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ORIGINAL REPORT

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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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.

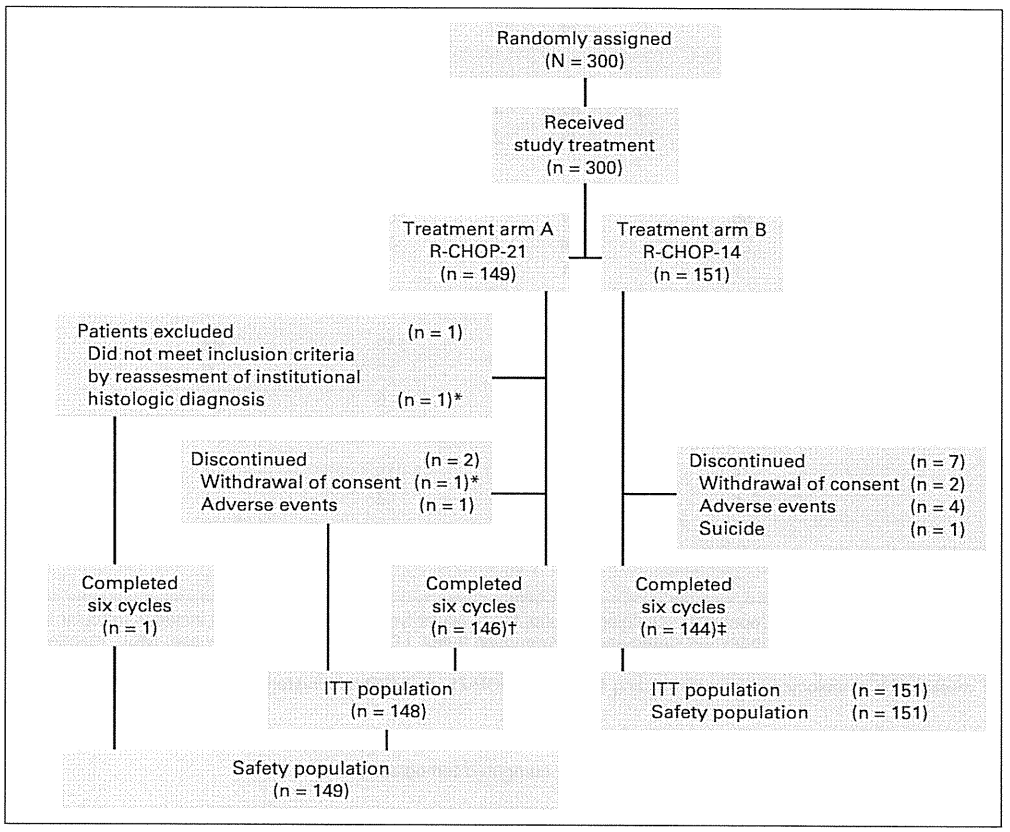

Fig 1. CONSORT diagram showing the flow of patient enrollment and disposition throughout the trial. ITT, intent to treat; R-CHOP-14, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) administered every 2 weeks with granulocyte colony-stimulating factor; R-CHOP-21, R-CHOP 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)			P*
	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 %	
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.

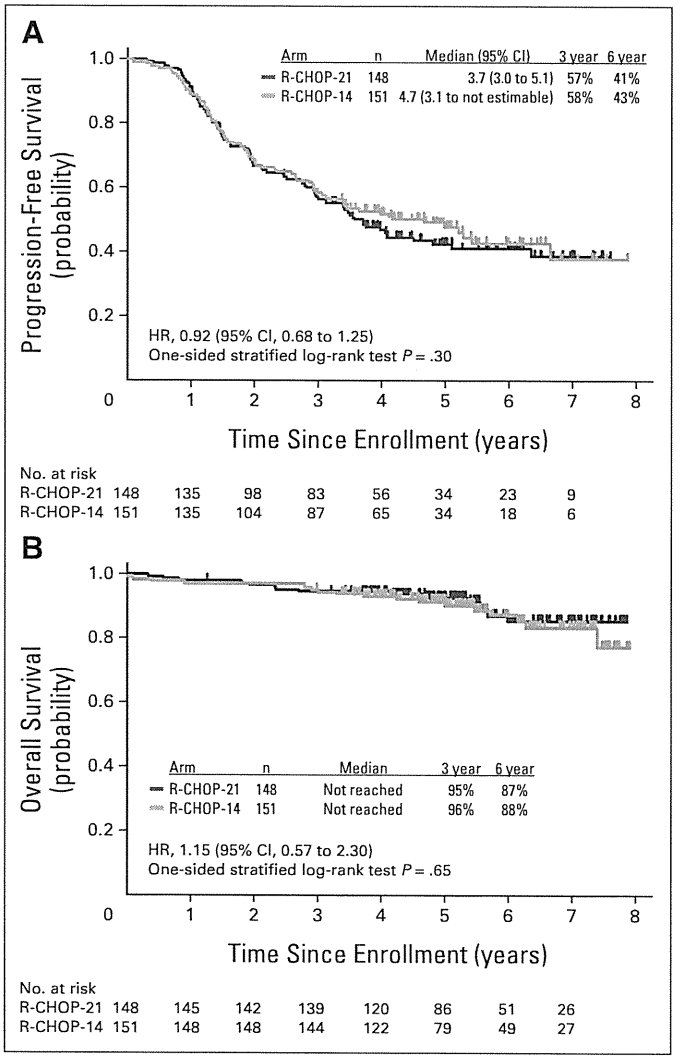

Fig 2. (A) Progression-free survival and (B) overall survival by treatment for patients with previously untreated, advanced-stage indolent B-cell non-Hodgkin's lymphoma. The median follow-up time was 5.2 years. HR, hazard ratio; R-CHOP-14, rituximab plus cyclophosphamide, doxorubicin, vincristine, and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

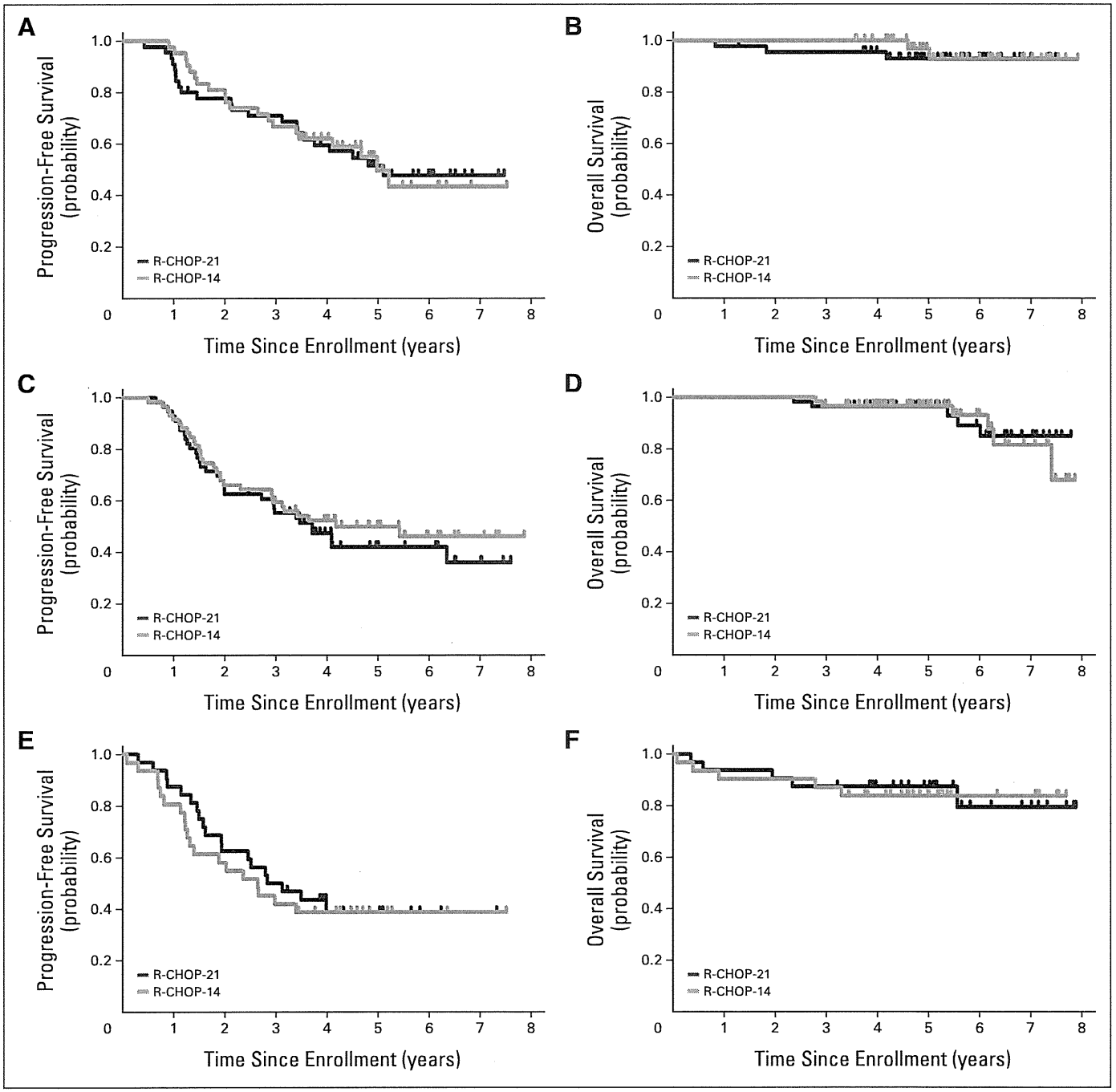

Fig 3. Progression-free survival (A, C, E) and overall survival (B, D, F) by treatment for patients in the low-risk (n = 87; A, B), intermediate-risk (n = 115; C, D), and high-risk (n = 63; E, F) groups according to the Follicular Lymphoma International Prognostic Index for the 265 patients with follicular 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.

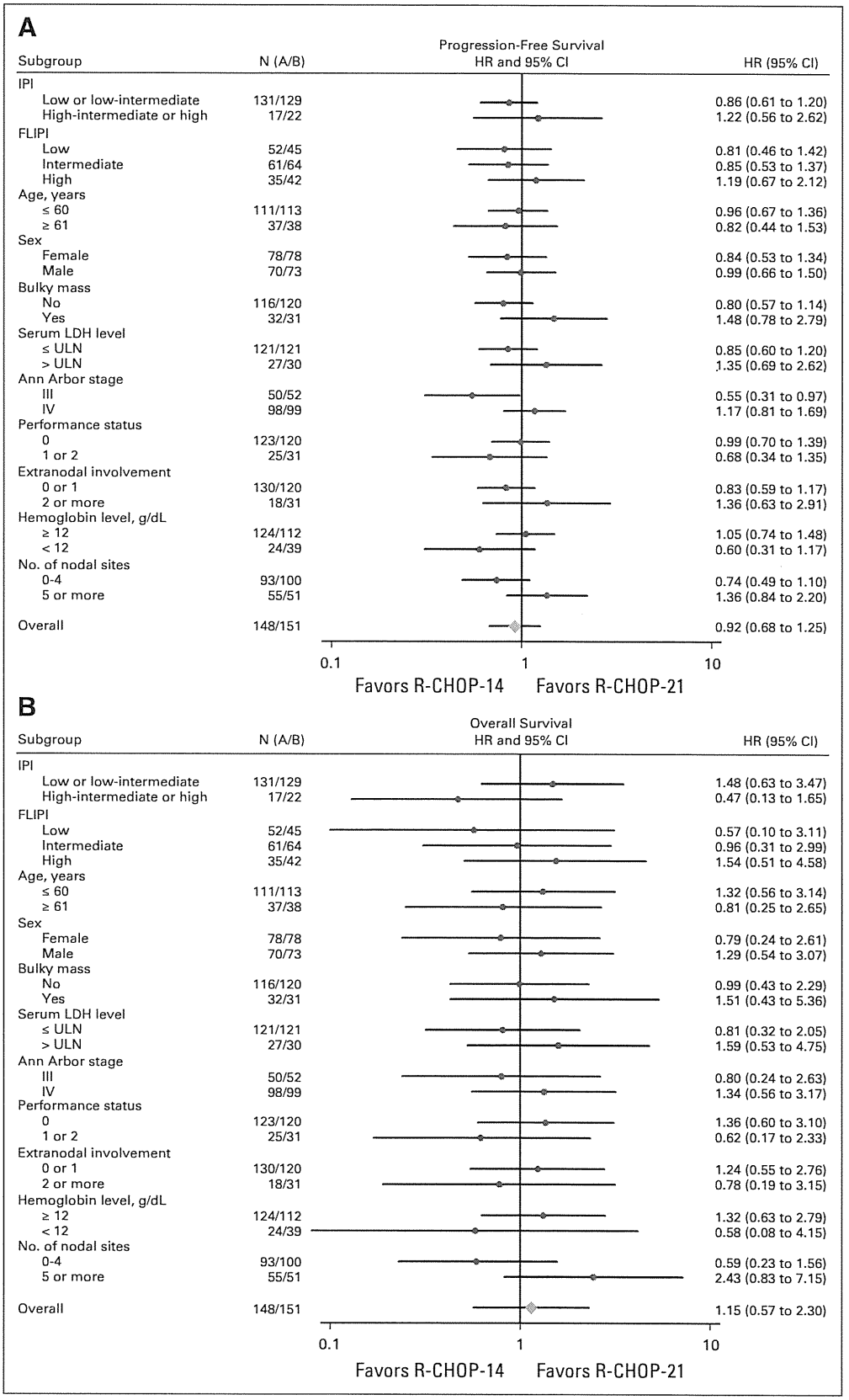

Fig 4. Forest plots of hazard ratios (HRs), comparing (A) progression-free survival and (B) overall survival among patients with previously untreated, advanced-stage indolent B-cell non-Hodgkin's lymphoma assigned to immunochemotherapy with either R-CHOP-14 (rituximab plus cyclophosphamide, doxorubicin, 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, $\leq$ 4 *v* $\geq$ 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; ULN, 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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Phase III trial of CHOP-21 versus CHOP-14 for aggressive non-Hodgkin's lymphoma: final results of the Japan Clinical Oncology Group Study, JCOG 9809

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Background: CHOP-21 has remained the standard chemotherapy for aggressive non-Hodgkin's lymphoma (NHL), and dose intensification is a potential strategy for improving therapeutic results. We conducted a phase III trial to determine whether dose-dense strategy involving interval shortening of CHOP (CHOP-14) is superior to CHOP-21.
Patients and methods: A total of 323 previously untreated patients (aged 15–69 years) with stages II–IV aggressive NHL were randomized. The primary end point was progression-free survival (PFS).
Results: Treatment compliance was comparable in both study arms. At 7-year follow-up, no substantial differences were observed in PFS and overall survival (OS) between CHOP-21 (n = 161) and CHOP-14 (n = 162) arms. Median PFS was 2.8 and 2.6 years with CHOP-21 and CHOP-14, respectively (one-sided log-rank P = 0.79). Eight-year OS and PFS rates were 56% and 42% [95% confidence interval (CI) 47% to 64% and 34% to 49%], respectively, with CHOP-21 and 55% and 38% (95% CI 47% to 63% and 31% to 46%), respectively, with CHOP-14. Subgroup analyses showed no remarkable differences in PFS or OS for patients stratified as per the International Prognostic Index or by age.
Conclusion: Dose-intensification strategy involving interval shortening of CHOP did not prolong PFS in advanced, aggressive NHL.
Key words: aggressive non-Hodgkin's lymphoma, CHOP-14, CHOP-21, phase III trial

introduction

CHOP-21 [cyclophosphamide (CPA), doxorubicin (DXR), vincristine (VCR), and prednisone (PDN)] has remained a standard treatment for patients with aggressive non-Hodgkin's lymphoma (NHL) since 30 years [1]. However, CHOP-21 only cures 30%–50% of patients [2]. Several multidrug combinations with promising efficacy in phase II trials have been developed for improving outcome. However, several randomized phase III trials revealed that these regimens are not superior to CHOP-21 with respect to survival [3–6] partly due to lower dose intensities of CPA and DXR, key drugs for NHL, in the former than latter regimen [7].

Upfront high-dose chemotherapy with autologous stem-cell transplantation might be beneficial for high-intermediate and high-risk group patients [classified by the International Prognostic Index (IPI)] [8, 9]. Therefore, a dose-intensified strategy for NHL is still of interest to clinicians. Previously, we conducted a randomized phase II trial to investigate the effects of increasing dose intensity of CHOP along with interval shortening; biweekly CHOP (CHOP-14) was compared with dose-escalated CHOP in aggressive NHL patients [10]. Seventy aggressive NHL patients classified as high-intermediate or high-risk groups as per IPI randomly received either CHOP (eight courses; every 2 weeks) or dose-escalated CHOP (six courses; every 3 weeks). The biweekly regimen showed better complete response (CR) and 3-year progression-free survival (PFS) rates. Thus, CHOP-14 was suggested as a more suitable regimen to be evaluated in subsequent phase III trials.

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To determine whether dose-dense chemotherapy involving interval shortening of CHOP is superior to CHOP-21, the Lymphoma Study Group of the Japan Clinical Oncology Group conducted a phase III trial.

patients and methods

eligibility criteria

Forty-two centers participated in this trial. Inclusion criteria were as follows: previously untreated intermediate- or high-grade NHL according to the Working Formulation (D through H and J) [11]; clinical stage II–IV disease (Ann Arbor classification) [12]; age 15–69 years; Eastern Cooperative Oncology Group performance status 0–2; white blood cell count $\geq 3.0 \times 10^9$/l; absolute neutrophil count (ANC) $\geq 1.2 \times 10^9$/l; platelet count $\geq 75 \times 10^9$/l; aspartate aminotransferase (AST) and alanine aminotransferase levels less than or equal to five times the upper limit of the normal range; total bilirubin level ≤2.0 mg/dl; serum creatinine level ≤2.0 mg/dl; $PaO_2 \geq 65$ mmHg; and normal electrocardiogram and cardiac function.

Exclusion criteria included any other malignancy, prior chemotherapy or radiotherapy, central nervous system involvement with lymphoma, HIV infection, positive test for hepatitis B virus surface antigen and/or hepatitis C virus antibody, pregnancy or breast-feeding, severe concomitant disease, or uncontrolled diabetes mellitus.

Written informed consent was obtained from all patients before enrollment, and the protocol was approved by the Protocol Review Committee of Japan Clinical Oncology Group (JCOG) and the Institutional Review Board of each participating center.

treatment

Patients were randomized at the JCOG Data Center after telephonic or fax registration to receive either CHOP-21 or CHOP-14 as per the minimization method of balancing the groups according to the institution, low/low-intermediate or high-intermediate/high-risk classification according to IPI, and informed consent available for *p53* gene analysis. CHOP-21 administered every 3 weeks consisted of CPA 750 mg/m^2 IV, DXR 50 mg/m^2 IV, VCR 1.4 mg/m^2 (maximum 2 mg) IV administered on day 1, and PDN 100 mg p.o. administered on days 1–5; same dosages of CHOP-14 were administered at every 2 weeks. Patients in the CHOP-14 arm received granulocyte colony-stimulating factor (G-CSF; filgrastim, lenograstim, or nartograstim) on days 6–13 or until their ANC was $>10 \times 10^9$/l. Patients in the CHOP-21 arm received G-CSF, if necessary. All patients in both study arms received eight courses of chemotherapy except those with progressive disease (PD) after two courses or no response (NR) after four courses when salvage chemotherapy was recommended.

If necessary, after eight courses of chemotherapy, patients were recommended for involved-field radiotherapy (dose 30–50 Gy), if they had initial bulky disease (masses of diameter > 5 cm) or if they only had a partial response (PR) in nonbulky disease.

response assessment

Tumor responses were assessed as per the World Health Organization (WHO) criteria [13] by clinical examination and computed tomography scan after two, four, six, and eight courses of chemotherapy and at 12 weeks after completing chemotherapy or radiotherapy and classified as CR, complete response unconfirmed (CRu), PR, NR, and PD.

statistical methods

All analyses were carried out according to an intent-to-treat principle, using SAS release 9.1 (SAS Institute, Cary, NC). The primary end point was PFS, which was calculated from the date of randomization to that of progression, relapse, or death from any cause. If patients survived without progression, PFS was censored on the latest date when no progression was confirmed. Secondary end points included overall survival (OS) calculated from the date of randomization to the date of death from any cause, CR rate (%CR), and toxicity. PFS and OS curves were generated using the Kaplan–Meier method. Toxicity was assessed as per the JCOG Toxicity Criteria (expanded and modified version of the National Cancer Institute Common Toxicity Criteria, version 1.0) [14]. All patient information forms were collected and managed at the JCOG Data Center where in-house interim monitoring was carried out, and the reports were semiannually reviewed by their Data and Safety Monitoring Committee.

This trial aimed to detect 10% improvement in 5-year PFS rates with CHOP-14 compared with CHOP-21, which was anticipated to have 5-year PFS rate of 50%. This study design required the enrollment of 410 patients with a one-sided α-level of 0.05 to attain 80% power over 4 years of accrual and 7 years of follow-up (including ineligibility and cases lost to follow-up). Two interim analyses were planned. The first involved comparing %CR after half of the patients had been assessed for response. However, blinded in-house monitoring showed poorer PFS than expected; the sample size was then amended to 330 patients, and the end point for the first interim analysis was changed from %CR to PFS.

Superiority of CHOP-14 was assessed by the one-sided log-rank test. Multiplicity was adjusted using an alpha-spending function of the O'Brien–Fleming type. To summarize the difference between the two arms at interim analysis, hazard ratios (HRs) with confidence intervals (CIs) were calculated [15]. If CHOP-14 proved inferior, the predictive distribution of HR [16] was used to decide whether to stop the trial for futility monitoring. Updated data and estimate HRs between the two arms were analyzed by Cox regression analysis.

central pathology review

Collected biopsy specimens (290 specimens) of enrolled patients were forwarded for central pathology review. Four hematopathologists classified them according to the Working Formulation and WHO classification (third edition) [17].

results

interim analysis

The first planned interim analysis was carried out in December 2002. Because CHOP-14 was deemed highly unlikely to be superior to CHOP-21 with respect to PFS, the trial was terminated early following recommendations by the JCOG Data and Safety Monitoring Committee on 18 December 2002. At the first interim analysis of 286 patients, median PFS was 33.9 and 24.3 months for patients in CHOP-21 ($n = 143$) and CHOP-14 ($n = 143$) arms, respectively (one-sided log-rank $P = 0.68$). The 2-year PFS rate was 54.4% (95% CI 45.0% to 63.7%) in the CHOP-21 arm and 51.1% (95% CI 41.4% to 60.8%) in the CHOP-14 arm with a HR of 1.10 (95% CI 0.76% to 1.57%). Two-year OS rates were 73.8% (95% CI 65.4% to 82.3%) and 74.8% (95% CI 66.1% to 83.5%) in CHOP-21 and CHOP-14 arms, respectively.

patient characteristics

Between February 1999 and December 2002, 323 enrolled patients were randomly assigned to CHOP-21 (161 patients) and CHOP-14 arms (162 patients). Patient characteristics in both groups were well balanced (Table 1). Among the 323

Table 1. Patients' characteristics

	CHOP-21		CHOP-14		Total	%
	n	%	*n*	%		
Number of patients	161	49.8	162	50.2	323	
Age						
Median (range)	58 (18–69)		57 (17–69)		57 (17–69)	
<61	103	64.0	111	68.5	214	66.3
≥61	58	36.0	51	31.5	109	33.7
Gender						
Male	94	58.4	96	59.3	190	58.8
Female	67	41.6	66	40.7	133	41.2
ECOG performance status						
0	79	49.1	88	54.3	167	51.7
1	68	42.2	61	37.7	129	39.9
2	14	8.7	13	8.0	27	8.4
Number of extranodal sites						
0, 1	127	78.9	132	81.5	259	80.2
>2	34	21.1	30	18.5	64	19.8
LDH greater than normal	80	49.7	74	45.7	154	47.7
Stage						
I[a]	3	1.9	1	0.6	4	1.2
II	56	34.8	58	35.8	114	35.3
III	42	26.1	43	26.5	85	26.3
IV	60	37.3	60	37.0	120	37.2
Bulky mass	82	50.9	86	53.1	168	52.0
IPI risk group						
Low	65	40.4	78	48.1	143	44.3
Low-intermediate	51	31.7	45	27.8	96	29.7
High-intermediate	36	22.4	26	16.0	62	19.2
High	9	5.6	13	8.0	22	6.8
Working formulation						
Institutional [consensus] diagnosis						
Small lymphocytic	[2]		[0]		[2]	
Follicular small cleaved	[1]		[3]		[4]	
Follicular mixed	[6]		[5]		[11]	
Follicular large	17 [8]		17 [13]		34 [21]	
Diffuse small cleaved	8 [6]		9 [6]		17 [12]	
Diffuse mixed	21 [13]		20 [13]		41 [26]	
Diffuse large	112 [93]		111 [94]		223 [187]	
Immunoblastic	3 [0]		4 [4]		7 [4]	
Small noncleaved	0 [2]		1 [2]		1 [4]	
Miscellaneous	[3]		[5]		[8]	
Others	[6]		[5]		[11]	
WHO classification						
MCL	2		2		4	
FL	11		12		23	
FL, follicular large plus diffuse large	4		9		13	
MZBCL	4		2		6	
DLCL	88		99		187	
BCL, unclassified	1		1		2	
BCL, low grade	4		2		6	
HL	4		3		7	
Miscellaneous	2		3		5	
NK/T lymphoma	2		1		3	
AILT	6		5		11	
PTCL	9		7		16	
ATL	1		1		2	
ALCL	2		2		4	

Table 1. (*Continued*)

	CHOP-21		CHOP-14		Total	%
	n	%	*n*	%		
T-cell lymphoma, unclassified	0		1		1	
Not collected	21		12		33	

[a]Ineligible, but one of four patients was treated as eligible.

MCL, mantle cell lymphoma; FL, follicular lymphoma; MZBCL, marginal zone B-cell lymphoma; DLCL, diffuse large cell lymphoma; BCL, B-cell lymphoma; HL, Hodgkin lymphoma; NK, natural killer; AILT, angioimmunoblastic T-cell lymphoma; PTCL, peripheral T-cell lymphoma; ATL, adult T-cell leukemia-lymphoma; ALCL, anaplastic large cell lymphoma; IPI, International Prognostic Index; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group.

patients, 8 were ineligible [3, incorrect histopathological diagnosis immediately after registration (2 with adult T-cell leukemia–lymphoma and 1 with follicular mixed-type lymphoma); 3, stage I disease; 1, complicated gastric cancer; and 1, no measurable lesion]. Of 290 patients whose biopsy samples were reviewed, 38 (13.1%) (18, CHOP-21 and 20, CHOP-14) were considered ineligible.

After chemotherapy, involved-field radiotherapy (dose 30–50 Gy) was administered to 58 patients (28, CHOP-21 and 30, CHOP-14) with initial bulky disease and 7 with PR and with no initial bulky mass for residual disease (2, CHOP-21 and 5, CHOP-14).

toxic effects

Collected case report forms of 320 patients (including ineligible patients) were used for evaluating toxic effects (Table 2). At least one episode of grade 4 neutropenia was experienced by 83.6% and 52.2% patients in CHOP-21 and CHOP-14 arms, respectively. While 12.5% and 20.6% patients in CHOP-21 and CHOP-14 arms, respectively, experienced grade 3 anemia (hemoglobin < 8 g/dl). Only one patient experienced grade 4 thrombocytopenia.

Nonhematologic toxic effects were mild and equivalent in both arms. However, treatment in the CHOP-21 arm was discontinued for four patients [one, decreased left ventricular ejection fraction (<40%); one, hypertension with Wallenberg's syndrome; one, gastric perforation; and one, amebic abscesses in the intestine and liver]. Protocol treatment was discontinued for seven patients (three, pneumonitis; three, ≥grade 2 arrhythmias; and one, a vertebral compression fracture) in the CHOP-14 arm.

After the seventh course of CHOP-14, one patient died suddenly but the cause of death could not be determined. In the CHOP-14 arm, one male patient developed Pneumocystis pneumonia immediately after the eighth course of chemotherapy and died of respiratory failure.

Twenty-nine secondary malignancies cases (CHOP-21 arm: 8 and CHOP-14 arm: 21) were also observed. Median age at lymphoma diagnosis was 59 years (range 32–68 years) and 60 years (range 41–69 years) in CHOP-21 and CHOP-14 arms, respectively. Three and eight patients in CHOP-21 and CHOP-14 arms were >60 years. In the CHOP-21 arm, the cases included non-small-cell lung cancer ($n = 1$), breast cancer ($n = 1$), gastric cancer ($n = 2$), pancreatic cancer ($n = 2$),

Table 2. Toxic effects

	CHOP-21, $n = 160$	CHOP-14, $n = 160$
Leukopenia (% grade 4)	47.5	35.0
Neutropenia (% grade 4)	83.6	52.2
Anemia (% grade 3)	12.5	20.6
Thrombocytopenia (% grade 4)	0.6	0.6
T-bil (% grade 3, 4)	2.5	0
AST (% grade 3, 4)	3.1	0
ALT (% grade 3, 4)	5.0	3.1
Creatinine (% grade 3, 4)	0	0.6
Hyperglycemia (% grade 3, 4)	2.0	3.2
Arrhythmia (% grade 3, 4)	1.3	0.6
Cardiac ischemia (% grade 3, 4)	0.6	0.7
Infection (% grade 3, 4)	3.8	3.8
Neurotoxicity—sensory (% grade 3, 4)	1.3	5.7
Neurotoxicity—motor (% grade 3, 4)	1.3	2.5
Constipation (% grade 3, 4)	1.3	1.3

Toxicity forms collected 320 patients.

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

prostate cancer ($n = 1$), and diffuse large B-cell lymphoma ($n = 1$). Only one pancreatic cancer patient received consolidative radiotherapy. One patient whose lymphoma had progressed during CHOP-21 treatment received allogeneic hematopoietic stem-cell transplantation, and the patient later developed non-small-cell lung cancer. Lymphoma relapse was not observed among other patients. In the CHOP-14 arm, the cases included thyroid cancer ($n = 1$), non-small-cell lung cancer ($n = 2$), breast cancer ($n = 2$), gastric cancer ($n = 3$), pancreatic cancer ($n = 1$), colon cancer ($n = 3$), uterine cervical cancer ($n = 1$), prostate cancer ($n = 1$), Ewing's sarcoma ($n = 1$), mantle cell lymphoma ($n = 1$), and myelodysplastic syndrome ($n = 5$). Every patient with breast cancer, mantle cell lymphoma, and colon cancer received consolidative radiotherapy. Lymphoma relapsed in three cases. One patient received salvage and high-dose chemotherapy followed by autologous hematopoietic stem-cell transplantation and developed myelodysplastic syndrome 23 months after CHOP-14 treatment. Other patients developed gastric and colon cancer after salvage chemotherapy. Lymphoma relapse was not observed in patients with myelodysplastic syndrome;

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

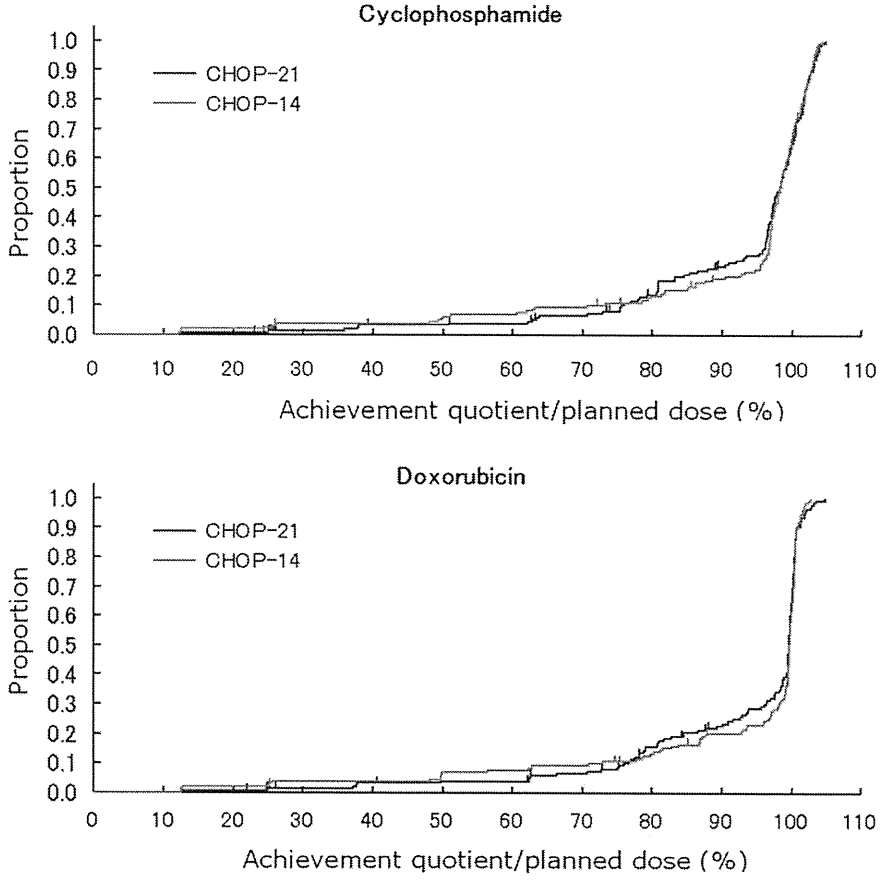


Figure 1. Distribution of the achievement quotient for planned doses of cyclophosphamide and doxorubicin.

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

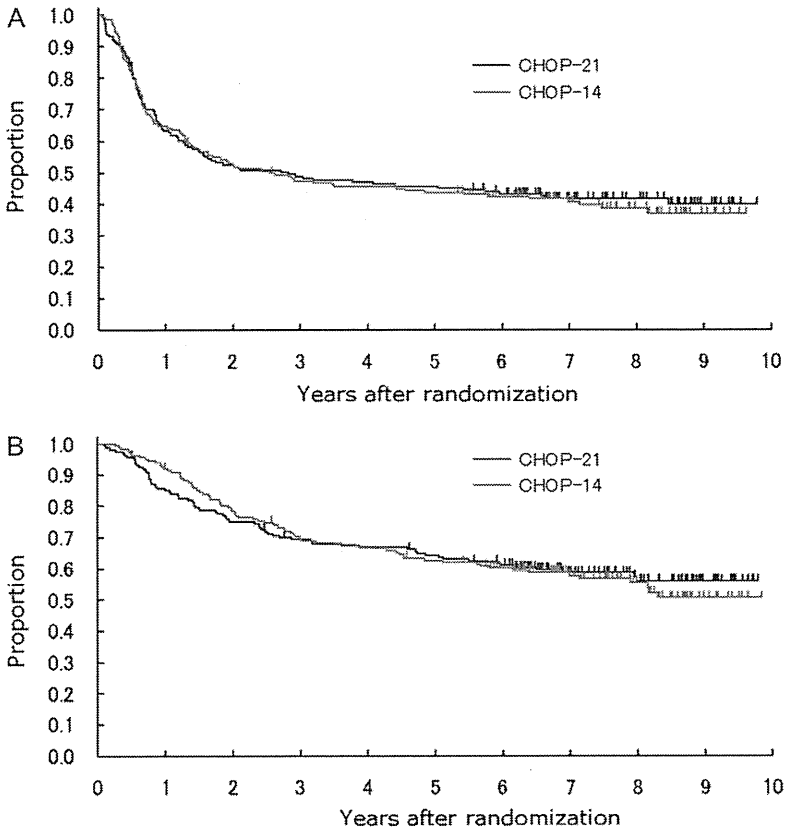
	CHOP-21 (%), $n = 161$	CHOP-14 (%), $n = 162$
CR	38.5	44.4
CRu	23.0	22.2
PR	0	0
NR	0	0
PD	12.4	9.3
Not evaluable	1.2	0
%CR (CR + CRu)	61.5	66.7
95% CI	53.5–69.0	58.8–73.9

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

conclusions

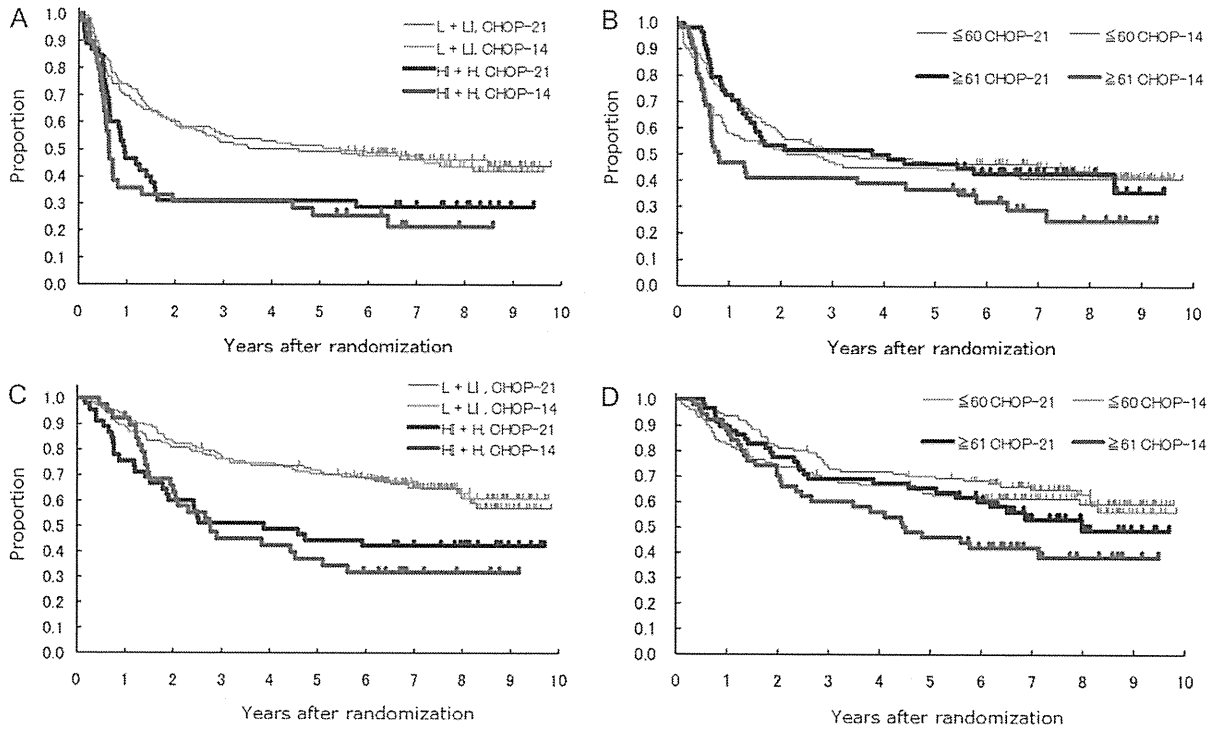
This trial failed to demonstrate the superiority of CHOP-14 over CHOP-21 for the treatment of aggressive NHL. PFS and OS after CHOP-14 were lower than those after CHOP-21 at the first interim analysis, and the trial was terminated early because the estimated predictive probability that CHOP-14 would 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 I study of LY2469298, an Fc-engineered humanized anti-CD20 antibody, in patients with relapsed or refractory follicular lymphoma

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Patients with follicular lymphoma (FL), where position 158 of FcγRIIIa is heterozygous valine/phenylalanine or homozygous phenylalanine (F-carriers), have natural killer cells with lower binding affinity to IgG than valine homozygote patients. In addition, F-carriers show less efficacy with rituximab treatment than patients homozygous for valine. LY2469298 is a humanized IgG1 monoclonal antibody targeting CD20, with human germline framework regions, and specific amino acid substitutions engineered into the Fc region to increase effector function in antibody-dependent cell-mediated cytotoxicity. This dose-escalation, phase I study was conducted to assess the safety, pharmacokinetics and preliminary efficacy of LY2469298 in Japanese patients with previously treated, CD20-positive FL who had not relapsed or progressed within 120 days of prior rituximab. LY2469298 was administered by intravenous infusion at 100 or 375 mg/m^2 weekly for 4 weeks. Ten patients were enrolled (median age, 60 years); all had previously been treated with rituximab. Nine patients were F-carriers while one was homozygous for valine at position 158 of FcγRIIIa. No patients developed dose-limiting toxicities, and the most frequent adverse events were lymphopenia, pyrexia, leukopenia, chills and neutropenia. Five (50%) of the ten patients responded to LY2469298 treatment (three complete responses, one unconfirmed complete response and one partial response). Serum LY2469298 was eliminated in a biphasic manner and the pharmacokinetic profiles were not different from those in a preceding study in the United States. In conclusion, LY2469298 was well tolerated and clinical activity was observed in FL patients pretreated with rituximab, mostly consisting of F-carriers. Further investigation of FL is warranted. (*Cancer Sci* 2011; 102: 432–438)

Follicular lymphoma (FL) is a low-grade B-cell non-Hodgkin lymphoma for which multiple treatment options exist; however, no uniform treatment approach has been established.[1] Lymphoma cells from almost all patients with FL express CD20 antigen on their cell surface.[2] Rituximab, a chimeric monoclonal antibody that targets CD20, has emerged over the past decade as a treatment of choice for patients with FL, either as a single agent or in combination with chemotherapies.[3–10] Recently, outcomes for patients with FL have improved, and some of this improvement has been attributed to rituximab.[11–13] Despite high response rates and a long duration of disease control for most patients, the majority of patients ultimately relapse with disease that is refractory to treatment, including rituximab.[10,14]

Rituximab is hypothesized to work through multiple mechanisms, including antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and direct induction of cellular signaling pathways that result in apoptosis. ADCC, considered to be particularly important for the clinical efficacy of rituximab in B-cell non-Hodgkin lymphoma,[15] is mediated by immune effector cells, including natural killer cells, and through IgG Fc-receptors (FcγR). Substitution of phenylalanine (F) for valine (V) at one or both alleles encoding for amino acid position 158 of the FcγRIIIa (CD16a) protein has been significantly correlated with a negative outcome for FL patients treated with rituximab. For example, an FcγRIIIa protein with F at position 158 has a lower binding affinity to IgG.[16,17] In addition, patients with heterozygous (VF) or homozygous (FF) *FcγRIIIA-158* alleles (F-carriers) have a significantly lower response rate and shorter time to progression following rituximab monotherapy compared with patients with homozygous (VV) *FcγRIIIA-158* alleles.[18–20]

LY2469298 is a humanized, IgG1, anti-CD20 monoclonal antibody with human germline framework regions, a higher affinity for CD20 compared with rituximab and a limited number of amino acid substitutions in the Fc region (selected to enhance ADCC). It had approximately sixfold more potent ADCC *in vitro* with approximately 50% less CDC, compared with rituximab (data at Eli Lilly on file). Thus, LY2469298 was hypothesized to have greater activity in patients with FL compared with rituximab, particularly in *FcγRIIIA-158* F-carrier patients. Furthermore, the humanization of LY2469298 was hypothesized to decrease immunogenicity.

In the United States, a phase I study of LY2469298 was conducted in patients with FL who expressed the low affinity forms of FcγRIIIa.[21] In this US study, five dose levels (ranging from 2 to 375 mg/m^2) were investigated for safety and tolerability and the maximum tolerated dose was not reached. Therefore, the dose level of 375 mg/m^2 was selected as the recommended dose for further study.

In the present study, Japanese patients with previously treated FL were treated with four weekly doses of LY2469298 at 100 or 375 mg/m^2. The primary objectives were to investigate the safety and tolerability of repeated administrations of LY2469298 at these two dose levels for establishing a recommended dose for a phase II study. The secondary objectives were to estimate the pharmacokinetic (PK) profile of LY2469298 and to explore the clinical activity of LY2469298 in this population.

Patients and Methods

Patients. Patients were eligible if they were 20 years of age or older with histologically confirmed, CD20-positive FL,

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