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

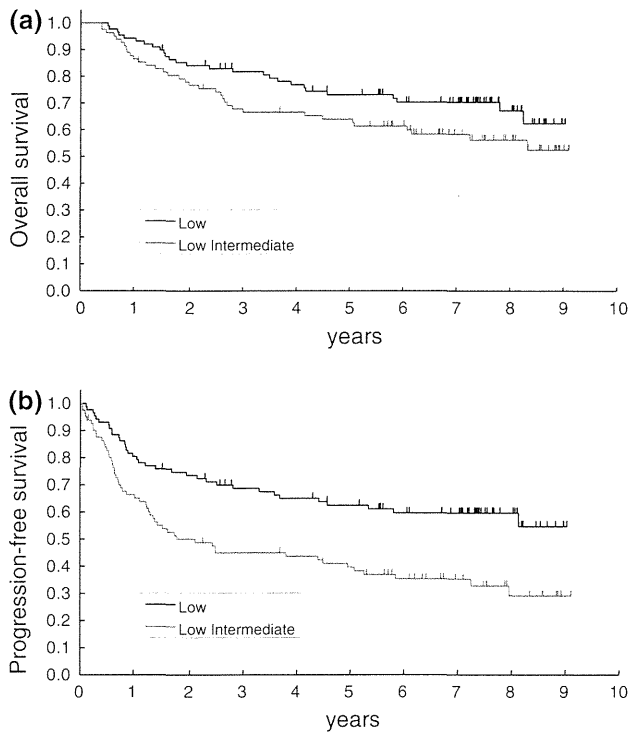

Fig. 1 Kaplan–Meier estimate of OS and PFS for pathologically eligible patients. **a** OS curves for patients in each risk category. The 5-year OS (95 % CI) in L risk and L–I risk cases was 73 % (63–82 %) and 64 % (53–74 %), respectively. **b** PFS curves for patients in each risk category. The 5-year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

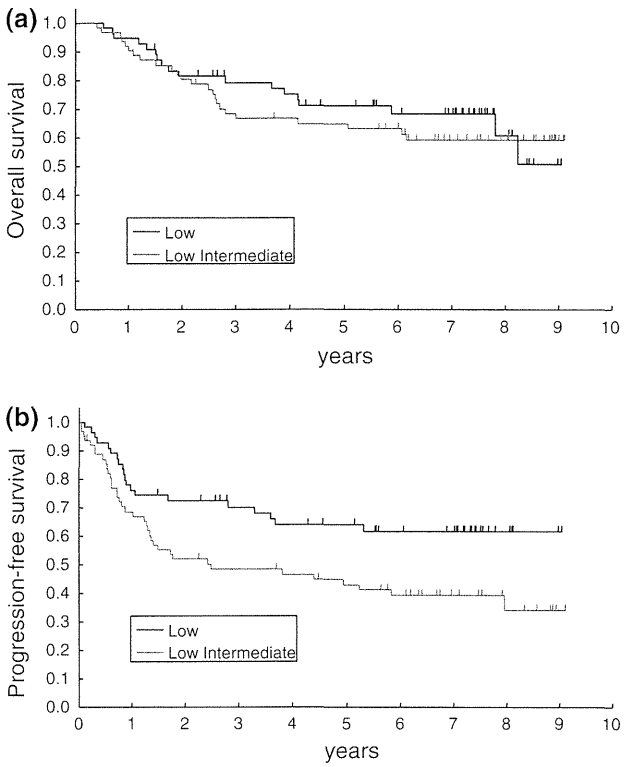

Fig. 2 Kaplan–Meier estimate of OS and PFS for DLBCL-NOS patients. **a** OS curves for patients in each risk category. The 5-year OS (95 % CI) in L risk and L–I risk patients was 71 % (58–83 %) and 65 % (53–77 %), respectively. **b** PFS curves for patients in each risk category. The 5-year PFS (95 %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

Participating institutions and principal investigators of the JCOG9508 study.

Hokkaido Cancer Center (C. Mikuni), Sapporo Hokuyu Hospital (M. Kasai), Akita University School of Medicine (A. Miura), Iwaki Kyoritsu General Hospital (T. Sai), Ota Nishinouchi Hospital (S. Matsuda), National Cancer Center Hospital East (T. Ohtsu), National Cancer Center Hospital (K. Tobinai), Kyorin Medical University (K. Kawano), Tokyo Metropolitan Komagome Hospital (T. Sasaki), Aoto Hospital of Tokyo Jikei Medical School (S. Yamada), The 3rd Hospital of Tokyo Jikei Medical School (F. Mizoroki), Tokai University School of Medicine (T. Hotta), St. Marianna University School of Medicine (H. Nagoshi), Niigata Cancer Center (T. Chou), Kanazawa Medical University (S. Shimizu), University of Fukui Faculty of Medical Science (T. Ueda), Aichi Cancer Center Hospital (M. Ogura), National Hospital Organization, Nagoya Medical Center (M. Shimoyama), Nagoya University School of Medicine (T. Kinoshita), Japanese Red Cross Nagoya Daiichi Hospital (S. Minami), Nagoya City University Graduate School of Medical Science and Medical School (R. Ueda), Shiga Medical Center for Adults (T. Suzuki), Ohtsu Red Cross Hospital (T. Ohno), Kyoto Prefectural University of Medicine (M. Abe), Kansai Medical School (S. Fukuhara), Tenri Yorozu Hospital (Y. Ohno), Okayama Medical Center (T. Sezaki), Shikoku Cancer Center (K. Okabe), National Hospital Organization Kyushu Medical Center (Y. Sakai), Kokura Memorial Hospital (Y. Izumi), Faculty of Medicine, Saga University (Y. Shimamoto), Nagasaki University School of Medicine (M. Tomonaga), Sasebo Municipal General Hospital (S. Ikeda), Faculty of Medical and Pharmaceutical Sciences Kumamoto University (K. Takatsuki), National Hospital Organization Kumamoto Medical Center (H. Kawano), Kagoshima University Faculty of Medicine (A. Utsunomiya), Kagoshima City Hospital (M. Tara), University of the Ryukyus Faculty of Medicine (K. Araki).

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ORIGINAL ARTICLE: CLINICAL

Phase II study of ABV (doxorubicin with increased dose, bleomycin and vinblastine) therapy in newly diagnosed advanced-stage Hodgkin lymphoma: Japan Clinical Oncology Group study (JCOG9705)

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Abstract

The role of dacarbazine in ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) therapy in Hodgkin lymphoma (HL) remains unclear. This phase II study assessed the efficacy and safety of ABV therapy with an increased doxorubicin dose (30 mg/m^2) in advanced-stage HL. The primary endpoint was complete response rate (%CR). Patients received six or eight cycles of ABV every 4 weeks followed by involved-field radiation therapy (IFRT) in residual disease and initial bulky mass. Seventy-two patients were enrolled. An interim analysis in 46 assessable patients showed that %CR had exceeded the stopping criteria. However, the 2-year progression-free survival (%PFS) rate of 49.4% (95% confidence interval [CI] 32.2–66.6) was markedly lower than the 79.2% PFS (95% CI 70.6–87.7) seen in our previously reported study (JCOG9305) of ABVd with two-thirds the dose of dacarbazine of the original ABVD. Therefore, the study was closed early. The %CR in the 70 eligible patients after ABV was 31.4% (95% CI 20.9–43.6) and was increased to 70.0% (95% CI 57.9–80.4) after the addition of IFRT. ABV was inferior to ABVd for PFS in patients with advanced HL, suggesting that dacarbazine is indispensable in ABVD/ABVd.

Keywords: ABV therapy followed by IFRT, first-line chemotherapy, Hodgkin lymphoma, phase II study

Introduction

Following the development of two representative curative combination chemotherapy regimens for advanced Hodgkin lymphoma (HL), the MOPP regimen (mechlorethamine, vincristine, procarbazine and prednisone) and the ABVD regimen (doxorubicin, bleomycin, vinblastine and dacarbazine) [1,2], several randomized trials were performed to establish the standard chemotherapy for patients with advanced HL. ABVD became the standard of treatment for patients with newly diagnosed advanced HL after a landmark phase III trial (the Cancer and Leukemia Group B [CALGB] 8251 study) showed that ABVD was as effective as alternating therapy of MOPP/ABVD, and more effective than MOPP, with fewer toxic events [3]. An American and Canadian intergroup phase III study also demonstrated that ABVD was as effective as the MOPP/ABV hybrid regimen, with fewer toxic effects [4].

The incidence of HL in Japan is approximately one-third that in Western countries [5,6]. Key drugs such as mechlorethamine in MOPP and dacarbazine in ABVD had not been approved by the Japanese government for clinical use in HL even as late as the 1990s. From October 1989 to February 1993, the Lymphoma Study Group of the Japan Clinical Oncology Group (JCOG-LSG) conducted a phase II study (JCOG8905)

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involving combination chemotherapy, alternating C-MOPP (cyclophosphamide, vincristine, procarbazine and prednisolone) and ABVd (with a lower dacarbazine dose than in ABVD) [7]. The dose of dacarbazine in ABVd was reduced to two-thirds (250 mg/m^2) that in the original ABVD (375 mg/m^2) regimen due to the side effect of intolerable severe emesis in a pilot study at that time. Subsequently, the emesis with dacarbazine has been greatly reduced with the development of promising anti-emetic regimens including 5-hydroxytryptamine 3 receptor and neurokinin 1 antagonists, which make standard ABVD more tolerable. The progression-free survival (PFS) rate at 4 years in patients with stage III/IV HL in the JCOG8905 study and that at 5 years in patients treated with MOPP/ABVD in the CALGB 8251 study were 65.7% and 65%, respectively [3,7]. Because the efficacy of C-MOPP/ABVd in the JCOG8905 study is considered almost equivalent to that of MOPP/ABVD in Western countries [4,8], the ABVd regimen is considered to be as effective as the original ABVD regimen.

After the results of CALGB 8251 were published [3], the JCOG-LSG conducted a multi-institutional phase II study (JCOG9305) to investigate the efficacy and safety of ABVd therapy for Japanese patients with newly diagnosed stage II–IV HL, although dacarbazine was administered off-label [9]. The complete response rate (CR) and 5-year PFS of all eligible patients were 81.4% and 78.4%, respectively. Thus, the JCOG9305 study showed sufficient efficacy and acceptable toxicity of ABVd therapy followed by post-chemotherapeutic involved-field radiation therapy (IFRT) for previously untreated patients with stage II–IV HL. The role of dacarbazine as a key drug in ABVd/ABVD therapy remains unclear, although dacarbazine was effective against HL as a single agent with an overall response rate of 56% in the Southwest Oncology Group study [10]. Phlebitis and emesis are serious side effects of this drug. Although the dacarbazine dose was reduced to two-thirds (250 mg/m^2) of that in the original ABVD regimen, grade 2 phlebitis and grade 2/3 nausea/vomiting were observed in 43% and 34%/11% of patients, respectively [9].

The JCOG-LSG conducted a phase II study (JCOG9705) to investigate the efficacy and safety of ABV therapy without dacarbazine and with the doxorubicin dose increased by 20%, in an effort to find a less toxic and equally effective treatment in patients with newly diagnosed advanced-stage HL. We report the results of JCOG9705 here.

Materials and methods

This trial was a prospective, multi-institutional phase II study conducted by the JCOG-LSG. The study protocol was approved by the Protocol Review Committee of the JCOG and by the institutional review board at each institution. Written informed consent was obtained from each patient before enrollment. This study was registered with UMIN-CTR (www.umin.ac.jp/ctr/), identification number C000000068.

Eligibility criteria

Eligible patients included: those who were newly diagnosed with HL according to the Rye classification [11]; those aged 15–69 years;those diagnosed at clinical stages IB, IIB, III, IV or any stage with bulky disease (>1/3 mediastinal widening by plain chest film or ≥ 10 cm maximum dimension of nodal mass on computed tomography [CT] scan) according to the Ann Arbor staging system [12] and the Cotswolds system [13]; those with evaluable lesions by CT scan; those with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, 2 or 3 [14]; and those with no involvement to the central nervous system and no other active malignancies. Other eligibility criteria included leukocytes ≥ 3000/μL, neutrophils ≥ 1200/μL, platelets ≥ 10×10^4/μL, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤ 2.5 times the upper limit of normal (ULN), total bilirubin ≤ 2.0 mg/dL, creatinine ≤ 1.5 mg/dL, PaO_2 ≥ 65 mmHg, ejection fraction (EF) ≥ 50%, and negative for hepatitis B surface antigen, anti-hepatitis C virus antibody, anti-human immunodeficiency virus antibody and anti-human T-lymphotropic virus type-I antibody. Exclusion criteria included women who were pregnant or nursing; patients with diabetes mellitus receiving insulin; those with severe infection or severe hepatic, pulmonary or psychiatric disease; or those with cardiac disease that could deteriorate due to administration of doxorubicin.

Treatment

The ABV regimen consisted of 6–8 cycles of doxorubicin (30 mg/m^2), bleomycin (9 mg/m^2; upper limit, 15 mg total) and vinblastine (6 mg/m^2; upper limit, 10 mg total), administered simultaneously as intravenous injections on days 1 and 15 of each cycle. The duration of each cycle was 4 weeks. Treatment was adjusted to six cycles of ABV if CR was obtained after four cycles or to eight cycles of ABV if CR or a partial response (PR) was obtained after six cycles. Bleomycin was omitted in cycles 7 and 8. The maximum total dose of bleomycin was defined to be 180 mg except for those patients in whom mediastinal radiation therapy was planned after ABV therapy. For these patients, the maximum total dose of bleomycin was defined to be 120 mg. If the pretreatment leukocyte and/or platelet counts were < 2500/μL and 7.5×10^4/μL, respectively, or the serum AST/ALT was ≥ 5 times the ULN, and/or total bilirubin was ≥ 2.1 mg/dL, treatment was postponed until recovery, with a maximum delay of 4 weeks. Vinblastine was discontinued if signs of neurotoxicity ≥ grade 3 were observed. Doxorubicin was discontinued if any of the following occurred: cardiac hypofunction (ejection fraction ≤ 40%), ≥ grade 2 arrhythmia, ischemic cardiac disease or pericarditis, or heart failure ≥ grade 3. Bleomycin was suspended until recovery if the PaO_2 level decreased to < 65 mmHg or decreased by > 15 mmHg of the previous PaO_2 level.

IFRT was indicated for patients with an initial bulky mass who experienced CR after six or eight cycles of ABV or PR after eight cycles of ABV. The first half of a total planned radiation dose of IFRT was delivered to cover the maximum diameter of the initial bulky mass. The latter half of the total planned radiation dose of IFRT was delivered to the residual mass after chemotherapy. IRFT to the residual mass in patients with stage IB, IIB, III or IV who achieved PR after ABV therapy was defined as follows: (1) no IFRT to bone marrow involved by HL; (2) IFRT (30 Gy) every 4–5 weeks should be delivered to lymph nodal lesions followed by booster radiation of 4–10 Gy if necessary; (3) both paraaortic nodes and spleen should be irradiated simultaneously if the HL lesion is observed in either tissue or both; (4) solitary ipsilateral pulmonary lesions should be

irradiated with IFRT of 18 Gy, but bilateral pulmonary lesions or pulmonary lesions more than 50% of the lateral lung area should not be irradiated; (5) hepatic lesions should be irradiated with 20 Gy; (6) bone lesions should be irradiated with 24 Gy followed by an IFRT boost of 10 Gy if necessary.

Patients with no bulky disease who achieved PR after eight cycles of ABV therapy received radiation therapy; antiemetic drugs were recommended as appropriate.

Central pathology review

A central pathology review was performed according to the method reported previously [9]. Names of the participating reviewers are provided in the "Appendix." Antigens routinely examined by immunohistochemistry included CD3, CD20, CD15 and CD30. Antibodies against CD79a, CD5, cyclinD1, CD10, bcl-2 and CD56 were utilized as necessary. Six hematopathologists and two hematologists reviewed the pathology specimens and classified them according to the World Health Organization (WHO) classification system [15]. The diagnosis by the central pathology review committee was used in this study.

Response and toxicity criteria

CR was defined as the disappearance of all measurable lesions and symptoms of disease for at least 4 weeks. PR was defined as a reduction of at least 50% in the sum of the products of the perpendicular diameters of all measurable lesions and the lack of appearance of new lesions for at least 4 weeks. An unconfirmed CR (CRu) was defined as maintenance of PR without chemotherapy for ≥ 3 months after completion of the study. Progressive disease was defined as a 25% increase in the size of any existing lesion or the development of any new lesions. All other circumstances were considered to indicate stable disease. Response was evaluated by CT scan after cycles 2, 4, 6 and 8 of ABV therapy, and after IFRT.

Pulmonary toxicity was evaluated by monitoring the partial pressure of oxygen in arterial blood just before the administration of ABV therapy. Cardiac toxicity was evaluated by electrocardiogram and echocardiography just before the administration of ABV therapy. Toxicities were evaluated according to the toxicity grading criteria of the JCOG [16], which include the expanded and modified version of the National Cancer Institute (NCI) Common Toxicity Criteria version 1.0.

Statistical analysis and endpoints

The primary endpoint was the CR rate (CR + CRu) in all eligible patients. Secondary endpoints were toxicity, overall survival (OS) and CR duration. At the time of analysis, PFS was used instead of CR duration. OS was calculated from the date of registration until death due to any cause or censored at the last follow-up date. PFS was calculated from the date of registration to the date of relapse or progression, death due to any cause, or censored at the date of the last follow-up for patients with no reported adverse events. Analyses of the CR and overall response rate (ORR: CR + PR) were performed using point estimates and the 95% confidence interval (CI). OS and PFS were estimated according to the Kaplan–Meier method. Sample size was determined using Simon's two-stage minimax design ($P_0 = 0.7$, $P_1 = 0.8$, alpha = 0.1, beta = 0.2) [17]. At the first-stage decision, if the total number of responders (CR + PR) was 32 of the 46 eligible patients or fewer (i.e.ORR $\leq$ 69.6%), the study was to be discontinued. At the second (final) stage, if the total number of responders (CR + PR) was 65 of the 86 eligible patients or fewer (i.e.ORR $\leq$ 75.6%), the protocol treatment was deemed ineffective.Because up to 20% of patients were ineligible based on the central pathology review, the sample size was decided to be 108 patients who were enrolled for 3 years.The analyses were performed using SAS release 9.1 (SAS Institute, Cary, NC).

Role of the funding source

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Results

Decision process using Simon's two-stage minimax design

Twenty-five hospitals participated in JCOG9705. The participating institutions and investigators are listed in the "Appendix." Between January 1998 and May 2000, 72 patients were enrolled in JCOG9705. In May 2000, according to the decision rule, the first-stage decision to stop enrollment and compare the PFS of this study to that of JCOG9305 was made for 36 patients, since the PFS of JCOG9705 was poor. In October 2000, an updated analysis was performed for 46 patients (as per the first-stage decision criteria) who were evaluable for response. The CR rate and 2-year PFS were 71.7% (95% CI 56.5–84.0) and 49.4% (95% CI 32.2–66.6), respectively.The PFS at 2 years (49.4%) in this study was markedly lower than that of JCOG9305 (79.2% [95% CI 70.6–87.7]), excluding those with non-bulky, stage IIA disease [9].The low PFS was considered to reflect too many early relapses after ABV–IFRT.Therefore, in accordance with the recommendations of the JCOG Data and Safety Monitoring Committee, the study was closed early in December 2000.

Patient characteristics

The final analysis of the results of JCOG9705 was conducted in December 2005. Seventy-two patients were enrolled in JCOG9705; two were deemed ineligible, one due to a change of pathological diagnosis after enrollment and the other due to a change in clinical stage from IIIA to non-bulky IIA. The clinical characteristics of the 70 eligible patients are shown in Table I. There were 36 men and 34 women, and the median age was 31.5 years. B symptoms at entry were observed in 39 patients (55.7%). PS was 0 or 1 for the majority (94.3%) of eligible patients. Bulky disease (maximum diameter $\geq$ 10 cm) was present in 34 patients (48.6%). Unfavorable localized disease (bulky stage IA, bulky IIA, IB and IIB) and advanced disease (stages III and IV) were present in 29 (41.4%) and 41 patients (58.6%), respectively. The numbers of patients with an International Prognostic Score (IPS) [18] of 0–2 and ≥ 3 were 33 (47.1%) and 37 (52.9%), respectively. Fourteen percent of patients had stage IV disease. In the JCOG8905 and

Table I. Patient characteristics.

Characteristic	Enrolled cases ($n = 72$)	Eligible cases ($n = 70$)
Age, median (range) years	31.5 (15–69)	31.5 (15–69)
Male sex	38 (52.8%)	36 (51.4%)
PS		
0	45 (62.5%)	43 (61.4%)
1	23 (31.9%)	23 (32.9%)
2	3 (4.2%)	3 (4.3%)
3	1 (1.4%)	1 (1.4%)
Clinical stage		
IA/IB	1 (1.4%)/2 (2.8%)	1 (1.4%)/2 (2.9%)
IIA/IIB	11 (15.3%)/15 (20.8%)	11 (15.7%)/15 (21.4%)
IIIA/IIIB	15 (20.8%)/18 (25.0%)	14 (20.0%)/17 (24.3%)
IVA/IVB	5 (6.9%)/5 (6.9%)	5 (7.1%)/5 (7.1%)
Bulky mass	34 (47.2%)	34 (48.6%)
B symptoms	40 (55.6%)	39 (55.7%)
Histological subtype		
NLPHL	1 (1.4%)	1 (1.4%)
Nodular sclerosis	43 (59.7%)	41 (58.6%)
NS grade 1	1 (1.4%)	1 (1.4%)
Mixed cellularity	11 (15.3%)	11 (15.7%)
LD	3 (4.2%)	3 (4.3%)
Unclassified	1 (1.4%)	1 (1.4%)
Other neoplasms	5 (6.9%)	5 (7.1%)
Samples uncollected*	7 (9.7%)	7 (10%)

PS, performance status; NLPHL, nodular lymphocyte predominant Hodgkin lymphoma; NS, nodular sclerosis; LD, lymphocyte depleted.
*Samples uncollected: pathological diagnosis of each institute was adopted in the seven patients whose pathological samples could not be collected.

JCPG9305 studies, in which the target clinical stage was II–IV, 16.4% and 24.6% of patients had stage IV disease, respectively [7,9]. The reason for the relatively low percentage of stage IV disease in the present study is unclear.

Responses

Responses of the 70 eligible patients are shown in Table II. The CR rate after ABV therapy or ABV therapy followed by IFRT (ABV–IFRT) was 70.0% (95% CI 57.9–80.4). Twenty-two patients (31.4%; 95% CI 20.9–43.6) achieved a CR or CRu after ABV therapy and 49 patients (70.0%; 95% CI 57.9–80.4) achieved a CR or CRu after ABV–IFRT. A total of 37 patients underwent IFRT after the completion of chemotherapy. While seven patients (9.7%) did not receive planned radiation therapy at the end of chemotherapy, five had unplanned IFRT after ABV therapy. After IFRT, the CR rates in the lower risk (IPS: 0–2) and higher risk groups (IPS: 3–7) increased from 33.3% to 81.8% and from 29.7% to 59.5%, respectively (data not shown).

Progression-free survival

The PFS curve is shown in Figure 1(A). The 5-year PFS was estimated to be 43.5% (95% CI 31.7–54.8). The PFS at 5 years in patients with bulky stage IIA/IIB/III/IV treated with ABVd in JCOG9305 ($n = 85$) and ABV in JCOG9705 ($n = 68$) was 72.2% (95% CI 61.2–80.6) and 43.3% (95% CI 31.3–54.8), respectively [Figure 1(B)]. The PFS at 5 years in patients with stage III/IV treated in JCOG9305 ($n = 62$) and the present study ($n = 40$) was 66.7% (95% CI 53.2–77.1) and 46.2% (95% CI 30.1–60.9), respectively [Figure 1(C)].

Overall survival

OS is shown in Figure 2(A). Sixteen patients died and OS at 5 years was estimated to be 80.9% (95% CI 69.4–88.5).OS at 5 years in patients with bulky stage IIA/IIB/III/IV treated with ABVd in JCOG9305 ($n = 85$) and ABV in JCOG9705 ($n = 68$) was 86.6% (95% CI 77.1–92.4) and 80.4% (95% CI 68.6–88.1), respectively [Figure 2(B)]. OS at 5 years in patients with stage III/IV treated in JCOG9305 ($n = 62$) and the present study ($n = 40$) was 83.2% (95% CI 71.0–90.6) and 79.1% (95% CI 62.5–89.0), respectively [Figure 2(C)].

Toxicity

All 72 treated patients were evaluated for toxicity (Table III), with the most common being hematological toxicities. No treatment-related deaths occurred. The most frequent grade 4 hematological toxicity was neutropenia, which was observed in 36 patients (50.7%). No grade 4 non-hematological toxicities were observed. Grade 3 non-hematological toxicities included hypoxemia, elevation of ALT, peripheral neuropathy and cardiac ischemia (one patient each). The most frequent grade 2 non-hematological toxicity was elevation of ALT in 14 patients (19.4%).

Diffuse large B-cell lymphoma (DLBCL) as a secondary malignancy was observed within 3 years after the completion of ABV therapy in two of 72 patients (2.8%) throughout the study. Neither of these patients received IFRT. There was no other report of malignancy including solid tumor in either of these patients. One patient died from progression of DLBCL.

Pathological characteristics

A central review of the pathological diagnosis was performed for 65 of the 72 enrolled patients and the pathological diagnosis of each institution was adopted for the remaining seven patients. Among the 65 centrally reviewed patients, five were deemed ineligible, all with non-Hodgkin lymphoma (NHL), including four diffuse large cell types (one with lymphomatoid granulomatosis subtype, one with pyothorax-associated lymphoma, one with T-cell rich B-cell lymphoma, and one with primary mediastinal large B-cell lymphoma) and one with B-cell lymphoma not otherwise specified. In addition

Table II. Responses of eligible patients ($n = 70$).

Response	After chemotherapy	%	After radiation*	%
CR	19	27.1	27	38.6
CRu	3	4.3	22	31.4
PR	39	55.7	8	11.4
NC	0	0	0	0
PD	7	10.0	11	15.7
NE	2	2.9	2	2.9
CR + CRu(95% CI)	22	31.4 (20.9–43.6)	49	70.0 (57.9–80.4)

CR, complete response; CRu, CR unconfirmed; PR, partial response; NC, no change; PD, progressive disease; NE, not evaluable; CI, confidence interval.
*Of the 70 patients enrolled in this study, 37 patients underwent radiation therapy after the completion of chemotherapy.

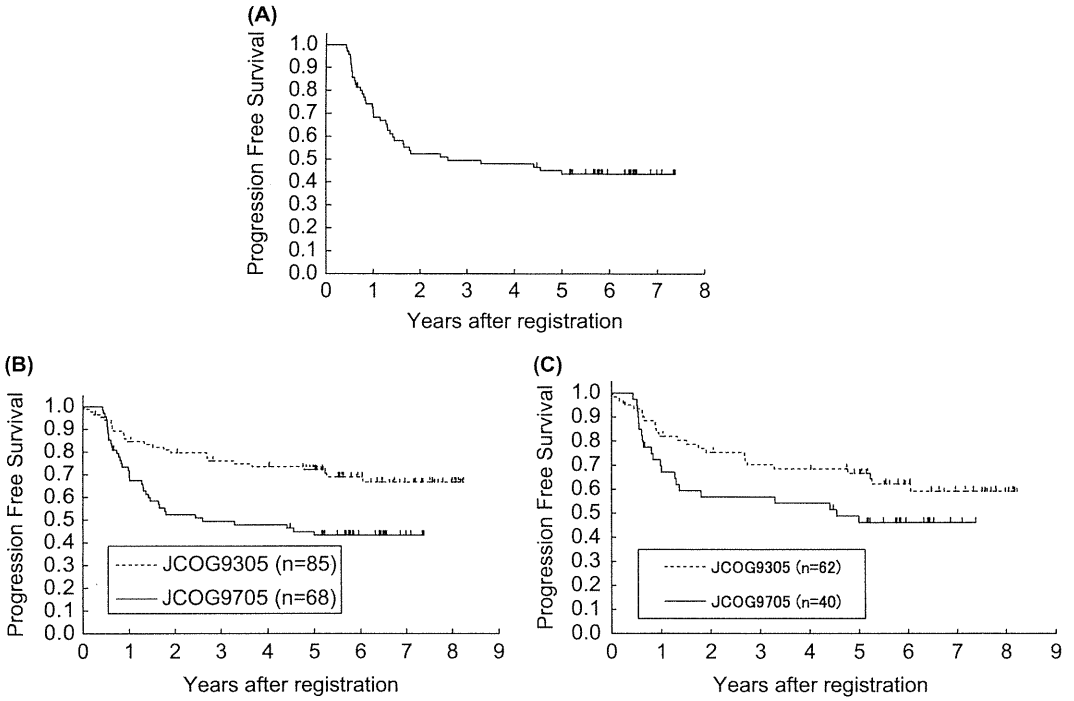

Figure 1. Progression-free survival (tick marks indicate censored data). (A) All 70 eligible patients. (B) Comparison according to study group; dotted and solid lines represent JCOG9305 (ABVd therapy, subgroup 1: $n = 85$) and JCOG9705 (ABV therapy, subgroup 2: $n = 68$), respectively. Target population is stage IIA bulky, IIB, III or IV in both studies. (C) Comparison according to study group;dotted and solid lines represent JCOG9305 (ABVd therapy, subgroup 1: $n = 62$) and JCOG9705 (ABV therapy, subgroup 2: $n = 40$), respectively. Target population is stage III or IV in both studies.

to these five pathologically ineligible patients, two other patients were deemed ineligible, one due to pathology after enrollment and the other due to a change in clinical stage from IIIA to non-bulky IIA. Therefore, 58 of the 65 patients who underwent pathological review were deemed pathologically eligible. The histological subtype of these patients was determined by the central pathological review and the distribution is also shown in Table I. Nodular sclerosis was present in 70.7% of the 58 patients with HL and mixed cellularity (19.0%) was the next most-common subtype. These histological distributions were similar to those reported in a study based in Western countries [19].

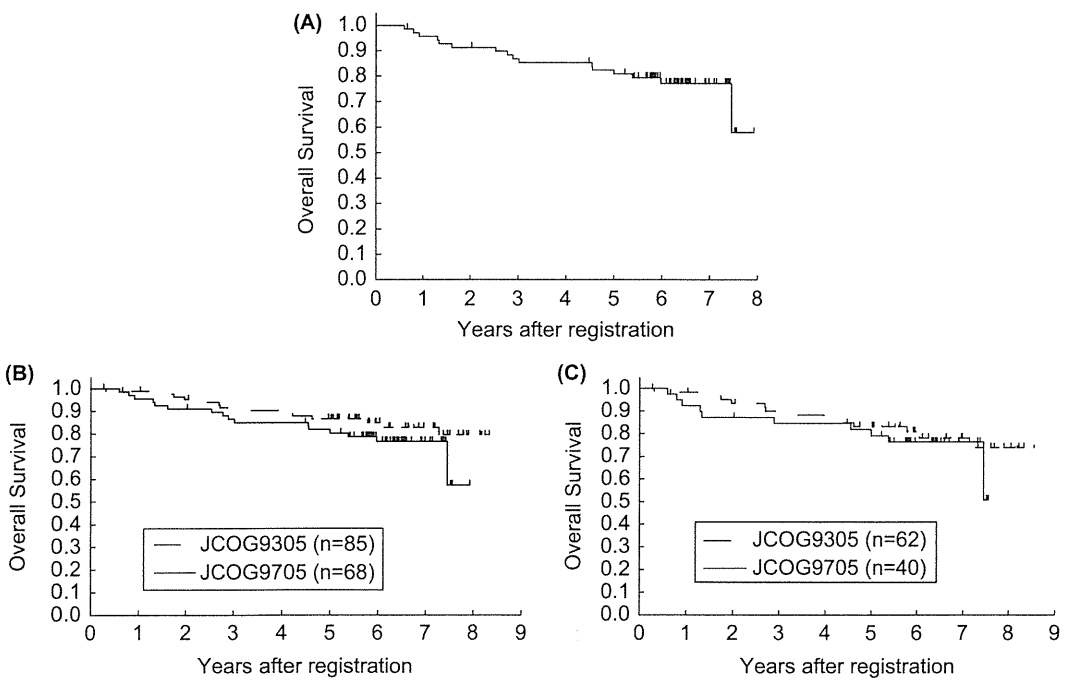

Figure 2. Overall survival (tick marks indicate censored data). (A) All 70 eligible patients. (B) Comparison according to study group;dotted and solid lines represent JCOG9305 (ABVd therapy, subgroup 1: $n = 85$) and JCOG9705 (ABV therapy, subgroup 2: $n = 68$), respectively. Target population is stage IIA bulky, IIB, III or IV in both studies. (C) Comparison according to study group; dotted and solid lines represent JCOG9305 (ABVd therapy, subgroup 1: $n = 62$) and JCOG9705 (ABV therapy, subgroup 2: $n = 40$), respectively. Target population is stage III or IV in both studies.

Table III. Toxicities in all enrolled patients ($n = 72$).

Toxicity	Toxicity grade by JCOG toxicity criteria			
	Grade 1	Grade 2	Grade 3	Grade 4
Hematological				
Leukopenia	5 (6.9%)	31 (43.1%)	29 (40.3%)	5 (6.9%)
Neutropenia	1 (1.4%)	10 (14.1 %)	22 (31.0%)	36 (50.7%)
Anemia	21 (29.2%)	21 (29.2 %)	7 (9.7%)	–
Thrombocytopenia	10 (13.9%)	2 (2.8%)	0	1 (1.4%)
Non-hematological				
AST elevation	24 (33.3%)	10 (13.9 %)	0	0
ALT elevation	24 (33.3%)	14 (19.4%)	1 (1.4%)	0
Creatinine elevation	4 (5.6%)	0	0	0
Hypoxemia*	25 (44.6%)	6 (10.7%)	1 (1.8%)	0
Diarrhea	8 (11.1%)	1 (1.4%)	0	0
Stomatitis	16 (22.2%)	3 (4.2%)	0	0
Arrythmia	3 (4.2%)	0	0	0
Esophagitis	9 (12.5%)	2 (2.8%)	0	0
Pharyngitis	31 (43.1%)	4 (5.6%)	0	0
Fever† (non-infectious)	3 (8.3%)	3 (8.3%)	0	0
Cardiac ischemia	1 (1.4%)	0	1 (1.4%)	0
Neuropathy	17 (23.6%)	7 (9.7%)	1 (1.4%)	-

AST, aspartate aminotransferase; ALT, alanine aminotransferase; JCOG, Japan Clinical Oncology Group.
*Toxicity data for hypoxemia were collected from 56 patients.
†Toxicity data for non-infectious fever were collected from 36 patients.

Discussion

This phase II study demonstrated that PFS in patients treated with ABV with an increased dose of doxorubicin and without dacarbazine followed by IFRT to initial bulky disease or residual mass in PR was markedly inferior to that with ABVd, although the comparison was not direct. To the best of our knowledge, this is the first report suggesting that dacarbazine is a key drug in ABVd/ABVD therapy in patients with advanced-stage HL.

We compared the 5-year PFS rate of ABV therapy in JCOG9705 to that of ABVd therapy in JCOG9305 in comparable patient populations. The 5-year PFS rate of the 70 eligible patients in the present study was 43.5%. This outcome is very poor compared to the 61% 5-year failure-free survival rate with ABVD therapy found in the CALGB 8251 study for newly diagnosed patients with stage IIIA2–IV HL [3].

The low CR rate after the completion of ABV therapy (31.4%) increased to 70.0% after IFRT, although this high CR rate after IFRT did not translate into high PFS in JCOG9705. These data imply that a high CR rate by induction chemotherapy itself is essential to achieve better PFS. ABV proved inadequate to achieve the high CR rate that is essential to good PFS. Thus, the present study strongly suggested that dacarbazine is an indispensable drug in ABVd/ABVD to achieve both a high CR rate and good PFS.

The important role of dacarbazine in ABVD in patients with early favorable HL was reported in 2010 based on the interim analysis of the HD13 trial comparing two cycles of AVBD, ABV, AVD or AV followed by IFRT conducted by the German Hodgkin Lymphoma Study Group (GHSD) [20]. The second interim analysis of the HD13 trial showed a four-fold increase of adverse events in the ABV and AV arms, which led them to close these two arms. This suggests that dacarbazine is also an essential drug in ABVD in early favorable HL.

The median dose intensities of doxorubicin in the present study and the JCOG9305 study were 93.3% (range, 49.6–103.2%) and 98.8% (range, 50.3–123.1%), respectively, based on the maximum planned dose in each protocol. The median dose intensities of bleomycin in the present study and the JCOG9305 study were 72.6% (range, 32.7–102.0%) and 81.3% (range, 11.5–128.2%), respectively. Thus, a high dose intensity of doxorubicin in the present study was maintained. The relatively low dose intensity of bleomycin seemed to have no significant impact on the poor PFS in JCOG9705, since there was no reported difference in outcome for patients in whom bleomycin was omitted during treatment (due to toxicity) compared with patients who completed the full ABVD with bleomycin [21,22].

In JCOG9705, the protocol required that patients with initial bulky disease underwent IFRT in CR or PR following ABV therapy, and those with a residual mass underwent IFRT in PR after eight cycles of ABV therapy. Protocol deviations occurred in seven patients (one in CR and six in PR), all of whom had an initial bulky mass and should have received IFRT (per protocol) but did not. A phase III study by the European Organisation for Research and Treatment of Cancer (EORTC) demonstrated that IFRT did not improve the outcome in patients with advanced-stage HL who were in CR after MOPP/ABV chemotherapy, although radiotherapy may benefit patients in PR after chemotherapy [23]. This suggests that the protocol deviation in one patient with initial bulky disease in CR (no IFRT) had no influence on the outcome of patients in JCOG9705, although chemotherapy was not different between the EORTC study (MOPP/ABV) and JCOG9705 (ABV). However, the six patients with initial bulky mass who were protocol deviations due to not receiving IFRT in PR may have had a negative influence on PFS.

OS at 5 years in JCOG9705 (80.9%) was comparable to that in patients receiving ABVd therapy in JCOG9305 (91.3%). As reported previously [4,8,9], the major toxicity in ABVD/ABVd was grade 4 neutropenia. In ABVd therapy, the occurrence of grade 4 neutropenia was 45.3% [9]. Although the ABV therapy in the present study included a 20% increased dose of doxorubicin, the incidence of grade 4 neutropenia (50.7%) was similar to that seen with ABVd therapy, possibly due to the deletion of dacarbazine. However, no severe (grade 3 or 4) infection was observed in JCOG9705, as has been seen with ABVd. Although the ABVd regimen included bleomycin and an increased dose of doxorubicin, the incidence of severe pulmonary or cardiac toxicity was very low (1.8%).

In JCOG9705, two patients developed DLBCL after completion of protocol treatment. Although ABVD therapy is less leukemogenic or carcinogenic [3], it is possible that the development of DLBCL in these two patients was related to the ABV regimen; these patients did not undergo IFRT. Scholz *et al.* [24] reported no differences in cumulative risk between the primary therapies for developing secondary NHL (2.9%) in a retrospective analysis of 5357 individuals in eight randomized trials of the German Hodgkin Lymphoma Study Group. The incidence of DLBCL in their study was similar to that in the present study (2.8%). Therefore, ABV therapy also seemed less leukemogenic in our study, although the dose of doxorubicin was increased.

In conclusion, the present study showed that the efficacy of ABV with an increased dose of doxorubicin and no dacarbazine was inferior to ABVd, although the comparison was not direct. Dacarbazine is thus indispensable in ABVD/ABVd therapy.

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Appendix

Participating institutions and principal investigators of the JCOG9705 study included: National Sapporo Hospital (Mikuni C.), Sapporo Hokuyu Hospital (Kasai M.), Ota Nishinouchi Hospital (Matsuda S.), National Cancer Center Hospital East (Ohtsu T.), National Cancer Center Hospital (Tobinai K.), Kyorin Medical University (Kawano K.), Tokyo Metropolitan Komagome Hospital (Sasaki T.), The 3rd Hospital of Tokyo Jikei Medical School (Mizoroki F.), Tokai University School of Medicine (Hotta T.), Niigata Cancer Center Hospital (Chou T.), Fukui Medical University (Ueda T.), Fukui Prefectural Hospital (Haba T.), Hamamatsu University School of Medicine (Ohnishi K.), Aichi Cancer Center Hospital (Morishima Y.), Nagoya University School of Medicine (Murate T.), National Nagoya Hospital (Shimoyama M.), Fujita Health University School of Medicine (Hirano M.), Nagoya City University School of Medicine (Ueda R.), Tenri Yorozu Hospital (Ohno Y.), Hiroshima Red Cross Hospital & Atomic-Bomb Survivors Hospital (Asaoku H.), Sasebo Municipal General Hospital (Ikeda S.), National Kyushu Cancer Center (Kotsuru M.), Kumamoto University School of Medicine (Yamaguchi K.), National Kumamoto Hospital (Kawano F.) and Ryukyu University (Masuda M).

Central review of pathological diagnosis

Reviewers included Drs. Yoshihiro Matsuno (National Cancer Center Hospital, Tokyo), Shigeo Nakamura (Aichi Cancer Center Hospital, Nagoya), Tadashi Yoshino (Okayama University, Okayama), Koichi Oshima and Masahiro Kikuchi (Fukuoka University, Fukuoka) and Kiyoshi Mukai (Tokyo Medical University) as pathologists for the Pathology Panel, and Masanori Shimoyama (National Cancer Center Hospital) and Michinori Ogura (Aichi Cancer Center) as hematologists for the Panel.

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Concurrent Chemoradiotherapy for Localized Nasal Natural Killer/T-Cell Lymphoma: An Updated Analysis of the Japan Clinical Oncology Group Study JCOG0211

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Concurrent Chemoradiotherapy for Localized Nasal Natural Killer/T-Cell Lymphoma: An Updated Analysis of the Japan Clinical Oncology Group Study JCOG0211

To the Editor: Extranodal natural killer (NK)/T-cell lymphoma (NKTCL), nasal type,[1,2] is a predominantly extranodal lymphoma associated with Epstein-Barr virus. Before the early 2000s, no prospective clinical trials had been conducted for localized nasal NKTCL. In the November 20, 2009, issue of *Journal of Clinical Oncology*, we reported the results of our first analysis of a phase I/II study of concurrent chemoradiotherapy for newly diagnosed localized nasal NKTCL (Japan Clinical Oncology Group study JCOG0211).[3] Our first analysis demonstrated improved overall survival (OS) and progression-free survival (PFS) at 2 years with a median follow-up of 32 months (range, 24 to 62 months) compared with a historical control of radiotherapy (RT) alone.[3,4] Soon after the publication of our study, a Korean group reported promising results from a phase II study of concurrent chemoradiotherapy.[5] Since then, concurrent chemoradiotherapy has been regarded as one of the reasonable treatment options for newly diagnosed localized nasal NKTCL.[6] However, to our knowledge, no long-term follow-up studies on survival or complications of concurrent chemoradiotherapy have been published. We report the results of a long-term follow-up of the JCOG0211 study.

A total of 33 patients were enrolled and received concurrent chemoradiotherapy that consisted of 50 Gy of RT and three cycles of dexamethasone, etoposide, ifosfamide, and carboplatin (DeVIC). Two doses, which consisted of a two-thirds dose of DeVIC (2/3DeVIC) and a full dose of DeVIC (100%DeVIC), were evaluated in the phase I portion, and 2/3DeVIC was selected for the phase II portion.[3] In total, 27 patients were treated with RT and 2/3DeVIC (RT-2/3DeVIC), and six patients were treated with RT and 100%DeVIC (RT-100%DeVIC). Clinical parameters of all 33 patients were comparable with those of the 27 patients treated with RT-2/3DeVIC.

The data used for this analysis were updated as of December 2011. No patients received prophylactic therapy for CNS relapse. Moreover, no patient with an objective response underwent consolidative hematopoietic stem-cell transplantation. The median follow-up time for the 27 patients who were treated with RT-2/3DeVIC was 67 months (range, 61 to 94 months). The OS at 5 years was 70% (90% CI, 53% to 82%; 95% CI, 49% to 84%; Fig 1A), which was superior to the historical control of RT alone (40%)[4] that we used in the previous analysis. The PFS at 5 years was 63% (90% CI, 46% to 76%; 95% CI, 42% to 78%; Fig 1B). No disease progression was observed after the first analysis. These results demonstrate that RT-2/3DeVIC provides reasonably long response durability for newly diagnosed localized nasal NKTCL. The median follow-up time for all 33 patients was 68 months (range, 61 to 94 months). The OS at 5 years was 73% (90% CI, 57% to 83%; 95% CI, 54% to 85%), and the PFS at 5 years was 67% (90% CI, 51% to 78%; 95% CI, 48% to 80%; Fig 2). Recurrence within the RT field was observed in only two patients. Thus, the planning target-volume control rate at 5 years was 94% (31 of 33 patients).

The late toxicities were acceptable and manageable (Table 1). One patient treated with RT-2/3DeVIC experienced perforation of the nasal skin and received plastic surgery 18 months after RT. This event was scored as a grade 4 late RT adverse event (AE), although the patient had massive involvement of the nasal skin and subcutaneous tissue before the protocol treatment. One patient treated with RT-100%DeVIC experienced grade 3 irregular menstruation. No other grade 3 or higher late AEs were observed. Eleven patients (33%) experienced grade 1 or 2 late RT AEs of the eye, but none of these patients required ophthalmologic surgery as a result of late RT AEs other than cataracts. However, five of the 11 patients had not recovered from the late RT AEs of the eye at the last follow-up.

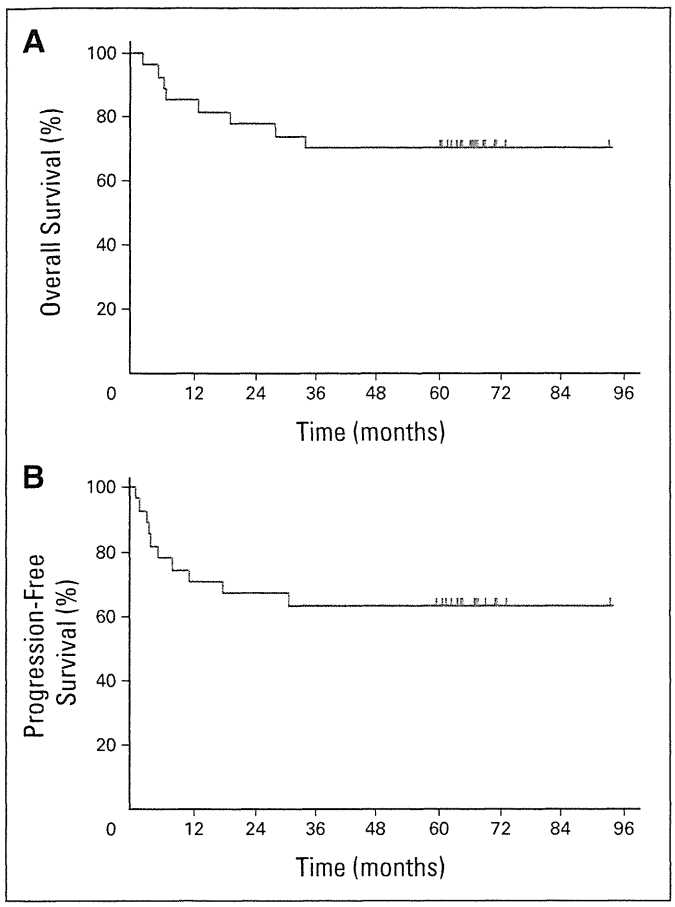

Fig 1. (A) Overall survival and (B) progression-free survival of 27 patients treated with radiotherapy and a two-thirds dose of dexamethasone, etoposide, ifosfamide, and carboplatin.

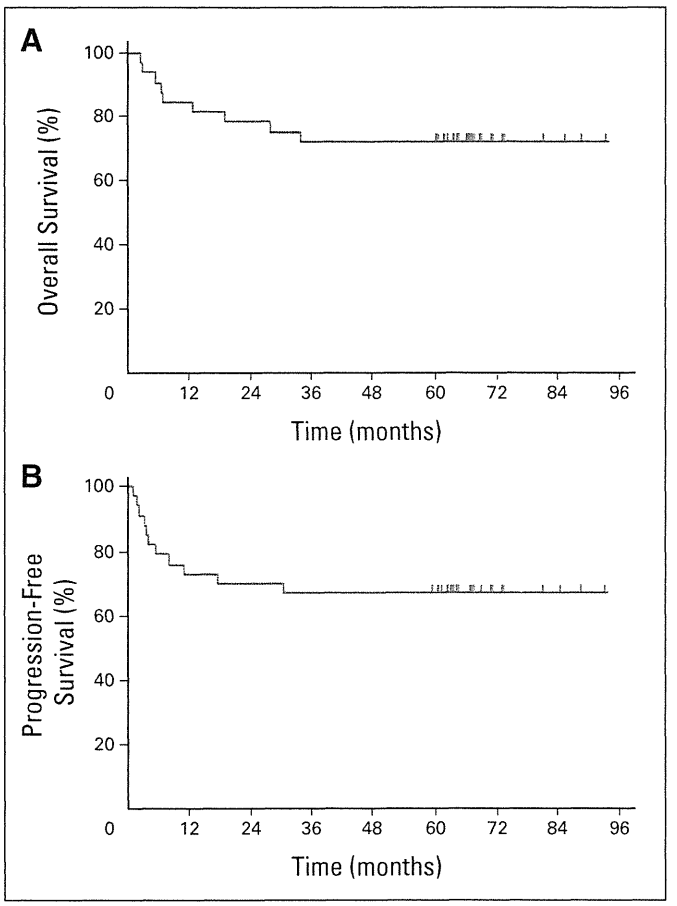

Fig 2. (A) Overall survival and (B) progression-free survival of 33 patients treated with radiotherapy and dexamethasone, etoposide, ifosfamide, and carboplatin.

Of note, four of the five patients had been treated with RT-100%DeVIC. With consideration of these results, and because the patient who experienced grade 3 amenorrhea had been treated with RT-100%DeVIC, it is unlikely that the full dose of DeVIC is appropriate for concurrent chemoradiotherapy because of the excessive acute and late toxicities, although the number of evaluated patients was small.

Our updated analysis confirmed that both the survival benefit and disease control provided by concurrent chemoradiotherapy with RT and DeVIC were maintained for more than 5 years, and to our knowledge, this analysis is the first to reveal the profile of late AEs of concurrent chemotherapy for this disease. We conclude that RT-2/3DeVIC is one of the most recommendable options as a first-line treatment for localized nasal NKTCL.

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Table 1. Incidence and Maximum Severity of Late Adverse Events During Follow-Up (N = 33)

Adverse Event	Grade 1		Grade 2		Grade 3		Grade 4	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Late RT adverse event, RTOG/EORTC Late Radiation Morbidity Scoring Scheme								
Mucous membrane, head and neck	11	33	3	9	0	0	0	0
Salivary glands	3	9	5	15	0	0	0	0
Skin, head and neck	7	21	0	0	0	0	1*	3
Subcutaneous tissue, head and neck	2	6	0	0	0	0	1*	3
Spinal cord	0	0	0	0	0	0	0	0
Brain	1	3	0	0	0	0	0	0
Eye	7	21	4	12	0	0	0	0
Other late adverse event, NCI-CTC 2.0								
Irregular menses	0	0	0	0	1†	3	0	0
Secondary malignancy							0	0

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; NCI-CTC, National Cancer Institute Common Toxicity Criteria; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group.
*The same patient underwent plastic surgery.
†This 30-year-old patient had been treated with RT and full-dose dexamethasone, etoposide, ifosfamide, and carboplatin and recovered from this adverse event after 3 years.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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