they received no additional therapy. In the CHOP-14 arm, the tendency toward development of secondary malignancies, including myelodysplastic syndrome, was significant.

treatment interval and dose intensity

To confirm treatment compliance, we assessed actual treatment duration, course interval, and actual dose administered. Total treatment duration was calculated as the duration from day 1 of the first course to day 1 of the eighth course. The planned duration of CHOP-21 and CHOP-14 treatment were 148 and 99 days, respectively. The relative dose (%) was calculated as the dose actually administered divided by the total dose planned for all eight courses.

The course interval was 21 days for 79.3% patients and 14 days for 83.2% patients in CHOP-21 and CHOP-14 arms, respectively. The treatment duration in each arm almost matched the planned duration. Figure 1 shows the distribution of the achievement quotient for planned CPA and DXR doses. In the CHOP-21 arm, median relative doses of CPA and DXR were 97.2% (actual dose range 752–6285 mg per body weight) and 99.4% (actual dose range 50–419 mg/body weight), respectively. In the CHOP-14 arm, median relative doses of CPA and DXR were 98.1% (actual dose range 724–6259 mg/body weight) and 99.6% (actual dose range 50–411 mg/body weight), respectively. With patients stratified by age (>60 or <60 years), in elderly patients, median relative doses of CPA and DXR were 97.1% and 99.2% in the CHOP-21 arm and were 97.4% and 99.0% in the CHOP-14 arm. In younger patients, median relative doses of CPA and DXR were 97.5% and 99.5% in the CHOP-21 arm and were 98.2% and 99.8% in the CHOP-14 arm. Thus, small variations from the planned course interval and dosage were observed, but compliance was good in both arms.

responses

Responses were assessed 12 weeks after chemotherapy or radiotherapy. Among all randomized patients, CR (including CRu) was observed in 61.5% (95% CI 53.5% to 69.0%) and 66.7% (95% CI 58.8% to 73.9%) patients in CHOP-21 and CHOP-14 arms, respectively (Table 3). Similar results were observed in eligible patients, and no significant difference was observed between the two arms.

survival

Figure 2 shows the PFS and OS curves for all randomized patients. At 7-year follow-up after enrollment termination, no substantial differences were observed in PFS and OS between the two arms. Median PFS was 2.8 and 2.6 in CHOP-21 and CHOP-14 arms, respectively. Eight-year PFS rates were 41.5% (95% CI 33.7% to 49.1%) and 38.4% (95% CI 30.5% to 46.1%) in CHOP-21 and CHOP-14 arms, respectively ($P = 0.79$, HR

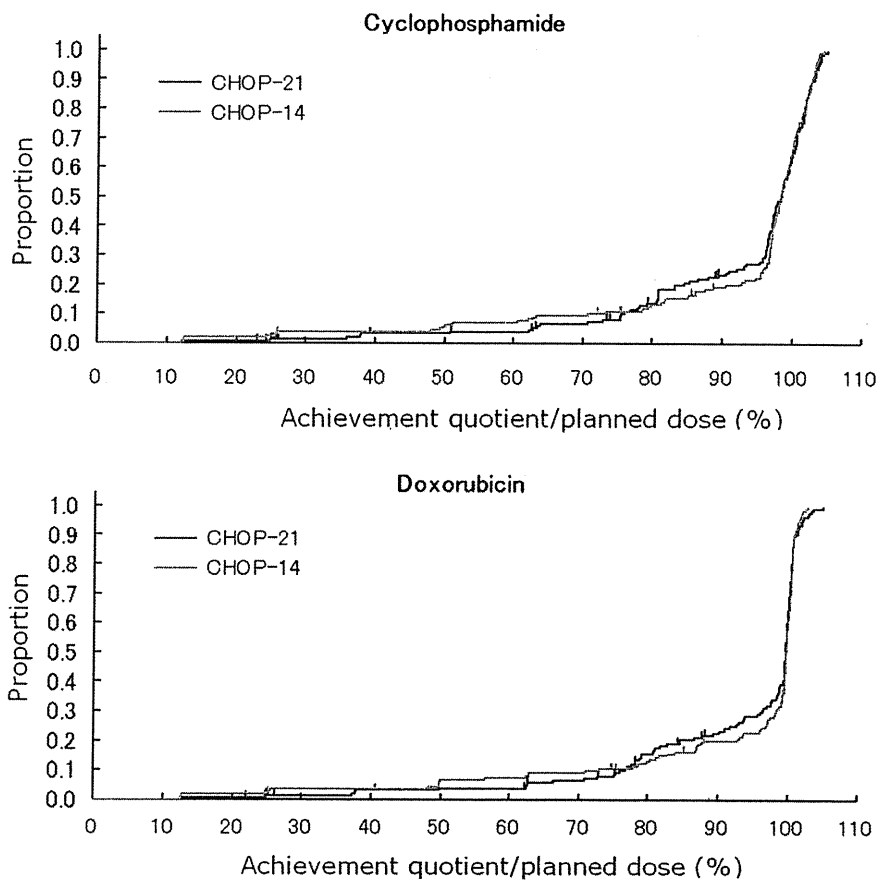


Figure 1. Distribution of the achievement quotient for planned doses of cyclophosphamide and doxorubicin.

1.04, 95% CI 0.78% to 1.38%), and 8-year OS rates were 55.9% (95% CI 47.3% to 63.7%) and 55.4% (95% CI 46.9% to 63.0%) in CHOP-21 and CHOP-14 arms, respectively ($P = 0.82$, HR 1.04, 95% CI 0.75% to 1.45%).

Subgroup analyses were also carried out for risk groups classified as per IPI and for patients stratified in two age groups; no remarkable differences were observed between the two arms for each subgroup (Figure 3).

Among patients with diffuse large B-cell lymphoma (the major subtype of aggressive NHL identified by central pathological review), 8-year PFS rates were 47.5% (95% CI 36.3% to 57.9%) and 44.1% (95% CI 32.8% to 54.8%) in CHOP-21 and CHOP-14 arms, respectively, and 8-year OS rates were 55.4% (95% CI 42.9% to 66.2%) and 55.4% (95% CI 43.0% to 66.1%) in CHOP-21 and CHOP-14 arms, respectively.

Table 3. Response after completion of the protocol treatment

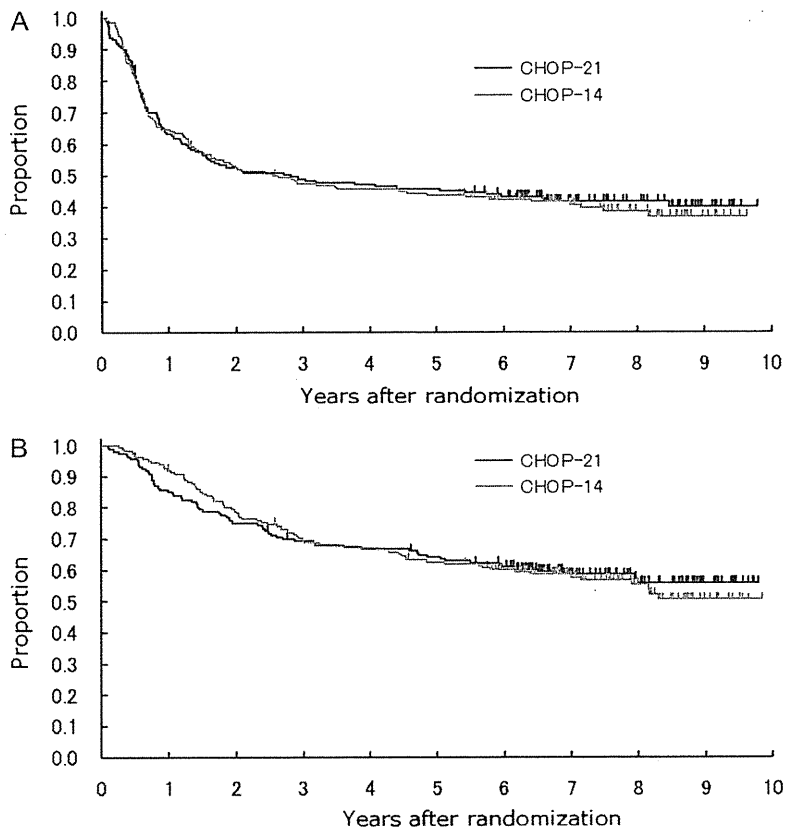
	CHOP-21 (%), $n = 161$	CHOP-14 (%), $n = 162$
CR	38.5	44.4
CRu	23.0	22.2
PR	0	0
NR	0	0
PD	12.4	9.3
Not evaluable	1.2	0
%CR (CR + CRu)	61.5	66.7
95% CI	53.5–69.0	58.8–73.9

CI, confidence interval, CR, complete response; CRu, complete response unconfirmed, %CR, CR rate; NR, no response; PD, progressive disease; PR, partial response.

conclusions

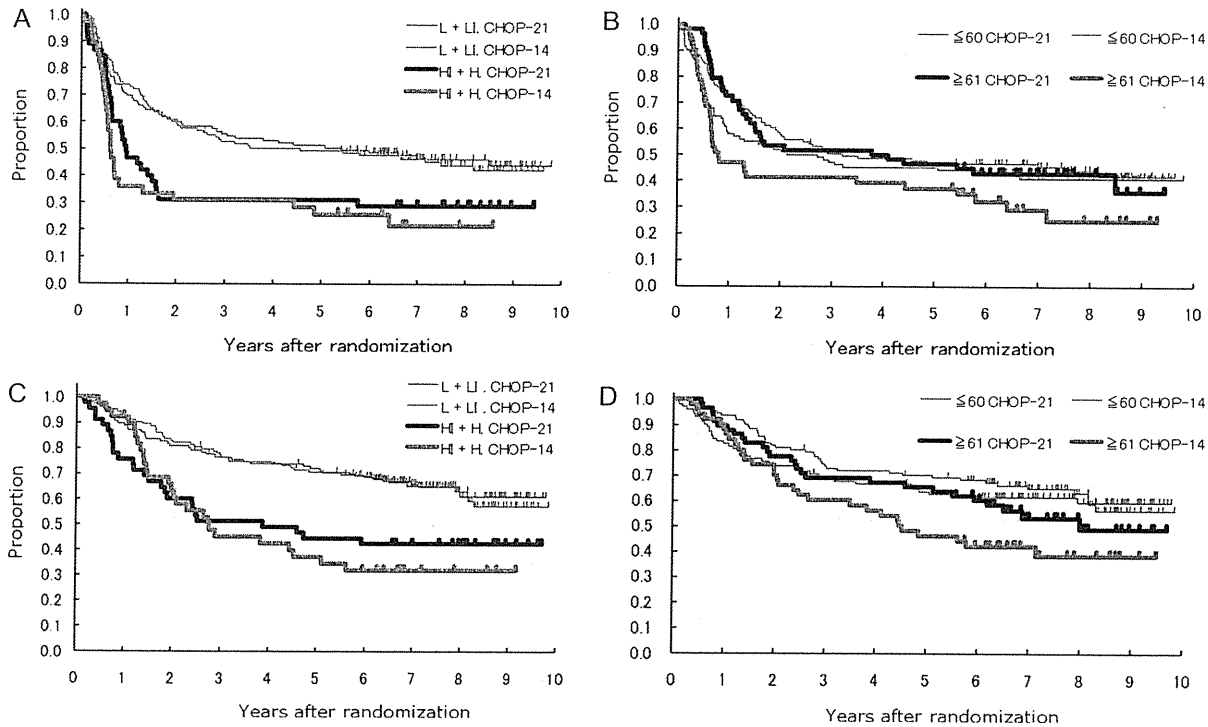
This trial failed to demonstrate the superiority of CHOP-14 over CHOP-21 for the treatment of aggressive NHL. PFS and OS after CHOP-14 were lower than those after CHOP-21 at the first interim analysis, and the trial was terminated early because the estimated predictive probability that CHOP-14 would be significantly superior to CHOP-21 was only 19%, even if the trial was continued. This result did not change even during long-term follow-up.

During treatment, there was no tendency for the interval of CHOP-14 to be postponed. No differences in planned dose and



arm	n	Median PFS	Median OS	8-year PFS (95%CI)	8-year OS (95%CI)
CHOP-21	161	2.8 years	not reached	41.5% (33.7%–49.1%)	55.9% (47.3%–63.7%)
CHOP-14	162	2.6 years	not reached	38.4% (30.5%–46.1%)	55.4% (46.9%–63.0%)

Figure 2. Progression-free survival (PFS) and overall survival (OS) curves for all randomized patients. (A) PFS curve and (B) OS curve.



			n	event	HR of CHOP-14 vs CHOP-21	95%CI of HR	
PFS	L/LI	CHOP-21	116	62			
		CHOP-14	123	68	1.019	0.722	1.438
	HI/H	CHOP-21	45	32			
		CHOP-14	39	30	1.284	0.779	2.116
PFS	AGE • 60	CHOP-21	103	60			
		CHOP-14	111	62	0.851	0.597	1.214
	AGE > 60	CHOP-21	58	34			
		CHOP-14	51	36	1.623	1.014	2.595
OS	L/LI	CHOP-21	116	41			
		CHOP-14	123	46	1.018	0.668	1.550
	HI/H	CHOP-21	45	26			
		CHOP-14	39	26	1.150	0.667	1.983
OS	AGE • 60	CHOP-21	103	40			
		CHOP-14	111	42	0.888	0.576	1.369
	AGE > 60	CHOP-21	58	27			
		CHOP-14	51	30	1.488	0.884	2.506

Figure 3. Progression-free survival (PFS) and overall survival (OS) curves for all randomized patients of the risk group classified as per International Prognostic Index (IPI) and for all randomized patients classified as per age. (A) PFS curve for the risk group classified as per IPI, (B) PFS curve for patients classified as per age, (C) OS curve for the risk group classified as per IPI and (D) OS curve for patients classified as per age.

accumulation ratios of key drugs were observed between the two arms, and treatment compliance was not only equivalent but also good in both arms. We therefore do not consider poor compliance, the cause of the lack of difference in efficacy between the two arms. Only 8.4% of the patients had a performance status of 2, and 26% of the patients belonged to high-intermediate and high-risk groups. These values were slightly low, thus implying that more patients with good prognoses were enrolled. However, patient characteristics did not differ completely, and subgroup analysis showed that survival in the high-risk group tended to be equivalent between the two arms. Thus, patient population may not have caused a bias in the study end points.

Other trials using dose-dense chemotherapy have been conducted by two groups. The German High-Grade Non-Hodgkin Lymphoma Study Group reported that CHOP-14 showed higher event-free survival (EFS) and OS in elderly patients than CHOP-21 in the NHL-B2 trial [18], and CHOEP-21 (CHOP-21 with etoposide) significantly improved survival compared with CHOP-21 in younger patients with normal lactate dehydrogenase (LDH) in the NHL-B1 trial [19]. As for the difference of these results, Pfreundschuh and Loeffler [20], in response to Coiffier and Salles [21], pointed out that the

schedule of CHOP-14 in our trial was well maintained; however, DXR doses were different from those in the NHL-B2 trial. In our trial, 24% patients received <90% of the planned dose of DXR, and 16% of patients received <80%, whereas in the NHL-B2 trial, only 11% and 9% of patients received <90% and 80% of DXR, respectively. Therefore, Pfreundschuh and Loeffler [20] argued that both planned dose and treatment interval must be maintained to preserve the superiority of the two-weekly regimen over the three-weekly regimen. However, results from cumulative dose analyses may differ according to the manner in which cases of early discontinuation of treatment (early off-treatment) are treated. Because relative dose curves in NHL-B1 and -B2 trials do not reflect the early off-treatment rate [18, 19, 22], Pfreundschuh's argument may not be derived from intention to treat analysis. In our trial, the cumulative percentage of patients receiving <90% of the planned dose of DXR decreases from 20% to 9% if we do not include the early off-treatment rate. Thus, comparison of results using different definitions is irrelevant. In NHL-B1 and -B2 trials, although both total chemotherapy duration and relative dose intensity tended to be better maintained in younger than elderly patients [22], the dose-dense regimen was not always superior to the 3-weekly regimen for younger patients. Even our trial showed a similar tendency. Moreover, no differences were maintained between our two treatment arms in terms of planned DXR or CPA doses administered or in any other background variable, and comparisons between the treatment arms were reliable.

In exploratory subgroup analysis, unlike in the NHL-B2 trial, CHOP-14 showed no survival advantage for elderly patients and appeared less effective in terms of OS and PFS. The planned CPA and DXR doses for elderly patients were well maintained in CHOP-14 and CHOP-21 arms. Secondary malignancies in elderly patients were observed more often in the CHOP-14 arm, but the cause of death in elderly patients was mostly due to lymphoma in both arms. Consequently, poorer outcomes were not derived from dose reduction of key drugs and secondary malignancies. On the other hand, subgroup analysis indicated that the efficacy of CHOP-14 was slightly greater than that of CHOP-21 in terms of OS and PFS in patients <60 years. In multivariate analysis using Cox regression, elevated LDH was identified as a negative prognostic factor in terms of both PFS and OS (Table 4). Age-based patient characteristics showed that the number of elderly patients with elevated LDH was greater in the CHOP-14 arm than in the CHOP-21 arm and that of younger patients with elevated LDH was lower in the CHOP-14 arm than in the CHOP-21 arm (Table 5). Thus, these deviations may have somewhat influenced our results. However, these results were based on a small number of patients and are not statistically significant. In the NHL-B1 trial, CHOP-14 did not exceed CHOP-21 in EFS but slightly exceeded CHOP-21 in OS. Furthermore, the Dutch–Belgian Group conducted a randomized trial comparing Intensified CHOP (I-CHOP), consisting of dose-dense chemotherapy, with CHOP-21, and reported that I-CHOP improved OS in low-intermediate risk patients according to age-adjusted IPI [23]. These results do not show similar tendencies, but taken together, dose-dense chemotherapy may be beneficial for some patients.

Frequency of secondary malignancies in the CHOP-14 arm was also determined in this trial. In the CHOP-14 arm, 9.9% and 3.1% patients developed solid tumors and myelodysplatsic syndrome, respectively, whereas in the CHOP-21 arm, 5.5% patients developed solid tumors and no patient developed myelodysplastic syndrome. Radiation, alkylating agents, and high-dose chemotherapy influence secondary malignancy development, and epipodophyllotoxin, G-CSF, and greater dose intensity are particularly involved with secondary myelodysplastic syndrome and acute myeloid leukemia [24–27]. Secondary myelodysplastic syndrome development might be greatly affected by G-CSF because such developments were only observed in the CHOP-14 arm. In terms of solid tumors, no differences were observed between the two arms with regard to patient background, such as receiving radiotherapy, dose of alkylating agent, and use of etoposide during or after treatment; thus, preexisting factors are not responsible for these results. Because dose-dense chemotherapy may cause more secondary solid tumors, long-standing careful follow-up of patients is needed.

Our trial did not use rituximab in combination with CHOP because rituximab was unavailable under the Japanese National Health Insurance at the time of patient enrollment. Since the superiority of this combination therapy over CHOP alone has been proven for elderly and younger low-risk patients with diffuse large B-cell lymphoma [28, 29], it has been recognized as a current standard treatment worldwide. The efficacy of dose-dense chemotherapy combined with rituximab remains yet to be clarified. Delarue et al. [30] recently reported that CHOP-14 was not superior to CHOP-21 plus rituximab in an interim analysis. A similar result was reported by Pfreundschuh et al. [29], who noted that the benefit achieved with etoposide plus CHOP-21 was absent for CHOP-21 plus rituximab, and he reasoned that this was due to the equalizing effect of rituximab.

Table 4. Result of multivariate analysis using COX regression

	PFS			OS		
	P	HR	95% CI	*P*	HR	95% CI
CHOP-21 versus CHOP-14	0.6074	1.078	0.810–1.433	0.5614	1.104	0.790–1.543
Stage I, II versus III, IV	0.0002	1.922	1.369–2.698	0.1052	1.389	0.933–2.068
PS 0, 1 versus 2	0.0393	1.637	1.024–2.616	0.0309	1.773	1.054–2.982
Age <60 versus >61	0.2506	1.191	0.884–1.603	0.0135	1.539	1.093–2.166
Extranodal disease 0, 1 versus >2	0.3834	1.171	0.821–0.671	0.1075	1.389	0.931–2.071
LDH normal versus elevated	0.0098	1.486	1.100–2.007	0.0017	1.768	1.239–2.524

CI, confidence interval; HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival.

Table 5. Patients' characteristics according to age

	Age ≤ 60				Age ≥ 61			
	CHOP-21		CHOP-14		CHOP-21		CHOP-14	
	n	%	*n*	%	*n*	%	*n*	%
Stage								
I, II	37	35.9	42	37.8	22	37.9	17	33.3
III, IV	66	64.1	69	62.2	36	62.1	34	66.7
Performance status								
0, 1	92	89.3	103	92.8	55	94.8	46	90.2
2	11	10.7	8	7.2	3	5.2	5	9.8
Extranodal disease								
0.1	79	76.7	91	82.0	48	82.8	41	80.4
≥2	24	23.3	20	18.0	10	17.2	10	19.6
Lactate dehydrogenase								
Normal	51	49.5	65	58.6	30	51.7	23	45.1
Elevated	52	50.5	46	41.4	28	48.3	28	54.9

In the rituximab era, the efficacy of dose-dense chemotherapy may thus not be as significant as before.

Here, CHOP-14 reduced the frequency of febrile neutropenia and shortened the total treatment duration. However, it did not improve survival, was more inconvenient to use, and was significantly more often associated with secondary malignancies. Thus, CHOP-14 is not suitable as a standard regimen to replace CHOP-21, and dose-dense chemotherapy with shortened treatment interval is not useful for improving the outcome in aggressive NHL patients.

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disclosure

The authors declare no conflict of interest.

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Phase II/III Study of R-CHOP-21 Versus R-CHOP-14 for Untreated Indolent B-Cell Non-Hodgkin's Lymphoma: JCOG 0203 Trial

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Clinical Trials repository link available on JCO.org.

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See accompanying editorial on page 3954; listen to the podcast by Dr Friedberg at www.jco.org/podcast

ABSTRACT

Purpose
Rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is one of the most effective front-line therapies to treat indolent B-cell lymphoma. Granulocyte colony-stimulating factor (G-CSF), which potentiates antibody-dependent rituximab cytotoxicity, is used to shorten CHOP intervals. To improve progression-free survival (PFS) in patients treated with R-CHOP as the primary end point, we conducted a phase III study.

Patients and Methods
Patients with untreated stages III to IV indolent B-cell lymphoma were randomly assigned to six cycles of R-CHOP every 3 weeks (R-CHOP-21) or every 2 weeks (R-CHOP-14) with G-CSF. Maintenance rituximab was not allowed.

Results
Three hundred patients were enrolled. At the median follow-up time of 5.2 years, there was no significant difference in PFS between arms for the 299 eligible patients; the median was 3.7 (R-CHOP-21) *v* 4.7 (R-CHOP-14) years, 57% *v* 58% at 3 years, and 41% *v* 43% at 6 years, respectively (hazard ratio [HR], 0.92; 95% CI, 0.68 to 1.25; one-sided $P = .30$). The median overall survival (OS) time was not reached in either arm, and there was no significant difference (6-year OS: 87% [R-CHOP-21] *v* 88% [R-CHOP-14]; HR, 1.15; 95% CI, 0.57 to 2.30; one-sided $P = .65$). Although grade 4 neutropenia and grade 3 infections were more frequent in the R-CHOP-21 group, R-CHOP was feasible in both arms.

Conclusion
The R-CHOP dose-dense strategy failed to improve PFS of patients with untreated indolent B-cell lymphoma. Further improvement of first-line treatment or investigations on postremission therapy following R-CHOP should be explored.

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INTRODUCTION

In randomized clinical trials (RCTs), rituximab in combination with chemotherapy has been shown to improve the outcome for patients with previously untreated, advanced-stage follicular lymphoma (FL) relative to combination chemotherapy alone.[1,2] Currently, rituximab with chemotherapy is used as the standard therapy for most patients with FL. Rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is regarded as one of the most effective first-line treatments for indolent B-cell non-Hodgkin's lymphoma (NHL).[1,3,4] Currently, there is no standard therapy for advanced-stage indolent B-cell NHL and FL grade 3B. A first-line intensive chemotherapy regimen has been shown to cause durable remission in patients with indolent B-cell NHL,[5] although there is no evidence to suggest that dose-intensified chemotherapy led to prolonged survival of the patients in the pre-rituximab era.[6] It is currently unknown whether a dose-dense strategy can improve the outcome for patients with indolent B-cell NHL who receive R-CHOP. A short interval of rituximab administration can achieve a higher serum concentration and, consequently, a better antitumor

response.[7,8] Furthermore, the clinical utility of any immunomodulators has not yet been evaluated in RCTs. Granulocyte colony-stimulating factor (G-CSF) has often been used to shorten CHOP intervals,[9-12] and it potentiates the antibody-dependent cell-mediated cytotoxicity of rituximab.[13,14]

In this prospective trial, we attempted to determine whether patients with indolent B-cell NHL would have long-term benefits from dose-dense immunochemotherapy.

PATIENTS AND METHODS

Study Design

We considered whether R-CHOP-21 (R-CHOP administered every 3 weeks) could be used as a putative standard first-line therapy for indolent B-cell NHL. In addition, R-CHOP-14 (R-CHOP administered every 2 weeks with G-CSF) was selected as a promising therapeutic strategy for the future. However, there was no available evidence to support using either of those rituximab-containing therapies as the treatment arm of an RCT. An RCT comparing the two treatments should be planned after R-CHOP-21 is confirmed to be the standard of care for patients with advanced-stage indolent B-cell NHL from the preceding RCT results. Moreover, the incidence of FL is low in Japan.[15,16] We therefore designed this clinical trial as a phase II/III study to confirm the necessary efficacy and feasibility of R-CHOP-21 or R-CHOP-14 versus a non–rituximab-containing regimen during phase II. Furthermore, these phase II patients would be included in the analysis of phase III.

Patient Selection

Patients with previously untreated stage III to IV indolent B-cell NHL and FL grade 3B were randomly assigned by using a minimization method to receive six cycles of either R-CHOP-21 (arm A) or R-CHOP-14 (arm B). Age, bulky disease, and institution were used as dynamic allocation adjustment factors.

The major eligibility criteria were as follows: age 20 to 69 years; $CD20^+$ histologically confirmed indolent B-cell NHL, including grades 1 to 3 FL, according to the 2001 WHO classification[17]; stage III or IV disease; an Eastern Cooperative Oncology Group performance status of 0 to 2; at least one measurable lymphomatous lesion more than 1.5 cm detected by computed tomography (CT); and adequate organ function. Patients were excluded if they had histologic transformation to aggressive lymphoma, more than 10×10^9/L circulating $CD20^+$ lymphoma cells, hepatitis B virus (HBV) surface antigens or antibodies to hepatitis C virus, glaucoma,[18] or if they wished to receive hematopoietic stem-cell transplantation. A requirement for therapeutic intervention was not well defined and, consequently, some of the patients enrolled were treated immediately after diagnosis without watchful waiting.

All patients gave written, informed consent before enrollment. All case report forms were collected, managed, and analyzed at the Japan Clinical Oncology Group [JCOG] Data Center. The report was monitored (without any comparative data between the two arms) through a semiannual review by the JCOG Data and Safety Monitoring Committee. The study protocol was approved by the JCOG Protocol Review Committee and the institutional review boards at all study sites.

Study Treatment

CHOP consisted of 750 mg/m^2 cyclophosphamide, 50 mg/m^2 doxorubicin, and 1.4 mg/m^2 vincristine (capped at 2.0 mg) taken intravenously on day 1 and 100 mg oral prednisone taken daily on days 1 to 5. CHOP cycles were repeated every 3 weeks (arm A) or every 2 weeks (arm B) for a total of six cycles. In both arms, rituximab was given 2 days before CHOP cycles 1, 2, 4, and 6, for a total of four doses, following R-CHOP dosage in the preceding study.[4] In the R-CHOP-14 arm, G-CSF was administered daily for a period of 6 days, starting on day 8 and ending 2 days before CHOP of the subsequent cycle.

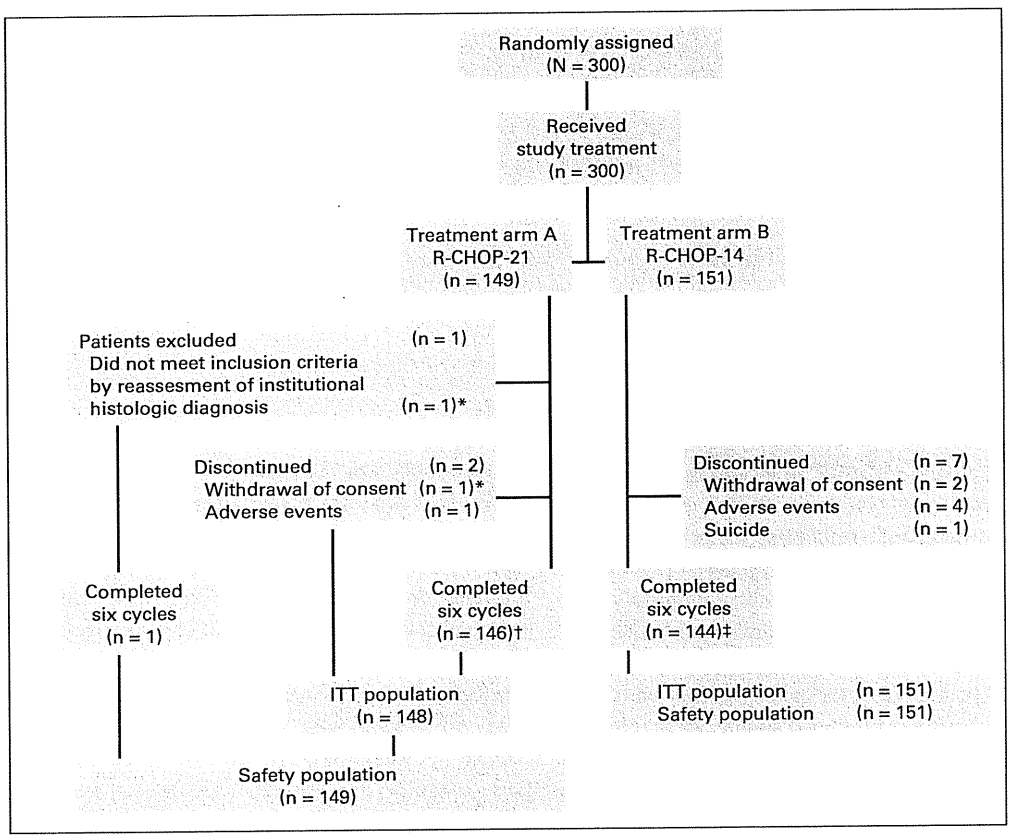

Fig 1. CONSORT diagram showing the flow of patient enrollment and disposition throughout the trial. ITT, intent to treat; R-CHOP-14, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) administered every 2 weeks with granulocyte colony-stimulating factor; R-CHOP-21, R-CHOP administered every 3 weeks. (*) Patients enrolled onto the phase II trial. (†) Thirty-five and (‡) 36 patients were enrolled onto the phase II trial for R-CHOP-21 and R-CHOP-14, respectively.

In the R-CHOP-21 arm, G-CSF was administered according to the American Society of Clinical Oncology guidelines.[19] Maintenance use of rituximab was not allowed.

After 74 patients had been enrolled onto this study, the Japanese National Health Insurance policy regarding rituximab treatment changed. In October 2003, the protocol was revised so that rituximab could be given in every CHOP cycle for a total of six doses. Consequently, of the 291 patients who completed the protocol treatment, 76 patients received four doses of rituximab, three patients received five doses, and 212 patients (71% of the total) received six doses. During the accrual period, seven of 134 of the patients treated with R-CHOP-21 developed interstitial pneumonitis, which was caused by *Pneumocystis jiroveci* in six of these patients. The original protocol stipulated prophylaxis only for the patients treated with R-CHOP-14; the protocol was thus amended to include both arms. To prevent HBV reactivation, we revised the protocol in March 2006 to allow the prescription of anti-HBV medication to patients in both treatment arms with a high titer of antibodies against the HBV core antigen.[20-22]

Assessments

Tumor assessments were performed on all target lesions identified at baseline by CT scans after three R-CHOP cycles and at different times after completion of six-cycle R-CHOP (ie, around the eighth week, every 6 months for the first 2 years, and annually thereafter). Tumor response was assessed by using the International Workshop Criteria.[23] CT films from patients who achieved a complete response (CR) or an unconfirmed CR (CRu) during phase II were evaluated by an independent CT review board consisting of two

Table 1. Baseline Patient Characteristics

Characteristic	R-CHOP-21 (n = 149)			R-CHOP-14 (n = 151)			Total (N = 300)			
	No. of Patients	No. of Patients With FL	Percent of Patients With FL %	No. of Patients	No. of Patients With FL	Percent of Patients With FL %	No. of Patients	No. of Patients With FL	Percent of Patients With FL %	*P**
Age, years†										
Median	54			55			54.5			.93
Range	27 to 69			33 to 69			27 to 69			
≥ 61	37		25	38		25	75		25	1.00
Male sex	70		47	73		48	143		48	.82
Bulky disease†‡	32		21	31		21	63		21	.89
Elevated LDH	28		19	30		20	58		19	.88
Stage IV	99		66	99		66	198		66	.90
B symptoms	17		11	11		7	28		9	.24
ECOG PS 1 or 2	26		17	31		21	57		19	.56
More than one extranodal site	18		12	31		21	49		16	.06
Hemoglobin < 12 g/dL	25		17	39		26	64		21	.07
At least five affected nodal areas	55		37	51		34	106		35	.63
FLIPI risk group										
Low	52	45	35 34	45	42	30 32	97	87	32 33	
Intermediate	61	56	41 42	64	59	42 45	125	115	42 43	.60
High	36	32	24 24	42	31	28 23	78	63	26 24	
IPI risk group										
Low	82		55	73		48	155		52	
Low-intermediate	50		34	56		37	106		35	.70
High-intermediate	16		11	21		14	37		12	
High	1		1	1		1	2		1	
Histology (central review)										
FL (grades 1, 2, and 3A)	125		84	123		81	248		83	
FL (grade 3B)	8		5	9		6	17		6	
MZL	0		0	6		4	6		2	
SLL	1		1	1		1	2		1	
Other indolent B-cell NHLs	8		5	5		3	13		4	.28
MCL§	2		1	2		1	4		1	
DLBCL§	4		3	2		1	6		2	
Plasmacytoma§	0		0	1		1	1		0.3	
Others§	1		1	2		1	3		1	

Abbreviations: DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma (FL grade 3B includes follicular large plus diffuse large); FLIPI, Follicular Lymphoma International Prognostic Index; IPI, International Prognostic Index; LDH, lactate dehydrogenase; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin's lymphoma; PS, performance status; R-CHOP-14, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) every 2 weeks with granulocyte colony-stimulating factor; R-CHOP-21, R-CHOP administered every 3 weeks; SLL, small lymphocytic lymphoma.

*Wilcoxon rank sum test.

†Dynamic allocation adjustment factors in randomization.

‡Bulky disease was defined as a nodal or extranodal mass of ≥10 cm horizontal diameter on a computed tomography scan.

§Patients judged ineligible by the central pathologic review.

radiologists (T.N. and T.T.) and one oncologist (T.W.). Histopathologic specimens from all 300 patients were reviewed by three hematopathologists (K.T., Y. Matsuno, MD, and Tadashi Yoshino, MD), as previously described.[24] Toxicity was assessed on the basis of the National Cancer Institute Common Toxicity Criteria Version 2.0.

Study End Points and Statistical Analyses

The primary end points of phase II and the whole phase III study were CR/CRu rate and progression-free survival (PFS), respectively; the secondary end points of phase II were overall response rate and toxicities and those of phase III were overall survival (OS) and toxicities. PFS was calculated from the date of random assignment to the date of relapse, progression, or death from any cause, and it was censored at the last verifiable progression-free date. OS was calculated from the date of random assignment to the date of death from any cause and censored at the last follow-up. PFS and OS were estimated by using the Kaplan-Meier method, and curves were compared (significance level of one-sided $\alpha = .05$) by using a log-rank test stratified by bulky disease and age (≥ 61 or ≤ 60 years). Hazard ratios (HRs) of treatment effects were estimated through the stratified Cox regression model with bulky disease and age as the strata. PFS and OS were subsequently analyzed by using the Cox regression model exploratorily to assess the effects of treatment with the prognostic factors, including the components of the Follicular Lymphoma International Prognostic Index (FLIPI)[25] or the International Prognostic Index (IPI),[26] bulky disease, and sex.

The planned sample size was 200 patients to detect a prolongation of 3-year PFS in the R-CHOP-14 arm from 50% with R-CHOP-21 to 65% with an 80% power and a one-sided $\alpha = .05$. The planned study period was 4 years for accrual and an additional 3 years for follow-up. Two interim analyses were planned. The first interim analysis was conducted during phase II to test whether the CR/CRu rate for each arm was superior to the predefined threshold (35%) with a one-sided $\alpha = .15$ and $\beta = .10$ to detect a 20% increase. The threshold data were based on the results of the standard CHOP regimen without rituximab.[27] The second interim analysis was conducted when all of the patients had registered in phase III to assess necessity of further follow-up; this analysis compared the arms that used the O'Brien and Fleming stopping boundaries by using the Lan and DeMets α-spending function to control the type I error for the primary end point. Throughout the study period, the researchers were blind to the primary end point interim analysis results. The sample size was re-evaluated independently from the interim analysis results when the accrual rate was higher than expected, and the protocol was subsequently revised. To maintain the required statistical power and to detect a 12% increase in the 3-year PFS of patients treated with R-CHOP-14, the sample size was increased to 300 patients (expected number of events, 181) over 4.5 years, using the same initial follow-up plan for these patients. All statistical analyses were performed by using SAS software, release 9.1 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

A total of 300 patients were enrolled from 44 institutions between September 2002 and February 2007 (Fig 1). The median age of the patients was 54.5 years. The patient characteristics were well balanced between arms except for B symptoms, hemoglobin levels, the number of extranodal sites, and the FLIPI risk group (Table 1). The doses delivered were the same between arms, except for vincristine (Appendix Fig A1, online only).

Response Rate

At the first interim analysis, the CR/CRu rates of the 73 patients enrolled in phase II of the R-CHOP-21 and R-CHOP-14 arms were 49% (17 CRs plus one CRu in 37 patients) and 50% (13 CRs plus five CRus in 36 patients), respectively, according to the central CT review.

Since one patient was excluded because of histologic transformation by institutional diagnosis, 299 patients were eligible for the survival analysis (Fig 1). The CR/CRu rates obtained from the case report forms for the 299 patients of the entire phase III study were 78% (68 CRs plus 48 CRu's in 148 patients) and 76% (76 CRs plus 39 CRus in 151 patients), respectively. The overall response rate was 97% for each arm. According to the FLIPI, CRs and CRus were achieved in 24 and 18 (93% in total) of the 45 patients with low-risk FL undergoing R-CHOP-21, respectively, and 29 and eight (88%) of the 42 patients with low-risk FL undergoing R-CHOP-14, respectively. For the patients with intermediate-risk FL, 82% of 56 patients (26 CRs and 20 CRus) undergoing R-CHOP-21 and 80% of 59 patients (26 CRs and 21 CRus) undergoing R-CHOP-14 achieved a CR or CRu. For the patients with high-risk FL, 15 and seven (69%) of 32 patients undergoing R-CHOP-21 and 14 and six (65%) of 31 patients undergoing R-CHOP-14 achieved a CR or CRu, respectively.

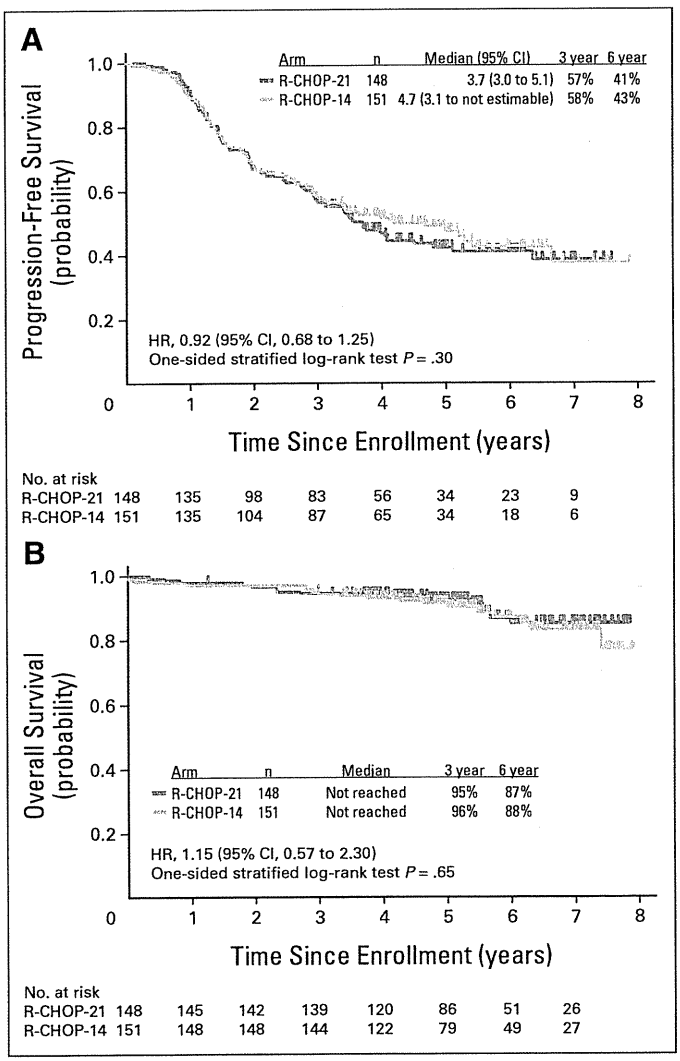

Fig 2. (A) Progression-free survival and (B) overall survival by treatment for patients with previously untreated, advanced-stage indolent B-cell non-Hodgkin's lymphoma. The median follow-up time was 5.2 years. HR, hazard ratio; R-CHOP-14, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) administered every 2 weeks with granulocyte colony-stimulating factor; R-CHOP-21, R-CHOP administered every 3 weeks.

PFS and OS

In the primary analysis for PFS in the eligible population at 4.7 years (median follow-up time), there was no significant difference between the arms (one-sided $P = .35$ with stratified log-rank test; multiplicity-adjusted one-sided significance level = 0.045; HR, 0.94; 95% CI, 0.69 to 1.28). At 5.2 years (the median follow-up time), 82 (R-CHOP-21) and 78 (R-CHOP-14) patients had a documented progression, and two patients from each treatment died before progression. Although we used a post hoc power calculation, we expected at least 80% power, as designed, to detect a difference between the arms with these events. The median PFS times were 3.7 and 4.7 years for R-CHOP-21 and R-CHOP-14, respectively, and the 3-year PFS (R-CHOP-21: 57%; R-CHOP-14: 58%) and 6-year PFS (R-CHOP-21: 41%; R-CHOP-14: 43%) were almost identical (HR, 0.92; 95% CI, 0.68 to 1.25; $P = .30$; Fig 2A). There was no significant difference between arms in OS (HR, 1.15; 95% CI, 0.57 to 2.30; $P = .65$; Fig 2B).

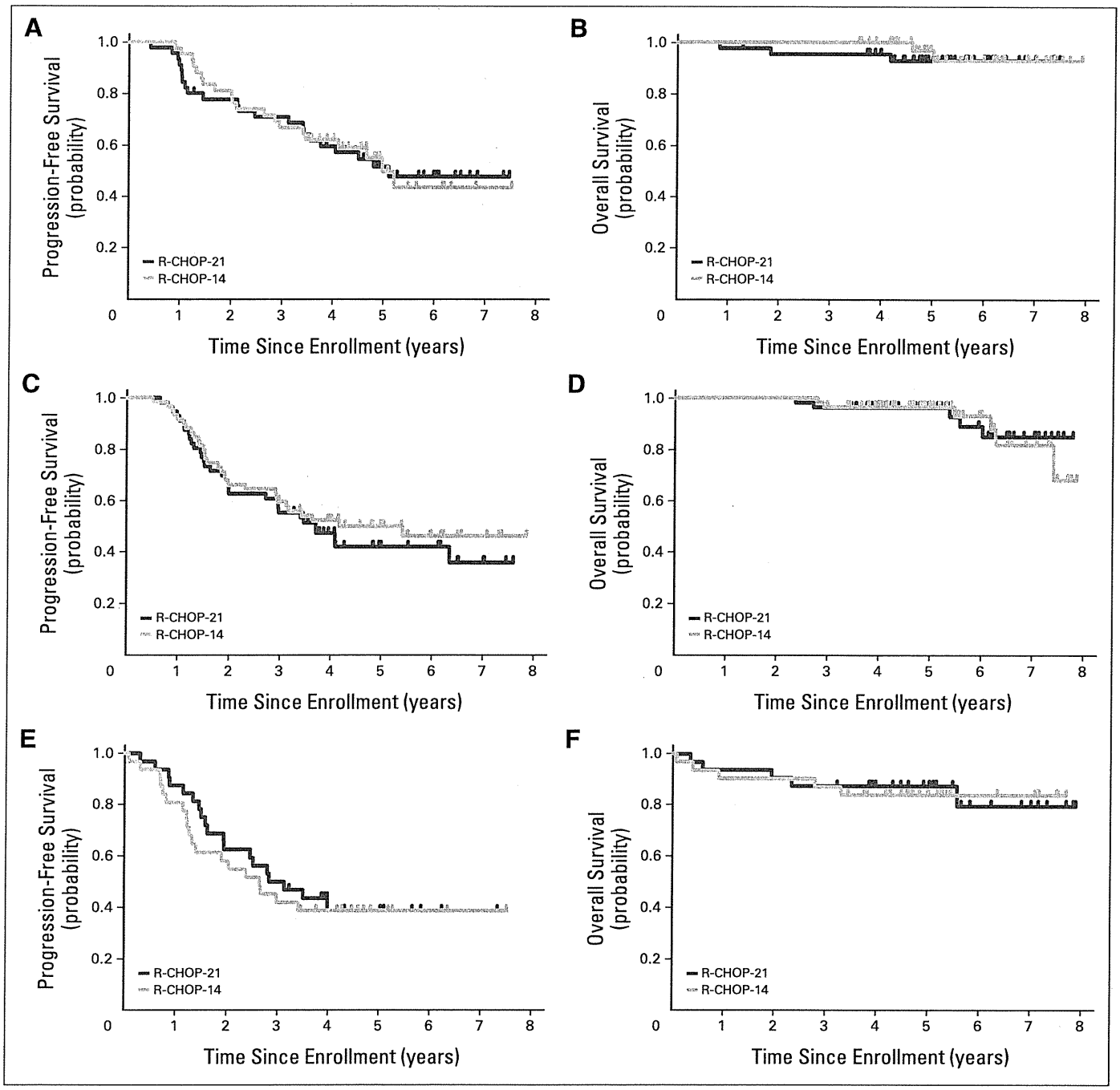

Fig 3. Progression-free survival (A, C, E) and overall survival (B, D, F) by treatment for patients in the low-risk (n = 87; A, B), intermediate-risk (n = 115; C, D), and high-risk (n = 63; E, F) groups according to the Follicular Lymphoma International Prognostic Index for the 265 patients with follicular lymphoma who were eligible for survival analysis. R-CHOP-14, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) every 2 weeks with granulocyte colony-stimulating factor; R-CHOP-21, R-CHOP administered every 3 weeks.

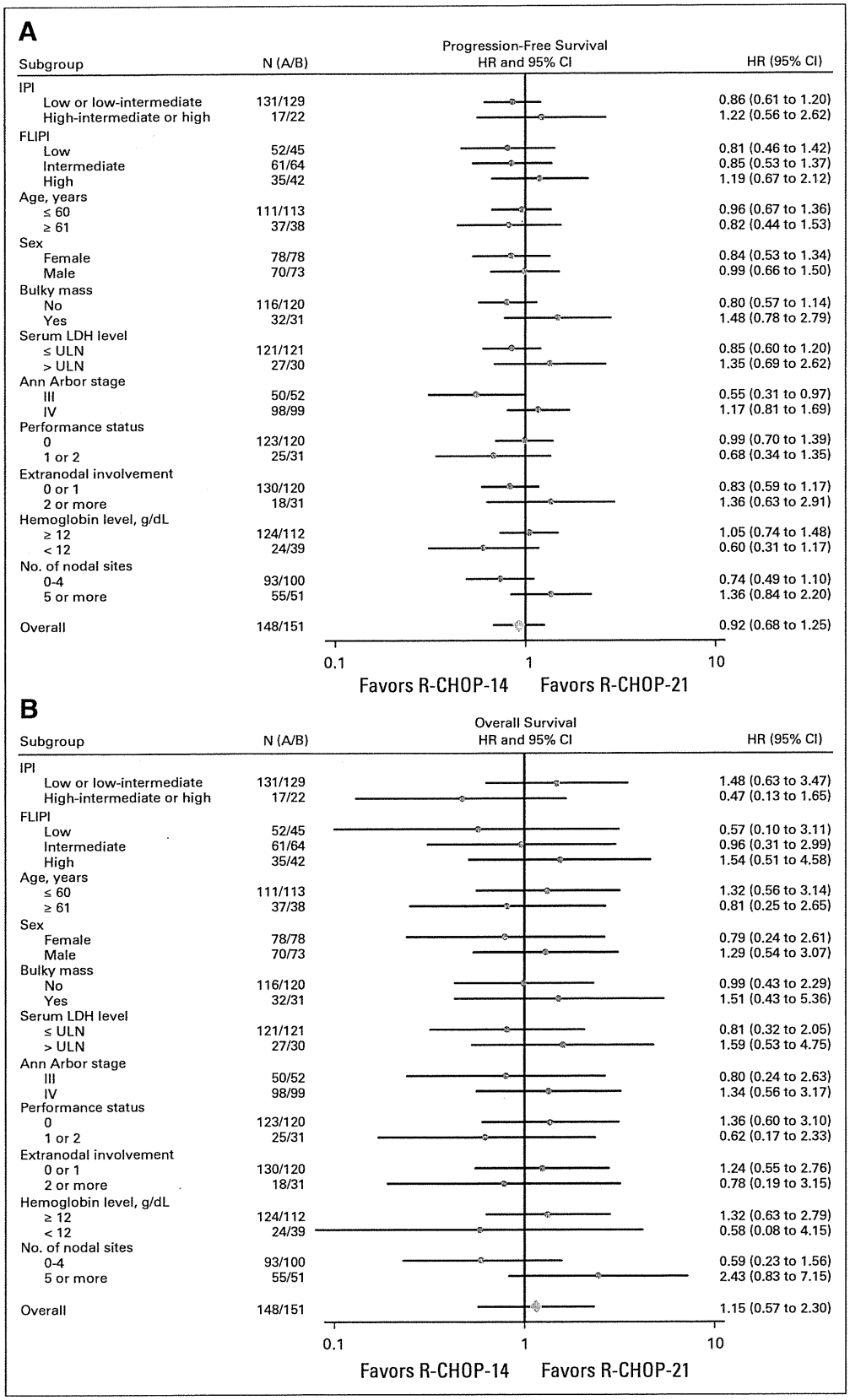

Fig 4. Forest plots of hazard ratios (HRs), comparing (A) progression-free survival and (B) overall survival among patients with previously untreated, advanced-stage indolent B-cell non-Hodgkin's lymphoma assigned to immunochemotherapy with either R-CHOP-14 (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP] administered every 2 weeks with granulocyte colony-stimulating factor) or R-CHOP-21 (R-CHOP administered every 3 weeks), according to the risk subgroups classified by the International Prognostic Index (IPI), the Follicular Lymphoma International Prognostic Index (FLIPI), or age. Closed circles represent the hazard ratios, and the horizontal bars represent the 95% CIs. LDH, lactate dehydrogenase; ULN, upper limit of normal.

The median PFS results for the 286 histopathologically eligible patients were similar (R-CHOP-21: 3.7 years; R-CHOP-14: 4.2 years). The exploratory subgroup analysis of the 34 patients with grade 3 FL indicated no significant difference in PFS (R-CHOP-21: 3.5 years; R-CHOP-14: not estimable; HR, 0.73; 95% CI, 0.27 to 1.94; $P = .26$).

Twenty patients (7% of all patients; 10 from each treatment) died as a result of progressive disease. Six patients (2%; three from each treatment) died as a result of other diseases; three patients treated with R-CHOP-21 died as a result of acute myeloid leukemia, subarachnoid hemorrhage, or pneumonia during glucocorticoid treatment for pemphigus vulgaris, and three patients treated with R-CHOP-14 died as a result of colon cancer, acute lymphoblastic leukemia, or cerebral hemorrhage. Five patients (2%; two, R-CHOP-21; three, R-CHOP-14) died as a result of treatment-related events after salvage therapies, including four relevant to allogenic stem-cell transplantation and one liver cirrhosis associated with HBV reactivation after rituximab-alone treatment for relapse (R-CHOP-21). One suicide (R-CHOP-14) occurred during the protocol treatment.

According to the FLIPI, the 6-year PFS of patients with FL treated with R-CHOP-21 or R-CHOP-14 were 48% and 43% in the low-risk group, 42% and 46% in the intermediate-risk group, and 39% each in the high-risk group (Figs 3A, 3C, and 3E). The 6-year OS of patients with FL treated with R-CHOP-21 or R-CHOP-14 were 93% each in the low-risk group, 89% and 93% in the intermediate-risk group, and 80% and 84% in the high-risk group, respectively (Figs 3B, 3D, and 3F). There were no differences found for any of the three risk groups in the 6-year PFS or OS. Moreover, the two treatments did not differ with respect to PFS or OS according to the IPI risk categories (low or low-intermediate versus high-intermediate or high) or on the basis of patient age (≤ 60 *v* $\geq$ 61 years; Fig 4).

A Cox proportional hazard regression analysis was used to assess the effects of various parameters on the primary analysis. These factors did not affect the point estimate of the treatment arms (Fig 4). Only male sex was a significantly unfavorable PFS parameter (Table 2).

Table 2. Clinicopathologic Parameters Influencing the PFS of Previously Untreated, Advanced, Indolent B-Cell NHL in a Multivariate Analysis

Parameter	HR*	95% CI	*P*
Treatment arm, R-CHOP-21 *v* R-CHOP-14	0.93	0.68 to 1.27	.64
Age (years), ≤ 60 *v* ≥ 61	1.00	0.70 to 1.43	.99
Sex, female *v* male	1.65	1.18 to 2.30	< .01
Bulky disease, < 10 cm *v* $\geq$ 10 cm	1.03	0.68 to 1.54	.91
LDH, $\leq$ ULN *v* > ULN	1.36	0.90 to 2.07	.15
Stage, III *v* IV	1.20	0.84 to 1.72	.32
ECOG PS, 0 *v* 1 or 2	1.13	0.76 to 1.68	.54
No. of extranodal sites, 0 or 1 *v* $\geq$ 2	1.20	0.79 to 1.83	.39
Hemoglobin, $\geq$ 12 g/dL *v* < 12 g/dL	1.15	0.77 to 1.74	.49
No. of affected nodal areas, ≤ 4 *v* ≥ 5	1.25	0.89 to 1.76	.20

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; NHL, non-Hodgkin's lymphoma; PFS, progression-free survival; PS, performance status; R-CHOP-14, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) every 2 weeks with granulocyte colony-stimulating factor; R-CHOP-21, R-CHOP administered every 3 weeks; UNL, upper limit of normal.

*HRs are presented as the risk of the right-side category (ie, right side of *v* in Parameter column) to the left-side category (ie, left side of *v*).

Male sex and increased lactate dehydrogenase were unfavorable predictors of OS (Appendix Table A1, online only).

Toxicity

We compared adverse events between treatments for all 300 patients who underwent the protocol treatment (Table 3). Grade 4 neutropenia and grade 3 infection were encountered more frequently during treatment with R-CHOP-21 than during treatment with R-CHOP-14 (35 of 149 [23%] *v* 18 of 151 [12%], respectively). Nevertheless, no patient experienced grade 4 infection following either treatment. More patients experienced a grade 3 to 4 hemoglobin decrease with R-CHOP-14; however, more patients in the R-CHOP-14 arm were diagnosed with anemia before treatment (Table 1). Furthermore, patients assigned to R-CHOP-14 experienced grade 3 peripheral neuropathy more frequently than did patients withR-CHOP-21 (three of 149 [2%] *v* 11 of 151 [7%],

Table 3. Comparison of Grade 3 or 4 Adverse Events* Between the R-CHOP-21 and R-CHOP-14 Treatment Arms

		Arm A (R-CHOP-21) (n = 149)		Arm B (R-CHOP-14) (n = 151)	
Adverse Events	Grade	No.	%	No.	%
Hematologic					
Neutropenia	3 or 4	144	97	102	68
Neutropenia	4	126	85	56	37
Hemoglobin	3 or 4	3	2	24	16
Thrombocytopenia†	3	2	1	4	3
Nonhematologic					
AST	3	4	3	4	3
ALT	3	7	5	8	5
Hyperglycemia	3	8	6	7	5
Hypocalcemia‡	4	0	0	1	1
Hyponatremia	3	4	3	4	3
Hypokalemia	3	2	1	1	1
Supraventricular arrhythmia	3	1	1	0	0
Fever	3	0	0	2	1
Appetite loss	3	6	4	11	7
Constipation	3	6	4	10	7
Diarrhea	3	1	1	2	1
Ileus	3	2	1	5	3
Nausea	3	7	5	8	5
Stomatitis/pharyngitis	3	2	1	0	0
Vomiting	3	4	3	3	2
Hematuria	3	1	1	1	1
Febrile neutropenia§	3	22	15	10	7
Infection with grade 3 neutropenia§	3	21	14	8	5
Infection without neutropenia§	3	7	5	5	3
Peripheral neuropathy	3	3	2	11	7
Dyspnea (shortness of breath)	3	4	3	0	0
Interstitial pneumonitis	3	5	3	0	0

Abbreviations: R-CHOP-14, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) every 2 weeks with granulocyte colony-stimulating factor; R-CHOP-21, R-CHOP administered every 3 weeks.

*Adverse events were evaluated by the worst grades throughout all of the cycles per patient, according to the National Cancer Institute-Common Toxicity Criteria, Version 2.0.

†No grade 4 thrombocytopenia was observed.

‡Except for hypocalcemia, no grade 4 nonhematologic toxicities were observed.

§Grade 3 infection. The number of patients who experienced any of these three was 35 (23%) in arm A and 18 (12%) in arm B.

respectively). Grade 3 appetite loss, constipation, and ileus followed the same trend. Three hematologic malignancies were found in total: in the R-CHOP-21 arm, myelodysplasia (patient remains alive) and acute myeloid leukemia were diagnosed in one patient each, and in the R-CHOP-14 arm, one patient was diagnosed with acute lymphoblastic leukemia.

DISCUSSION

The results from this phase II/III study demonstrate that R-CHOP-14 is not superior to R-CHOP-21 in terms of PFS, although R-CHOP is highly effective as an initial treatment for indolent B-cell NHL, regardless of the administration schedule, as determined by a long-term follow-up. The median follow-up time for all randomly assigned patients was 5.2 years at the planned analysis time point 3 years after the last patient enrollment. Therefore, our mature analysis results have not been reported from other RCTs that use rituximab to treat FL.[1,2] However, our attempt to improve PFS by using a dose-dense strategy with the immunomodulatory agent G-CSF failed.

The 3-year PFS for patients treated with R-CHOP-21 in this study matched that for the control patients in the Primary RItuximab and MAintenance (PRIMA) study (58%).[28] The lower CR/CRu rates in the first interim analysis (compared with the entire phase III population) could be due to two reasons: First, the central CT review was used to judge the transition to phase III. Second, the majority of patients enrolled in phase II received four doses of rituximab.

Our subset analysis (according to the FLIPI) demonstrates that there are no differences in PFS or OS between treatments for any of the three risk groups. The proportion of high-risk patients in our study was smaller than that in the German Low-Grade Lymphoma Study Group (GLSG)[29] (24% *v* 45%). The difference in the proportions of high-risk patients between the two studies was partly due to different inclusion criteria.

Grade 4 neutropenia and grade 3 infection occurred more often during R-CHOP-21 than during R-CHOP-14. However, no grade 4 infections were observed in either arm, although a total of 59 patients (40%) received G-CSF (13 in one cycle, nine each in two and three cycles, six in four cycles, 10 in five cycles, and 12 in six cycles) with R-CHOP-21.[1] Seven patients (4.7% of patients treated with R-CHOP-21) developed interstitial pneumonitis, and six of these cases were caused by *Pneumocystis jiroveci*. No cases of interstitial pneumonitis were observed in the patients treated with R-CHOP-14 because they were prescribed prophylactic treatment early in the study period. In our previous study, CHOP-14 treatment was frequently complicated by *Pneumocystis carinii* pneumonitis.[11] Alveolar damage caused by rituximab-induced cytokine production and lymphopenia might have partially contributed to the development of *Pneumocystis carinii* pneumonitis.[30,31] Furthermore, as a result of prophylaxis, there were no reports of hepatitis caused by HBV reactivation during the trial treatment, except for one patient who died as a result of liver cirrhosis associated with HBV reactivation following salvage treatment with rituximab.

Three and five secondary malignancies were found following R-CHOP-21 and R-CHOP-14, respectively. The incidence of secondary hematologic malignancies for the combined treatments was 1% at the time of analysis.

Potentially efficacious treatment options that will further improve the PFS of patients with untreated advanced indolent B-cell NHL include consolidative radioimmunotherapy[32] and/or rituximab maintenance.[28] Another potential efficacious first-line treatment is R-bendamustine.[33]

In summary, to the best of our knowledge, the JCOG 0203 study provides the first phase III data illustrating that a dose-dense strategy using the immunomodulatory agent G-CSF does not prolong PFS in previously untreated indolent B-cell NHL and that R-CHOP-21 is still one of the standard treatments for this population.

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Review Article: Study Group

Lymphoma Study Group of JCOG

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The Lymphoma Study Group (LSG) of the Japan Clinical Oncology Group (JCOG) was initiated in 1978 by five institutions and now has 47 members. JCOG-LSG has focused on combined modalities, dose intensification and the incorporation of new agents for major disease entities of lymphoid malignancies. More than 30 trials including 10 randomized trials have been conducted for aggressive non-Hodgkin's lymphoma (NHL), adult T-cell leukemia–lymphoma (ATL), lymphoblastic lymphoma/acute lymphoblastic leukemia, Hodgkin's lymphoma (HL), multiple myeloma, NK/T-NHL and indolent B-NHL, and correlative epidemiological and pathological studies have been performed on human T-lymphotropic virus type-I and T/B cell phenotypes. The first trials for aggressive NHL revealed significant differences in the prognosis of ATL, non-ATL T-NHLs and B-NHLs, establishing a subclassification of ATL, and leading to the establishment of standard therapies for ATL and localized nasal natural killer/T-NHL. Recently, for B-NHLs including diffuse large B-cell lymphoma, mantle cell lymphoma, and indolent B-NHLs, regimens incorporating rituximab have been evaluated. The JCOG-LSG trials for HL led to the approval of dacarbazine for the National Health Insurance in Japan. The multicenter trials by the JCOG-LSG combining new modalities such as molecular-targeting agents will contribute to further improvements in the treatment of lymphoid malignancies.

Key words: clinical trial – lymphoid malignancy – Lymphoma Study Group – Japan Clinical Oncology Group – T- and B-cell lymphoma

INTRODUCTION

Lymphoid malignancies consist of B-cell and T/natural killer (NK)-cell neoplasms, which are clonal tumors of mature and immature B cells, T cells or NK cells at various stages of differentiation (1). Paradigm shifts in the management of lymphoid malignancies have been achieved by the discovery of new disease entities, revision of classifications and development of new agents. The diagnosis of lymphoid malignancies improved significantly in the 1980s mainly with the development of immunophenotypic analyses using monoclonal antibodies. This resulted in the discovery of several new disease entities. Among them, adult T-cell leukemia–lymphoma (ATL) was first described in Japan by Takatsuki and colleagues (2) in 1977 and was found to be associated with human T-lymphotropic virus type-I (HTLV-1), the first RNA retrovirus associated with human diseases, in the early 1980s (3–5).

Treatment of lymphoid malignancies has been improved by the development of standard combination chemotherapy such as CHOP, secondary in association with the advances in diagnosis and classification described above, and by the development of new agents and modalities such as an anti-CD20 antibody for CD20-expressing B cell

malignancies, autologous/allogeneic (auto/allo)-hematopoietic stem cell transplantation (HSCT) with the prophylactic use of granulocyte colony-stimulating factor (G-CSF), and thalidomide and its derivatives and proteasome inhibitor for multiple myeloma (MM) (6,7).

Along with these advances in research for lymphoid malignancies, JCOG-LSG, which was initiated in 1978, has conducted more than 30 clinical trials including 10 randomized trials to establish new standard therapies for lymphoid malignancies (Tables 1–7 and Fig. 1) (8–10). In this article, we summarize the development of JCOG-LSG with the results of clinical trials.

HISTORY OF JCOG-LSG

Conducting clinical trials for the development of standard therapies requires investigators, a coordinating center and committees under the support of grant providers (8–10). Now, LSG, as in the case of other cancer study groups in JCOG, is conducting trials under the organization of JCOG. At first in 1978, following the success of multi-institutional clinical trials of oncology in the USA, a directed research project entitled 'A Study on Multidisciplinary Treatment for Solid Cancer' was started. Several disease committees including LSG have been supported since then by Grants-in-Aid for Cancer Research from the Ministry of Health, Labor and Welfare (MHLW) in Japan. LSG was initiated in 1978 with only five institutions chaired by Masanori Shimoyama, MD, and included the T- and B-cell Malignancy Study Group as a subgroup to conduct epidemiological studies of ATL. It then grew to 17 institutions during 1980–84 to perform virological studies on ATL, resulting in the discovery of an etiological retrovirus called ATL virus by Yorio Hinuma, MD, in 1981. Meanwhile, LSG has conducted clinical trials for non-Hodgkin's lymphoma (NHL) and later formed the Lymphoma Clinico-Pathological Panel to evaluate the reproducibility agreement rates of the pathological diagnosis of NHL. Then, the Autologous Bone Marrow Transplantation Study Group was initiated by Kensei Tobinai, MD, in 1990, which was later integrated into the LSG and the Breast Cancer Study Group in 1999. [LSG now consists of 47 institutions as an active disease committee in JCOG.]

Along with the development of standing committees and a statistical center, the multicenter cooperative oncology group was named the Japan Clinical Oncology Group (JCOG) in 1990. JCOG has now a common Data Center, a Steering Committee and each of 13 cancer study groups including LSG. JCOG-LSG has conducted consecutive studies for

Table 1. Results of the JCOG-LSG trials for advanced aggressive non-Hodgkin's lymphoma (NHL)

Protocol	Regimen	Patients risk category	Phase	No. of patients	%CR and uncertified CR	MST (months)	Survival (%)	Reference
JCOG7801	VEPA	All	II	100	52	NA	NA	11
JCOG8101		All	III	163				12
	VEPA			81	52	17	27 (4 years)	
	VEPA-M			82	62	24	37 (4 years)	
JCOG8701	LSG4	All	II	267	72	39	48 (5 years)	13
JCOG9002		All	III	447	67	NA	56 (5 years)	14
	LSG9			230	70	91	57 (5 years)	
	modified LSG4			217	65	78	55 (5 years)	
JCOG9203	VEPA/FEPP	Elderly	II	45	60	52	42 (5 years)	58
JCOG9505	upfront ASCT	HI/H	R-II	70	56	12	42 (4 years)	18
	CHOP-14			35	60	NA	42 (4 years)	
	DE-CHOP			35	51	NA	42 (4 years)	
JCOG9506		HI/H	II	43	NA	NA	58 (3 years)	NA
JCOG9508	CHOP	L/LI	II	213	NA	NA	74 (4 years)	17
JCOG9809		All	III	323[a]			74 (2 years)	19, 20
	CHPO-14			162	67	NR	55 (8 years)	
	CHOP			161	62	NR	56 (8 years)	

VEPA consisting of vincristine (VCR), cyclophosphamide (CPA), prednisone (PSL) and doxorubicin (DOX); VEPA-M consisting of VEPA + methotrexate (MTX); LSG4 consisting of VEPA-B, M-FEPA and VEPP-B, where VEPA-B consisting of VEPA + bleomycin (BLM), M-FEPA consisting of moderate dose of MTX, vindesine (VDS), CPA, PSL and DOX, and VEPP-B consisting of VCR, CPA, PSL and procarbazin (PCZ); LSG9 consisting of dose-intensified mLSG4; DE-CHOP: dose-escalated CHOP; CR, complete response; MST, median survival time; NA, not applicable; NR, not reached, R-II, randomized Phase II study; ASCT, autologous stem cell transplantation.
[a]Number of enrolled patients until the early termination.

Table 2. Results of the JCOG trials for adult T-cell leukemia–lymphoma

Protocol	Regimen	Phase	No. of patients	%CR	MST (months)	Survival (%)	Reference
JCOG7801	VEPA	II	18	17	5	0 (3 years)	11
JCOG8101		III	54	28	8	8.3 (4 years)	12
	VEPA		24	17	NA	NA	
	VEPA-M		30	37	NA	NA	
JCOG8701	LSG4	II	42	43	8	12 (5 years)	13
JCOG9109	LSG11	II	60	28	7	16 (2 years)	31
JCOG9303	LSG15	II	93	36	13	31 (2 years)	32
JCOG9801		III	118				33
	mLSG15		57	40	13	24 (3 years)	
	CHOP-14		61	25	11	13 (3 years)	

For abbreviations, see Table 1. LSG 11 consists of 2′-deoxycoformycin, VCR, ETP, PSL and DOX; LSG15 consists of VCAP (VCR, CPA, PSL and DOX), AMP [DOX, raimustine (MCNU), VECP [VDS, ETP, carboplatin (CBDCA) and PSL], intrathecal MTX + PSL, with each intensified by the prophylactic use of G-CSF (granulocyte colony-stimulating factor); mLSG15 is a modified LSG15.

Table 3. Results of the JCOG trials for lymphoblastic lymphoma/acute lymphoblastic leukemia

Protocol	Regimen	Phase	No. of patients	%CR	PFS (%)	MST (months)	Survival (%)	Reference
JCOG8702	LSG 5	II	46	78	NA	14	15 (7 years)	38
JCOG9004	LSG10	II	143	83	26 (5 years)	26	32 (7 years)	39
JCOG9402	LSG16	II	108	81	28 (5 years)	21	28 (7 years)	40

For abbreviations, see Tables 1 and 2. PFS, progression-free survival; LSG5 consists of VEPA-L [VEPA with L-asparaginase (L-ASP) and intrathecal (IT) MTX/PSL] and M-VEPA (moderate-dose methotrexate plus VEPA); LSG10 consists of induction by LSG5/consolidation by DCMP (DOX, AraC, VDS, PSL, IT-MTX/PSL)/MEVP (mitoxantron, ETP, VCR, PSL, IT-MTX/PSL)/maintenance by 6-mercaptopurine (6-MP)/MTX, with allowing HSCT; LSG16 consists of induction by VEPA-L/consolidation by DCMP and CCMOL (CPA, AraC, 6-MP, VCR, L-ASP with IT-MTX/PSL)/intensified maintenance with allowing HSCT.

Table 4. Results of the JCOG trials for advanced Hodgkin's lymphoma

Protocol	Regimen	Phase	No. of patients	%CR	PFS (%)	Survival (%)	Reference
JCOG8905	C-MOPP/ABVd	II	79	84	73 (4 years)	85 (5 years)	41
JCOG9305	ABVd	II	128	81	78 (5 years)	91 (5 years)	42
JCOG9705	ABV + R	II	72[a]	72	49 (2 years)	92 (2 years)	44

For abbreviations, see Tables 1–3. C-MOPP consists of CPA, VLB, PCZ and PDN; ABVd consists of DOX, BLM, VLB and dacarbazine (DTIC); ABV + R consists of DOX, BLM, VLB with radiation.
[a]No. of enrolled patients with eligibility until the early termination.

lymphoid malignancies since 1978 with the help of the Central Pathology Review, the Radiation Therapy Quality Assurance and the Central CT Review Committees.

The research on treatments for lymphoid malignancies by JCOG-LSG is now supported by four grants for the principal investigators of the LSG studies by MHLW and Grants-in-Aid for Cancer Research (23A-17). JCOG-LSG has conducted more than 30 clinical trials including 10 randomized trials for several entities of lymphoid malignancies, meta-analyses of them, and correlative epidemiological and pathological studies on HTLV-1 and T/B-cell phenotype, respectively, providing several standard treatments, classifications and prognostic indexes for lymphoid malignancies as shown in the following sections.

Table 5. Results of the JCOG trials for advanced multiple myeloma

Protocol	Regimen	Phase	No. of patients	%RR (no)	Median PFS	MST (months)	Survival (%)	Reference
JCOG8906	COP/MP	II	69	51	13	39	51/27 (3/5 years)	48
JCOG9301		III	210					49
	MCNU-COP/MP		107	56	23	50	38 (5 years)	
	mCOP/MP		103	44	16	44	40 (5 years)	
JCOG0005-DI	VAD and up-front auto-HSCT	II	16[a]	NA	NA	NA	NA	NA
JCOG0112	MP/VAD with IFN + PSL versus PSL	III	34[a]					50
	VAD		16	44	NA	NA	NA	
	MP		17	47	NA	NA	NA	

For abbreviations, see Tables 1–4. DI, Data Center independent; IFN, interferon-α; COP consists of CPA, VCR and PSL; MP consists of melphalan and PSL; mCOP/MP is a modified COP/MP; VAD consists of VCR, DOX and dexamethasone.
[a]No. of enrolled patients until the early termination.

Table 6. Results of the JCOG trials for indolent B-cell lymphomas and localized nasal natural killer/T-cell lymphoma

Protocol	Regimen	Diseases	Phase	No. of patients	%CR/CRu (no)	PFS (%)	Survival (%)	Reference
JCOG0203		Indolent B	III	300				52
	CHOP-14			151	76	43 (6 years)	88 (6 years)	
	CHOP-21			149	78	41 (6 years)	87 (6 years)	
JCOG0211-DI	DEVIC/50 Gy	Nasal NK/T	I/II	33	77 (20/26)	67 (2 years)	78 (2 years)	56

For abbreviations, see Tables 1–5. DEVIC consists of DEX, ETP, ifosfamide (IFM) and CBDCA.

Table 7. Summaries of the JCOG-LSG correlative studies on trials for malignant lymphomas

Protocol	Trials	Disease	No. of patients	Reference
JCOG0108-A	9305, 0705	Hodgkin	167	45
JCOG0108-A	9002, 9203, 9505, 9506, 9508, 9809	NHL	1141	55
		DLBCL		NA
		T/NK	136	55
JCOG0103-A		NHL	499	59

For abbreviations, see Tables 1–6. NHL, non-Hodgkin's lymphoma; DLBCL, diffuse large B-cell lymphoma; T/NK, peripheral T and NK-cell lymphomas.

CONSECUTIVE AND ONGOING TRIALS FOR MAJOR LYMPHOID MALIGNANCIES BY JCOG-LSG

ADVANCED-STAGE, AGGRESSIVE NHL

Since 1978, chemotherapy trials have been consecutively conducted for patients with advanced-stage, aggressive NHL in JCOG-LSG (Table 1 and Fig. 1). After the completion of JCOG7801, a Phase II study of VEPA therapy (vincristine, cyclophosphamide, prednisone and doxorubicin), with promising results, JCOG-LSG started in 1981 a randomized Phase III trial (JCOG8101) to evaluate VEPA versus VEPA-M [VEPA plus methotrexate (MTX)] for advanced-stage NHL (11,12). The difference in survival between the two arms was not significant; however, unique pretreatment variables predictive for efficacy were found. Three factors, leukemic change, poor performance status (PS) and T-cell phenotype, were negatively associated with both the complete remission rate (%CR) and overall survival (OS). In addition, ATL was found to have a much poorer in prognosis than non-ATL peripheral T-cell lymphoma (26).

In 1987, JCOG-LSG initiated a Phase II study (JCOG8701) of a multiagent combination chemotherapy (LSG4 protocol) for advanced aggressive NHL (10). The LSG4 protocol consisted of three regimens: (i) VEPA-B (VEPA plus bleomycin), (ii) M-FEPA (MTX, vindesine, cyclophosphamide, prednisone and doxorubicin) and (iii) VEPP-B (vincristine, etoposide, procarbazine, prednisone and bleomycin). A central pathology review revealed 84 patients with T-NHL, including 42 with ATL, 151 with B-NHL and 33 with NHL of undetermined lineage

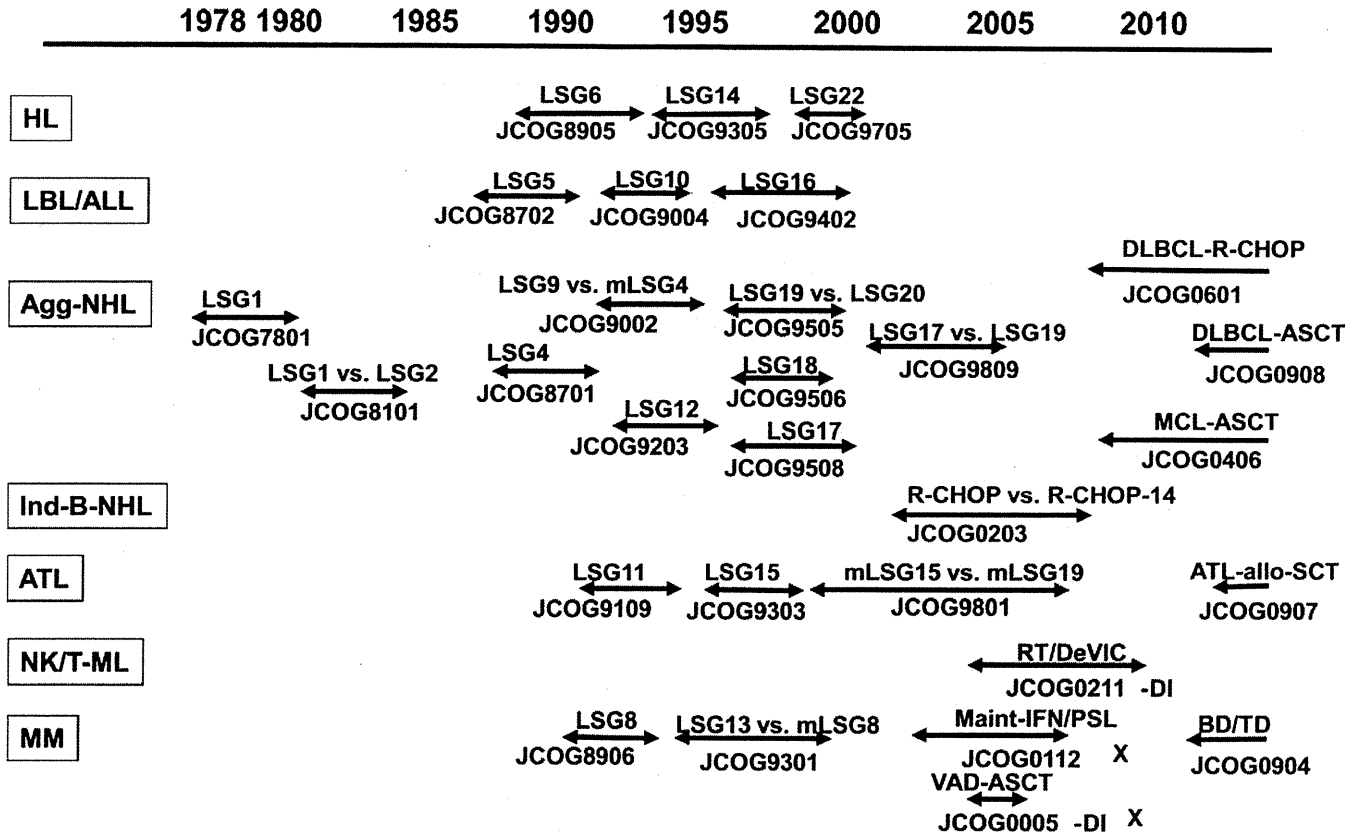

Figure 1. Consecutive studies by JCOG-LSG. HL, Hodgkin's lymphoma; LBL/ALL, lymphoblastic lymphoma/acute lymphoblastic leukemia; Agg-NHL, aggressive non-Hodgkin's lymphoma; Ind-B-NHL, indolent B-NHL, ATL; adult T-cell leukemia–lymphoma; NK/T ML, localized nasal natural killer/T-cell lymphoma; MM, multiple myeloma; DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma. LSG1, VEPA, consists of vincristine (VCR), cyclophosphamide (CPA), prednisone (PSL) and doxorubicin (DOX); LSG2, VEPA-M, consists of VEPA plus methotrexate (MTX); LSG4 consists of VEPA-B, M-FEPA and VEPP-B, where VEPA-B consists of VEPA plus Bleomycin (BLM), M-FEPA consists of a moderate dose of MTX, vindesine (VDS), CPA, PSL and DOX, and VEPP-B consists of VCR, CPA, PSL and procarbazin (PCZ); LSG5 consists of VEPA-L [VEPA with L-asparaginase (L-ASP) and intrathecal (IT) MTX/PSL] and M-VEPA (moderate-dose methotrexate plus VEPA); LSG6 consists of C-MOPP/ABVd; C-MOPP consists of CPA, VLB, PCZ and PDN; ABVd consists of DOX, BLM, VLB and dacarbazine (DTIC); LSG8 consists of COP/MP; COP consists of CPA, VCR and PSL; MP consists of melphalan and PSL; mLSG8 is a modified LSG8; LSG9 consists of dose-intensified mLSG4; LSG10 consists of induction by LSG5/consolidation by DCMP (DOX, AraC, VDS, PSL, IT-MTX/PSL)/MEVP (mitoxantron, ETP, VCR, PSL, IT-MTX/PSL)/maintenance by 6-mercaptopurine (6-MP)/MTX, with HSCT; LSG11 consists of DCF, VCR, ETP, PSL and DOX; LSG12 consists of VEPA/FEPP, where FEPP consists of vindesine, etoposide, procarbazine and prednisolone; LSG13 consists of raimustine (MCNU)-COP/MP; LSG14 consists of ABVd; LSG15 consists of VCAP (VCR, CPA, PSL, DOX), AMP (DOX, MCNU, PSL), VECP [VDS, ETP, carboplatin (CBDCA), PSL], intrathecal MTX + PLS, with each intensified by the prophylactic use of G-CSF (granulocyte colony-stimulating factor); mLSG15 is a modified LSG15; LSG16 consists of induction by VEPA-L/consolidation by DCMP and CCMOL (CPA, cytarabine, 6-MP, VCR; L-ASP with IT-MTX/PSL)/intensified maintenance with allowing HSCT; LSG17, CHOP, consists of CPA, DOX, VCR and PSL; LSG18 consists of CHOP-14 followed by up-front autologous hematopoietic stem cell transplantation (auto-HSCT); LSG19 consists of CHOP-14; LSG22, ABV + R, consists of DOX, BLM, VLB with radiation; RT/DeVIC in JCOG0005DI consisting of VAD (VCR, DOX and DEX) followed by up-front auto-HSCT; Maint-IFN/PSL in JCOG0112 consisting of MP/VAD induction therapy followed by maintenance therapy with interferon plus PSL versus PSL; R-CHOP and R-CHOP-14 in JCOG0203 consisting of rituximab plus CHOP and rituximab plus CHOP-14, respectively; MCL-ASCT in JCOG0406 consisting of R-high-CHOP followed by CHASER, LEED and auto-HSCT; DLBCL-R-CHOP in JCOG0601 consisting of weekly rituximab plus CHOP versus R-CHOP; BD/TD in JCOG0904 consisting of bortezomib plus dexamethasone versus thalidomide plus dexamethasone; ATL-allo-HSCT in JCOG0907 consisting of mLSG15 followed by allo-HSCT; DLBCL-ASCT in JCOG0908 consists of R-CHOP-14 versus R-CHOP-14 followed by CHASER as induction therapy prior to LEED and auto-HSCT.

(U-NHL). After a median follow-up of 56 months, the estimated overall 5-year OS rate was 48%: 60% in B-NHL, 45% in U-NHL, 35% in PTCL and 12% in ATL (Fig. 2). Unfavorable factors influencing OS that remained independently significant in Cox's analyses were clinical diagnosis of ATL, total number of involved lesions $\geq$4, C-reactive protein-positivity and Eastern Cooperative Oncology Group PS $\geq$ 2. JCOG8701 led to the following conclusions: (i) T-cell phenotype was an important pretreatment variable for aggressive NHL in Japan, and (ii) LSG4 protocol was effective against B-NHL. Since the clinical diagnosis of ATL was an independent unfavorable factor, ATL patients were excluded from subsequent JCOG trials for aggressive NHL, but LSG has started clinical trials specialized for ATL since then.