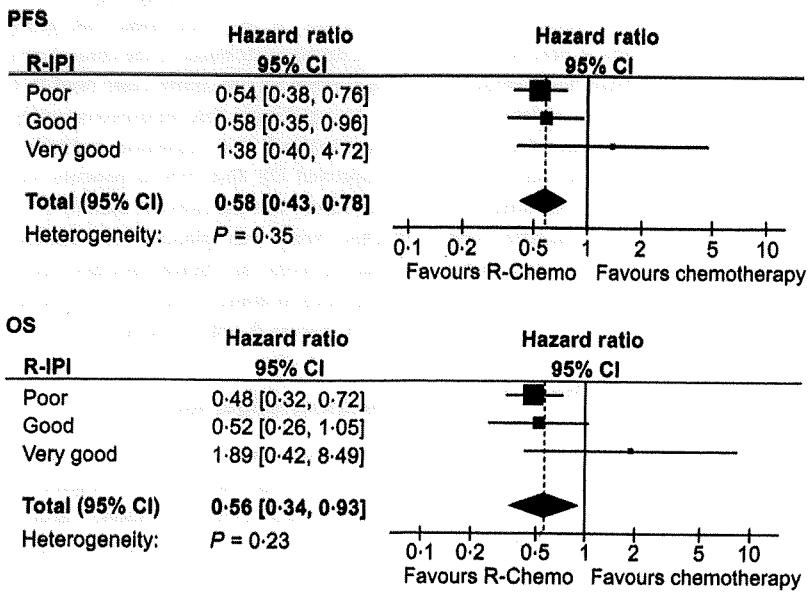

Fig 5. Disease control for DLBCL in each R-IPI risk group receiving rituximab with chemotherapy (R-chemo) or chemotherapy alone. Disease control is shown as the hazard ratio (HR) for a disease event (progression or death). Solid squares represent risk estimates for the each R-IPI risk group. The size of squares represents the weight assigned to each R-IPI risk group and is proportional to inverse variance of the estimate. Horizontal lines indicate 95% confidence intervals (CIs). The diamond indicates the 95% CIs for the overall HR. Values less than 1·0 indicate HRs that favour R-chemo.

Table III. Characteristics of follicular lymphoma patients (n = 215).

Characteristics	Rituximab group (n = 111)	Non-rituximab group (n = 104)	P
Age (years), median (range)	56 (26–83)	57 (23–91)	0·497*
Gender male/female	49/62	48/56	0·767†
PS at diagnosis			
0	60	53	0·395*
1	38	31	
2	8	13	
3	4	6	
4	1	1	
LDH > normal	42	47	0·274†
Clinical stage			
I	4	7	0·065*
II	28	15	
III	41	32	
IV	38	50	
Receiving anthracyclin-containing regimen	104	91	0·159†

PS, ECOG performance status; LDH, lactate dehydrogenase.
*Mann–Whitney U-test.
†Chi-squared test.

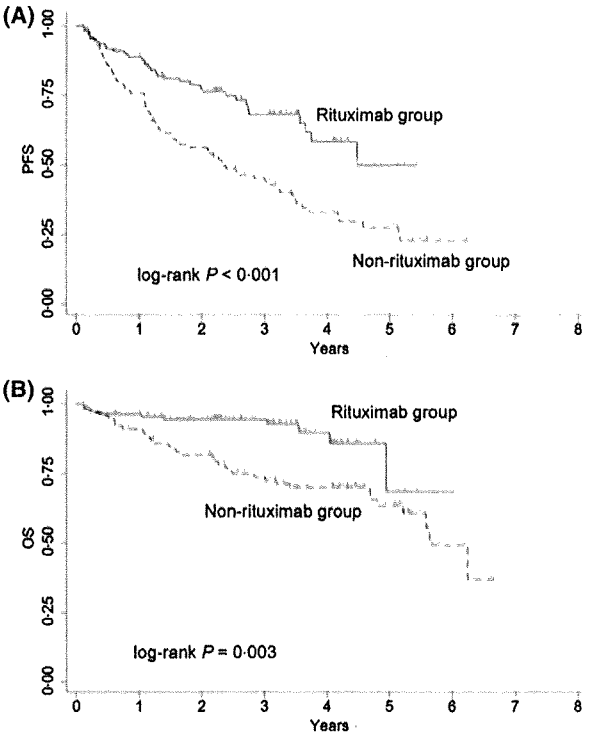

Fig 6. Progression-free survival (A) and overall survival (B) of 215 follicular lymphoma patients. The rituximab group received rituximab in addition to systemic chemotherapy as first remission induction. The non-rituximab group received systemic chemotherapy alone as first remission induction.

combination with a CHOP-like regimen for the younger DLBCL population was indicated by the intergroup cooperative study (MInT study) (Pfreundschuh *et al*, 2006). Therefore, the clinical merits of the use of rituximab in the induction treatment of mature B cell lymphoma have now been established by these well controlled, phase III studies, but the actual benefits of rituximab benefits in clinical practice have not been addressed. Prospective clinical trials for treatment have critical inclusion and exclusion criteria, and patients with poor PS or organ dysfunction are usually excluded. One population-based retrospective analysis, by the British Columbia Cancer Registry, assessed the effect of rituximab in combination with CHOP for DLBCL and demonstrated improvement in treatment outcome in clinical practice (Sehn *et al*, 2005). However, this study was limited to patients who were treated with curative intent. The present study serially enrolled all patients with mature B cell lymphoma who were newly diagnosed, and all patients receiving systemic chemotherapy, whether or not the intent was curative, were included in the analysis to evaluate the effect of rituximab. This approach reflects the actual state of management of mature B cell lymphoma patients in clinical practice.

In DLBCL, PFS and OS were better in the rituximab group than in the non-rituximab group. When DLBCL was classified by R-IPI, the benefit of rituximab was statistically identified in the good and poor risk group but not in the very good risk group. The favourable effect of rituximab seemed to be restricted in higher risk patients, but the significant heterogeneity between these subgroups was not identified by the forest plot (Fig 5). This finding might be a result of small patient numbers in the very good risk group. To clarify whether rituximab contributes to the clinical outcomes of the very good risk group or not, more cases need to be analysed.

In conclusion, this retrospective analysis showed that the use of rituximab for remission induction therapy significantly improved OS and PFS in patients with FL or DLBCL, who constitute the majority of mature B cell lymphoma patients. This study was planned to elucidate the state of NHL management in clinical practice and found that rituximab appeared to dramatically improve clinical outcomes in patients with mature B cell lymphoma.

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