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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

A B S T R A C T

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

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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.

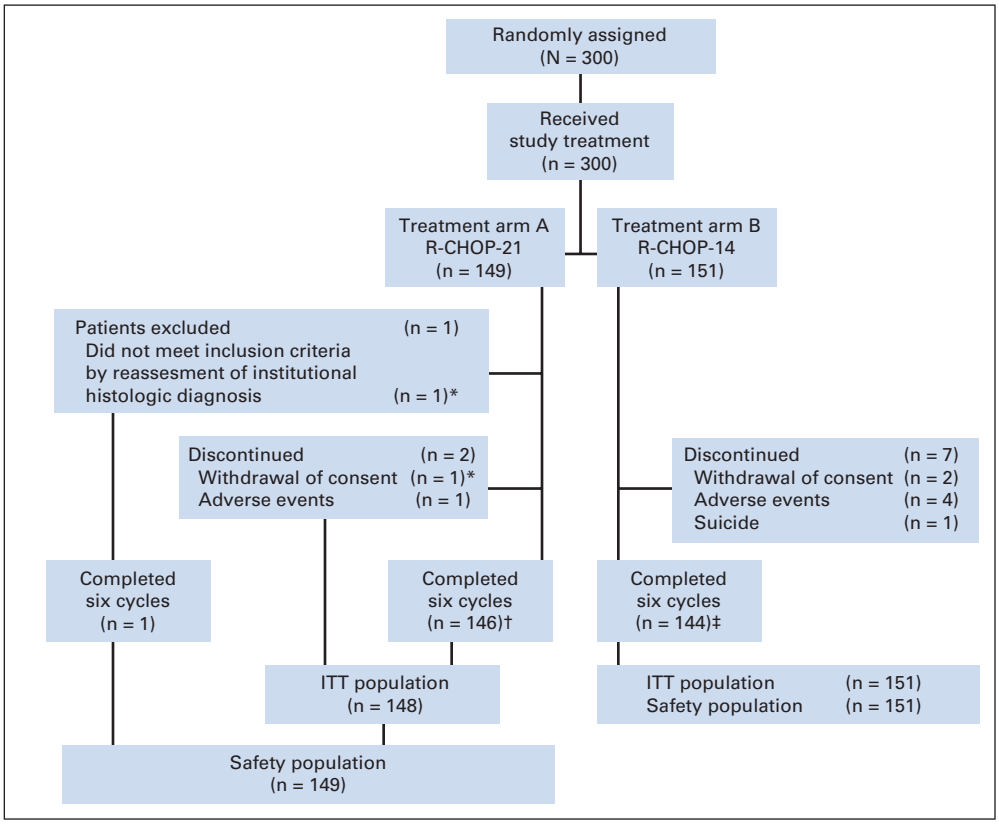

Fig 1. CONSORT diagram showing the flow of patient enrollment and disposition throughout the trial. ITT, intent to treat; R-CHOP-14, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) administered every 2 weeks with granulocyte colony-stimulating factor; R-CHOP-21, R-CHOP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

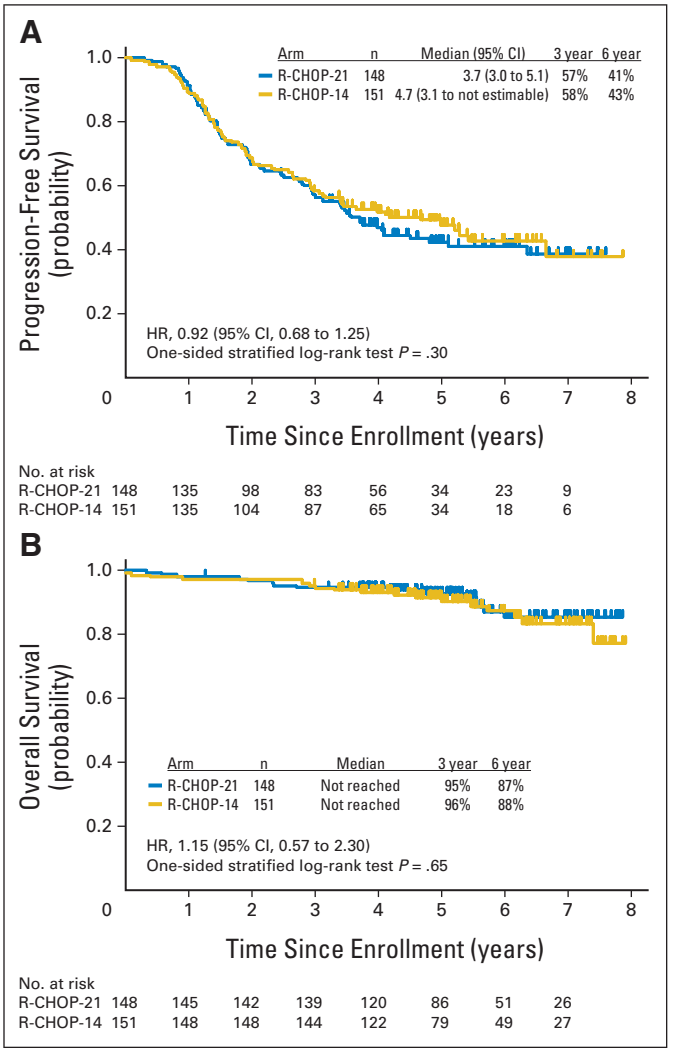

Fig 2. (A) Progression-free survival and (B) overall survival by treatment for patients with previously untreated, advanced-stage indolent B-cell non-Hodgkin's lymphoma. The median follow-up time was 5.2 years. HR, hazard ratio; R-CHOP-14, rituximab plus cyclophosphamide, doxorubicin, vincristine, and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

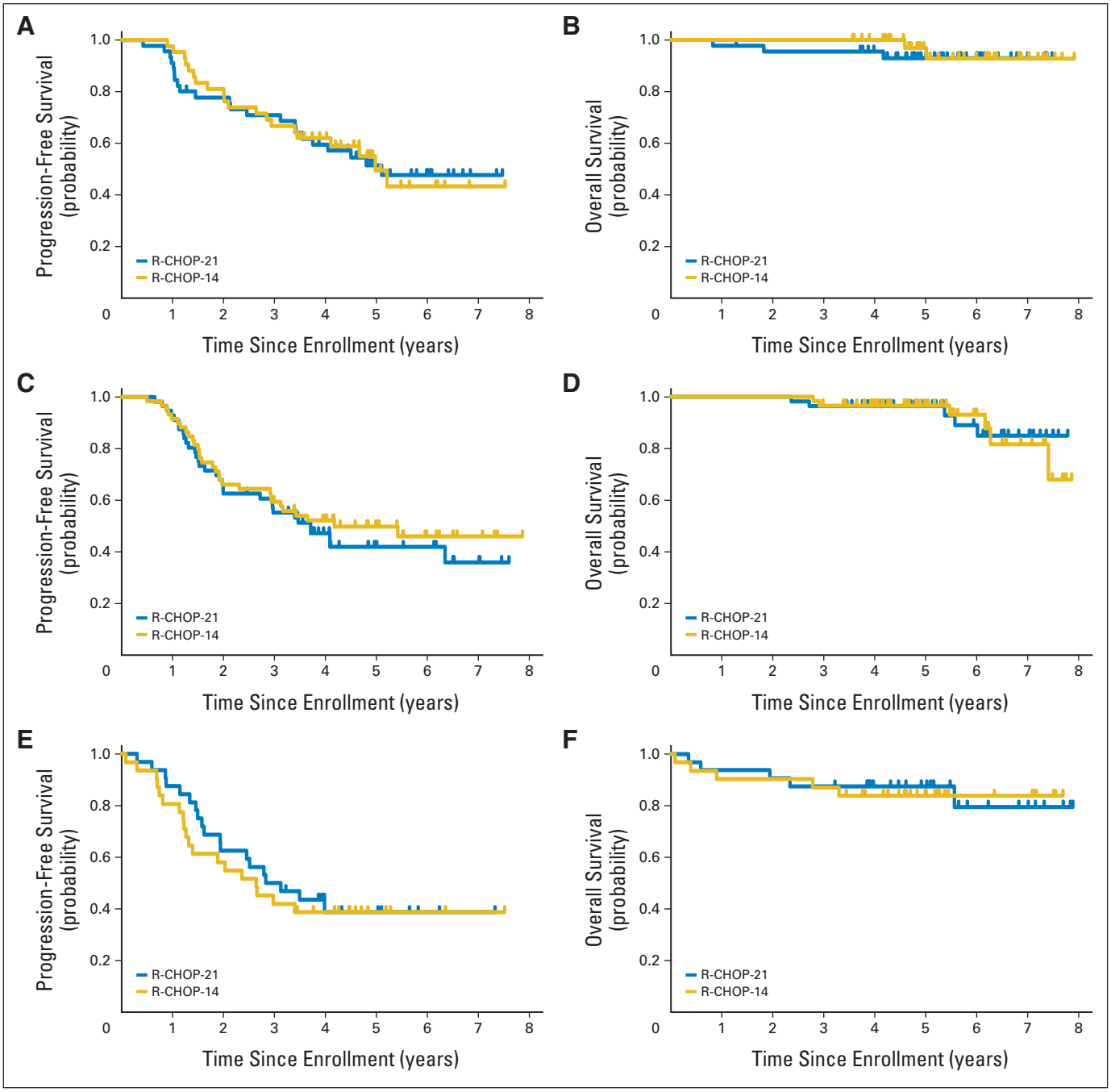

Fig 3. Progression-free survival (A, C, E) and overall survival (B, D, F) by treatment for patients in the low-risk (n = 87; A, B), intermediate-risk (n = 115; C, D), and high-risk (n = 63; E, F) groups according to the Follicular Lymphoma International Prognostic Index for the 265 patients with follicular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

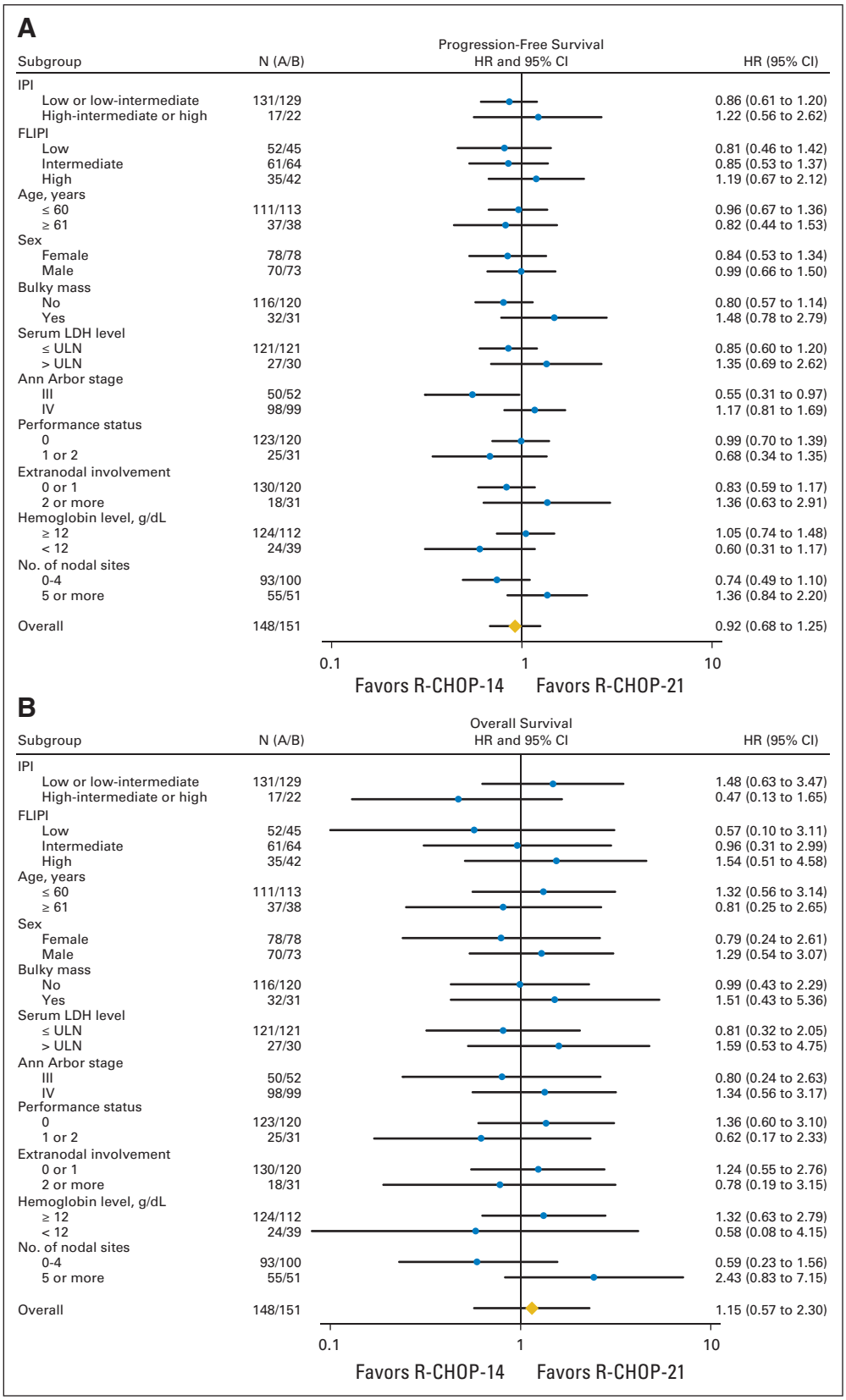

Fig 4. Forest plots of hazard ratios (HRs), comparing (A) progression-free survival and (B) overall survival among patients with previously untreated, advanced-stage indolent B-cell non-Hodgkin's lymphoma assigned to immunochemotherapy with either R-CHOP-14 (rituximab plus cyclophosphamide, doxorubicin, 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). Male sex and increased lactate dehydrogenase were unfavorable predictors of OS (Appendix Table A1, online only).

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*).

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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