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.

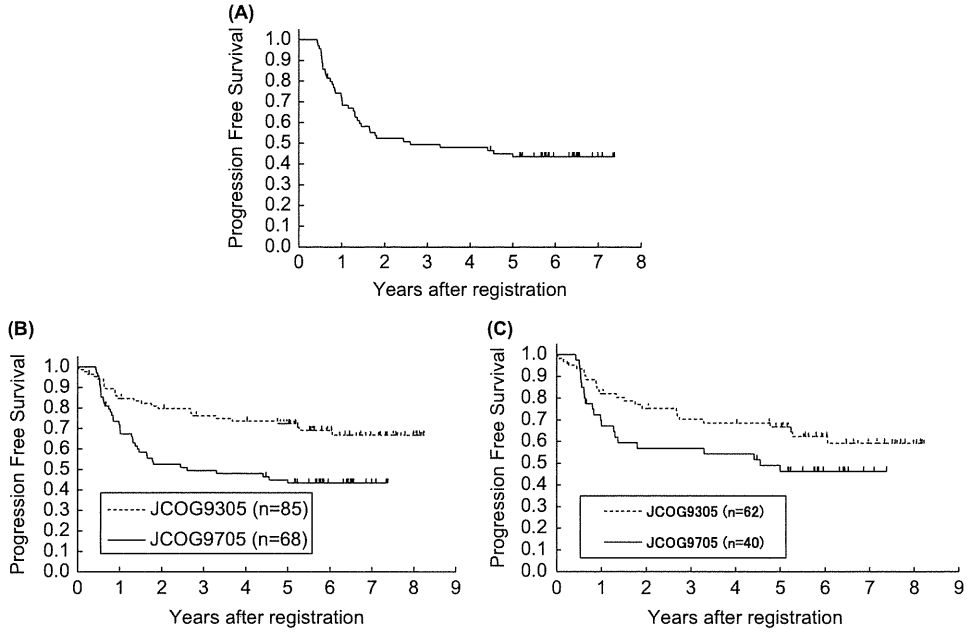

Figure 1. Progression-free survival (tick marks indicate censored data). (A) All 70 eligible patients. (B) Comparison according to study group; dotted and solid lines represent JCOG9305 (ABVd therapy, subgroup 1: $n = 85$) and JCOG9705 (ABV therapy, subgroup 2: $n = 68$), respectively. Target population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

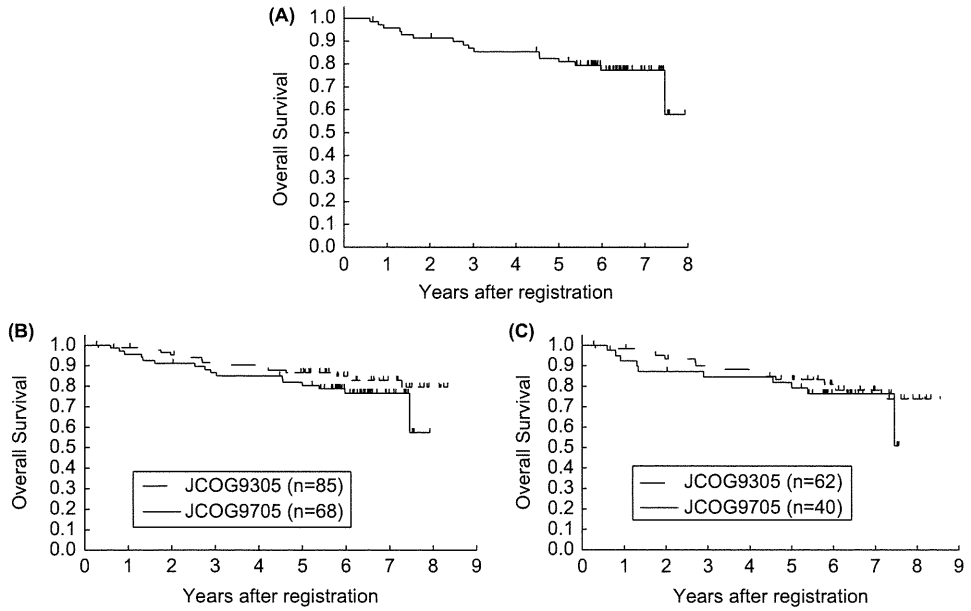

Figure 2. Overall survival (tick marks indicate censored data). (A) All 70 eligible patients. (B) Comparison according to study group;dotted and solid lines represent JCOG9305 (ABVd therapy, subgroup 1: $n = 85$) and JCOG9705 (ABV therapy, subgroup 2: $n = 68$), respectively. Target population is stage 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 grade by JCOG toxicity criteria			
Toxicity	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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Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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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.

Reply to H. Charalambous et al

Brenda Breuer, Ricardo A. Cruciani, and Russell K. Portenoy
Beth Israel Medical Center, New York, NY

We agree with Charalambous and Silbermann[1] that action needs to be taken to improve the skills of oncologists to manage chronic cancer pain. Their suggestion for clinical training programs at first seems logical; they cite findings that classroom training did not improve residents' knowledge,[2] a finding consistent with ours, that is, that continuing medical education in cancer pain management seemed to be ineffective.[3] They also cite a study showing that clinically based training in palliative care is effective.[4] In that study, however, there was only a 10% improvement, with statistically significant improvement in only six of 25 questions. In addition, the program was optional, which might suggest that those who took it were more motivated than most, making the generalizability of these findings questionable. Thus, although we agree that change is critically needed, the way to accomplish that change remains elusive. We continue to study this issue and hope that a more complete characterization of this problem will inform the development of more effective programs to support best practices in pain management and palliative care for the broad oncology community.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
The author(s) indicated no potential conflicts of interest.

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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.

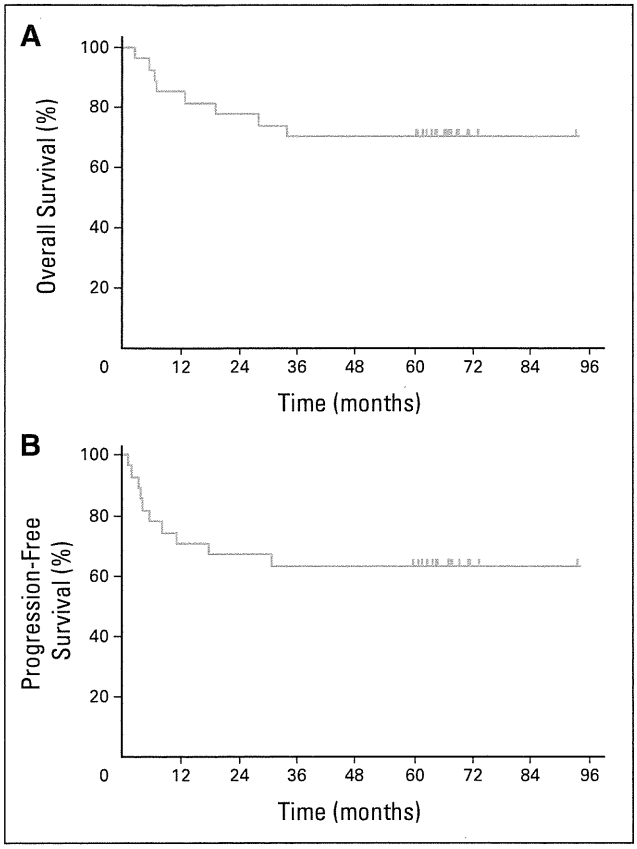

Fig 1. (A) Overall survival and (B) progression-free survival of 27 patients treated with radiotherapy and a two-thirds dose of dexamethasone, etoposide, ifosfamide, and carboplatin.

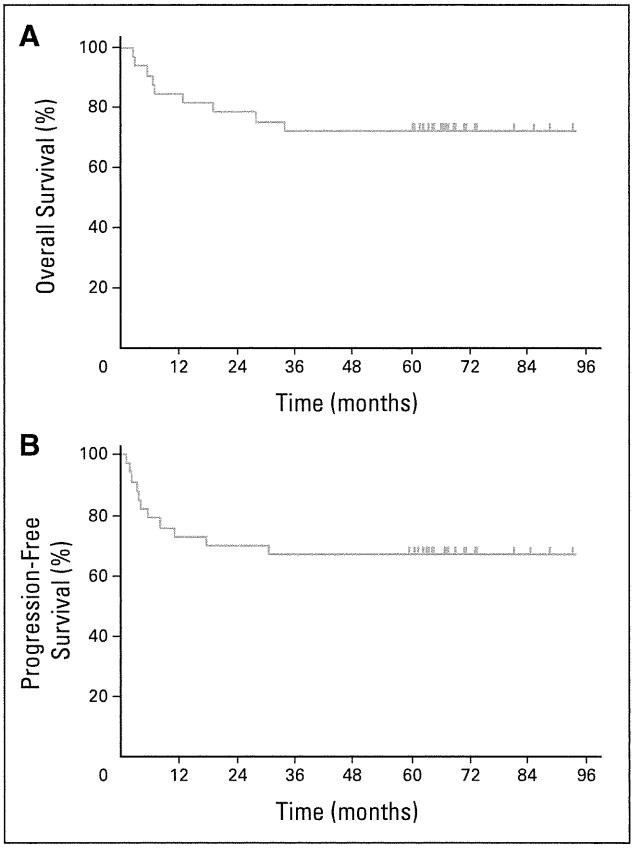

Fig 2. (A) Overall survival and (B) progression-free survival of 33 patients treated with radiotherapy and dexamethasone, etoposide, ifosfamide, and carboplatin.

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

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
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Cancer Rehabilitation Evaluation System (CARES) and CARES-SF Now Publicly Available

To the Editor: I was very pleased to read your special issue of *Journal of Clinical Oncology* (April 10, 2012) focused on "Caring for the Whole Patient: The Science of Psychosocial Care." The issue does an excellent job of amplifying the findings of the recent Institute of Medicine report[1] by including review articles that provide in-depth presentation of strategies that can be used to implement the recommendations of the committee report. One of the major failures of our current oncology practice is the lack of a systematic approach to evaluating the unmet needs of patients with cancer, and this is well described in the article by Carlson et al.[2]

Early in the 1980s, my colleagues Coscarelli (Schag) and Heinrich developed a needs assessment tool, initially called the Cancer Inventory of Problem Situations[3] and then later refined as the Cancer Rehabilitation Evaluation System (CARES)[4] and a short form called the CARES-SF.[5] I have used this tool for intervention research,[6] outcomes in clinical trials,[7] and clinical care. It is described among a variety of instruments in Table 2 of the article by Carlson et al[2] as a reliable and useful tool for assessing the unmet needs of patients with cancer. Unfortunately, the widespread use of the CARES and CARES-SF was limited by a copyright and user fee that the developers chose to impose. Fortunately, this is no longer the case. The CARES, CARES-SF, user manual and scoring sheets, along with a listing of many related publications are now publicly available at the Jonsson Comprehensive Cancer Center Web site.[8] I would encourage anyone interested in a comprehensive needs assessment tool to review the CARES and consider its use. It is well

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ORIGINAL ARTICLE

Phase II study of cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) therapy for newly diagnosed patients with low- and low–intermediate risk, aggressive non-Hodgkin's lymphoma: final results of the Japan Clinical Oncology Group Study, JCOG9508

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

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

Keywords Clinical trial · Aggressive lymphoma · Chemotherapy · CHOP

Introduction

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

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

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

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

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

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Patients and methods

Patients

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

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

Registration

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

Treatment

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

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

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

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

Central review of pathological diagnosis

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

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

Response and toxicity criteria

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

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

Endpoints and study design

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

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

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

Results

Patient characteristics

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

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

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

Pathological characteristics

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

Clinically and pathologically eligible patients

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

Table 1 Patients characteristics

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

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

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

[a] Ineligible type

MALT Mucosa-associated lymphoid tissue

CLL/SLL Chronic lymphocytic leukemia/small lymphocytic lymphoma

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

Responses and survival of clinically and pathologically eligible patients

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

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

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

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

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

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

Response and survival in patients with DLBCL

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

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

Toxicity

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

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

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

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

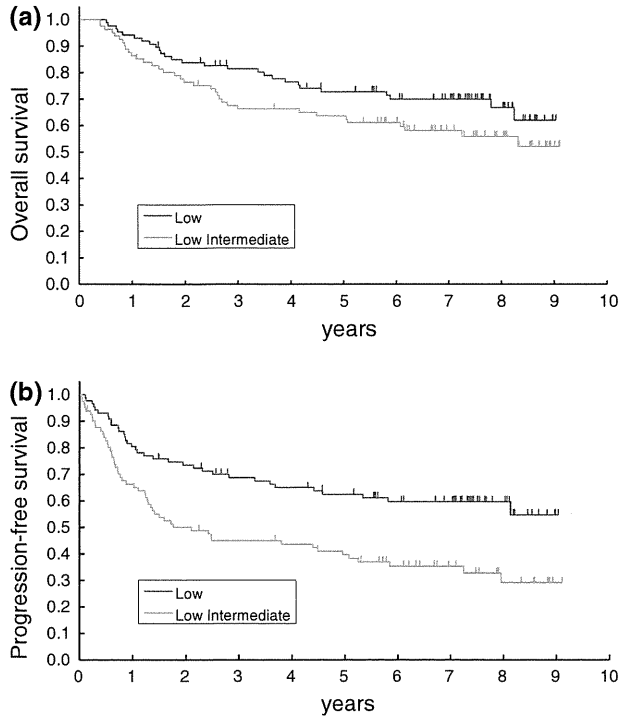

Fig. 1 Kaplan–Meier estimate of OS and PFS for pathologically eligible patients. **a** OS curves for patients in each risk category. The 5-year OS (95 % CI) in L risk and L–I risk cases was 73 % (63–82 %) and 64 % (53–74 %), respectively. **b** PFS curves for patients in each risk category. The 5-year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

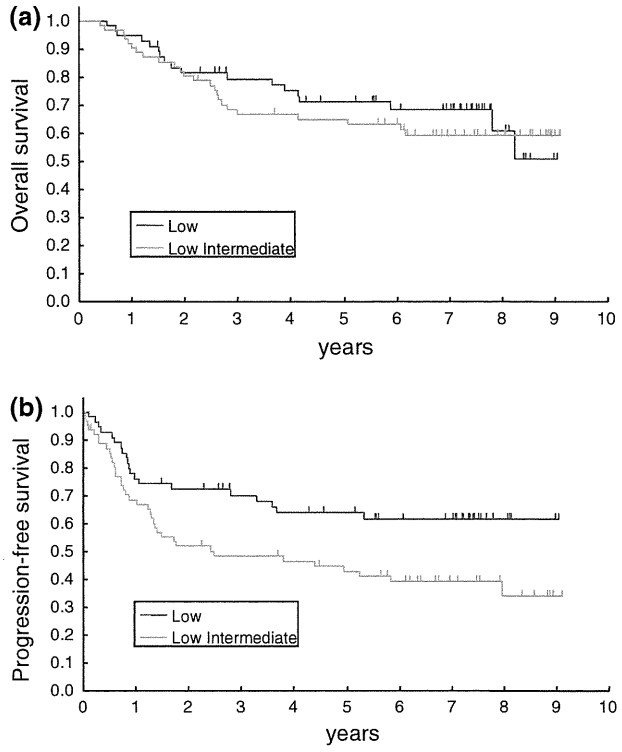

Fig. 2 Kaplan–Meier estimate of OS and PFS for DLBCL-NOS patients. **a** OS curves for patients in each risk category. The 5-year OS (95 % CI) in L risk and L–I risk patients was 71 % (58–83 %) and 65 % (53–77 %), respectively. **b** PFS curves for patients in each risk category. The 5-year PFS (95 %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

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

Prognostic factors

To investigate other prognostic factors not included in IPI, Cox multivariate regression analyses were carried out to determine OS and PFS with the prognostic factors in Table 4 (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

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

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

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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Short Communication

Melphalan–Prednisolone and Vincristine–Doxorubicin–Dexamethasone Chemotherapy followed by Prednisolone/Interferon Maintenance Therapy for Multiple Myeloma: Japan Clinical Oncology Group Study, JCOG0112

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A multicenter phase III study for untreated multiple myeloma was conducted to investigate a switch-induction chemotherapy with melphalan–prednisolone and vincristine–doxorubicin–dexamethasone followed by randomization on maintenance therapy for patients achieving plateau. Between November 2002 and November 2005, 34 patients were registered. The study was closed early because of poor accrual. Thirty-three eligible patients, with a median age of 65 years (range: 47–77 years) were analyzed for the secondary purpose. For induction therapy, 16 patients were treated with vincristine–doxorubicin–dexamethasone and 17 with melphalan–prednisolone initially. In eight cases, induction therapy was switched because of a poor response. Both regimens were well tolerated, but neutropenia, anorexia, constipation and infection with neutropenia were more frequent for vincristine–doxorubicin–dexamethasone. Best response rates were 44% (95% confidence interval, 20–70) and 47% (95% confidence interval, 23–72), respectively, for vincristine–doxorubicin–dexamethasone and melphalan–prednisolone. Vincristine–doxorubicin–dexamethasone/melphalan–prednisolone switch-induction therapy might be feasible and effective for Japanese patients with multiple myeloma.

Key words: myeloma – Chemo-Phase III – MP/VAD – IFN/PSL

INTRODUCTION

The administration of melphalan and prednisone (MP) has been the standard treatment for multiple myeloma (MM) since the 1960s. A review of clinical trials found that MP results in a 60% overall response rate (ORR) with the response lasting 18 months and an overall survival (OS) period of 24–36 months (1). To develop more effective treatments that both produce a higher response rate and lengthen OS, combination chemotherapy using various regimens has been compared with MP or MP-like regimens in numerous randomized studies including ours (2). Among the many alternatives to MP, vincristine, doxorubicin and dexamethasone (VAD), first reported as an effective salvage therapy for MM refractory to melphalan or other alkylators, is frequently chosen especially for patients with significant symptoms related to MM partly because the achievement of a response with relief of symptoms occurs sooner than with MP (3). Also, VAD has been chosen for patients undergoing

high-dose chemotherapy followed by autologous stem cell transplantation (HDC-aSCT), because of less damage to hematopoietic stem cells after this regimen when compared with an alkylator-containing regimen such as MP (4). Therefore, VAD has been considered a standard treatment for untreated MM. However, VAD is more toxic than MP and requires hospitalization for continuous drip infusion. It was reported that MP was also effective as a salvage treatment for relapse after VAD and HDC-aSCT (5).

Despite the effective induction chemotherapies, most patients with MM will ultimately relapse. Therefore, attempts to prolong the remission with maintenance treatment have been made. Meta-analyses suggested that MM patients receiving α2 interferon (IFN) as maintenance therapy have a slightly prolonged OS (6,7). It is well documented that glucocorticoids have antitumor activity in MM patients (8,9). In a prior Southwest Oncology Group (SWOG) study, 89 patients responding to induction of VAD chemotherapy receive maintenance therapy with either prednisone at 50 mg three times per week with IFN, or IFN alone (10). Progression-free survival (PFS) was increased from 9 to 19 months for patients given the combination compared with those given IFN alone. A subsequent study by SWOG comparing alternate-day, oral treatment with prednisone at pharmacologic doses (50 mg) vs. physiologic doses (10 mg) for maintaining remission in MM patients who responded to chemotherapy revealed the benefit of the former regimen (OS: 37 vs. 26 months; $P = 0.05$) (11). However, the role of maintenance therapy in MM patients remains controversial, especially the usefulness of IFN when compared with prednisone. We considered that both the MP and VAD were standard as the induction therapy for untreated MM and each was substitutable for the other as salvage therapy. Therefore, we conducted a multicenter prospective randomized controlled trial to investigate switch-induction chemotherapy with MP and VAD followed by maintenance therapy to compare less toxic prednisolone (PSL) alone with PSL + IFN-α for the treatment of overt MM.

PATIENTS AND METHODS

Patients

Patients were eligible for the first registration if they were <80 years and had overt MM diagnosed according to the SWOG criteria and not previously treated with chemotherapy (12). Patients were required to have a performance status (PS) of 0–3 according to the criteria of the Eastern Cooperative Oncology Group (13), to have no severe organ dysfunction (Hgb ≥6.0 g/dl, neutrophils $\geq 1.0 \times 10^9$/l, platelets $\geq 20 \times 10^9$/l, alanine aminotransferase/aspartate aminotransferase ≤2.5 times the upper normal limit, total bilirubin ≤2.0 mg/dl, serum creatinine ≤5.0 mg/dl, PaO_2 ≥60 torr or SaO_2 ≥90%, electrocardiogram without arrhythmia and/or ischemia requiring treatment) and to be negative for hepatitis B virus surface antigen and/or hepatitis C virus antibody. Patients were not eligible if they had indolent myeloma or non-secretory MM, active primary cancer in other organs or any serious concomitant disease, including diabetes mellitus requiring insulin therapy, uncontrolled hypertension, psychiatric disease, a history of myocardial infarction, unstable angina, renal diseases with abnormal function, interstitial pneumonitis or autoimmune hepatitis, or if they were pregnant and/or breast feeding. The study protocol and the informed consent document were approved by both the Japan Clinical Oncology Group (JCOG) Protocol Review Committee and the institutional review board of each participating institution.

Eligibility for the second registration was identical to that of the first except for the achievement of a plateau phase of MM, a PS of two or less, a platelet count of $\geq 50 \times 10^9$/l and a serum creatinine concentration of ≤2.0 mg/dl.

Treatment

As for induction therapy, either VAD or MP was chosen. After the achievement of a plateau phase, maintenance therapy with either IFN + PSL or PSL alone was applied by randomization with a minimization method for balancing institution, induction chemotherapy and risk grouping by β2 microglobulin and C-reactive protein.

Switch-induction Chemotherapy

As for induction chemotherapy, patients received either MP or VAD following the primary physician's decision. If the response was less than partial response just before the fifth course of VAD or the seventh course of MP, a switch to the other induction therapy was allowed. The maximum number of courses for VAD and MP was 10 and 15, respectively. The maximum number in cases with switching was 20.

VAD consists of 0.4 mg vincristine per day and 10 mg/m^2 of doxorubicin per day, both administered by continuous infusion on Days 1–4; 40 mg of dexamethasone per day by drip infusion on Days 1–4. Treatment was repeated at 21 day intervals. MP consists of oral melphalan given at 8 mg/m^2 on Days 1–4 and oral PSL at 60 mg/m^2 on Days 1–4, every 4 weeks.

Maintenance Therapy

For maintenance therapy, after the achievement of a plateau phase and an evaluation of eligibility, patients were assigned to receive either PSL alone or PSL + IFN-α. IFN-α and PSL consist of natural IFN-α (NAMALWA, Sumiferon®) 3 MU s.c. ×3/week and PSL 50 mg p.o. ×3/week. PSL alone consists of PSL 50 mg p.o. ×3/week. The therapy was continued unless progressive disease or severe toxicity occurred.

Evaluation of Response and Adverse Events

Response criteria followed those of the European Group for Blood and Marrow Transplantation/International Blood and Marrow Transplant Research/Autologous Blood and Marrow

Transplant Registry (14). An objective response was evaluated after every two courses of induction and maintenance therapy by the following five factors: serum M-protein concentration, 24 h urine Bence-Jones protein, plasma cells in bone marrow, extramedullary plasmacytoma detected by computed tomography or magnetic resonance imaging and radiological changes in bone lesion.

Adverse events were graded according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC, version 2.0, 30 April 1999) (15).

Statistical Analysis

The primary endpoint was PFS, defined as the time from randomization at the second registration until death from any cause, relapse or progressive disease and censored at the last follow-up. The secondary endpoints were toxicity and OS after the second registration, and toxicity, ORR and OS after the first registration for induction therapy. The planned duration of patient accrual was 4 years, and the planned follow-up time was 4 years.

The study was designed as a non-inferiority trial of maintenance therapy comparing less toxic PSL alone with PSL + IFN-α. The required sample size for the second registration was 160 with 75% power, non-inferiority margin with a hazard ratio of 1.32 (corresponding to a 10% difference in the 4 year PFS rate when that in the PSL + IFN-α arm is 35%), and a one-sided alpha value of 0.05. The planned sample size for the first registration was 230 assuming that 70% of the registered patients would achieve a plateau phase of MM after induction therapy and randomization.

The JCOG Data Center collected and managed case report forms. In-house interim monitoring for quality control was performed at the Center, and the monitoring reports were semi-annually submitted to the JCOG Data and Safety Monitoring Committee.

RESULTS AND DISCUSSION

Between November 2002 and November 2005, 34 patients were enrolled from 15 participating institutions. The study was then closed early because of poor accrual. One patient was deemed ineligible after randomization because he was judged to have smoldering myeloma. Thirty-three eligible patients were analyzed for the secondary purpose. For the first induction therapy, VAD and MP were chosen for 16 and 17 patients, respectively (Table 1). Median ages were 63 and 70 years in patients initially treated with VAD and MP, respectively. In eight cases (five for VAD and three for MP), the induction therapy was switched because of a poor response. The median numbers of courses of first induction therapy were six (range: 2–10) and nine (range: 1–15), respectively, for VAD and MP.

Both regimens were well tolerated, but Grade 4 neutropenia was more frequent for VAD than for MP (63 vs. 11%) and also, Grade 3/4 anorexia, constipation and infection with Grade 3/4 neutropenia were more frequent for VAD (25 vs. 17%, 31 vs. 6% and 25 vs. 6%, respectively). The ORR including that after the switch was 44% [95% confidence interval (CI), 20–70%] and 47% (95% CI, 23–72%), respectively, for VAD and MP (Table 2). In all of them the

Table 1. Patient characteristics

	Eligible patients ($n = 33$)[a]	Initial therapy	
		VAD ($n = 16$)	MP ($n = 17$)
Age, years [median (range)]	65 (47–77)	63 (47–70)	70 (56–77)
Gender			
Male	19 (58)	6 (38)	13 (77)
Female	14 (42)	10 (63)	4 (24)
Stage (Durie and Salmon)			
IIA	6 (18)	74 (25)	2 (12)
IIB	0	0	0
IIIA	24 (73%)	10 (63)	14 (82)
IIIB	3 (9)	2 (13)	1 (6)
PS (stratification: 0,1/2,3,4)			
0	5 (15)	1 (6)	4 (24)
1	18 (55)	11 (69)	7 (41)
2	2 (6)	1 (6)	1 (6)
3	8 (24)	3 (19)	5 (29)
Ig subtype			
G/A/D/BJP	19/7/2/5 (58/21/6/15)	11/2/1/2 (69/13/6/13)	8/5/1/3 (47/29/6/18)

Percentage values are represented in parenthesis. VAD, vincristine–doxorubicin–dexamethasone; MP, melphalan–prednisolone; PS, performance status; BJP, Bence-Jones protein.
[a]One patient was ineligible because of inaccurate staging.

Table 2. Response to treatment

	VAD as initial therapy ($n = 16$)	MP as initial therapy ($n = 17$)	*P* value
CR (%)	0	0	
PR (%)	44	47	
MR (%)	25	29	
NR (%)	31	12	
PD (%)	0	12	
Not evaluable	0	0	
CR + PR (%) (95% CI)	44 (20–70)	47 (23–72)	NS[a]

CR, cytogenetic response; PR, partial response; MR, minor response; NR, no response; PD, progressive disease; CI, confidence interval.
[a]Fisher's exact test (two sided).