Table 3 Toxicities

Toxicity	Toxicity grade by JCOG toxicity criteria				
	Grade 1	Grade 2	Grade 3	Grade 4	ND#
Hematological					
Leukopenia	11 (8.6%)	49 (38.3%)	60 (46.9%)	7 (5.5%)	
Neutropenia	8 (6.3%)	16 (12.5%)	44 (34.4%)	58 (45.3%)	
Anemia	34 (26.6%)	40 (31.3%)	9 (7.0%)	–	
Thrombocytopenia	11 (8.6%)	3 (2.3%)	1 (0.8%)	1 (0.8%)	
Non-hematological					
Bilirubin elevation	–	16 (12.5%)	4 (3.1%)	1 (0.8%)	
AST elevation	56 (43.8%)	14 (10.9%)	3 (2.3%)	0	
ALT elevation	53 (41.4%)	27 (21.1%)	6 (4.7%)	0	
Cr elevation	6 (4.7%)	2 (1.6%)	0	0	
Hypoxemia	56 (43.8%)	13 (10.2%)	1 (0.8%)	1 (0.8%)	4
Nausea/vomiting	50 (39.1%)	43 (33.6%)	14 (10.9%)	–	
Diarrhea	16 (12.5%)	2 (1.6%)	1 (0.8%)	0	2
Stomatitis	12 (9.4%)	3 (2.3%)	0	0	3
Proteinuria	7 (5.5%)	0	0	0	6
Arrythmia	2 (1.6%)	1 (0.8%)	0	0	4
Phlebitis	–	54 (42.2%)	0	0	2
Dyspnea	5 (3.9%)	5 (3.9%)	1 (0.8%)	0	4
Infection	21 (16.4%)	9 (7.1%)	0	1 (0.8%)	4
Alopecia	63 (49.2%)	40 (31.3%)	–	–	4
Fever (non-infectious)	27 (21.1%)	39 (30.5%)	3 (2.3%)	0	1
Neuropathy	33 (25.8%)	5 (3.9%)	1 (0.8%)	–	3
Constipation	34 (26.6%)	11 (8.6%)	1 (0.8%)	1 (0.8%)	3

Cr creatinine, *ND#* no data collected

hematological toxicity was nausea/vomiting that was observed in 14 patients (10.9%). Other grade 3 non-hematological toxicities were hyperbilirubinemia observed in 4 patients (3.1%), elevation of AST/ALT in 9 patients (7.0%), non-infectious fever in 3 patients (2.3%), and hypoxemia, diarrhea, dyspnea, peripheral neuropathy and constipation in each one patient (0.8% each). The frequent grade 2 non-hematological toxicities (≥30%) were phlebitis, nausea/vomiting, alopecia and non-infectious fever.

Secondary malignancies were observed within 3 years after ABVd therapy in 4 patients (3.1% of 128) throughout the study. Myelodysplastic syndrome (MDS), lung cancer, rectal cancer and gastric cancer were observed in each one patient. Diagnosis of lung cancer and gastric cancer was confirmed at 2.8 and 1.5 years after the treatment, respectively. A patient with MDS had involved-field radiation therapy to left cervical lymphatic area after ABVd therapy. A patient with rectal cancer had mantle-field radiation therapy after ABVd therapy. Each patient with MDS and gastric cancer died from progression of HL, and cerebral infarction followed by pneumonia, respectively. Another two patients died from their secondary malignancies.

Table 4 Responses of eligible patients ($n = 118$)

	Response after Cx		After Cx or Cx and Rx	
	No.	%	No.	%
CR	70	59.3	81	68.6
CRu	5	4.2	15	12.7
PR	32	27.1	10	8.5
NC	5	4.2	5	4.2
PD	5	4.2	6	5.1
NE	1	0.8	1	0.8
CR + CRu (95% CI)	75	63.6 (54.2–72.2%)	96[a]	81.4 (73.1–87.9%)

Cx chemotherapy, *Rx* radiation therapy, *CI* confidential interval

[a] 37 of 96 patients received Rx after the completion of Cx

3.4 Responses

The therapeutic efficacy was evaluated in 118 eligible patients. The ORR after ABVd therapy or ABVd therapy followed by radiation therapy in all 118 eligible patients was 89.8% (95% CI 82.9–94.6%) (Table 4). Seventy-five

Table 5 CR rate (including CRu) and 5-year PFS according to IPS or clinical stage

IPS/stage	CR rate after chemotherapy (%)	CR rate after radiation (%)/5-year PFS (%)
IPS		
0–2	65.4	84.6/83.1
3–7	60.0	75.0/69.0
Clinical stage		
II	67.2	86.9/86.8
III or IV	59.6	75.4/69.2
IIA	67.3	87.8/85.7
IIB, III or IV	60.9	76.8/73.1
Non-bulky IIA	74.4	87.2/87.2
Bulky IIA, IIB, III or IV	58.2	78.5/74.0

IPS International Prognostic Score

patients achieved CR (including CRu) (63.6%; 95% CI 54.2–72.2%) after ABVd therapy and 96 patients achieved CR (including CRu) (81.4%; 95% CI 73.1– 87.9%) after post-ABVd radiation therapy. A total of 39 patients (23 patients in PR and 16 patients in CR or CRu after ABVd) received radiotherapy after the completion of chemotherapy. While a total of 4 patients with initial bulky mass did not receive planned radiation therapy in CR at the end of chemotherapy, 23 patients who achieved PR after 4–8 cycles of ABVd therapy had unplanned radiation therapy. Twenty-one out of the 23 PR patients achieved CR or CRu after unplanned radiation therapy.

The responses according to the IPS category or clinical stage (II vs. III or IV, IIA vs. IIB, III or IV, and non-bulky IIA vs. bulky IIA, IIB, III or IV) are shown in Table 5. After involved-field radiation therapy, CR rate in lower (IPS: 0–2) and higher risk groups (IPS: 3–7) increased from 65.4 to 84.6%, and from 60.0 to 75.0%, respectively. Improved CR rate after radiation therapy was also observed in each clinical stage group. In the group of stage III or IV, the CR rate after ABVd therapy was 58.2%, but after radiation therapy, CR rate was increased to 78.5%.

3.5 Progression-free survival

The PFS curve of all 118 eligible patients is shown in (Fig. 1a), and 5-year PFS was estimated to be 78.4% (95% CI 70.9–85.9%). The PFS was analyzed according to the IPS risk groups and stages. The PFSs at 5 years in lower (IPS of 0–2) and higher risk groups (IPS of 3 or more) were 83.1% (95% CI 74.8–91.5%) and 69.0% (95% CI 54.4–83.7%), respectively (Fig. 1b). The PFSs at 5 years in stage II and III or IV were 86.8% (95% CI 75.4–93.2%) and 69.2% (95% CI 55.1–79.6%), respectively (Fig. 1c). The PFSs at 5 years in stage IIA non-bulky and stage IIA bulky, IIB, III or IV were 87.2 (95% CI 71.9–94.5%) and 74% (95% CI 62.6–82.4%), respectively (Fig. 1d).

3.6 Overall survival (OS)

The OS of all 118 eligible patients is shown in Fig. 2a. There have been 14 deaths among the 118 eligible patients. The OS at 5 years was estimated to be 91.3% (95% CI 86.1–96.5%). Median follow-up time for censored patients was 6.5 years.

The OS was analyzed according to the IPS risk groups and stages. The OS at 5 years in lower (IPS of 0–2) and higher risk groups (IPS of 3 or more) were 93.5% (95% CI 88.0–99.0%) and 87.0% (95% CI; 76.4–97.6%), respectively (Fig. 2b). The OS in stage II and III or IV were 96.7% (95% CI 87.5–99.2%) and 85.3% (95% CI 72.8–92.4%), respectively (Fig. 2c). The OS at 5 years in stage IIA non-bulky and stage IIA bulky, IIB, III or IV were 97.4% (95% CI 83.2–99.6%) and 88.2% (95% CI 78.5–93.7%), respectively (Fig. 2d).

4 Discussion

Our present phase II study confirmed that ABVd with lower dose of dacarbazine is as effective for Japanese patients with newly diagnosed HL with stages II–IV as ABVD with full dose of dacarbazine for the Western patients.

ABVD has been considered the standard of care for advanced-stage HL after the publication of a landmark CALGB study [7] and other large-scaled randomized phase III studies [9, 22–24]. The German Hodgkin Study Group has developed a dose-escalated and accelerated combined-modality program, escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine) plus radiation (+RT) for newly diagnosed patients with unfavorable stage IIB, III or IV [20]. The most recent analysis, also with a median follow-up of 9.3 years, included 1,196 evaluable patients and demonstrated superior freedom from treatment failure and overall survivals for the patients treated with escalated BEACOPP + RT [25]. In freedom from treatment failure (88% at 5 years), escalated BEACOPP + RT seems to be superior to failure-free survival (61% at 5 years) in ABVD therapy in CALGB study [8, 25]. Italian group compared ABVD with BEACOPP and CEC in randomized trial for the initial treatment of advanced HL [26]. Although BEACOPP may be associated with an improved PFS, it has greater toxicity; because of the success of salvage regimens, improvements in PFS may not translate to improved OS. Thus, ABVD still represents the standard initial treatment regimen for advanced HL.

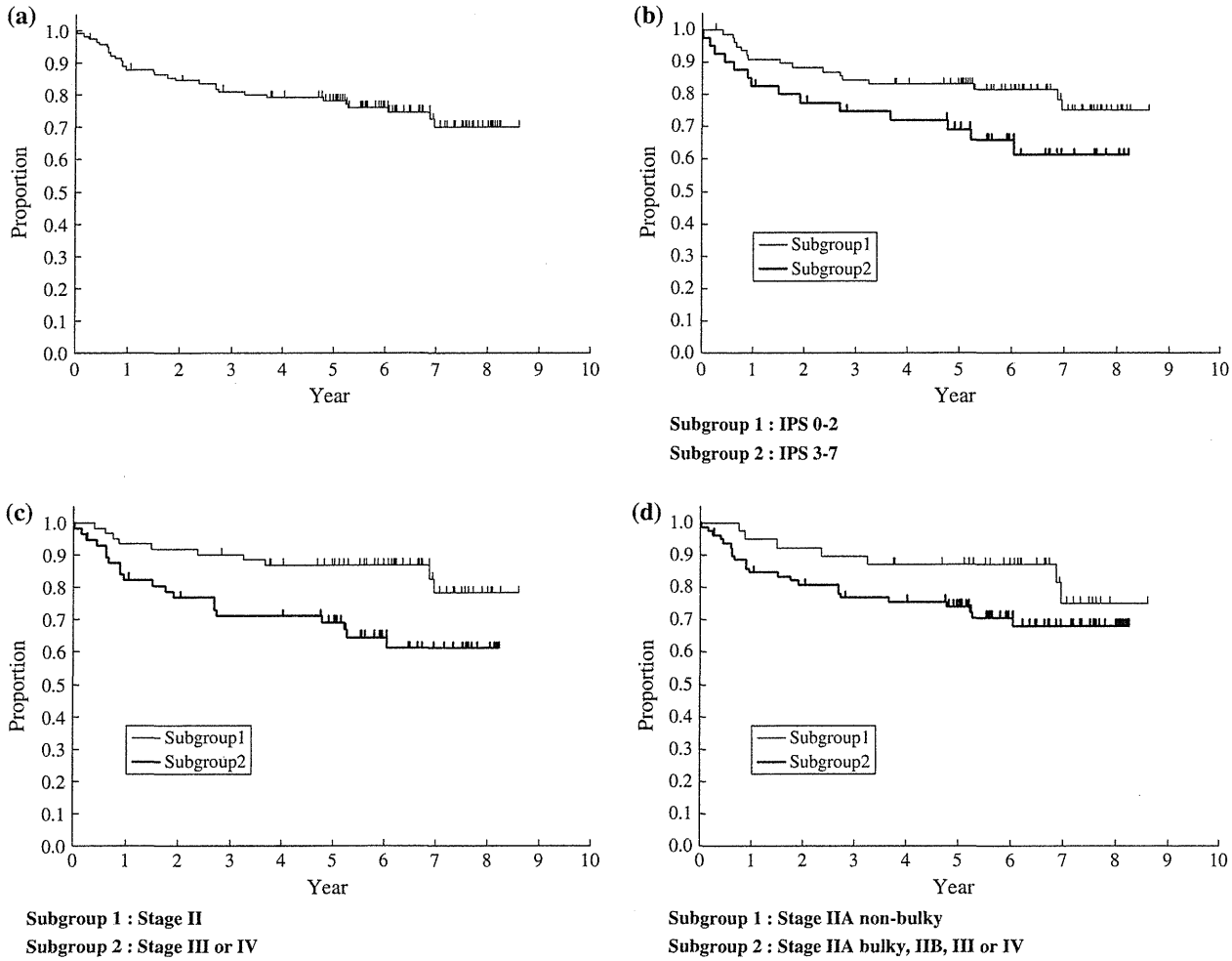

Fig. 1 Progression-free survival. *Tick marks* indicate censored data. **a** All 118 eligible patients. **b** Comparison according to IPS risk groups. *Fine* and *bold lines* represent lower risk group categorized by IPS of 0–2 ($n = 78$) and higher risk group categorized by IPS of 3 or more ($n = 40$), respectively. **c** Comparison according to stages. *Fine* and *bold lines* represent stage II group (subgroup 1; $n = 61$) and stage III or IV group (subgroup 2; $n = 57$), respectively. **d** Comparison according to stages in consideration of bulky disease and B symptom. *Fine* and *bold lines* represent stage IIA non-bulky group (subgroup 1; $n = 39$) and stage IIA bulky, IIB, III or IV group (subgroup 2; $n = 79$), respectively

Hoskin et al. reported the results of the randomized comparison of the Stanford V regimen and ABVD followed by involved-field radiation therapy in both arms to sites of previous bulk (>5 cm) in the treatment of advanced HL conducted by United Kingdom National Cancer Research Institute Lymphoma Group [27]. In that UK study, patients with stage IIB, III, or IV disease or with stages I–IIA disease with bulky disease (>5 cm) or other adverse features were eligible. There was no evidence of a difference in ORR, projected 5-year PFS and OS (92, 76 and 90%, respectively, for ABVD; 91, 74 and 92%, respectively, for Stanford V). They concluded that the efficacies of Stanford V and ABVD were comparable when given in combination with appropriate radiotherapy, and that ABVD is likely to remain standard therapy for initial treatment of HL.

In the present study, stages II–IV were eligible, while in CALGB study and German Hodgkin's Lymphoma Study Group's trial, stages IIIA2, IIIB, IVA or IVB, and unfavorable stages IIB–IV were eligible, respectively. Thus, direct comparison of efficacies of the present study with those in CALGB study or German Hodgkin's Lymphoma Study Group's trial is difficult. However, in UK study, stages I–IIA disease with bulky disease (>5 cm) or other adverse features and stage III or IV were eligible. And, the percentage of patients with stage III or IV in the present study and UK study was 48 and 54%, respectively. In the present study, CR rate and 5-year PFS of the patients with IIA-bulky, IIB, III, or IV (67% of all eligible patients) were 78.5 and 74%, respectively, while CR rate and 5-year PFS of the patients in ABVD arm in UK study were 67 and

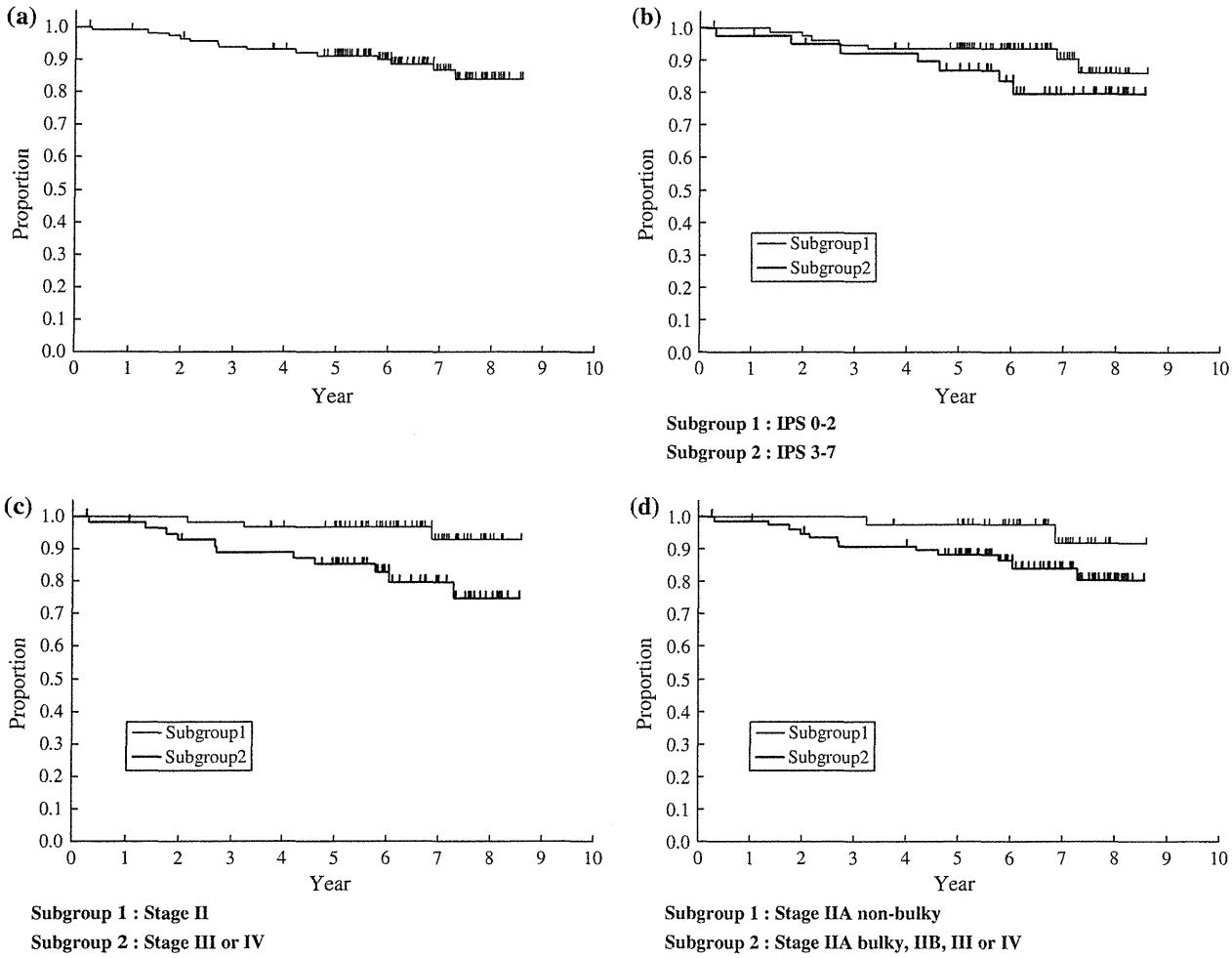

Fig. 2 Overall survival. *Tick marks* indicate censored data. **a** All 118 eligible patients. **b** Comparison according to IPS risk groups. *Fine* and *bold lines* represent lower risk group categorized by IPS of 0–2 ($n = 78$) and higher risk group categorized by IPS of 3 or more ($n = 40$), respectively. **c** Comparison according to stages. *Fine* and *bold lines* represent stage II (subgroup 1; $n = 61$) group and stage III or IV group (subgroup 2; $n = 57$), respectively. **d** Comparison according to stages in consideration of bulky disease and B symptom. *Fine* and *bold lines* represent stage IIA non-bulky (subgroup 1; $n = 39$) and stage IIA bulky, IIB, III or IV group (subgroup 2; $n = 79$), respectively

76%, respectively. Thus, the efficacies of ABVd therapy of advanced-stage patients in the present study seem to be comparable to those of ABVD therapy in UK study, although there is a limitation due to historical comparison.

Combined-modality treatment (CMT) using multidrug chemotherapy and radiotherapy is currently considered the standard of care in early stage HL. Its role in advanced stages, however, continues to be debated [28, 29]. In the present study, radiotherapy was planned to deliver to the initial sites of bulky mass for the patients in CR after ABVd therapy. As a result, it is possible that radiation to patients in PR might contribute to good PFS in the present study. Those tendencies were reported in UK study [27].

In the present study, 39 patients (33% of all eligible patients) were stage IIA without bulk disease (non-bulky) defined as early stage. Although CMT of short courses of ABVD followed by involved-field radiation therapy has been established as a standard of care in early stage HL since 2004 [30], extended-field radiation therapy was utilized as a standard of care of early stage HL, and full courses of chemotherapy was considered as an optional therapy in late 1980s to early 1990s when the present study was planned. Meyer et al. [31] reported the results of a randomized trial conducted by National Cancer Institute of Canada Clinical Trials Group (NCIC) and the ECOG comparing ABVD chemotherapy alone with CMT in patients with early stage HL. The 5-year PFS of patients with non-bulky stage IIA in the present study, and 5-year freedom from disease progression of patients with favorable early stage in NCIC and ECOG study was 87.2 and 87%,

respectively. Although a direct comparison is difficult, the outcome of early stage HL in the present study seems to be comparable with that in the NCIC and ECOG study.

According to the international comparison of survival data by Cancer Registries [32], OS at 5 years of the patients with HL treated in 1997–1999 was 68.3% in Japan, while it was 84.9% in the USA and 83.0% in the Europe in the same period. One of the reasons why the 5-year survival rate in Japan was about 15% lower than those in the USA and Europe is that dacarbazine was not commercially available in 1990s, then ABVD therapy could not be delivered to Japanese patients with HL. In this context, the present study contributed to get a governmental approval of dacarbazine for HL in 2000s and may contribute to improve greatly the treatment outcome for patients with HL in Japan.

As reported previously [7], major toxicity was grade 4 neutropenia (45.3%) in ABVd therapy in the present study. However, no severe (grade 3 or 4) infection was observed in the present study. As Boeti et al. reported, ABVD administration irrespective of granulocyte counts may allow the treatment to be given at full dose without delays or significant number of infective episodes [33]. Although four kinds of grade 4 non-hematological toxicity were observed in 4 patients as described above, all toxicities were transient, and all patients fully recovered. Although ABVd regimen contains doxorubicin and bleomycin, no severe cardiac toxicity such as congestive heart failure or ischemic heart disease, and no severe pulmonary toxicities were observed in the present study. Although the dose of dacarbazine in the present study was as same as that in JCOG8905, the incidence of grade 3/4 nausea/vomiting was decreased from 25%/12% in JCOG8905 to 11%/−% in the present study [12]. This improvement was mainly due to the development of 5HT3 antagonist such as granisetron that was launched in May 1992 in Japan. Since acute emesis due to dacarbazine is now well known to be controlled by these 5HT3 antagonists and new anti-emetic drug called substance P antagonist, dose reduction of dacarbazine in ABVD therapy may not be quite necessary.

In this study, four secondary malignancies including one MDS and three solid tumors developed after the completion of protocol treatment. Although ABVD therapy was reported to be less leukemogenic or carcinogenic [7, 34], development of MDS in one patient in the present study might be related to ABVd regimen. Although radiation is known to be carcinogenic, a patient with rectal cancer received mantle-field radiation without any radiation to abdomen. Thus, this case with rectal cancer also seems to be incidental development. Other two patients with lung cancer and gastric cancer, respectively, received only ABVd therapy. It might be less possible that ABVd therapy caused these solid cancers.

In summary, the present phase II study, JCOG 9305, showed the expecting efficacy and acceptable toxicity of ABVd therapy including post-chemotherapeutic involved-field radiation therapy for previously untreated patients with stage II–IV HL, despite the dose reduction of dacarbazine to two-thirds of that in the original ABVD therapy. These data should be useful for future clinical trials.

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Appendix

Participating institutions and principal investigators of the JCOG9305 study included: Sapporo National Hospital (C. Mikuni), Sapporo Hokuyu Hospital (M. Kasai), Akita University School of Medicine (A. Miura), Iwaki Kyoritsu General Hospital(T. Sai), Ota Nishinouchi Hospital (S. Ohta), National Cancer Center Hospital East (T. Ohtsu), National Cancer Center Hospital (K. Tobinai), Kyorin Medical University (K. Kawano), Tokyo Metropolitan Komagome Hospital (T. Sasaki), National Medical Center (A. Togawa), The 3rd Hospital of Tokyo Jikei Medical School (F. Mizoroki),Tokai University School of Medicine (T. Hotta), Niigata Cancer Center (T. Chou), Saku General Hospital (S. Seki), Hamamatsu University School of Medicine (K. Ohnishi), Aichi Cancer Center Hospital (Y. Morishima), Nagoya University School of Medicine (T. Kinoshita), Nagoya National Hospital (M. Tanaka), Fujita Health University (M. Hirano), Mie University School of Medicine (H. Shiku), Kyoto Prefectural University of Medicine (M. Taniwaki), Kyoto University School of Medicine (H. Ohno), Shiga Medical Center for Adults (T. Suzuki), Ohtsu Red Cross Hospital (T. Ohno), Osaka Red Cross Hospital (K. Nasu), Kansai Medical School (S. Fukuhara), Tenri Yorozu Hospital (Y. Ohno), Hiroshima Red Cross Atomic Bomb Hospital (H. Asaoku), Kagawa Medical School (M. Nagai), Shikoku National Hospital (K. Okabe), Sasebo Municipal General Hospital (S. Ikeda), National Kyushu Cancer Center (N. Uike), Nagasaki University School of Medicine (M. Tomonaga), Kagoshima University (S. Hanada), Kagoshima Municipal Hosipital (M. Tara).

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) as a hematologist for the Panel.

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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.

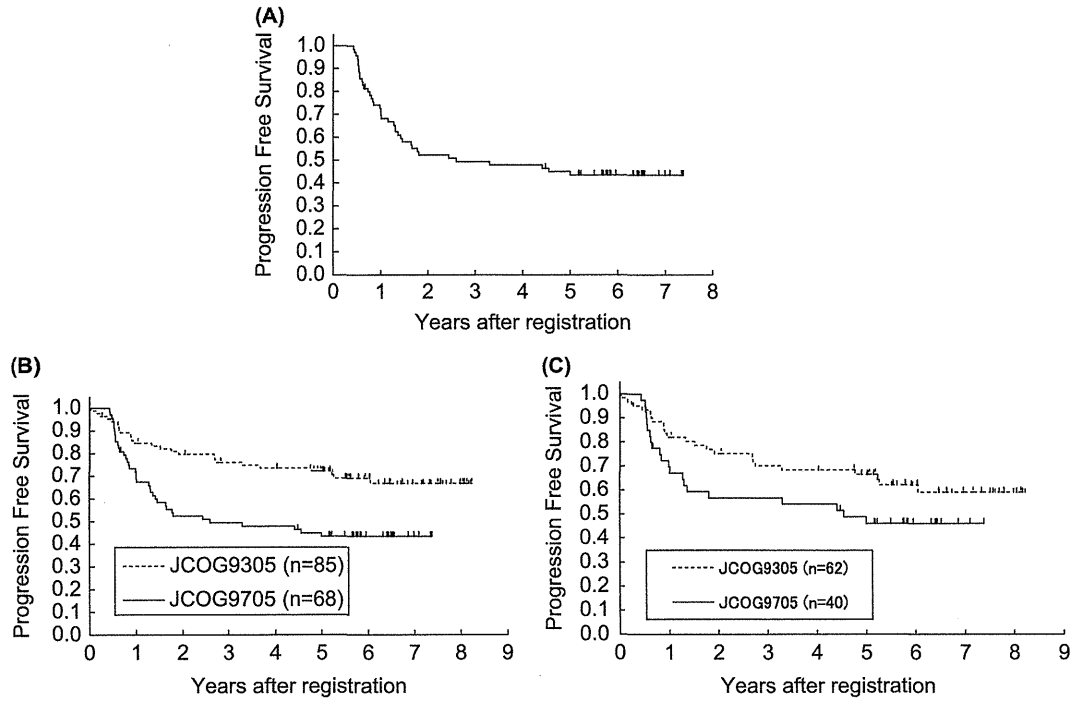

Figure 1. Progression-free survival (tick marks indicate censored data). (A) All 70 eligible patients. (B) Comparison according to study group; dotted and solid lines represent JCOG9305 (ABVd therapy, subgroup 1: $n = 85$) and JCOG9705 (ABV therapy, subgroup 2: $n = 68$), respectively. Target population 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].

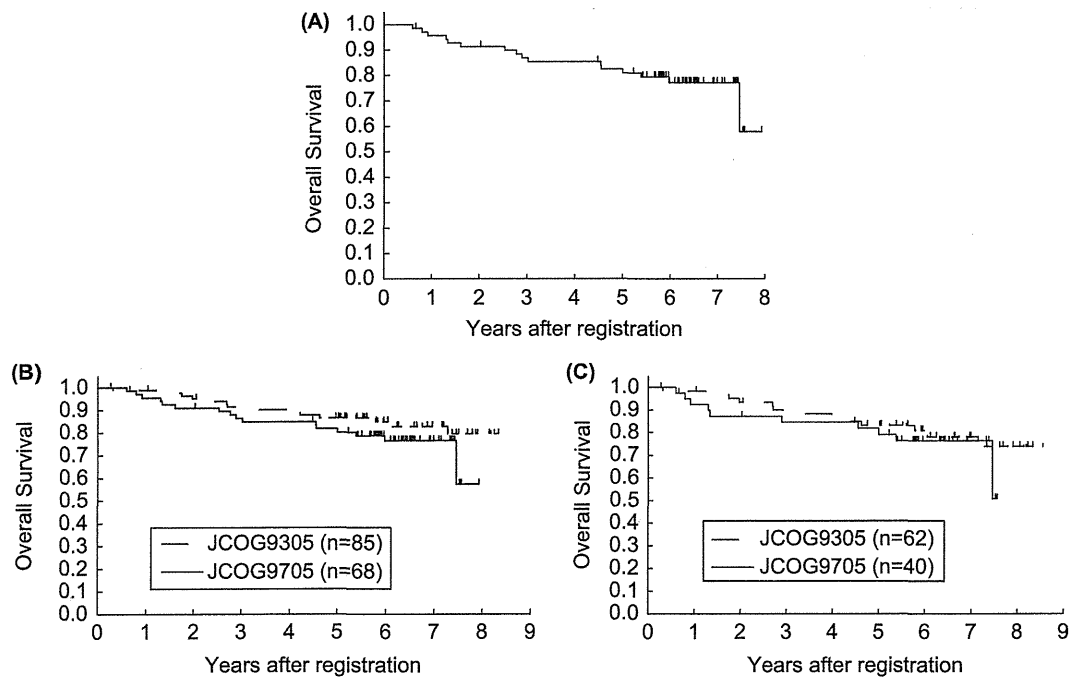

Figure 2. Overall survival (tick marks indicate censored data). (A) All 70 eligible patients. (B) Comparison according to study group;dotted and solid lines represent JCOG9305 (ABVd therapy, subgroup 1: $n = 85$) and JCOG9705 (ABV therapy, subgroup 2: $n = 68$), respectively. Target population is stage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

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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.

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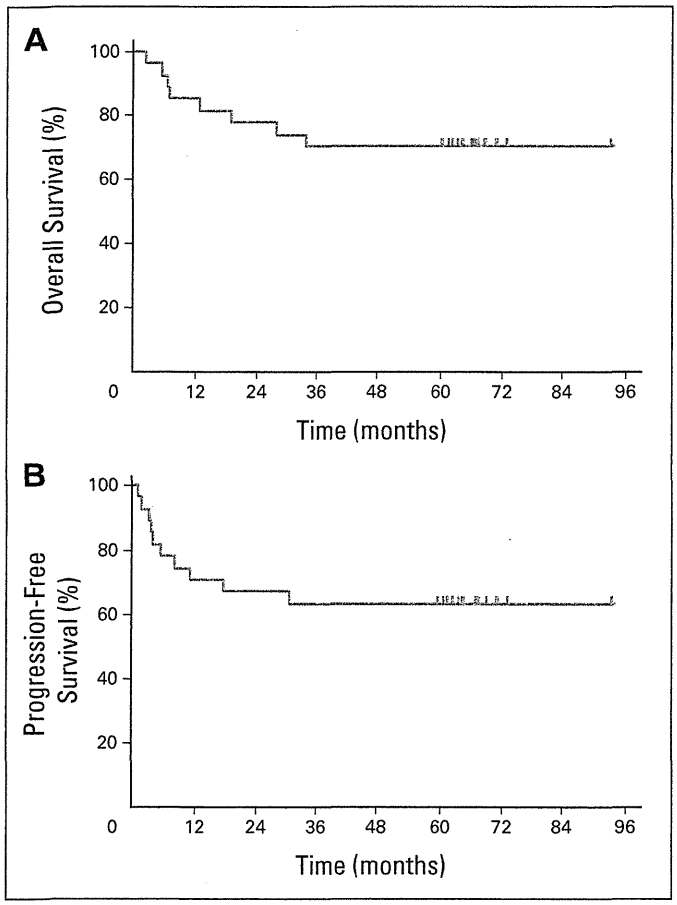

Fig 1. (A) Overall survival and (B) progression-free survival of 27 patients treated with radiotherapy and a two-thirds dose of dexamethasone, etoposide, ifosfamide, and carboplatin.

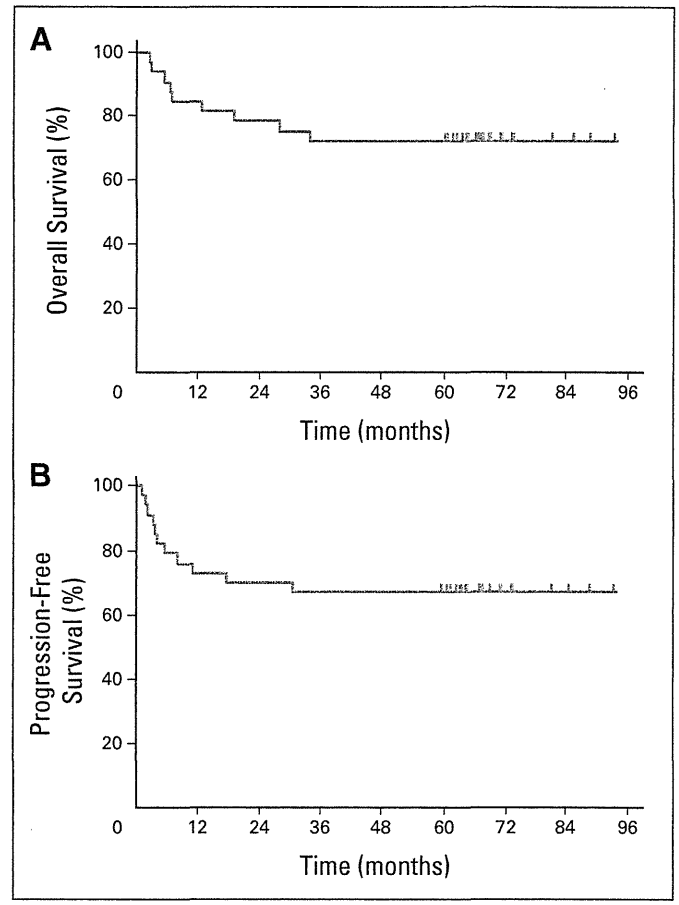

Fig 2. (A) Overall survival and (B) progression-free survival of 33 patients treated with radiotherapy and dexamethasone, etoposide, ifosfamide, and carboplatin.

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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Review Article: Study Group

Lymphoma Study Group of JCOG

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The Lymphoma Study Group (LSG) of the Japan Clinical Oncology Group (JCOG) was initiated in 1978 by five institutions and now has 47 members. JCOG-LSG has focused on combined modalities, dose intensification and the incorporation of new agents for major disease entities of lymphoid malignancies. More than 30 trials including 10 randomized trials have been conducted for aggressive non-Hodgkin's lymphoma (NHL), adult T-cell leukemia–lymphoma (ATL), lymphoblastic lymphoma/acute lymphoblastic leukemia, Hodgkin's lymphoma (HL), multiple myeloma, NK/T-NHL and indolent B-NHL, and correlative epidemiological and pathological studies have been performed on human T-lymphotropic virus type-I and T/B cell phenotypes. The first trials for aggressive NHL revealed significant differences in the prognosis of ATL, non-ATL T-NHLs and B-NHLs, establishing a subclassification of ATL, and leading to the establishment of standard therapies for ATL and localized nasal natural killer/T-NHL. Recently, for B-NHLs including diffuse large B-cell lymphoma, mantle cell lymphoma, and indolent B-NHLs, regimens incorporating rituximab have been evaluated. The JCOG-LSG trials for HL led to the approval of dacarbazine for the National Health Insurance in Japan. The multicenter trials by the JCOG-LSG combining new modalities such as molecular-targeting agents will contribute to further improvements in the treatment of lymphoid malignancies.

Key words: clinical trial – lymphoid malignancy – Lymphoma Study Group – Japan Clinical Oncology Group – T- and B-cell lymphoma

INTRODUCTION

Lymphoid malignancies consist of B-cell and T/natural killer (NK)-cell neoplasms, which are clonal tumors of mature and immature B cells, T cells or NK cells at various stages of differentiation (1). Paradigm shifts in the management of lymphoid malignancies have been achieved by the discovery of new disease entities, revision of classifications and development of new agents. The diagnosis of lymphoid malignancies improved significantly in the 1980s mainly with the development of immunophenotypic analyses using monoclonal antibodies. This resulted in the discovery of several new disease entities. Among them, adult T-cell leukemia–lymphoma (ATL) was first described in Japan by Takatsuki and colleagues (2) in 1977 and was found to be associated with human T-lymphotropic virus type-I (HTLV-1), the first RNA retrovirus associated with human diseases, in the early 1980s (3–5).

Treatment of lymphoid malignancies has been improved by the development of standard combination chemotherapy such as CHOP, secondary in association with the advances in diagnosis and classification described above, and by the development of new agents and modalities such as an anti-CD20 antibody for CD20-expressing B cell

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malignancies, autologous/allogeneic (auto/allo)-hematopoietic stem cell transplantation (HSCT) with the prophylactic use of granulocyte colony-stimulating factor (G-CSF), and thalidomide and its derivatives and proteasome inhibitor for multiple myeloma (MM) (6,7).

Along with these advances in research for lymphoid malignancies, JCOG-LSG, which was initiated in 1978, has conducted more than 30 clinical trials including 10 randomized trials to establish new standard therapies for lymphoid malignancies (Tables 1–7 and Fig. 1) (8–10). In this article, we summarize the development of JCOG-LSG with the results of clinical trials.

HISTORY OF JCOG-LSG

Conducting clinical trials for the development of standard therapies requires investigators, a coordinating center and committees under the support of grant providers (8–10). Now, LSG, as in the case of other cancer study groups in JCOG, is conducting trials under the organization of JCOG. At first in 1978, following the success of multi-institutional clinical trials of oncology in the USA, a directed research project entitled 'A Study on Multidisciplinary Treatment for Solid Cancer' was started. Several disease committees including LSG have been supported since then by Grants-in-Aid for Cancer Research from the Ministry of Health, Labor and Welfare (MHLW) in Japan. LSG was initiated in 1978 with only five institutions chaired by Masanori Shimoyama, MD, and included the T- and B-cell Malignancy Study Group as a subgroup to conduct epidemiological studies of ATL. It then grew to 17 institutions during 1980–84 to perform virological studies on ATL, resulting in the discovery of an etiological retrovirus called ATL virus by Yorio Hinuma, MD, in 1981. Meanwhile, LSG has conducted clinical trials for non-Hodgkin's lymphoma (NHL) and later formed the Lymphoma Clinico-Pathological Panel to evaluate the reproducibility agreement rates of the pathological diagnosis of NHL. Then, the Autologous Bone Marrow Transplantation Study Group was initiated by Kensei Tobinai, MD, in 1990, which was later integrated into the LSG and the Breast Cancer Study Group in 1999. [LSG now consists of 47 institutions as an active disease committee in JCOG.]

Along with the development of standing committees and a statistical center, the multicenter cooperative oncology group was named the Japan Clinical Oncology Group (JCOG) in 1990. JCOG has now a common Data Center, a Steering Committee and each of 13 cancer study groups including LSG. JCOG-LSG has conducted consecutive studies for

Table 1. Results of the JCOG-LSG trials for advanced aggressive non-Hodgkin's lymphoma (NHL)

Protocol	Regimen	Patients risk category	Phase	No. of patients	%CR and uncertified CR	MST (months)	Survival (%)	Reference
JCOG7801	VEPA	All	II	100	52	NA	NA	11
JCOG8101		All	III	163				12
	VEPA			81	52	17	27 (4 years)	
	VEPA-M			82	62	24	37 (4 years)	
JCOG8701	LSG4	All	II	267	72	39	48 (5 years)	13
JCOG9002		All	III	447	67	NA	56 (5 years)	14
	LSG9			230	70	91	57 (5 years)	
	modified LSG4			217	65	78	55 (5 years)	
JCOG9203	VEPA/FEPP	Elderly	II	45	60	52	42 (5 years)	58
JCOG9505	upfront ASCT	HI/H	R-II	70	56	12	42 (4 years)	18
	CHOP-14			35	60	NA	42 (4 years)	
	DE-CHOP			35	51	NA	42 (4 years)	
JCOG9506		HI/H	II	43	NA	NA	58 (3 years)	NA
JCOG9508	CHOP	L/LI	II	213	NA	NA	74 (4 years)	17
JCOG9809		All	III	323[a]			74 (2 years)	19, 20
	CHPO-14			162	67	NR	55 (8 years)	
	CHOP			161	62	NR	56 (8 years)	

VEPA consisting of vincristine (VCR), cyclophosphamide (CPA), prednisone (PSL) and doxorubicin (DOX); VEPA-M consisting of VEPA + methotrexate (MTX); LSG4 consisting of VEPA-B, M-FEPA and VEPP-B, where VEPA-B consisting of VEPA + bleomycin (BLM), M-FEPA consisting of moderate dose of MTX, vindesine (VDS), CPA, PSL and DOX, and VEPP-B consisting of VCR, CPA, PSL and procarbazin (PCZ); LSG9 consisting of dose-intensified mLSG4; DE-CHOP: dose-escalated CHOP; CR, complete response; MST, median survival time; NA, not applicable; NR, not reached, R-II, randomized Phase II study; ASCT, autologous stem cell transplantation.
[a]Number of enrolled patients until the early termination.