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16.8. 病理判定委員

中村 栄男（名古屋大学大学院医学系研究科）

菊地 昌弘（福岡大学医学部）

大島 孝一（久留米大学医学部）

吉野 正（岡山大学医学部）

向井 清（東京医科大学）

16.9. 参加施設

参加施設の追加や登録可能施設の追跡協力施設への変更、研究責任者、コーディネーターの変更などによる内容変更は、プロトコール改訂・改正申請時に合わせて行い、それ以外の時に記載の変更は行わない。なお、最新の参加施設一覧は JCOG ホームページ（http://www.jcog.jp/）で 1 か月に 1 度更新されているので、確認可能である。（2011 年 10 月現在）

	医療機関名	科名	研究責任者	コーディネーター	年間登録見込み
○	国立病院機構北海道がんセンター	血液内科	黒澤 光俊	三上 祥博	7
○	札幌北楡病院	血液内科	中田 匡信	中田 匡信	5～7
○	東北大学病院	血液・免疫科	張替 秀郎	石澤 賢一	3
○	秋田大学医学部	血液腎膠原病内科	澤田 賢一	亀岡 吉弘	2
○	太田西ノ内病院	血液疾患センター	松田 信	斉藤 由理恵	1～2
○	群馬大学医学部附属病院	第3内科	塚本 憲史	横濱 章彦	2～3
○	埼玉県立がんセンター	血液内科	小林 泰文	久保田 靖子	1
○	国立がん研究センター東病院	化学療法科	伊藤 國明	伊藤 國明	10
○	千葉県がんセンター	腫瘍血液内科	熊谷 匡也	辻村 秀樹	3
○	国立がん研究センター中央病院	血液腫瘍科	飛内 賢正	小林 幸夫	10
○	杏林大学医学部	第2内科	高山 信之	高山 信之	5
○	東京医科大学病院	第1内科	大屋敷 一馬	後藤 明彦	2～3
○	がん・感染症センター都立駒込病院	化学療法科	前田 義治	岡元るみ子	4
○	東京慈恵会医科大学附属病院	腫瘍・血液内科	矢萩 裕一	齋藤 健	10
○	東京慈恵会医科大学第三病院	腫瘍・血液内科	薄井 紀子	土橋 史明	2
○	癌研究会有明病院	血液腫瘍科	畠 清彦	横山 雅大	
○	NTT 東日本関東病院	血液内科	臼杵 憲祐	半下石 明	
○	東海大学医学部	血液・腫瘍内科	安藤 潔	種田 いずみ	4
○	新潟県立がんセンター新潟病院	内科	張 高明	張 高明	5～7
○	金沢医科大学	血液リウマチ・膠原病科/血液免疫制御学	正木 康史	正木 康史	2
○	福井大学医学部附属病院	血液・腫瘍内科	上田 孝典	岸 慎治	1～2
○	浜松医科大学	腫瘍センター	大西 一功	大西 一功	4
○	愛知県がんセンター中央病院	血液細胞療法部	木下 朝博	山本 一仁	7～10
○	国立病院機構名古屋医療センター	血液内科	永井 宏和	永井 宏和	2
○	名古屋大学医学部	血液内科	冨田 章裕	徳永 隆之	5～7
○	名古屋市立大学病院	血液・膠原病内科	飯田 真介	楠本 茂	5
○	名古屋第二赤十字病院	血液・腫瘍内科	小椋 美知則	内田 俊樹	10
○	愛知医科大学附属病院	血液内科	仁田 正和	花村 一朗	2
○	三重大学医学部	血液内科	山口 素子	宮崎 香奈	3
○	滋賀県立成人病センター	血液・腫瘍内科	鈴木 孝世	内海 貴彦	5

○	京都府立医科大学	血液内科	谷脇 雅史	黒田 純也	7
○	兵庫県立がんセンター	血液内科	村山 徹	五明 広志	
○	国立病院機構四国がんセンター	血液腫瘍科	吉田 功	吉田 功	1～2
○	愛媛大学医学部附属病院	第1内科	安川 正貴	薬師神 芳洋	4
○	国立病院機構九州がんセンター	血液内科	鵜池 直邦	末廣 陽子	5
○	福岡大学医学部	腫瘍・血液・感染症内科	田村 和夫	高松 泰	3
○	国立病院機構九州医療センター	血液内科	岡村 精一	原田 直樹	3
○	産業医科大学	化学療法センター・血液科	塚田 順一	森本 浩章	2～3
○	佐賀大学医学部	血液・呼吸器・腫瘍内科	木村 晋也	福島 伯泰	5～7
○	国立病院機構長崎医療センター	血液内科	吉田 真一郎	吉田 真一郎	3
○	佐世保市立総合病院	内科	森内 幸美	森内 幸美	2
○	長崎大学医学部・歯学部附属病院	原研内科	塚崎 邦弘	福島 卓也	4～5
○	熊本大学医学部	血液内科	畑 裕之	野坂 生郷	5～7
○	国立病院機構熊本医療センター	内科	日高 道弘	井上 佳子	5
○	大分県立病院	血液内科	佐分利 能生	大塚 英一	2～3
○	鹿児島大学医学部・歯学部附属病院	血液・膠原病内科	魚住 公治	魚住 公治	2～3
○	今村病院分院	内科	宇都宮 與	宇都宮 與	2～3

合計 183～208 名

上記の JCOG リンパ腫グループ参加施設のうち、本試験参加は、○印のある施設である

16.10. プロトコール審査委員会

本プロトコールは参加施設の IRB 審査への提出に先立ち JCOG プロトコール審査委員会の審査承認を得たものである。

（委員の構成・所属は承認時のもの　更新なし

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16.11. JCOG 効果・安全性評価委員会

研究期間中は効果・安全性評価委員会による監視（有害事象報告、中間解析審査、モニタリングレポート審査、プロトコール改訂審査など）を受ける。

（委員の構成はホームページ http://www.jcog.jp/basic/org/committee/jury.html 参照。ただし、本試験を実施する研究グループの委員は、本試験の審査には直接加わらない。）

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16.12. JCOG 監査委員会

研究期間中は監査委員会による施設訪問監査を受ける。
(委員の構成はホームページ http://www.jcog.jp/basic/org/committee/audit.html 参照)
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16.13. データセンター/運営事務局

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JCOG 運営事務局

研究支援部門　　高島淳生/金戸啓介

16.14. プロトコール作成

プロトコール作成

東海大学医学部血液腫瘍リウマチ内科　　大間知謙

プロトコール作成支援

JCOG データセンター

統計部門　　柴田大朗

DM 部門　　加幡晴美

JCOG 運営事務局

研究支援部門　　齋藤勇/三浦弥生

17. 研究結果の発表

主たる公表論文は英文誌に投稿する。

プロトコールで規定された主たる解析・最終解析または公表目的での中間解析がプロトコールに明記されていない場合は、効果・安全性評価委員会の承認を得た場合を除いて発表は行わない。

ただし、研究代表者または研究事務局は、研究の endpoint の解析結果を含まない、研究の紹介目的の学会・論文(総説)発表は研究グループ代表者および JCOG データセンター長の了承を得て行うことができる。

原則として、研究結果の主たる公表論文の著者は筆頭を研究事務局とし、以下、研究代表者、データセンターの統計担当(公表のための解析を行った時点での担当者1名)、グループ代表者の順とする。それ以下は、論文の投稿規定による制限に従って、登録数の多い順に施設研究責任者または施設コーディネーターを施設毎に選び共著者とする。

すべての共著者は投稿前に論文内容を review し、発表内容に合意した者のみとする。内容に関して、議論にても合意が得られない場合、研究代表者はグループ代表者の了承の上で、その研究者を共著者に含めないことができる。

学会発表は複数回に及ぶ可能性があるため、研究事務局、研究代表者、登録の多い施設の研究責任者または施設コーディネーターの中から、持ち回りで発表を行うこととする。発表者は研究代表者がグループ代表者の了承を得て決定する。ただし、学会発表に際しては、発表準備および発表内容について研究事務局が責任を持ち、原則としてデータセンターとの連絡は研究事務局が行う。研究事務局以外の発表者が、研究事務局と JCOG データセンター長の了承なく、直接データセンターから集計・解析結果を受け取ることはできない。

18. 参考文献

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19. 付表 Appendix

- 説明文書・同意書
- 薬剤添付文書
- 付表 6・付表 7
- Performance status scale(ECOG)※
- 体表面積表※
- 毒性規準(CTCAE v3.0 日本語訳 JCOG 版)◎
- ケースレポートフォーム一式※(一次審査提出時は CRF ドラフトを添付)

※印の資料は一次審査では添付不要。

Ⅱ. 研究成果の刊行に関する一覧表

別紙４

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Watanabe T, Tobinai K, Tsukasaki K, Kinoshita T, Suzuki T, Taniwaki M,et al.:	Phase II/III Study of R-CHOP-21 Versus R-CHOP-14 for Untreated Indolent B-Cell Non-Hodgkin's Lymphoma:JCOG 0203 Trial	J ClinOncol	29	3990-3998	2011
Kagami Y, Itoh K, Tobinai K, Kinoshita T, Suzuki T, Tsukasaki K,et al.:	Phase II study of cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) therapy for newly diagnosed patients with low- and low-intermediate risk, aggressive non-Hodgkin's lymphoma: final results of the Japan Clinical Oncology Group Study, JCOG9508.	Int J Hematol	96	74-83	2012
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Tobinai K.	Guest editorial: Management of malignant lymphoma is continuously improving.	Int J Hematol	96	533-4	2012
Tanaka T, Kinoshita T,et al,:	Retrospective analysis of primary gastric diffuse large B cell lymphoma in the rituximab era:a multicenter study of 95 patients in Japan	Ann Hematol	91	383-390	2012
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木下　朝博	悪性リンパ腫(ホジキンリンパ腫・非ホジキンリンパ腫)	臨床血液	第53巻第２号	145-154	2012
木下朝博	びまん性大細胞型Ｂ細胞リンパ腫	成人病と生活習慣病	42巻６号	720-725	2012
木下朝博	リンパ腫の最近の診療キーポイント 胃悪性リンパ腫の病態・病気分類と治療の考えかた	Medical Practice	Vol. 29 no. 8	1316-1318	2012

Ⅲ. 研究成果の刊行物・別刷

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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

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Clinical Trials repository link available on JCO.org.

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ABSTRACT

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

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

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

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

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INTRODUCTION

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

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

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

PATIENTS AND METHODS

Study Design

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

Patient Selection

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

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

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

Study Treatment

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

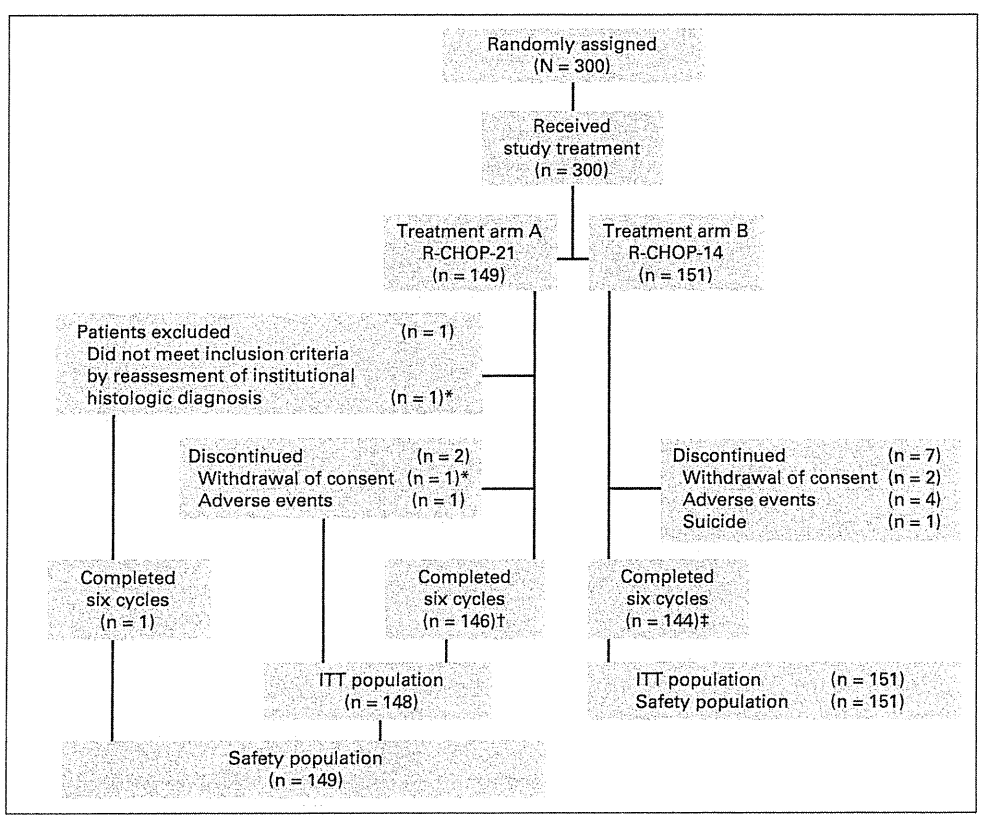

Fig 1. CONSORT diagram showing the flow of patient enrollment and disposition throughout the trial. ITT, intent to treat; R-CHOP-14, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) administered every 2 weeks with granulocyte colony-stimulating factor; R-CHOP-21, R-CHOP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

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

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

Assessments

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

Table 1. Baseline Patient Characteristics

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

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

*Wilcoxon rank sum test.

†Dynamic allocation adjustment factors in randomization.

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

§Patients judged ineligible by the central pathologic review.

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

Study End Points and Statistical Analyses

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

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

RESULTS

Patient Characteristics

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

Response Rate

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

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

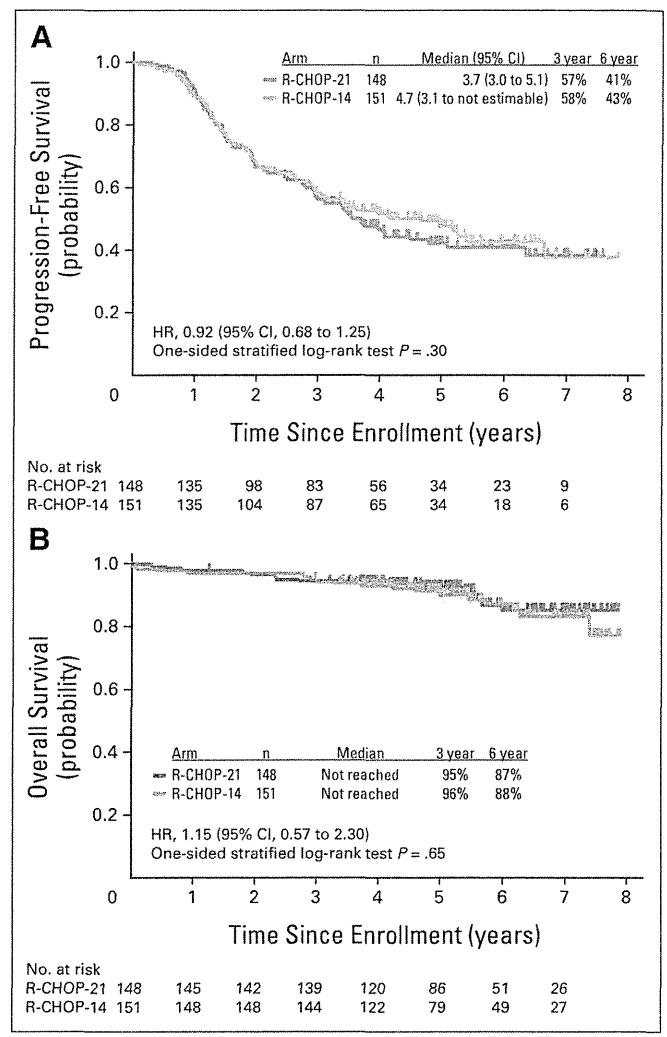

Fig 2. (A) Progression-free survival and (B) overall survival by treatment for patients with previously untreated, advanced-stage indolent B-cell non-Hodgkin's lymphoma. The median follow-up time was 5.2 years. HR, hazard ratio; R-CHOP-14, rituximab plus cyclophosphamide, doxorubicin, vincristine, and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