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).

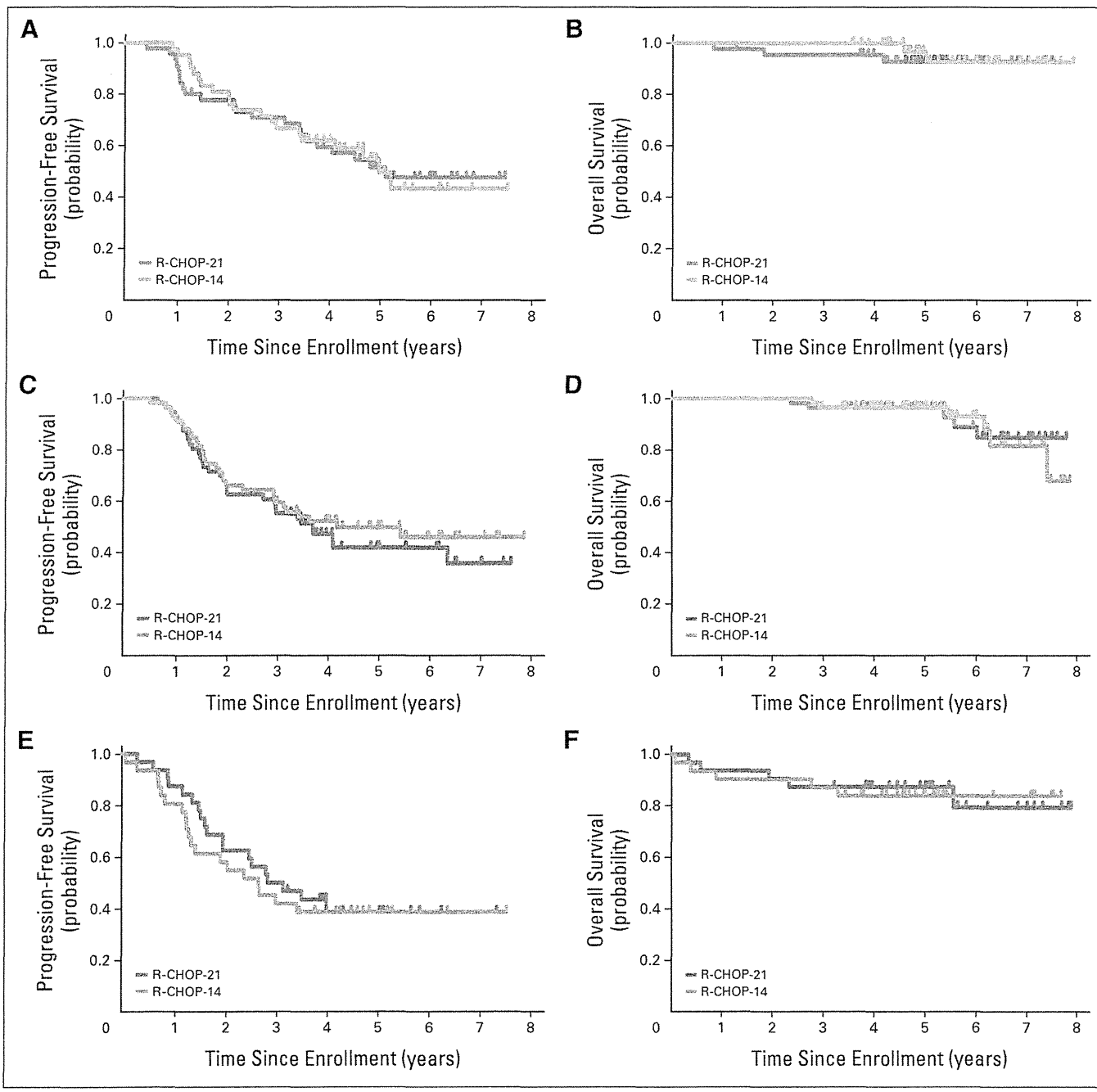

Fig 3. Progression-free survival (A, C, E) and overall survival (B, D, F) by treatment for patients in the low-risk (n = 87; A, B), intermediate-risk (n = 115; C, D), and high-risk (n = 63; E, F) groups according to the Follicular Lymphoma International Prognostic Index for the 265 patients with follicular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

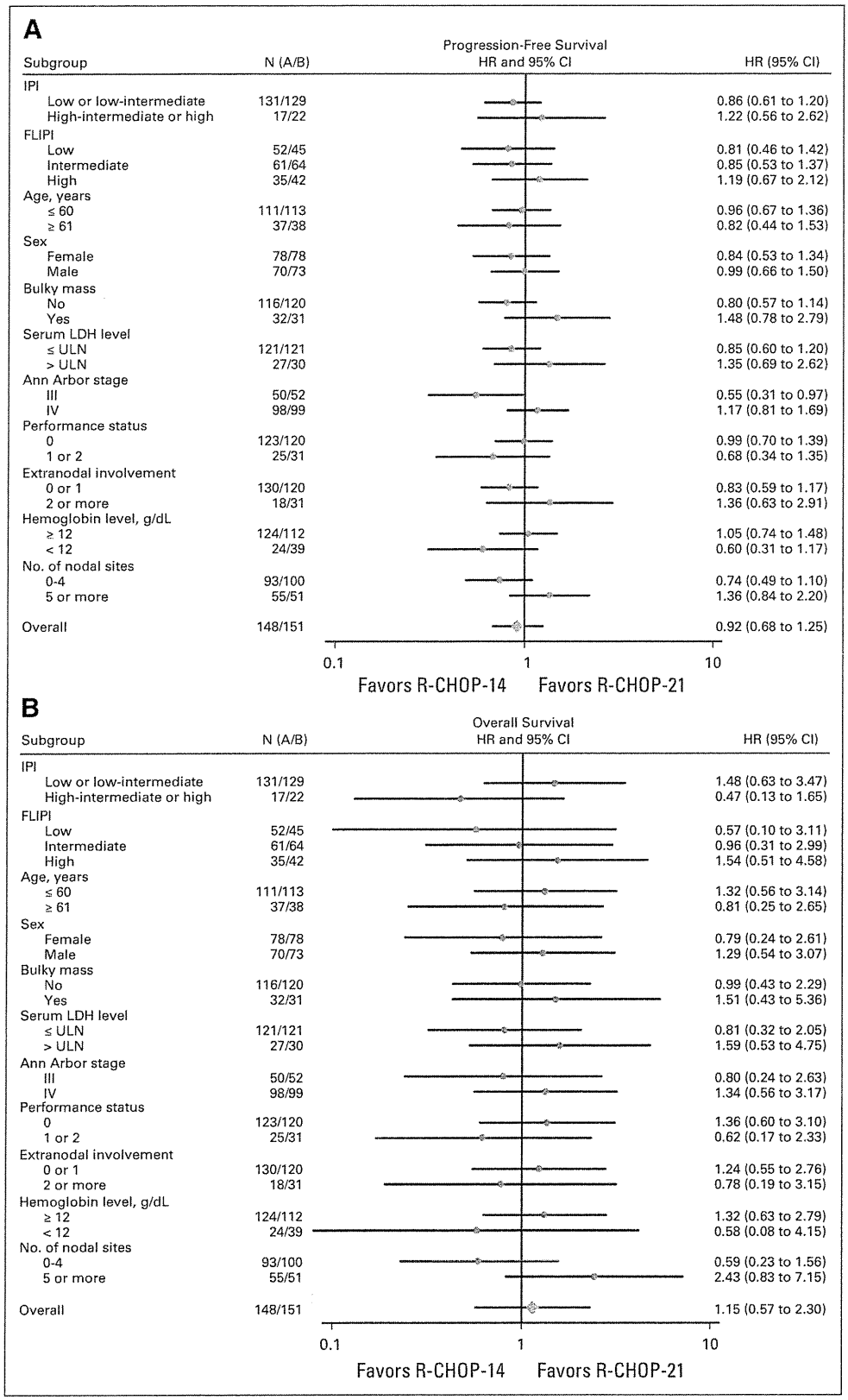

Fig 4. Forest plots of hazard ratios (HRs), comparing (A) progression-free survival and (B) overall survival among patients with previously untreated, advanced-stage indolent B-cell non-Hodgkin's lymphoma assigned to immunochemotherapy with either R-CHOP-14 (rituximab plus cyclophosphamide, doxorubicin, 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* ≥ 2	1.20	0.79 to 1.83	.39
Hemoglobin, $\geq$ 12 g/dL *v* < 12 g/dL	1.15	0.77 to 1.74	.49
No. of affected nodal areas, ≤ 4 *v* ≥ 5	1.25	0.89 to 1.76	.20

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

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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ORIGINAL ARTICLE

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

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Abstract The regimen of cyclophosphamide, doxorubicin, vincristine, and prednisolone, known as CHOP therapy, has been established as the standard treatment for aggressive non-Hodgkin's lymphoma (NHL). Although patients categorized as low (L) and low–intermediate (L–I) risk using the International Prognostic Index have favorable prognoses in Western countries, the efficacy and safety of CHOP therapy has not been prospectively evaluated in Japan. We conducted a phase II study of CHOP in L and L–I risk Japanese patients, evaluating overall survival (OS) as the primary endpoint. A total of 213 patients were enrolled and treated with eight courses of CHOP. Efficacy was evaluated in 168 eligible patients (L risk, 87; L–I risk, 81). Five-year OS rates in all eligible, L, and L–I risk patients were 68 % [95 % confidence interval (CI): 61–76 %], 73 % (95 % CI: 63–82 %), and 64 % (95 % CI: 53–74 %), respectively. The major toxicity observed was grade 4 neutropenia (64 %). Grade 4 non-hematological toxicities were observed as follows: one case each of paralytic ileus, convulsions, hypoxemia due to interstitial pneumonia, and reactivated fulminant hepatitis B. These results show reasonable efficacy and safety of the CHOP

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regimen in Japanese patients with lower risk aggressive NHL (UMIN-CTR Number C000000053).

Keywords Clinical trial · Aggressive lymphoma · Chemotherapy · CHOP

Introduction

The cyclophosphamide (CPM), doxorubicin (DXR), vincristine (VCR), prednisolone (CHOP) regimen was developed in the 1970s in the United States. Because CHOP yielded long-term survival in only 20–40 % of patients with advanced stage non-Hodgkin's lymphoma (NHL) [1], more intensive chemotherapies, referred to as second- and third-generation regimens, were devised [2–6]. It was reported that these chemotherapy regimens yielded higher complete response (CR) rates and longer survival in single arm, phase II studies [2, 3, 5].

Between February 1991 and March 1995, the Lymphoma Study Group of the Japan Clinical Oncology Group (JCOG-LSG) conducted a randomized phase III study (JCOG 9002) of the second- (mLSG4) and third-generation (LSG9) chemotherapy regimens [6]. The 5-year overall survival (OS) rates were 55 % with mLSG4 and 57 % with LSG9 (logrank $P = 0.42$), and there was no difference between the two arms in terms of toxicity [6].

In 1993, the results of a randomized phase III trial comparing the CHOP regimen with three second- or third-generation chemotherapies were reported as an intergroup study in the United States [7]. The outcome revealed equivalent OS with all four regimens, with the lowest toxicity reported for CHOP, demonstrating that this regimen remains the standard treatment for aggressive NHL.

In the same year, the International non-Hodgkin's Lymphoma Prognostic Factors Project identified five risk factors, designated as the International Prognostic Index (IPI), for predicting the prognosis of patients with aggressive NHL. IPI stratified patients into four groups on the basis of risk levels as follows: high risk (H), high–intermediate risk (H–I), low–intermediate risk (L–I), and low risk (L) [8]. According to IPI, 5-year OS in the H, H–I, L–I, and L groups was 26, 43, 51, and 73 %, respectively. Since then, a risk-adapted strategy has been considered a reasonable approach for the investigational treatment of aggressive NHL.

Until 1995, the safety and efficacy of the CHOP regimen had not been prospectively evaluated in multicenter trials in Japan. Thus, the JCOG-LSG planned prospective studies of the CHOP or dose-intensified CHOP regimen as an IPI risk-adapted therapy for aggressive NHL. In H and H–I risk patients, the JCOG-LSG planned two clinical trials: a randomized phase II trial comparing a dose-dense CHOP regimen (CHOP-14) with a dose-intensified CHOP regimen (high CHOP-21) and a phase II study of CHOP-14 followed by high-dose chemotherapy with autologous stem cell transplantation [9, 10]. In L and L–I risk patients, the JCOG-LSG conducted a phase II study of the CHOP regimen for the establishment of reference data in Japan.

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Patients and methods

Patients

Eligibility criteria were as follows: 15–69 years of age, L and L–I risk based on IPI, histopathological diagnosis of intermediate- or high-grade NHL, excluding mycosis fungoides, Sézary syndrome, adult T-cell leukemia–lymphoma (ATLL), and T-lymphoblastic lymphoma according to the Working Formulation [11], no previous treatment, stages I bulky (≥10 cm maximum diameter on computed tomography [CT] scans), II, III, or IV according to the Ann Arbor staging system [12–14], lesions evaluable by CT scanning, an Eastern Cooperative Oncology Group performance status (PS) of 0, 1, 2, or 3 [15], no involvement of the central nervous system, no other malignancies, adequate organ function as indicated by neutrophils ≥1200/μL, platelets ≥7.5 × 10^4/μL, asparate:2-oxoglutarate aminotransferase (AST) and alanine:2-oxoglutarate aminotransferase (ALT) levels ≤5 times the normal upper limit, serum creatinine ≤2.0 mg/dl, and total bilirubin ≤2.0 mg/dl. The exclusion criteria were as follows: severe infection; severe hepatic, pulmonary, psychological, or cardiac disease; and human immunodeficiency virus infection. All pathological and clinical data were evaluated before enrollment and a primary lymphoma lesion was determined if the lesion was the maximum mass of the patient's lesions, or determined according to each case history.

The protocol was approved by the Protocol Review Committee of JCOG and by the institutional review boards at each institution. Informed consent was obtained from all patients prior to enrollment in accordance with the Declaration of Helsinki.

Registration

Patients were centrally registered at the JCOG Data Center via telephone or fax after the assessment of inclusion and exclusion criteria. The Data Center was in charge of data management and central monitoring throughout the study.

Treatment

The CHOP regimen consisted of eight courses of CPM (750 mg/m^2), DXR (50 mg/m^2), VCR (1.4 mg/m^2, maximum 2 mg) intravenously on day 1, and oral prednisolone (100 mg/day) on days 1–5. The regimen was administered every 3 weeks up to eight courses if disease progression was not observed during treatment. Treatment was postponed if the pretreatment neutrophil count was <1200/μl or the platelet count was <7.5 × 10^4/μl, serum AST or ALT levels were >5 times the normal upper limit, serum creatinine was >2.0 mg/dl, total bilirubin was >2.0 mg/dl, or any non-hematological toxicity except nausea/vomiting and alopecia was >grade 1.

CPM and DXR doses were reduced to 75 % in the subsequent course if the following adverse events occurred: grade 4 leukopenia lasting for >2 days, platelet counts <5.0 × 10^4/μl, or neutropenic fever lasting >2 days. The DXR dose was reduced to 50 % in the subsequent courses if the bilirubin level was elevated from 1.2 mg/dl to ≤2.0 mg/dl, and was reduced to 75 % if ≥grade 2 mucositis occurred. In the event of DXR dose reduction, CHOP therapy was prolonged until the total dose of DXR reached 400 mg/m^2. The CPM dose was reduced to 75 % if ≥grade 2 hemorrhagic cystitis occurred. The VCR dose was reduced to 50 or 0 % in the event of grades 2 or 3/4 neurotoxicity, respectively. Prednisolone was excluded in patients with poorly controlled diabetes mellitus, active peptic ulcers, hepatitis B virus (HBV) surface antigen positivity, or hepatitis C virus antibody positivity. The protocol treatment was discontinued if cardiotoxicity ≥grade 2, grade 3 or greater heart failure, or an ejection fraction ≤40 % was observed. In addition, the protocol treatment was terminated if chemotherapy was delayed for more than 4 weeks or in the event of progressive disease (PD) or patient refusal.

In patients who had a bulky mass (≥10 cm maximum diameter on CT scan or a mediastinal mass covering more than one-third of the maximum intrathoracic dimension), involved-field radiotherapy (IFRT) of 30–40 Gy was administered after CHOP therapy was completed. IFRT was optionally administered to the region that contained initial masses ≥5 cm maximum diameter or to residual masses of uncertain CR (CRu).

Prophylactic use of 5HT3 antagonist, amphotericin B syrup, and trimethoprim-sulfamethoxazole was recommended. Transfusion was recommended when hemoglobin level or platelet count was decreased to <8.0 g/dl or 2 × 10^4/μl, respectively. The prophylactic use of granulocyte-colony stimulating factor (GCS-F) was not mandatory. G-CSF was delivered if needed in neutropenic fever or grade 4 neutropenia.

Central review of pathological diagnosis

Unstained 3-μm sections of biopsied specimens at initial diagnosis were collected. Hematoxylin–eosin and immunohistochemical staining were performed as previously described [9]. Briefly, anti-cluster of differentiation (CD)-3 and anti-CD20 antibodies were used for all patients, and the following antigens or molecules were additionally examined for further diagnosis: CD10, CD15, CD30, CD56, cyclin D1, BCL-2, TIA1, granzyme B, terminal deoxynucleotidyl transferase, anaplastic lymphoma kinase, and Epstein–Barr virus-encoded small RNAs. Specimens

were examined on the basis of the Working Formulation [11] and the third edition of the World Health Organization (WHO) classification [16, 17] by a central pathology review committee composed of six hematopathologists as listed in Acknowledgments.

Response and toxicity criteria

Tumor response was assessed on the basis of the WHO criteria [18] by CT scanning and bone marrow aspiration if necessary. CR was defined as disappearance of all clinical evidence of disease and normalization of all laboratory values and radiographic results lasting for at least 4 weeks. On the basis of the Cotswolds consensus report [14], patients with residual mass(es) were termed CRu, which denotes complete resolution of all disease with residual radiologic abnormalities (<50 % of initial volume) without signs of relapse or progression lasting for at least 3 months. Partial response (PR) was defined as a reduction of ≥50 % in the sum of the products of the cross-sectional diameters of all known lesions lasting for at least 4 weeks. PD was defined as the occurrence of new lesions, or as an increase of ≥25 % in the sum of the products of the cross-sectional diameters of all previously detected lesions. All other categories of tumor response were defined as no change.

Hematologic and non-hematologic toxicities were evaluated in all treated patients according to the toxicity grading criteria of JCOG [19], which is a modified and expanded version of the National Cancer Institute Common Toxicity Criteria version 1.0. Blood cell counts were examined once or twice every week, and clinical observations and other routine laboratory tests were performed weekly.

Endpoints and study design

The primary endpoint was OS in all eligible patients, which was calculated from the date of registration to death due to any cause or was censored at the last follow-up date. The secondary endpoints included toxicity, CR + CRu rate (%CR), and progression-free survival (PFS). Analysis of %CR was carried out using point estimates and 95 % confidence intervals (CIs). PFS was defined as the interval from the date of registration to the date of relapse, progression, or death due to any cause, and it was censored at the last follow-up date. OS and PFS were estimated using the Kaplan–Meier method, and the 5-year survival rate was measured as a 95 % CI using Greenwood's formula. As an exploratory method to investigate pretreatment prognostic factors for OS and PFS, Cox regression analysis was performed. All statistical analyses were carried out using the SAS software Release 8.1 (SAS Institute Inc., Cary, NC, USA).

We hypothesized that the 5-year OS would be equivalent to that of our previous second-generation chemotherapy LSG4 in JCOG8701 [20]. From the retrospective subgroup analysis of JCOG8701, the 5-year OS in 132 L and L–I risk patients (except ATLL) was 64 %. The sample included 158 eligible patients so that the 95 % CI for the estimated 5-year OS would be ±7.5 % of the expected value of 64 %, and a projected accrual was set at 160 patients.

All case report forms were collected and managed at the JCOG Data Center (JCOG-DC). In-house interim monitoring was performed at the JCOG-DC for quality control, and the monitoring reports were submitted to and reviewed by the Data and Safety Monitoring Committee of the JCOG on a semi-annual basis.

Results

Patient characteristics

A total of 213 patients were enrolled between June 1995 and May 1999. In the L risk group, registration was completed in July 1997 when the number of accrued patients reached 119. Registration in the L–I risk group was continued up to May 1999, until a total of 94 patients were enrolled.

Clinical characteristics of patients are shown in Table 1. The median age was 55 years and the male-to-female ratio was approximately 1.4:1. The proportion of patients in clinical stage III or IV was 54 %, and there were 11 patients with PS 2 or 3 (5 %).

The ratio of nodal to extranodal onset was approximately 4.2:1. Frequent primary sites were the cervical lymph nodes (39 %), Waldeyer's ring (14 %), and the retroperitoneal lymph nodes (13 %). A bulky mass (≥10 cm) was detected in 38 (18 %) patients.

Pathological characteristics

A central review of the pathological diagnosis was performed on 195 of 213 enrolled patients (92 %). The diagnoses according to the third edition of the WHO classification and Working Formulation are shown in Table 2. The most common subtype was diffuse large B-cell lymphoma (DLBCL) (64 %). Other B-cell lymphomas were confirmed in 44 patients (23 %). The proportion of patients with T-cell and NK-cell lymphoma was small (9 %), and the pathological subtypes were variable in these patients.

Clinically and pathologically eligible patients

Five patients were judged to be clinically ineligible due to H–I risk ($n = 3$), non-bulky stage I disease ($n = 1$), and

Table 1 Patients characteristics

Age	
Median (range)	55 (17–69)
Sex	
Male	126 (59 %)
Female	87 (41 %)
IPI	
Low	118 (55 %)
Low–Int	92 (43 %)
High–Int	3 (1 %)
High	0
PS	
0	131 (62 %)
1	71 (33 %)
2	10 (5 %)
3	1 (0.5 %)
Clinical stage	
I	14 (7 %)
II	84 (39 %)
III	58 (27 %)
IV	57 (27 %)
B symptom	
Yes	42 (20 %)
Primary site	
Nodal	172 (81 %)
Extranodal	41 (19 %)
Maximum tumor size	
<5 cm	109 (51 %)
≥5 cm, <10 cm	66 (31 %)
≥10 cm	38 (18 %)

Table 2 Histopathology of central review in 195 patients based on WHO classification and Working Formulation

WHO classification	
B-cell lymphoma: 168 (86 %)	
Diffuse large B-cell	124
Follicular grade 1, 2[a]	13
Follicular large with diffuse area	8
Mantle cell	7
Extranodal marginal zone of MALT	5
Mediastinal (thymic) large B-cell	3
CLL/SLL[a]	1
Marginal zone	1
Unclassified	6
T-cell and NK-cell lymphoma: 18 (9 %)	
Peripheral T cell	7
Angioimmunoblstic T cell	3
NK/T cell, nasal type	3
Anaplastic large cell	2
Subcutaneous panniculitis-like T cell	1
Enteropathy-type T cell	1
T lymphoblastic[a]	1
Non-B, non-T, non-NK lymphoma: 6 (3 %)	
Non-B, non-T lymphoma-large	1
Hodgkin's lymphoma[a]	4
Dysplastic lesion	1
Miscellaneous: 3 (2 %)	
Non-hematopoietic neoplasm[a]	1
Others[a]	2
Working Formulation	
Small lymphocytic[a]	1
Follicular small cleaved[a]	2
Follicular mixed[a]	9
Follicular large	10
Diffuse medium	10
Diffuse mixed	18
Diffuse large	123
Immunoblastic	5
Lymphoblastic[a]	1
Small non-cleaved	2
Miscellaneous	6
Dysplastic lesion[a]	1
Others[a]	7

[a] Ineligible type

MALT Mucosa-associated lymphoid tissue

CLL/SLL Chronic lymphocytic leukemia/small lymphocytic lymphoma

history of prior treatment ($n = 1$). For the pathological central review, 18 of 213 enrolled patients could not be examined because of loss of biopsied specimens. Twenty-two (11 %) of 195 patients were judged to be histopathologically ineligible: 13 with follicular lymphoma, 4 with Hodgkin lymphoma, 1 with chronic lymphocytic leukemia/small lymphocytic lymphoma, 1 with T-cell lymphoblastic lymphoma, and 3 with miscellaneous diseases. Finally, a total of 168 clinically and pathologically eligible patients were assessed for response and survival.

Responses and survival of clinically and pathologically eligible patients

Efficacy of CHOP was evaluated and analyzed in 168 clinically and pathologically eligible patients (87 with L risk and 81 with L–I risk). The %CR (95 % CI) of all 168 patients after CHOP and IFRT was 80 % (73–86 %). In the L risk group and the L–I risk group, %CR (95 % CI) after CHOP and IFRT was 85 % (76–92 %) and 74 % (63–83 %), respectively (Table 3).

After 6.3 years (range, 0.4–9.1 years) of the median follow-up period, the estimated 5-year OS (95 % CI) of all

Table 3 Response rate in pathological eligible patients after CHOP and after radiotherapy

	Low		Low–Int		L + LI	
	n	(%)	*n*	(%)	*n*	(%)
After CHOP						
CR	68	78	56	69	124	74
CRu	2	2	4	5	6	4
PR	7	8	6	7	13	8
NR	2	2	1	1	3	2
PD	5	6	12	15	17	10
NE	3	3	2	2	5	3
Total	87	100	81	100	168	100
CR + CRu (95 % CI)		80 (71–88)		74 (63–83)		77 (70–84)
After radiotherapy						
CR	70	80	56	69	126	75
CRu	4	5	4	5	8	5
PR	2	2	6	7	8	5
NR	2	2	1	1	3	2
PD	6	7	12	15	18	11
NE	3	3	2	2	5	3
Total	87	100	81	100	168	100
CR + CRu (95 % CI)		85 (76–92)		74 (63–83)		80 (73–86)

168 patients was 68 % (61–76 %), and that of L risk and L–I risk patients was estimated to be 73 % (63–82 %) and 64 % (53–74 %), respectively. (Fig. 1a) The estimated 5-year PFS (95 % CI) of 168 patients, L risk patients, and L–I risk patients was 52 % (44–59 %), 62 % (52–73 %), and 40 % (29–50 %), respectively (Fig. 1b).

In 31 patients with bulky disease, 20 patients completed CHOP and 10 patients received IFRT. After IFRT, 8 patients showed a CR and 1 patient showed a PR. One patient showed PD. A total of 54 patients had an initial semi-bulky mass between 5 and 10 cm. Among them, 45 patients completed CHOP, 11 of whom received IFRT and were CR or CRu.

Response and survival in patients with DLBCL

Of the pathologically eligible patients with DLBCL, 115 were DLBCL, not otherwise specified (NOS). Their %CR (95 % CI) was 74 % (65–82 %) after CHOP and 77 % (68–84 %) after IFRT. The %CR in L and L–I risk patients after CHOP therapy was 74 % (60–85 %) and 74 % (61–84 %), respectively. After IFRT, the %CR (95 % CI) in L and L–I risk patients was 80 % (67–89 %) and 74 % (61–84 %), respectively.

The 5-year OS (95 % CI) in the entire group, L risk group, and L–I risk group of DLBCL-NOS patients was 68 % (59–76 %), 71 % (58–83 %), and 65 % (53–77 %), respectively (Fig. 2a). The 5-year PFS (95 % CI) in these three groups was 53 % (43–62 %), 64 % (51–77 %), and 43 % (30–56 %), respectively (Fig. 2b).

Toxicity

Of the 213 patients treated, 172 (81 %) completed eight courses of CHOP. The reasons for discontinuing treatment in the remaining patients were as follows: PD ($n = 19$, 9 %), toxicity ($n = 5$, 2 %), patient refusal ($n = 8$, 4 %), death ($n = 1$, 0.5 %), evidence of ineligibility after the start of protocol treatment ($n = 2$, 1 %), protocol violation ($n = 2$, 1 %), and other reasons ($n = 4$, 2 %).

Because the medical records of 1 patient were misplaced, toxicities were evaluated in 212 patients (Table 4). Regarding hematological toxicities, grade 4 leukopenia and neutropenia occurred in 55 (26 %) and 136 (64 %) patients, respectively, and most patients (88 %) experienced grade 3 or 4 neutropenia. However, grade 3 anemia and grades 3 or 4 thrombocytopenia were rare.

Grade 4 non-hematological toxicities were observed in 4 patients (paralytic ileus, convulsions, elevation of ALT, and hypoxemia due to interstitial pneumonia). The most frequent grade 3 non-hematological toxicity was elevation of ALT in 18 patients (8 %). However, the frequency of nausea/vomiting (3 %), infection (2 %), and peripheral neuropathy (3 %) was low.

Of the 2 HBV carrier patients, 1 completed the protocol treatment without significant hepatitis, and the other died

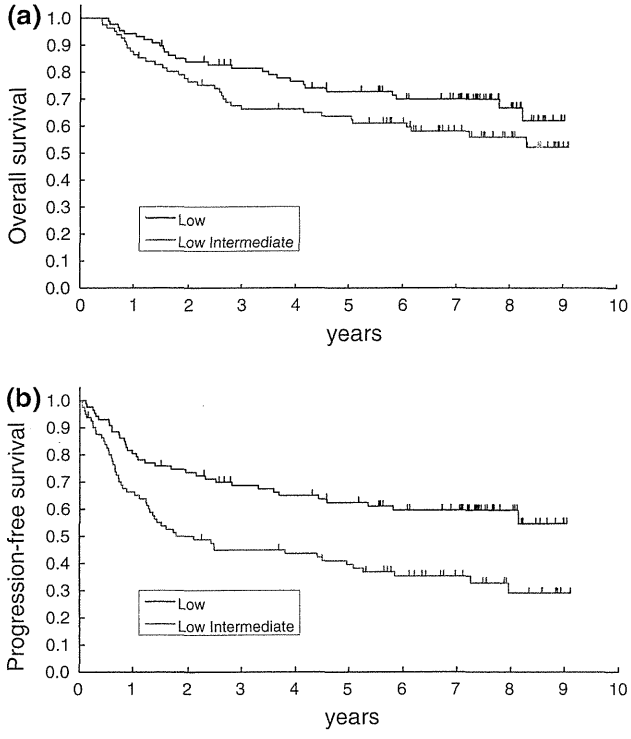

Fig. 1 Kaplan–Meier estimate of OS and PFS for pathologically eligible patients. **a** OS curves for patients in each risk category. The 5-year OS (95 % CI) in L risk and L–I risk cases was 73 % (63–82 %) and 64 % (53–74 %), respectively. **b** PFS curves for patients in each risk category. The 5-year PFS (95 % CI) in L risk and L–I risk patients was 62 % (52–73 %) and 40 % (29–50 %), respectively

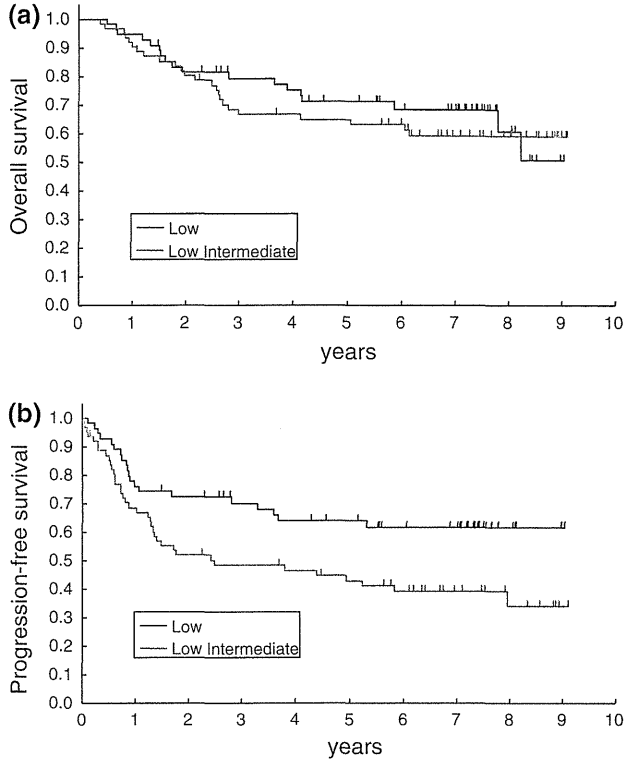

Fig. 2 Kaplan–Meier estimate of OS and PFS for DLBCL-NOS patients. **a** OS curves for patients in each risk category. The 5-year OS (95 % CI) in L risk and L–I risk patients was 71 % (58–83 %) and 65 % (53–77 %), respectively. **b** PFS curves for patients in each risk category. The 5-year PFS (95 % CI) in L risk and L–I risk patients was 64 % (51–77 %) and 43 % (30–56 %), respectively

from fulminant hepatitis, even though prednisolone was not administered and chemotherapy was discontinued when hepatic function became aggravated. Within 9 years from the first registration, secondary malignancies occurred in 5 patients (2 %), 2 of whom developed gastric cancer. Of the remaining 3, 1 each developed breast cancer, hepatocellular carcinoma, and cholangiocarcinoma.

Prognostic factors

To investigate other prognostic factors not included in IPI, Cox multivariate regression analyses were carried out to determine OS and PFS with the prognostic factors in Table 1 (Table 5). In OS, only IPI was statistically significant, and in PFS, IPI and B symptoms were significant.

Discussion

In this prospective multicenter phase II trial in Japan, we have shown the reasonable efficacy and safety of the CHOP regimen in Japanese L and L–I risk patients with newly diagnosed aggressive NHL for the first time. In the L risk patients, the %CR and 5-year OS were 85 and 73 %, respectively, which were similar to the %CR (87 %) and 5-year OS (73 %) reported in the IPI project [8]. However, the %CR (74 %) and 5-year OS (64 %) in the L–I risk patients in the present study were superior to the %CR (67 %) and 5-year OS (51 %) in the IPI project. In the present study, the proportion of patients >60 years of age was smaller than that in the IPI project (30 vs. 41 %, respectively). This fact may have contributed to the better OS of the L–I risk group in the present study.

The German High-Grade non-Hodgkin's Lymphoma Study Group (DSHNHL) conducted a randomized phase III trial (NHL-B1) to compare CHOP-21 or CHOP with etoposide (CHOEP)-21 with CHOP-14 or CHOEP-14 in younger patients younger than 60 years with lower risk aggressive NHL [21]. The proportion of B-cell lymphoma, DLBCL, and T-cell lymphoma was 85.8, 59.8 and 13.7 %, respectively, which was similar to the present study. Although the proportion of L risk was much higher (L risk, 64.8 %; L–I risk, 35.2 %), the CR rate and 5-year event-free survival of CHOP-21 were 80.1 and 54.7 %, respectively, which were comparable to those in the present

Table 4 Adverse toxicity

Grade (%)	1	2	3	4
Hematological				
Leukopenia	4	20	48	26
Anemia	23	38	5	–
Neutropenia	1	8	24	64
Thrombopenia	13	5	2	1
Non-hematological				
Infection	27	16	2	0
Nausea, vomiting	46	16	3	–
Diarrhea	13	3	1	0
Stomatitis	22	4	0.5	0
Arrhythmia	4	1	0.5	0
Dyspnea	2	1	0.5	0
Peripheral neuropathy	59	13	3	–
Constipation, paralytic ileus	35	6	2	0.5
Fever	13	7	0.5	0
Bilirubin	–	16	1	0
AST	35	9	4	0
ALT	40	12	8	0.5
Creatinine	8	1	0.5	0
Hypoxia	39	4	1	0.5

Table 5 Cox regression analysis: prognostic factors in OS and PFS

Factor	*P* value	Hazard ratio	95 % CI
OS			
IPI: LI (vs. L)	0.04	1.60	1.01–2.52
Sex: male (vs. female)	0.86	1.04	0.65–1.66
Maximum tumor diameter: ≥5 cm (vs. <5 cm)	0.80	0.94	0.60–1.49
Primary site: nodal (vs. extranodal)	0.52	0.83	0.47–1.47
B symptom: + (vs. −)	0.07	1.65	0.96–2.83
PFS			
IPI: LI (vs. L)	<0.01	1.78	1.23–2.58
Sex: male (vs. female)	0.80	0.95	0.65–1.39
Maximum tumor diameter: ≥5 cm (vs. <5 cm)	0.60	1.11	0.76–1.61
Primary site: nodal (vs. extranodal)	0.99	1.00	0.62–1.62
B symptom: + (vs. −)	0.01	1.86	1.20–2.88

study. The 5-year OS 74.9 % seems to be superior to the present study. This finding may be due to the higher proportion of younger subjects and their lower risk status.

High-dose chemotherapy (HDT) with autologous hematopoietic stem cell transplantation (auto HSCT) is the standard of care in patients of age younger than 65 years with first relapsed aggressive NHL [22]. In the present study, 83 of 168 eligible patients relapsed, and their median age at progression was 57 (range 19–71) years. HDT with auto HSCT was done in 14 relapsed or refractory patients, and 11 of them relapsed. The low proportion of HDT with auto-HSCT in patients with relapsed or refractory disease after the protocol treatment in the present study might imply that salvage chemotherapy followed by auto-HSCT had less impact on OS.

Although the sample size of the present study was calculated from the survival data of JCOG8701, more detailed data for comparison has not yet been analyzed. We compared the survival data of the present study with that of the previous randomized phase III study (JCOG9002), which showed no statistical difference in survival between mLSG4 and LSG9 [6]. In the subgroup analysis, 5-year OS (95 % CI) of L risk patients was 74 % (65–84 %) with mLSG4 and 74 % (64–83 %) with LSG9, which is comparable to the value of 73 % (63–82 %) with CHOP reported in the present study. On the other hand, 5-year OS (95 % CI) of L–I risk patients was 56 % (42–71 %) with mLSG4 and 48 % (35–60 %) with LSG9, which is not superior to the value of 64 % (53–74 %) with CHOP reported in the present study. In a randomized study of CHOP with third-generation regimens in the Nordic Lymphoma Group, 5-year OS of all the L and L–I risk patients was 72 %, which is comparable to that of the present study [23]. These results suggest that the efficacy of CHOP therapy in Japanese patients with L and L–I risk of aggressive NHL is equivalent to that of second- or third-generation therapies.

The proportion of DLBCL in the present study was 64 %, which is comparable with that of JCOG9002 (58 %). Recently, the therapeutic outcome of DLBCL patients has clearly improved due to the combined use of the anti-CD20 antibody (rituximab), and rituximab-CHOP has become the standard treatment for DLBCL according to the Groupe d'Etude des Lymphomes de l'Adulte (GELA) study [23] and the Mabthera International (MInT) trial [24]. In the GELA study [23], L and L–I risk patients aged between 60 and 80 years were administered CHOP with or without rituximab, and the 5-year OS for the two groups was 80 and 62 %, respectively. In the MInT trial [24], which was a randomized study where L and L–I patients aged between 18 and 60 years were administered CHOP-like chemotherapy with or without rituximab, 3-year OS was 93 and 84 %, respectively. The OS data of the present study, combined with the data from the CHOP arm of the abovementioned randomized studies, is potential reference data for DLBCL in the rituximab era in Japan.

Analysis of prognostic factors confirmed that the IPI score or individual factors of IPI independently influenced both OS and PFS (Table 5). Furthermore, the presence of B symptoms also affected PFS. Previously, B symptoms were reported to be a poor prognostic factor in several studies that included all risk patients [25–27]. Further validation

analysis may be necessary to decide the prognostic significance of B symptoms in L and L–I risk patients.

The major adverse events of CHOP therapy observed in this study were hematological toxicities. While grade 3 anemia and grade 3/4 thrombocytopenia occurred in 2 and 3 % of patients, respectively, grade 4 neutropenia occurred in 64 %, which was similar to the occurrence rates with mLSG4 (62 %) and LSG9 (51 %) [6]. Major grade 3/4 non-hematological toxicities were gastrointestinal (0–3 %), hepatic (1–9 %), and peripheral nerve related (2–3 %). The frequency of grade 3/4 infection or fever was <3 %.

In the present study, the incidence of grade 3/4 non-hematological toxicity with CHOP was lower than that with mLSG4 or LSG9 [6]. Non-hematological grade 4 toxicities were limited to 1 case each of paralytic ileus, convulsion, hypoxemia due to interstitial pneumonia, and fulminant hepatitis. Of these, 1 treatment-related death from fulminant hepatitis was caused in an HBV surface antigen-positive patient. Because of this adverse event, HBV antigen positivity was added to the exclusion criteria of the JCOG-LSG trials.

In conclusion, we demonstrated the reasonable efficacy and acceptable toxicity profiles of CHOP and post-chemotherapeutic IFRT in previously untreated Japanese patients with L and L–I risk advanced, (stage I bulky, II, III or IV) aggressive NHL. This data will provide the basis for future clinical trials and serve as reference data for CHOP therapy in Japan.

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Conflict of interst None.

Appendix

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ORIGINAL ARTICLE

Phase II study of ABVd therapy for newly diagnosed clinical stage II–IV Hodgkin lymphoma: Japan Clinical Oncology Group study (JCOG 9305)

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Abstract Although ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) therapy has been regarded as a standard of care for advanced-stage Hodgkin lymphoma (HL) since 1992, there has been no prospective data of ABVD therapy in Japan. To investigate the efficacy and safety of ABVd therapy with the lower dose of dacarbazine (250 mg/m^2) in patients with newly diagnosed stage II–IV HL, Lymphoma Study Group of Japan Clinical Oncology Group conducted a phase II study. The primary endpoints were complete response rate (%CR) and progression-free survival (PFS). A total of 128 patients with age less than 70 years were enrolled and received 6–8 cycles of ABVd followed by radiation to initial bulky mass. The %CR in 118 eligible patients was 81.4% [95% confidence interval (CI) 73.1–87.9%]. Major toxicity was grade 4 neutropenia (45.3%). Grade 3 nausea/vomiting was the most frequent non-hematological toxicity (10.9%). Transient grade 4 constipation, infection (abscess), hypoxemia and hyperbilirubinemia were observed in 4 patients. No treatment-related death was observed. PFS and overall survival at

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5 years were 78.4% (95% CI 70.9–85.9%) and 91.3% (95% CI 86.1–96.5%), respectively. In conclusion, ABVd is effective in Japanese patients with stage II–IV HL with acceptable toxicities (UMIN-CTR Number: C000000092).

Keywords Hodgkin lymphoma · Chemotherapy · ABVd therapy · Phase II study

1 Introduction

Since the development of two representative curative combination chemotherapy regimens for advanced Hodgkin lymphoma (HL), MOPP regimen (mechlorethamine, vincristine, procarbazine, and prednisone) and ABVD regimen (doxorubicin, bleomycin, vinblastine, and dacarbazine) [1–4], several randomized trials were performed to establish the standard chemotherapy for advanced HL. The ABVD has partial non-cross resistance with MOPP [3, 4], and less pronounced long-term toxicity, causing neither sterility nor premature menopause and being less leukemogenic [5–7]. Hybrid or alternating combinations of MOPP and ABVD were widely tested in the 1980s and shown superior to MOPP by virtue of curing approximately 10–15% more patients [8, 9]. As a landmark randomized phase III trial, the Cancer and Leukemia Group B (CALGB) compared MOPP, ABVD and MOPP/ABVD in advanced HL (stages $IIIA_2$, IIIB, IVA, IVB) [7]. Both ABVD and MOPP/ABVD were superior to MOPP in terms of failure-free survival. Although there was no statistically significant difference in overall survival (OS) across the three arms, this no difference might be partly explained by secondary treatments. These results were confirmed in a large intergroup study in which the MOPP/ABV hybrid regimen was tested against ABVD [9]. This trial enrolled 856 patients and found no differences in complete response rate, freedom from treatment failure or OS. The most reasonable conclusion to draw from this series of trials is that ABVD presently demonstrates the best combination in terms of efficacy and toxicity and should be considered the standard of care for advanced-stage HL.

In Japan, the incidence of HL is approximately one-third of that in Western countries [10, 11], and key drugs such as mechlorethamine and dacarbazine used in MOPP or ABVD were not approved by Japanese government for clinical use to HL even in 1990s. Therefore, there have been few prospective multi-institutional trials for HL in Japan. From October 1989 to February 1993 in that historical background, the Lymphoma Study Group of Japan Clinical Oncology Group (JCOG-LSG) conducted a phase II study

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(JCOG8905) of alternating combination chemotherapy of C-MOPP (cyclophosphamide, vincristine, procarbazine, and prednisolone) and ABVd with the lower dose of dacarbazine (doxorubicin 25 mg/m^2, days 1 and 15, bleomycin 9 mg/m^2 with the upper limit dose of 15 mg, days 1 and 15, vinblastine 6 mg/m^2 with the upper limit dose of 10 mg, days 1 and 15, and dacarbazine 250 mg/m^2, days 1 and 15) [12]. The dose of dacarbazine in ABVd had to be reduced to a two-thirds (250 mg/m^2) of that in original ABVD regimen due to intolerable severe emesis in a pilot study at that time. The progression-free survival (PFS) at 4 years of the patients with stage III or IV in JCOG8905 for Japanese patients with advanced-stage HL and that at 5 years in MOPP/ABVD in CALGB study was 65.7 and 65%, respectively [7, 12]. Because the efficacy of C-MOPP/ABVd in JCOG8905 study was thus excellent and is considered almost equivalent to that of MOPP/ABVD in the Western countries [7, 8], ABVd regimen is supposed to be as effective as original ABVD regimen. After the publication of the landmark randomized phase III trial by CALGB [7], JCOG-LSG decided to conduct a multi-institutional phase II study to investigate the efficacy and safety and to create the reference data of ABVd therapy for the Japanese patients with newly diagnosed HL with stages II–IV, although dacarbazine was administered in off-label use.

2 Patients and methods

2.1 Patients

A total of 128 patients with newly diagnosed HL were enrolled from 35 institutions listed in Appendix, between December 1993 and June 1997. Eligibility criteria included: ages less than 70 years; a histopathologic diagnosis of HL according to the Rye classification [13]; no previous treatment, stages II, III or IV disease according to the Ann Arbor staging system [14] and the Cotswolds system [15]; evaluable lesions by computed tomography (CT) scan; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, 2 or 3 [16]; having no other malignancies, no major organ dysfunction [neutrophils $\geq$ 1,500/μL, platelets $\geq 10 \times 10^4$/μL, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) $\leq$ 2 times normal upper limit, blood urea nitrogen (BUN) $\leq$ 1.25 times normal upper limit, creatinine $\leq$ 1.25 times normal upper limit and $PaO_2 \geq 70$ mmHg, ejection fraction (EF) $\geq$ 50%] and no complication of severe infection, severe hepatic, pulmonary, psychological or cardiac disease such as myocardial infarction.

The present trial was a prospective, multi-institutional phase II study conducted by JCOG-LSG. The protocol was approved by the Protocol Review Committee of the JCOG and by the institutional review boards at each institution. Written or oral informed consent was obtained from each patient before enrollment.

2.2 Treatment

The ABVd regimen consists of 6–8 cycles of the intermittent administration of doxorubicin (25 mg/m^2), bleomycin (9 mg/m^2 with the upper limit dose of 15 mg), vinblastine (6 mg/m^2 with the upper limit dose of 10 mg), and dacarbazine (250 mg/m^2), administered simultaneously as intravenous injections on days 1 and 15 of each cycle, and one cycle takes 4 weeks. The dose of dacarbazine is the two-thirds of that in original ABVD regimen [3]. The treatment was scheduled to give 6 or 7–8 cycles of ABVd, if complete response (CR) was obtained after 1–4 or 5–6 cycles, respectively. In 7 and 8 cycles, bleomycin was omitted. For patients of age $\geq$60 years, or for those with planned mediastinal radiation therapy after ABVd therapy due to bulky mass at initial presentation, bleomycin was omitted in 5th or later cycles. If the pretreatment leukocyte and/or platelet count was less than 2,500/μL and 7.5×10^4/μL, respectively, or serum AST/ALT and/or total bilirubin was more than 4 times normal upper limit and more than 2 mg/dL, respectively, treatment was postponed for at least 1 week or until recovery. Vinblastine was temporarily discontinued if signs of grade 3 or greater sensory neurotoxicity or grade 4 constipation appeared. Doxorubicin was discontinued if cardiac hypofunction (ejection fraction $\leq$ 40%), arrhythmia or heart failure appeared. Bleomycin was stopped if the PaO_2 level decreased under 70 mmHg or by more than 10 mmHg from the prior level. Bulky (maximum diameter $\geq$ 10 cm) tumors at initial presentation were irradiated after completion of chemotherapy at 30–40 Gy. Although as a rule, radiation therapy was indicated for the patients with bulky mass in CR at the end of chemotherapy, some patients who achieved PR after 6 cycles of ABVd therapy received

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radiation therapy. We did not define the use of any antiemetic drugs.

2.3 Central review of the pathological diagnosis

Thin-layer slide preparations of lymphoma tissues obtained at the initial diagnosis were collected. These specimens were stained with hematoxylin–eosin. In addition, immunohistochemical analyses were conducted on paraffin sections by means of the avidin–biotin–peroxidase complex technique and a panel of the monoclonal antibodies. Antibodies that were routinely employed in the central review of the pathological diagnosis were for CD3, CD20, CD15, and CD30. When further immunohistochemical stainings were necessary for differential diagnosis, antibodies to the following antigens were also used: CD79a, CD5, cyclinD1, CD10, bcl-2, CD56. Epstein–Barr virus was investigated by in situ hybridization or anti-P80 antibody if necessary. Preparations stained with hematoxylin–eosin and immunohistochemically were microscopically examined by a central pathology review committee composed of the six hemato-pathologists and one hematologist as listed in Appendix according to the World Health Organization (WHO) classification, version 2 [17]. The diagnosis by the central pathological review committee was used in this paper.

2.4 Response and toxicity criteria

The tumor response was assessed according to the WHO criteria [18]. The response was evaluated by CT scanning and gallium scintigraphy, and, if necessary, by bone marrow aspiration. CR was defined as disappearance of all clinical evidence of disease and normalization of all laboratory values and radiographic results lasting for at least 4 weeks. Patients with residual mass (es) were termed uncertain CR (CRu), which denotes complete resolution of all diseases but residual radiologic abnormalities (<50% of initial volume) of uncertain significance without any signs or symptoms of relapse or regrowth for at least 3 months, based on the Cotswold consensus report [15]. Partial response (PR) was defined as a reduction of 50% or more in the sum of the products of the cross-sectional diameters of all known lesions lasting for at least 4 weeks. Progressive disease (PD) was defined as the occurrence of new lesions, or as an increase of 50% or more in the sum of the products of the cross-sectional diameters of all previously detected lesions. All other categories of tumor response were defined as no change (NC).

Hematologic and non-hematologic toxicities were evaluated in all treated patients according to the toxicity grading criteria of the Japan Clinical Oncology Group (JCOG) [19], which is an expanded and modified version of the National Cancer Institute (NCI) Common Toxicity Criteria version 1.0. Blood cell counts were examined once or twice a week, and clinical observation and other routine laboratory tests were performed weekly.

2.5 Statistical analysis and endpoints

The primary endpoints were the CR rate (CR + CRu) and PFS in all eligible patients, defined as an interval from the date of registration to the date of relapse or progression, death due to any cause or date of the last follow-up date. The secondary endpoints were toxicity, overall response rate (ORR) (CR + CRu + PR), and 5-year OS rate. Survival was calculated from the date of registration to death due to any cause or the last follow-up date. Analysis of the CR rate and ORR was carried out using point estimates and the 95% confidence interval (CI). The OS and PFS were determined according to the Kaplan–Meier method, and 5-year survival rate was employed to estimate the 95% CI. Sample size was determined by the precision based to attain a 15% width of 95% CI of CR rate for each stage II and III + IV subgroups with expecting 80% of CR. Assuming 10% ineligible patients based on the central pathology review, at least 90 patients were required. The analyses were carried out with the SAS release 9.1 (Carry, NC).

3 Results

3.1 Pathological characteristics

Central review of pathological diagnosis was performed on 116 of 128 enrolled patients, and pathological diagnosis on each institute was adopted in the remaining 12 patients. As shown in Table 1, among 128 enrolled patients, 9 patients revealed to be ineligible by the central pathology review: 2 patients with histiocytic neoplasms, 7 with non-Hodgkin lymphoma including 5 with diffuse large cell lymphoma (3 with T cell rich B cell lymphoma subtype, one with anaplastic large B cell lymphoma subtype and one with not otherwise specified type), one with composite lymphoma and one with angioimmunoblastic T cell lymphoma.

The histological distribution of 102 patients in which histological subtype was determined by the central pathological review is also shown in Table 1. Nodular sclerosis ($n = 71$) represented 69.6% of the 102 patients of HL and mixed cellularity ($n = 23$; 22.5%) was the next common subtype. One (1.0%) had nodular lymphocyte predominance, four (3.9%) had lymphocyte depletion, three (2.9%) had lymphocyte-rich classical HL. These histological distributions were similar to those in western countries [20].

Pathologically eligible patients including subtype unclassified or undetermined accounted for 92.9% (119 of

Table 1 Central review of pathological diagnosis and distribution of histological subtype

Pathological diagnosis	Enrolled ($n = 128$)	Subtype[a] ($n = 102$)	Eligible ($n = 118$)
NLPHL	1	1 (1.0%)	1 (0.8%)
Nodular sclerosis	71	71 (69.6%)	71 (60.2%)
Mixed cellularity	23	23 (22.5%)	22 (18.6%)[b]
LRCHL	3	3 (2.9%)	3 (2.5%)
LD	4	4 (3.9%)	4 (3.4%)
Subtype unclassified/ undetermined	17		17 (14.4%)
Other neoplasms	9 (7.0%)		

NLPHL nodular lymphocyte predominance Hodgkin lymphoma, *LRCHL* lymphocyte-rich classical Hodgkin lymphoma, *LD* lymphocyte depletion

[a] Subtype distribution of the patients diagnosed by the central review

[b] One of 23 patients with mixed cellularity subtype was ineligible due to non-bulky stage I

128 patients), but one case was ineligible because of bulky stage I. Thus, a total of 118 patients were finally decided to be eligible in this study. The histological distribution of 118 eligible patients is also shown in the right column of Table 1. As subtype was unclassified or undetermined due to poor specimens for diagnosis or no available slides in 17 patients (14.4% of 118), each distribution rate of histological subtype was lowered at that rate.

3.2 Patient characteristics

The clinical characteristics of the 118 eligible patients are shown in Table 2. In eligible patients, the median age was 32.5 years, and the male:female was 66:52. B symptoms at entry were observed in 46 (39.0%) patients. Majority of PS in eligible patients was 0, or 1. Bulky disease with a maximum diameter $\geq$10 cm was present in 24 patients (20.3%). Localized disease (stage IIA non-bulky) and advanced disease (stage IIA bulky, IIB, III or IV) were present in 39 patients (33.1%), and 79 (66.9%), respectively. In a total of 49 patients with stage IIA, 10 patients were stage IIA bulky. Retrospectively, we analyzed the International Prognostic Score (IPS) [21] in all eligible patients. The numbers of patients with IPS of 0–2, and 3 or higher were 78 (66.1%) and 40 (33.9%), respectively.

3.3 Toxicities

All 128 patients treated were evaluated for toxicity. Eighty patients (62.5%) were treated with 6 cycles of ABVd and 5 (3.9%) and 21 (16.4%) were treated with 7 cycles and 8 cycles of ABVd, respectively. Twenty-two patients (17.2%) were treated with less than 6 cycles of ABVd.

Table 2 Patient characteristics

Characteristic	Eligible patients ($n = 118$)
Age	
Median	32.5 years
Range	15–69
Male sex	66 (55.9%)
PS	
0	75 (63.6%)
1	34 (28.8%)
2	7 (5.9%)
3	0
ND#	2
Clinical stage	
I[a]	0
II	61 (51.7%)
IIA non-bulky	39 (33.1%)
IIA bulky, IIB	22 (18.6%)
III	28 (23.7%)
IV	29 (24.6%)
Bulky mass	24 (20.3%)
B symptoms	46 (39.0%)
International Prognostic Score	
0	12 (10.2%)
1	34 (28.8%)
2	32 (27.1%)
3	20 (16.9%)
4	15 (12.7%)
5	4 (3.4%)
6	1 (0.8%)
7	0

ND# no data collected

[a] Ineligible because of stage I

A total of 24 patients (18.8%) were decided to discontinue protocol treatment because of disease progression (5 patients, 3.9%), toxicity (10 patients, 7.8%), refusal by patients (4 patients 3.1%), proving to be ineligible during chemotherapy (3 patients, 2.3%) and impossible pursuit of patients (2 patients, 1.6%). Table 3 lists the acute toxicities of the highest grade observed during 745 cycles in all 128 enrolled patients. There was no treatment-related death. The major toxicity was hematological ones. Grade 4 neutropenia was observed in 58 patients (45.3%). Grade 4 thrombocytopenia and leukopenia were observed in 1 patient (0.8%) and 7 patients (5.5%), respectively. Grade 3 neutropenia, thrombocytopenia and decrease of hemoglobin were observed in 44 patients (34.4%), 1 (0.8%) and 9 (7.0%), respectively.

Grade 4 non-hematological toxicities were observed in 4 patients (constipation, hyperbilirubinemia, hypoxemia and intramuscular abscess). The most frequent grade 3 non-