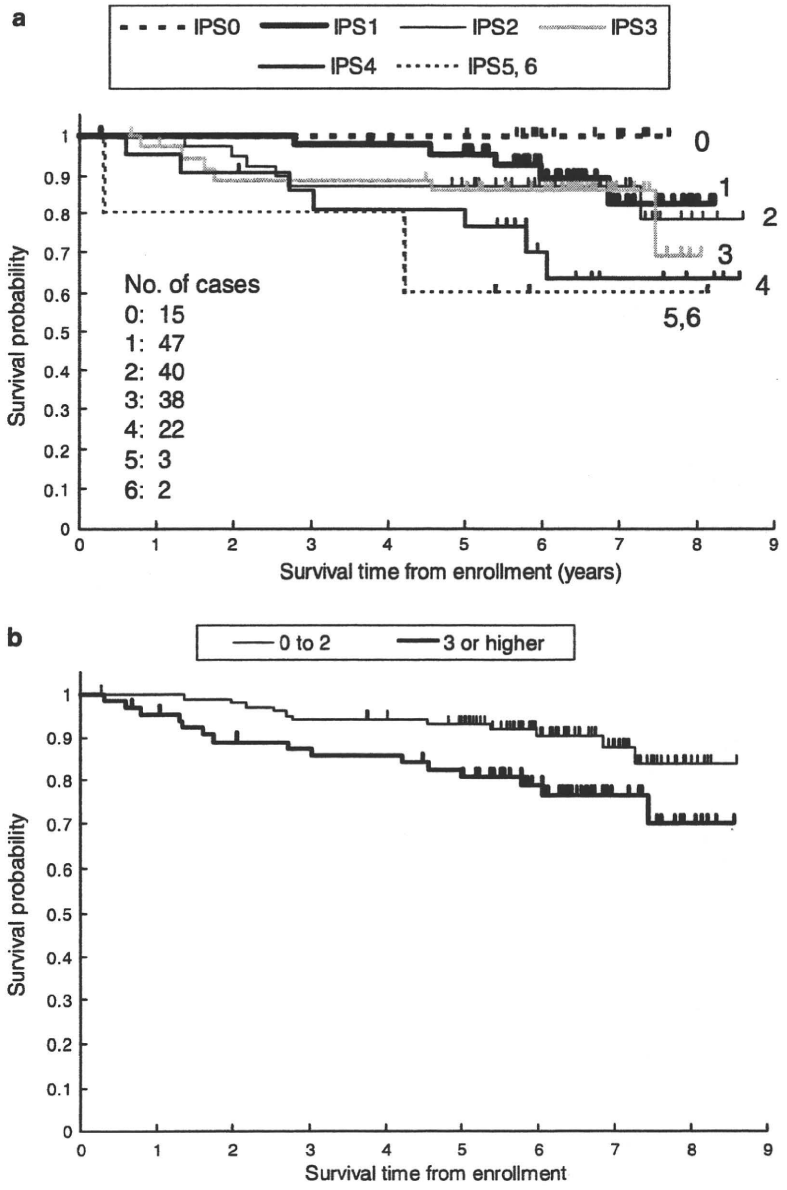

Fig. 2 Overall survival according to the international prognostic score (IPS) **a** 1, 2, 3, 4 and 5 + 6, and **b** 0–2 or 3 or higher

applicability of IPS or other prognostic factors to Japanese patients with advanced HL treated with an established protocol considered to be state-of-the-art combination chemotherapy or chemo-radiotherapy. To our knowledge, this is the first report to validate the IPS comprehensively and to analyze the conventional prognostic factors for OS in a large number of Japanese patients with advanced HL treated with established protocols of state-of-the-art combination chemotherapy or chemo-radiotherapy and diagnosed by central pathological review. The histopathological distributions of advanced HL according to the WHO classification in 167 patients in Japan were determined, and showed that the proportion of patients with nodular sclerosis in Japan (68.9%) was higher, while the proportion with mixed cellularity (20%) was similar to those in Western countries [12, 16]. The survival of each HL subtype in Japan was similar to those in Western countries [12].

In our study, there were only 5 patients with IPS score of 5 or higher, accounting for only 3% of the entire study population. Their 6-year OS was 60%, indicating that a distinct group of patients at very high risk could not be determined on the basis of IPS. Even in the original IPS paper, only 7% of the patients had a score of 5 or higher representing a very high risk and had a 59% of OS at 5 years. The results were very similar to our study.

Table 3 Univariate survival analysis

		Hazard ratio	95% CI	*p*
Sex	Male	4.30	(1.62–11.45)	0.004
β2-Microglobulin	>2 mg/l	4.78	(1.49–15.27)	0.008
B symptoms	Yes	0.31	(0.13–0.74)	0.009
Serum LDH	Elevated	2.55	(1.18–5.51)	0.02
Alkaline phosphatase	Elevated	2.53	(1.13–5.67)	0.03
Clinical stage	III/IV	2.41	(1.05–5.56)	0.04
Histopathology	MC&LD	2.21	(1.02–4.83)	0.05
Albumin	<4 g/dl	2.44	(0.98–6.09)	0.06
Age (years)	≥45	1.80	(0.82–3.96)	0.15
Hemoglobin	<10.5 g/dl	0.36	(0.08–1.51)	0.16
White blood cells	≥15000/μl	1.83	(0.73–4.55)	0.20
Lymphocytes	<600/μl or <8%	1.63	(0.69–3.88)	0.27
Clinical stage	IV	1.40	(0.59–3.32)	0.45
Extranodal sites	Yes	0.97	(0.40–2.39)	0.95

Table 4 Multivariate survival analysis

		Hazard ratio	95% CI	*p*
Sex	Male	3.30	(1.15–9.52)	0.03
Serum LDH	Elevated	2.41	(1.07–5.43)	0.03
B symptoms	Yes	2.26	(0.85–6.06)	0.10
Alkaline phosphatase	Elevated	1.94	(0.70–5.37)	0.21
Histopathology	MC&LD	1.73	(0.75–4.00)	0.20
Clinical stage	III/IV	0.87	(0.31–2.47)	0.80

Therefore, in our study, it can be concluded that a distinct group of patients at a very high risk could not be identified by IPS, as same as stated in the original IPS paper [7]. Furthermore, the survival curves of patients with an IPS score of 1, 2 or 3 were not clearly separated from each other (Fig. 2). Therefore, IPS was not closely associated with OS in our study. It has been reported that the IPS score 0–4 versus 5 or 6 was found to have prognostic significance for disease-specific survival in a report of large number of Japanese patients with HL treated variously, in which the presence of T cell and/or cytotoxic antigen in Hodgkin's and Reed-Sternberg cells also showed a significant poor prognosis [17]. However, in that study, neither patient number nor survival rate of patients in each IPS score was shown at all, thus it may be said that IPS was not adequately validated in Japanese patients with advanced HL treated with state-of-the-art combination chemotherapy or chemo-radiotherapy. As it had been concluded that a distinct group of patients at very high risk could not be identified by the IPS [7], attempts have been made to determine more suitable factors that could detect the poor-risk population among patients with HL [17–19]. Namely, it was reported that the number of involved anatomic sites combined with the IPS [18] or interleukin-10 (IL-10) level added to the IPS [19] could detect the subgroup of HL patients with poor prognosis.

As the initial treatments for HL led to excellent outcomes and the rescue treatments could improve the clinical outcomes, the prognostic factors for OS might be more important than the prognostic factors for progression-free survival (PFS) in patients with advanced HL. In our study in which the diagnosis of HL was based on central pathological review, OS was independently affected by male and elevated serum LDH on multivariate analysis. Only male and clinical stage of III or IV among the 7 factors in the IPS were significantly associated with poor OS in the univariate analysis, and male remained significant in the multivariate analysis. The German Hodgkin Study Group suggested that hematotoxicities were more pronounced in females although this did not translate into increased infection, and female patients had similar response rates as males but fewer relapses and deaths, leading to a significantly better freedom from treatment failure in a large retrospective analysis [20]. Sex might be associated with the metabolism of anticancer drugs [21]. Elevated serum LDH was previously reported to be prognostically unfavorable in advanced HL [22, 23] and is also one of the most important factors in the international prognostic index of non-HL [24]. Therefore, elevated serum LDH might reflect the total status of HL, including both constitutional and disease-related elements.

As a post hoc sensitivity analysis, we also performed the analysis using stepwise variable selection methods, and the results were shown that male [HR 6.18 (95% CI 2.28–16.70, $p < 0.001$)] and elevated serum LDH [HR 2.87 (95% CI 1.32–6.24, $p = 0.008$)] remained significant and serum albumin level of less than 4 g/dl [HR 3.38 (95% CI 1.35–8.51, $p = 0.01$)] was also significant. Although serum albumin was significantly correlated with B symptom ($p < 0.001$) and serum alkaline phosphatase ($p = 0.001$), serum albumin did not show the significancy over male and serum LDH as the prognostic factor and did not show the prognostic relevance for OS in univariate analyses. Although stepwise variable selection method was widely used, model by stepwise method is not necessarily considered the best with regard to the statistical issues, which were often discussed and criticized [25–28]. In this study, analysis was performed following the prospectively planned method, and the final model was evaluated by cross-validation, one of the internal validation methods to resolve these statistical issues. The OS curves between risk groups derived from our final model were significantly different, and the results were validated by cross-validation. Based

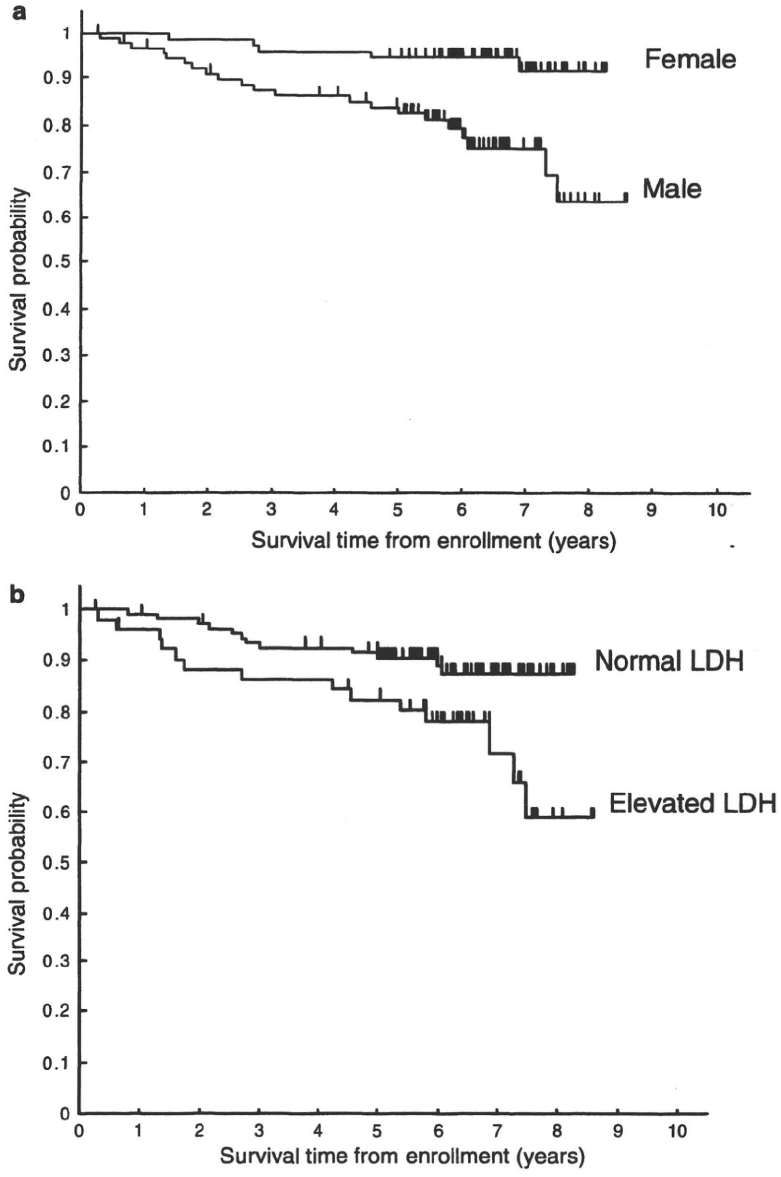

Fig. 3 Overall survival according to **a** sex ($n = 167$) and **b** serum LDH ($n = 166$)

on a combination of model fit and parsimony considerations, our final model incorporated two prognostic factors: male and elevated serum LDH.

Generally, complex models with a large number of prognostic predictors are not practical and simple models are easier to evaluate and are preferable in routine clinical practice. The prognostic model for advanced HL in our study, including sex and serum LDH, was considered to be very simple. However, it is discussed that prognostication with the prospective studies has a limitation by the exclusion of patients with poor condition and prognostic models using data of prospective study might be difficult for generalization. On this concern, adequate consideration should be necessary.

Prognosis of the patients with advanced HL is improved in advance of treatment, and then prognostic factors may differ according to the state of the treatment. In the original IPS paper, eligible patients with advanced HL for the original IPS study were limited to those who were 15–65 years old and were treated with an established protocol still considered to be state-of-the-art, with at least four planned cycles of combination chemotherapy (preferably containing doxorubicin) with or without radiotherapy. This means that IPS was established in the patients who could be safely treated with state-of-the-art therapy, excluding both elderly patients of more than 65 years and those who were poorly treated probably because of poor condition. Nonetheless, IPS has been used widely, because

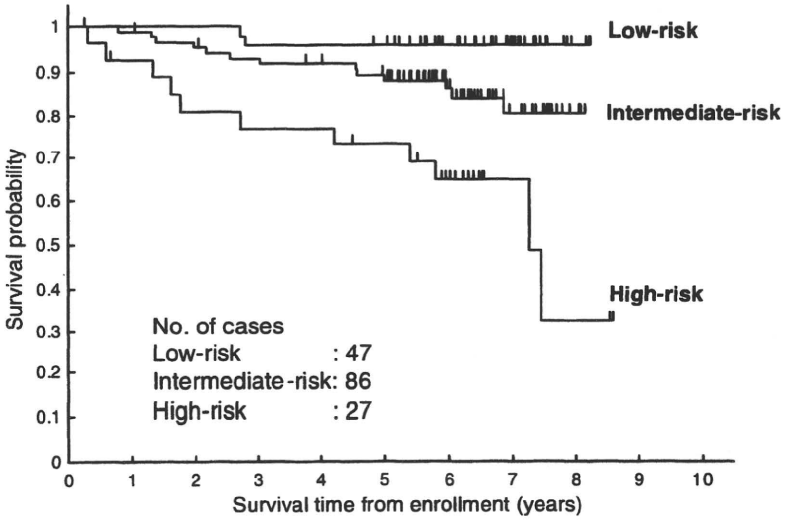

Fig. 4 Overall survival among patients with HL excluding those with unclassified histopathology according to the number of unfavorable prognostic factors (male and elevated serum LDH). Low risk, intermediate risk and high risk indicate 0, 1 and 2 risk factors, respectively. Data on serum LDH were not available in one patient, and this patient was excluded from this analysis

everybody wants to know the prognostic state of patients with advanced HL treated with state-of-the-art therapy. In our study, eligible patients for the prognostic analysis are almost same as patients for the original IPS study. Then, our prognostic model could be accepted for general use, although further studies should be warranted to validate our prognostic model.

Unfortunately, data on the β2-microglobulin level of 56 patients were missing. In univariate analysis, β2-microglobulin was found to be highly significant in 111 patients. However, multivariate analysis including β2-microglobulin revealed that there was no significant factor detected. Then, β2-microglobulin was excluded from the final multivariate analysis for OS. Serum β2-microglobulin levels are known to reflect renal function and membrane turnover, the latter of which is associated with tumor mass and growth rate. Elevated β2-microglobulin level was reported to predict poor survival in several hematological malignancies including low-grade lymphoma [29], large cell lymphoma [30] and HL [31–33]. Interestingly, Vassilakopoulos et al. [33] reported that the β2-microglobulin level was a powerful independent prognostic factor for OS, but not for failure-free survival in optimally treated patients with HL. The prognostic impact of β2-microglobulin on OS should be re-evaluated in future.

In conclusion, despite the limitation of a small number of patients, our prognostic model was considered to be a simple method of predicting OS in Japanese patients with advanced HL. Further studies to validate our prognostic model and to re-evaluate the prognostic impact on OS of sex and serum LDH combined with β2-microglobulin are warranted.

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Phase III trial of CHOP-21 versus CHOP-14 for aggressive non-Hodgkin's lymphoma: final results of the Japan Clinical Oncology Group Study, JCOG 9809

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Background: CHOP-21 has remained the standard chemotherapy for aggressive non-Hodgkin's lymphoma (NHL), and dose intensification is a potential strategy for improving therapeutic results. We conducted a phase III trial to determine whether dose-dense strategy involving interval shortening of CHOP (CHOP-14) is superior to CHOP-21.

Patients and methods: A total of 323 previously untreated patients (aged 15–69 years) with stages II–IV aggressive NHL were randomized. The primary end point was progression-free survival (PFS).

Results: Treatment compliance was comparable in both study arms. At 7-year follow-up, no substantial differences were observed in PFS and overall survival (OS) between CHOP-21 ($n = 161$) and CHOP-14 ($n = 162$) arms. Median PFS was 2.8 and 2.6 years with CHOP-21 and CHOP-14, respectively (one-sided log-rank $P = 0.79$). Eight-year OS and PFS rates were 56% and 42% [95% confidence interval (CI) 47% to 64% and 34% to 49%], respectively, with CHOP-21 and 55% and 38% (95% CI 47% to 63% and 31% to 46%), respectively, with CHOP-14. Subgroup analyses showed no remarkable differences in PFS or OS for patients stratified as per the International Prognostic Index or by age.

Conclusion: Dose-intensification strategy involving interval shortening of CHOP did not prolong PFS in advanced, aggressive NHL.

Key words: aggressive non-Hodgkin's lymphoma, CHOP-14, CHOP-21, phase III trial

introduction

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

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

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

patients and methods

eligibility criteria

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

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

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

treatment

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

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

response assessment

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

statistical methods

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

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

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

central pathology review

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

results

interim analysis

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

patient characteristics

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

Table 1. Patients' characteristics

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

Table 1. (*Continued*)

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

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

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

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

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

toxic effects

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

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

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

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

Table 2. Toxic effects

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

Toxicity forms collected 320 patients.

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

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

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

treatment interval and dose intensity

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

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

responses

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

survival

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

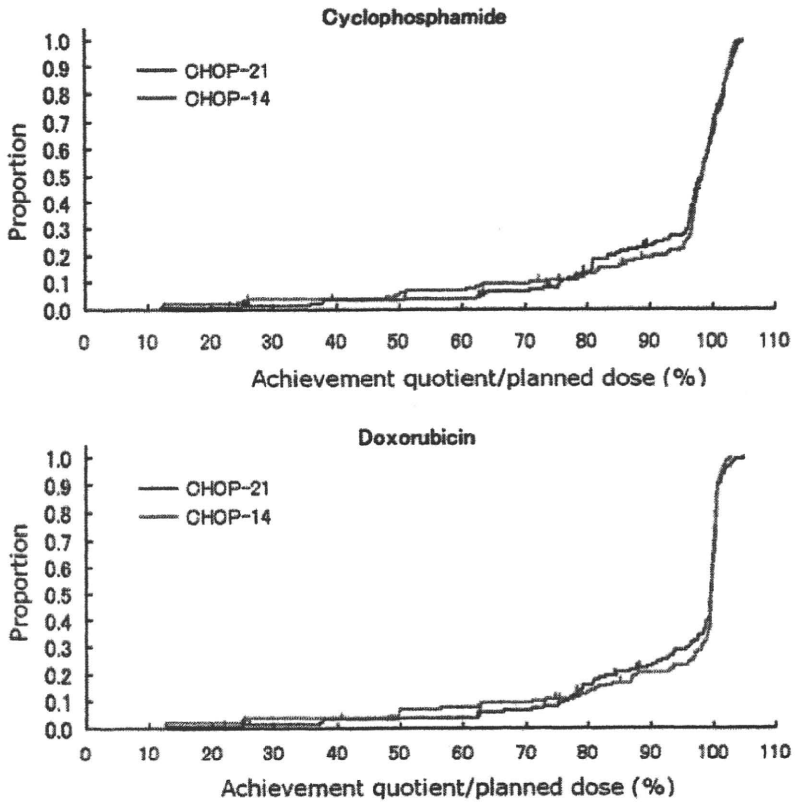


Figure 1. Distribution of the achievement quotient for planned doses of cyclophosphamide and doxorubicin.

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

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

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

Table 3. Response after completion of the protocol treatment

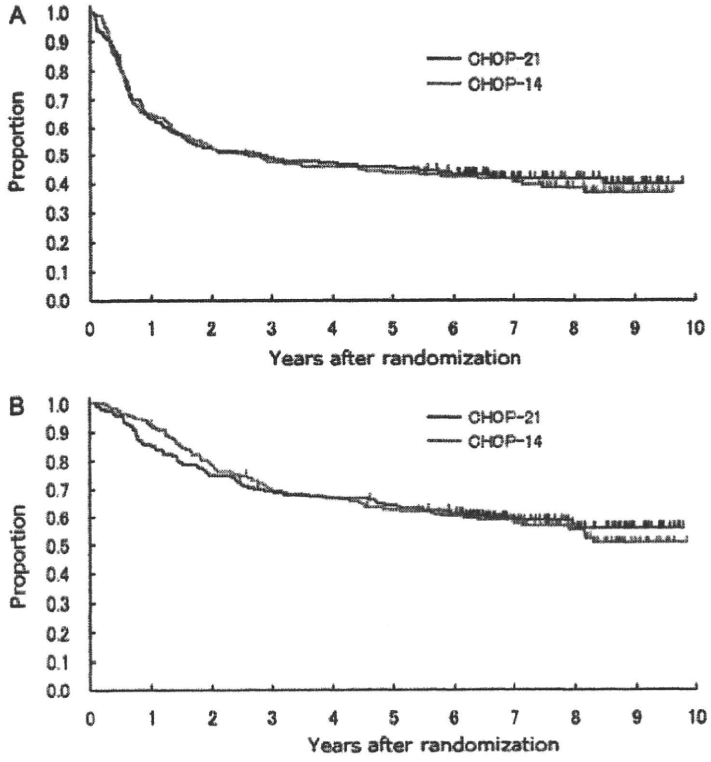
	CHOP-21 (%), $n = 161$	CHOP-14 (%), $n = 162$
CR	38.5	44.4
CRu	23.0	22.2
PR	0	0
NR	0	0
PD	12.4	9.3
Not evaluable	1.2	0
%CR (CR + CRu)	61.5	66.7
95% CI	53.5–69.0	58.8–73.9

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

conclusions

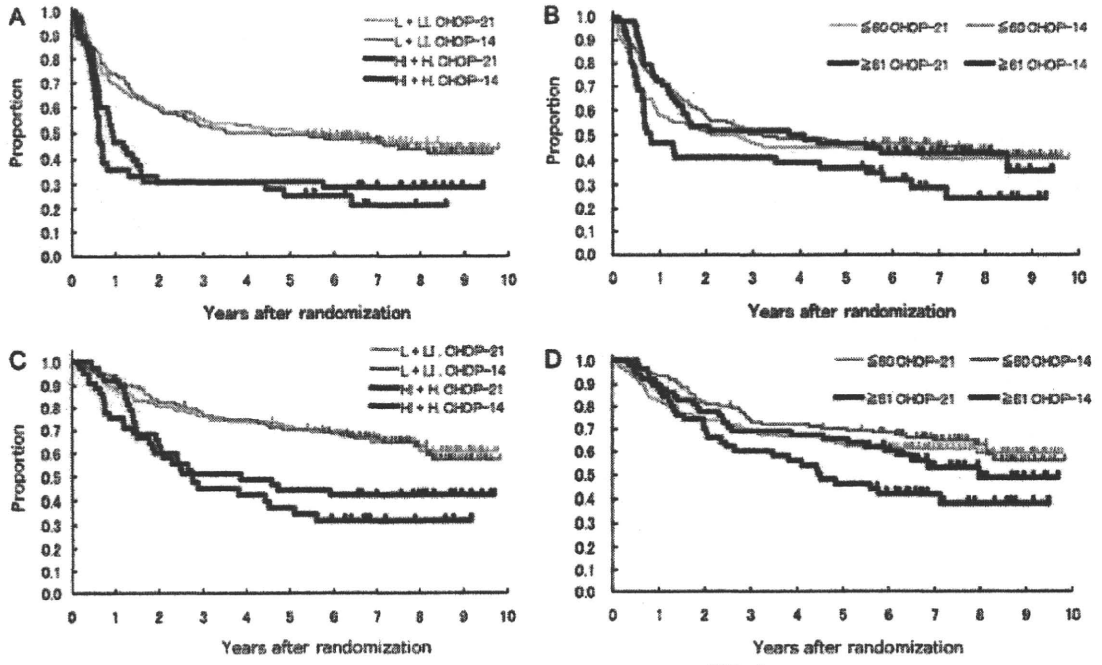
This trial failed to demonstrate the superiority of CHOP-14 over CHOP-21 for the treatment of aggressive NHL. PFS and OS after CHOP-14 were lower than those after CHOP-21 at the first interim analysis, and the trial was terminated early because the estimated predictive probability that CHOP-14 would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

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



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

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



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

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

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

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

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

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

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

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

Table 4. Result of multivariate analysis using COX regression

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

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

Table 5. Patients' characteristics according to age

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

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

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

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The authors declare no conflict of interest.

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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-