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References

[1] Devita VT Jr, Serpick AA, Carbone PP. Combination chemotherapy in the treatment of advanced Hodgkin's disease. Ann Intern Med 1970;73:881–895.
[2] Bonadonna G, Zucali R, Monfardini S, et al. Combination chemotherapy of Hodgkin's disease with adriamycin, bleomycin, vinblastine, and imidazole carboxamide versus MOPP. Cancer 1975;36:252–259.
[3] Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. N Engl J Med 1992;327:1478–1484.
[4] Duggan DB, Petroni GR, Johnson JL, et al. Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: report of an intergroup trial. J Clin Oncol 2003;21:607–614.
[5] The World Health Organization classification of malignant lymphomas in Japan: incidence of recently recognized entities. Lymphoma Study Group of Japanese Pathologists. Pathol Int 2000;50:696–702.
[6] Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008 . CA Cancer J Clin 2008;58:71–96.
[7] Takenaka T, Mikuni C, Miura A, et al. Alternating combination chemotherapy C-MOPP (cyclophosphamide, vincristine, procarbazine, prednisone) and ABVd (adriamycin, bleomycin, vinblastine, dacarbazine) in clinical stage II-IV Hodgkin's disease: a multicenter phase II study (JCOG 8905). Jpn J Clin Oncol 2000;30:146–152.
[8] Connors JM. Is cyclic chemotherapy better than standard four-drug chemotherapy for Hodgkin's disease? Yes.Important Adv Oncol 1993:189–195.
[9] Ogura M, Itoh K, Kinoshita T, et al. Phase II study of ABVd therapy for newly diagnosed clinical stage II-IV Hodgkin's lymphoma: Japan Clinical Oncology Group study (JCOG9305). Int J Hematol 2010;92:713–724.
[10] Costanzi JJ. DTIC (NSC-45388) studies in the Southwest Oncology Group. Cancer Treat Rep 1976;60:189–192.
[11] Lukes RJ, Butler JJ. The pathology and nomenclature of Hodgkin's disease. Cancer Res 1966;26:1063–1083.
[12] Carbone PP, Kaplan HS, Musshoff K, et al. Report of the committee on Hodgkin's disease staging classification. Cancer Res 1971;31: 1860–1861.
[13] Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol 1989;7:1630–1636.
[14] Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649–655.
[15] Jaffe ES, Harris NL, Stein H, et al. World Health Organization classification of tumours. Pathology and genetics of tumours of haematopoietic and lymphoid tissues, 3rd ed. Lyon, France: IARC Press; 2001 .
[16] Tobinai K, Kohno A, Shimada Y, et al. Toxicity grading criteria of the Japan Clinical Oncology Group. Jpn J Clin Oncol 1993;23:250–257.
[17] Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials 1989;10:1–10.
[18] Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease.International Prognostic Factors Project on Advanced Hodgkin's Disease. N Engl J Med 1998;339: 1506–1514.
[19] Diehl V, Franklin J, Pfreundschuh M, et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. N Engl J Med 2003;348: 2386–2395.
[20] Borchmann P, Diehl V, Goergen H, et al. Dacarbazine is an essential component of ABVD in the treatment of early favourable Hodgkin lymphoma: results of the second interim analysis of the GHSG HD13 trial. Haematologica 2010;95(Suppl.2): Abstract 1146.
[21] Straus DJ, Portlock CS, Qin J, et al. Results of a prospective randomized clinical trial of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by radiation therapy (RT) versus ABVD alone for stages I, II, and IIIA nonbulky Hodgkin disease. Blood 2004;104:3483–3489.
[22] Canellos GP, Duggan D, Johnson J, et al. How important is bleomycin in the adriamycin + bleomycin + vinblastine + dacarbazine regimen? J Clin Oncol 2004;22:1532–1533.
[23] Aleman BM, Raemaekers JM, Tirelli U, et al. Involved-field radiotherapy for advanced Hodgkin's lymphoma. N Engl J Med 2003;348:2396–2406.
[24] Scholz M, Engert A, Franklin J, et al. Impact of first- and second-line treatment for Hodgkin's lymphoma on the incidence of AML/MDS and NHL—experience of the German Hodgkin's Lymphoma Study Group analyzed by a parametric model of carcinogenesis. Ann Oncol 2011;22:681–688.

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.

Reply to H. Charalambous et al

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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
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REFERENCES
1. Charalambous H, Silbermann M: Clinically based palliative care training is needed urgently for all oncologists. J Clin Oncol 30:4042-4043, 2012
2. Fischer SM, Gozansky WS, Kutner JS, et al: Palliative care education: An intervention to improve medical residents' knowledge and attitudes. J Palliat Med 6:391-399, 2003
3. Breuer B, Fleishman SB, Cruciani RA, et al: Medical oncologist attitudes and practice in cancer pain management: A national survey. J Clin Oncol 29:4769-4777, 2011
4. von Gunten CF, Twaddle M, Preodor M, et al: Evidence of improved knowledge and skills after an elective rotation in a hospice and palliative care program for internal medicine residents. Am J Hosp Palliat Care 22:195-203, 2005

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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.

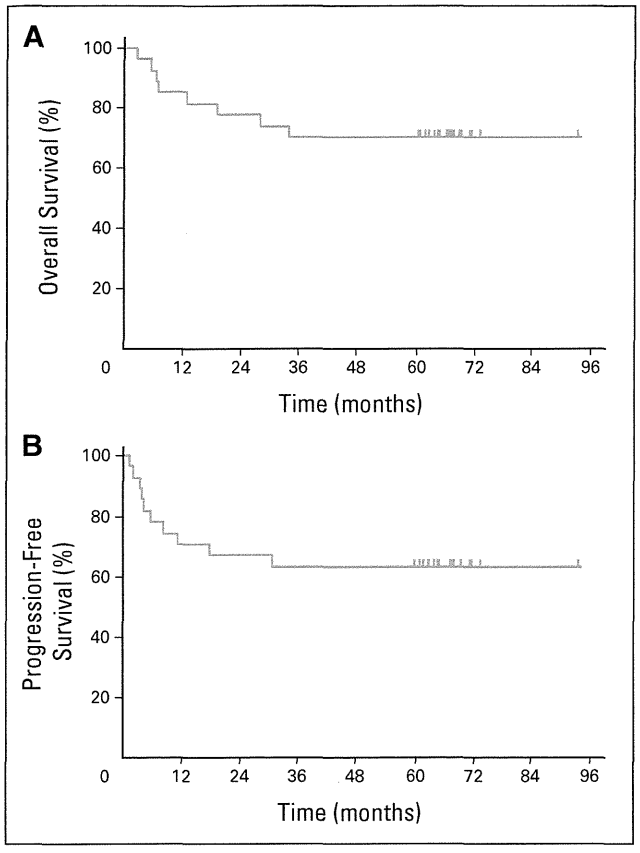

Fig 1. (A) Overall survival and (B) progression-free survival of 27 patients treated with radiotherapy and a two-thirds dose of dexamethasone, etoposide, ifosfamide, and carboplatin.

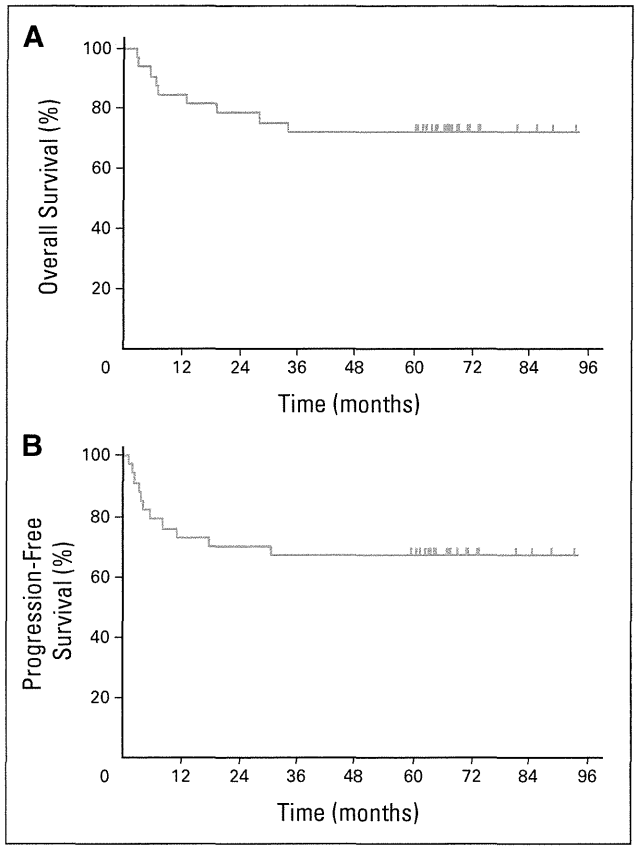

Fig 2. (A) Overall survival and (B) progression-free survival of 33 patients treated with radiotherapy and dexamethasone, etoposide, ifosfamide, and carboplatin.

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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REFERENCES

1. Jaffe ES, Harris NL, Stein H, et al (eds): World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France, IARC Press, 2001
2. Swerdlow SH, Campo E, Harris NL, et al (eds): WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France, IARC, 2008
3. Yamaguchi M, Tobinai K, Oguchi M, et al: Phase I/II study of concurrent chemoradiotherapy for localized nasal natural killer/T-cell lymphoma: Japan Clinical Oncology Group Study JCOG0211. J Clin Oncol 27:5594-5600, 2009
4. Kim GE, Cho JH, Yang WI, et al: Angiocentric lymphoma of the head and neck: Patterns of systemic failure after radiation treatment. J Clin Oncol 18:54-63, 2000
5. Kim SJ, Kim K, Kim BS, et al: Phase II trial of concurrent radiation and weekly cisplatin followed by VIPD chemotherapy in newly diagnosed, stage IE to IIE, nasal, extranodal NK/T-cell lymphoma: Consortium for Improving Survival of Lymphoma study. J Clin Oncol 27:6027-6032, 2009
6. Foss FM, Zinzani PL, Vose JM, et al: Peripheral T-cell lymphoma. Blood 117:6756-6767, 2011

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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

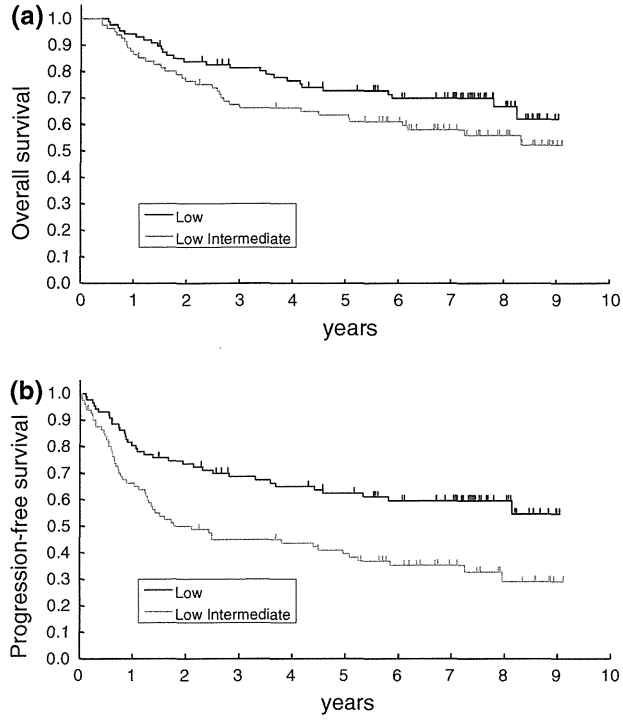

Fig. 1 Kaplan–Meier estimate of OS and PFS for pathologically eligible patients. **a** OS curves for patients in each risk category. The 5-year OS (95 % CI) in L risk and L–I risk cases was 73 % (63–82 %) and 64 % (53–74 %), respectively. **b** PFS curves for patients in each risk category. The 5-year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

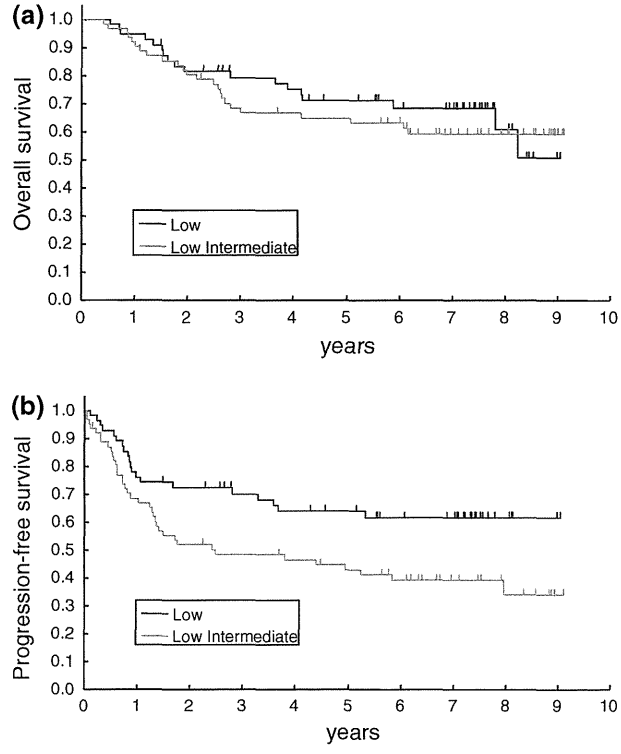

Fig. 2 Kaplan–Meier estimate of OS and PFS for DLBCL-NOS patients. **a** OS curves for patients in each risk category. The 5-year OS (95 % CI) in L risk and L–I risk patients was 71 % (58–83 %) and 65 % (53–77 %), respectively. **b** PFS curves for patients in each risk category. The 5-year PFS (95 % 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 1 (Table 5). In OS, only IPI was statistically significant, and in PFS, IPI and B symptoms were significant.

Discussion

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

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

Table 4 Adverse toxicity

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

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).

References

1. McKelvey EM, Gottlieb JA, Wilson HE, Haut A, Talley RW, Stephens R, et al. Hydroxyldaunomycin (adriamycin) combination chemotherapy in malignant lymphoma. Cancer. 1976;38(4):1484–93.
2. Klimo P, Connors JM. MACOP-B chemotherapy for the treatment of diffuse large-cell lymphoma. Ann Intern Med. 1985;102(5):596–602.
3. Shipp MA, Harrington DP, Klatt MM, Jochelson MS, Pinkus GS, Marshall JL, et al. Identification of major prognostic subgroups of patients with large-cell lymphoma treated with m-BACOD or M-BACOD. Ann Intern Med. 1986;104(6):757–65.
4. Coiffier B, Gisselbrecht C, Herbrecht R, Tilly H, Bosly A, Brousse N. LNH-84 regimen: a multicenter study of intensive chemotherapy in 737 patients with aggressive malignant lymphoma. J Clin Oncol. 1989;7(8):1018–26.

5. Longo DL, DeVita VT Jr. Superiority of ProMACE-CytaBOM over ProMACE-MOPP in the treatment of advanced diffuse aggressive lymphoma: results of a prospective randomized trial. J Clin Oncol. 1991;9(1):25–38.
6. Kinoshita T, Hotta T, Tobinai K, Kobayashi T, Ishizuka N, Tomonaga M, et al. A randomized controlled trial investigating the survival benefit of dose-intensified multidrug combination chemotherapy (LSG9) for intermediate- or high-grade non-Hodgkin's lymphoma: Japan Clinical Oncology Group Study 9002. Int J Hematol. 2004;80(4):341–50.
7. Fisher RI, Gaynor ER, Dahlberg S, Oken MM, Grogan TM, Mize EM, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med. 1993;328(14):1002–6.
8. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med. 1993;329(14):987–94.
9. Itoh K, Ohtsu T, Fukuda H, Sasaki Y, Ogura M, Morishima Y, et al. Randomized phase II study of biweekly CHOP and dose-escalated CHOP with prophylactic use of lenograstim (glycosylated G-CSF) in aggressive non-Hodgkin's lymphoma: Japan Clinical Oncology Group Study 9505. Ann Oncol. 2002;13(9):1347–55.
10. Takeyama K, Ogura M, Morishima Y, Kasai M, Kiyama Y, Ohnishi K, et al. A dose-finding study of glycosylated G-CSF (lenograstim) combined with CHOP therapy for stem cell mobilization in patients with non-Hodgkin's lymphoma. Jpn J Clin Oncol. 2003;33(2):78–85.
11. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas. Summary and description of a working formulation for clinical usage. The Non-Hodgkin's Lymphoma Pathologic Classification Project. Cancer. 1982;49(10):2112–35.
12. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the committee on Hodgkin's disease staging classification. Cancer Res. 1971;31(11):1860–1.
13. Rosenberg SA, Boiron M, DeVita VT Jr, Johnson RE, Lee BJ, Ultmann JE, et al. Report of the committee on Hodgkin's disease staging procedures. Cancer Res. 1971;31(11):1862–3.
14. Lister TA, Crowther D, Sutcliffe SB, Glatstein E, Canellos GP, Young RC, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol. 1989;7(11):1630–6.
15. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649–55.
16. Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. J Clin Oncol. 1999;17(12):3835–49.
17. Jaffe ES, Harris NL, Stein H, Vardiman JW. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues, 3 edn. Lyon: IARC Press; 2001.
18. WHO Handbook for Reporting Results of Cancer Treatment. 1979
19. Tobinai K, Kohno A, Shimada Y, Watanabe T, Tamura T, Takeyama K, et al. Toxicity grading criteria of the Japan Clinical Oncology Group. The Clinical Trial Review Committee of the Japan Clinical Oncology Group. Jpn J Clin Oncol. 1993;23(4):250–7.
20. Tobinai K, Shimoyama M, Minato K. Japan Clinical Oncology Group (JCOG) trial of second-generation "LSG4 protocol" in aggressive lymphoma including ATL: prognostic factors and a predictive model [abstract]. Proc Am Soc Clin Oncol. 1994;13:378.
21. Pfreundschuh M, Trumper L, Kloess M, Schmits R, Feller AC, Rudolph C, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: results of the NHL-B1 trial of the DSHNHL. Blood. 2004;104(3):626–33.
22. Philip T, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med. 1995;333(23):1540–5.
23. Jerkeman M, Anderson H, Cavallin-Stahl E, Dictor M, Hagberg H, Johnson A, et al. CHOP versus MACOP-B in aggressive lymphoma—a Nordic Lymphoma Group randomised trial. Ann Oncol. 1999;10(9):1079–86.
24. Feugier P, Van Hoof A, Sebban C, Solal-Celigny P, Bouabdallah R, Ferme C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol. 2005;23(18):4117–26.
25. Armitage JO, Dick FR, Corder MP, Garneau SC, Platz CE, Slymen DJ. Predicting therapeutic outcome in patients with diffuse histiocytic lymphoma treated with cyclophosphamide, adriamycin, vincristine and prednisone (CHOP). Cancer. 1982;50(9):1695–702.
26. Nakamine H, Bagin RG, Vose JM, Bast MA, Bierman PJ, Armitage JO, et al. Prognostic significance of clinical and pathologic features in diffuse large B-cell lymphoma. Cancer. 1993;71(10):3130–7.
27. Kojima H, Hasegawa Y, Suzukawa K, Mukai HY, Kaneko S, Kobayashi T, et al. Clinicopathological features and prognostic factors of Japanese patients with "peripheral T-cell lymphoma, unspecified" diagnosed according to the WHO classification. Leuk Res. 2004;28(12):1287–92.

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ORIGINAL ARTICLE

Tumor response evaluation criteria for HCC (hepatocellular carcinoma) treated using TACE (transcatheter arterial chemoembolization): RECIST (response evaluation criteria in solid tumors) version 1.1 and mRECIST (modified RECIST): JIVROSG-0602

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Abstract

Background. Two standard sets of criteria are used to evaluate the tumor response of hepatocellular carcinoma (HCC): RECIST (Response Evaluation Criteria in Solid Tumors) and modified RECIST (mRECIST). The purpose was to compare two tumor response evaluation criteria, RECIST version 1.1 and mRECIST, for HCC treated using transcatheter arterial chemoembolization (TACE).

Methods. The radiological findings of patients who underwent TACE for HCCs in a multicenter clinical trial were examined. Sixty-five lesions in 21 patients treated with TACE without mixing iodized-oil were evaluated. The tumor size was evaluated by measuring the entire lesion, including the necrotic part, using RECIST version 1.1, whereas only the contrast-enhanced part observed during the arterial phase was measured using mRECIST. Five radiologists independently measured each lesion twice. To evaluate the inter-criteria reproducibility, the complete response (CR) rate, the response rate, the kappa statistics, and the proportion of agreement (PA) for response categories were calculated. The same analyses were conducted for inter- and intra-observer reproducibility.

Results. In the inter-criteria reproducibility study, the CR rate and the response rate obtained using mRECIST (56.9% and 79.7%) were higher than those obtained using RECIST version 1.1 (9.2% and 43.1%). In the inter- and intra-observer reproducibility study, mRECIST exhibited an 'almost perfect agreement', while RECIST version 1.1 exhibited a 'substantial agreement'.

Conclusions. Considerable differences in the CR rate and the response rate were observed. From the viewpoint of the high inter- and intra-observer reproducibility, mRECIST may be more suitable for tumor response criteria in clinical trials of TACE for HCC.

Key words: *Hepatocellular carcinoma, modified RECIST, RECIST version 1.1, reproducibility, tumor response*

Introduction

Two standard sets of criteria are used to evaluate the tumor response of hepatocellular carcinoma (HCC) treated using loco-regional therapy, such as transcatheter arterial embolization (TACE): RECIST (Response Evaluation Criteria in Solid Tumors) criteria (1) and modified RECIST (mRECIST) criteria (2).

RECIST criteria were published by the National Cancer Institute in 2000 with the objective of unifying

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the criteria used for response assessments. These criteria evaluate the unidimensional measurement of the longest diameter of the tumor lesions and have been used in most oncology trials. However, a number of questions and issues have arisen, leading to the development of revised RECIST (version 1.1) criteria (3). In the RECIST version 1.1 criteria, the major changes included the number of lesions to be assessed, the assessment of pathological lymph nodes, confirmation of a response, disease progression, and the necrotic tumor size (i.e. in cases where a lesion which was solid at baseline has become necrotic in the center, the longest diameter of the entire lesion should be followed).

In 2000, a panel of experts on HCC from the European Association for the Study of the Liver (EASL) agreed that estimating the reduction in viable tumor volume (as recognized using enhanced spiral computed tomography (CT)) should be considered the optimal method for assessing the local response to treatment in patients with HCC (4). Since then, most authors reporting the results of loco-regional therapy for HCC have evaluated tumor response according to this recommendation (5,6).

The aforementioned expert panel continued the concept of viable tumor endorsed by EASL and adapted the unidimensional measurement as a substitute for the bidimensional one in the determination of tumor response for target lesions in HCC (7). These amendments confirmed the American Association for the Study of Liver Disease (AASLD)–Journal of the National Cancer Institute (JNCI) guidelines and were defined as 'modified RECIST (mRECIST)' criteria (2). Therefore, mRECIST criteria were developed for loco-regional therapies to HCC. On the other hand, RECIST version 1.1 criteria were developed for systemic therapies; however, RECIST version 1.1 criteria are used in many oncology trials including loco-regional therapies for the treatment of HCC.

A study investigating the inter-criteria reproducibility between the older versions of criteria (RECIST version 1.0 and EASL) has been reported (8). Furthermore, a comparative study of tumor response by the updated criteria (RECIST version 1.1 and mRECIST) has been published (9). However, to the best of our knowledge, the inter- and intra-observer reproducibility between RECIST version 1.1 and mRECIST has not been investigated or reported.

Using these standardized criteria for evaluating tumor response in clinical trials, reproducible results should be obtained by all investigators. For a surrogate marker such as tumor response for therapy, both 'precision' (observer consistency study) and 'accuracy' (validation study comparing to gold standard) are evaluated. From the viewpoint of 'precision', we compared RECIST version 1.1 and mRECIST criteria by evaluating the inter- and intra-observer reproducibility.

The purpose of the present study was to clarify the differences in tumor response as evaluated using two updated sets of criteria (RECIST version 1.1 and mRECIST) by assessing the inter-criteria reproducibility. Moreover, another purpose of the present study was to investigate which set of criteria was superior for use as tumor response evaluation criteria in clinical trials of TACE for HCC by assessing the inter- and intra-observer reproducibility.

Materials and methods

We analyzed the radiological findings of patients who underwent pan-hepatic TACE for multiple HCCs in a multicenter clinical trial. In this trial, the eligibility criteria included patients with untreated, bilobar multiple HCCs, compensated Child–Pugh A or B cirrhosis, and the absence of vascular invasion or extrahepatic spread. TACE was performed using cisplatin (IA call, Nihon-Kayaku; 35–65 mg/m^2) and gelatin particles without mixing iodized-oil. The present study was conducted in accordance with the Helsinki Declaration, and the protocols were approved by the institutional review board. Informed written consent for the treatment protocols, including the secondary use of treatment-associated documents, was obtained from each patient. Twenty-one patients were entered from 19 July 2005 to 15 May 2007.

Image analysis

All patients underwent a dynamic study performed using a multi-slice CT scanner with non-ionic contrast medium. CT scans were obtained within two weeks before TACE and one month after TACE. Tumor assessments were made using a 5-mm interval, and axial images were obtained during the unenhanced phase, the arterial phase, and the portal venous or equilibrium phase.

Tumor response evaluation

Response was defined according to RECIST version 1.1 criteria measuring the entire lesion, including the necrotic part. On the other hand, mRECIST were used to evaluate the lesion taking tumor necrosis, recognized by the non-enhanced areas, into account. Both guidelines adopted the unidimensional measurement (Figure 1).

According to RECIST version 1.1 criteria, a complete response (CR) was defined as the disappearance

of all target lesions; a partial response (PR) was defined as at least a 30% decrease in the sum of the longest diameter of the target lesions; progressive disease (PD) was defined as at least a 20% increase in the sum of the longest diameter of the target lesions; and stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor a sufficient increase to qualify for PD.

According to mRECIST criteria, CR was defined as the absence of enhanced tumor areas during the arterial phase, reflecting complete tissue necrosis; PR was defined as at least a 30% decrease, PD was defined as at least a 20% increase in the sum of the longest diameter in the enhanced tumor areas; and SD was defined using the same definition as that used in RECIST version 1.1 criteria.

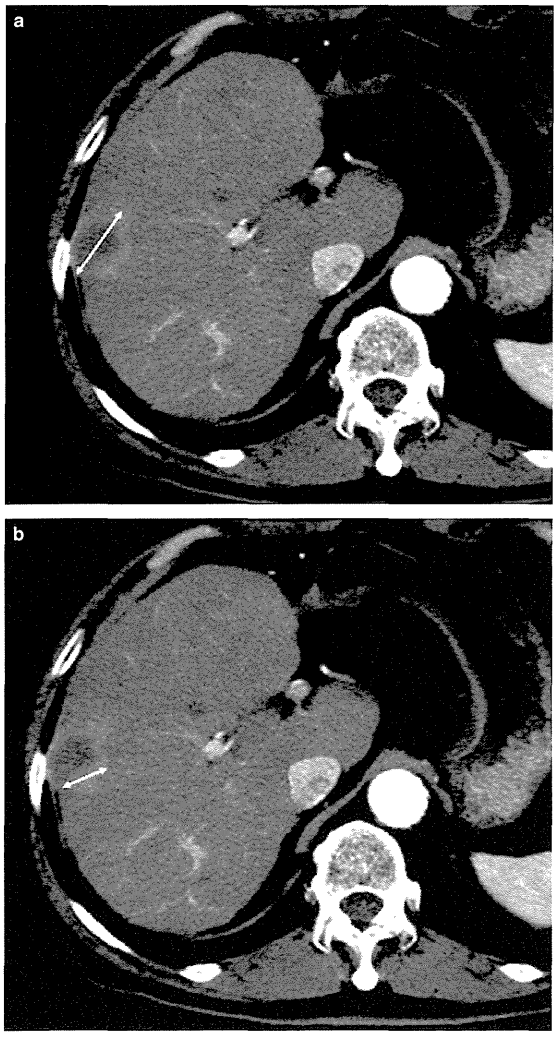

Figure 1. A: RECIST ver. 1.1: Response was defined according to a unidimensional measurement of the entire lesion, including the necrotic part. B: mRECIST: Response was defined according to a unidimensional measurement of the viable part, excluding the necrotic part.

Evaluation methods

Five observers measured 65 lesions in 21 patients independently. A total of 325 measurements were made for the first measurement. The second measurement was performed independently by the same five observers. The sum of the longest diameters for all the target lesions was calculated for baseline and post-treatment. The baseline sum was used as the reference from which the objective tumor response could be calculated. The percentage changes were calculated as the post-treatment value divided by the pre-treatment value. The percentage changes were then classified using RECIST version 1.1 and mRECIST tumor response classification systems. Tumor response was categorized as CR, PR, SD, or PD based on both sets of criteria. Furthermore, the CR rate and the response rate were also calculated.

All the images were collected from each institution and supplied to the Japan Interventional Radiology in Oncology Study Group (JIVROSG) Data Center using the WEB system.

Analysis of inter-criteria reproducibility

To examine the inter-criteria reproducibility between RECIST version 1.1 and mRECIST criteria, we estimated the kappa statistics and the proportion of agreement for the CR, PR, SD, and PD categories among the five observers. The data for the first measurements were analyzed to evaluate the inter-criteria reproducibility.

Analysis of inter-observer reproducibility

To examine the inter-observer reproducibility among the five observers, we estimated the kappa statistics and the proportion of agreement. Each pair yielded 10 pairs for comparison. The data for the first measurements were analyzed to evaluate the inter-observer reproducibility.

Analysis of intra-observer reproducibility

The data for the first and second measurements were compared to assess the intra-observer reproducibility for the same observer. The intra-observer reproducibility for the same observer yielded five pairs for comparison.

Statistics

Kappa statistics were performed to determine the concordance/agreement of the tumor response criteria. The potential kappa values ranged from −1.0 (complete disagreement) through 0 (chance agreement) to 1.0 (complete agreement). Interpretations of the strength of the agreement determined using the kappa values were given by adopting the criteria (9). The kappa values of the two agreements were compared for statistical significance using a paired *t* test. Comparisons between groups were done using the Fisher exact test. A conventional *P* value of 0.05 was considered statistically significant. All analyses were conducted using SPSS (version 17.0).

Results

Patient population

Sixty-five untreated lesions in 21 patients treated using pan-hepatic TACE were evaluated. The patients' characteristics were as follows (Table I), median age (range): 68 years (27–74 years); sex (male/female): 19/2; hepatitis C virus/hepatitis B virus/others: 12/3/6; Child–Pugh A/B: 20/1; total number of nodules (range): 65 nodules (1–5 nodules); mean tumor size (range): 20 mm (10–132 mm).

Inter-criteria reproducibility

The inter-criteria reproducibility using RECIST version 1.1 and mRECIST criteria is summarized in Tables II and III. Five observers measured 65 lesions independently, for a total of 325 measurements. According to RECIST version 1.1 criteria, the CR rate and the response rate were 9.2% and 43.1%, respectively; according to mRECIST criteria, the CR rate and the response rate were 56.9% and 79.7% (Table II).

Among the 185 CR lesions that were identified using mRECIST criteria, RECIST version 1.1 criteria classified the same responses as PR for 89 lesions, SD for 64 lesions, and PD for 2 lesions (Table III). The kappa value was 0.149 (95% CI 0.098–0.201), and the proportion of agreement was 35.5% (Table III).

Table I. Patients and characteristics.

No. of patients	21
Age, median (range)	68 (27–74)
Sex (male/female)	19/2
HCV/HBV/others	12/3/6
Child–Pugh A/B	20/1
No. of nodules, all (range)	65 (1–5)
Mean tumor size (range), mm	20 (10–132)

HCV = hepatitis C virus; HBV = hepatitis B virus.

Inter-observer reproducibility

The inter-observer reproducibility among the five observers was analyzed using the data for the first measurements, with each pair yielding 10 pairs for comparison. These 10 pairs for comparisons, or 650 measurements, are collectively shown in Table IV. For the inter-observer reproducibility for RECIST version 1.1, the kappa value was 0.628 (95% CI 0.571–0.684), and the proportion of agreement was 78.8%. For the inter-observer reproducibility for mRECIST, the kappa value was 0.829 (95% CI 0.792–0.866), and the proportion of agreement was 90.0%.

Intra-observer reproducibility

The intra-observer reproducibility was analyzed from the data for the first and second measurements, with each pair yielding five pairs for comparison. These five pairs for comparisons, or 325 measurements, are collectively shown in Table V. For the intra-observer reproducibility for RECIST version 1.1, the kappa value was 0.643 (95% CI 0.565–0.722), and the proportion of agreement was 79.4%. For the intra-observer reproducibility for mRECIST, the kappa value was 0.900 (95% CI 0.858–0.942), and the proportion of agreement was 94.2%.

Discussion

The inter-criteria reproducibility study between RECIST version 1.0 and EASL guidelines, and a comparative study of tumor response by RECIST and mRECIST have been reported (8,9). However, no information is available concerning the inter-observer reproducibility in those reports. In addition to performing an inter-criteria reproducibility study, we also estimated the inter- and intra-observer reproducibility to investigate which set of criteria (RECIST version 1.1 or mRECIST) is superior for performing tumor response evaluations in clinical trials of TACE for HCC.

Inter-criteria reproducibility

An evaluation of the tumor response according to RECIST version 1.0 and EASL guidelines after loco-regional therapies in patients with HCC has been reported. RECIST missed all the CRs obtained by

Table II. Inter-criteria reproducibility between RECIST version 1.1 and mRECIST criteria. Number of lesions (%).

Response category	Complete response	Partial response	Stable disease	Progressive disease	Overall response[a]
Response criteria					
RECIST	30 (9.2)	110 (33.8)	180 (55.4)	5 (1.5)	140 (43.1)
	$P < 0.001$				$P < 0.001$
mRECIST	185 (56.9)	74 (22.8)	65 (20)	1 (3)	259 (79.7)

[a]Complete response + partial response.
RECIST = Response Evaluation Criteria in Solid Tumors; mRECIST = modified RECIST.

Table III. Inter-criteria reproducibility between RECIST version 1.1 and mRECIST criteria: distribution chart.

		RECIST				
		Complete response	Partial response	Stable disease	Progressive disease	Total
mRECIST	Complete response	30	89	64	2	185
	Partial response	0	21	53	0	74
	Stable disease	0	0	63	2	65
	Progressive disease	0	0	0	1	1
Total		30	110	180	5	325

Proportion of agreement = 35.5%. Kappa = 0.149.

tumor necrosis and underestimated the extent of the partial tumor response because of tissue necrosis (8).

In our inter-criteria reproducibility study comparing RECIST version 1.1 and mRECIST criteria, similar results were obtained. The CR rate and the response rate obtained using mRECIST criteria were higher than those obtained using RECIST version 1.1 criteria (56.9% versus 9.2%, $P < 0.001$; 79.7% versus 43.1%, $P < 0.001$).

According to mRECIST criteria, if a tumor that was solid at baseline became entirely necrotic, all the tumors were evaluated as CR. On the other hand, using RECIST version 1.1 criteria, the necrotic tumor was evaluated as a non-CR based on the measurement of the entire lesion, leading to a different conclusion, such as PR, SD, or PD (Figure 2). Among 185 CR lesions that were identified using mRECIST criteria, 155 lesions (83.8%) were evaluated as non-CR using RECIST version 1.1 criteria. In particular, two lesions evaluated as CR using mRECIST criteria were categorized as PD using RECIST version 1.1 criteria; thus, two sets of criteria produced opposite conclusions (Table III). As the tumor size was very small and a 20% increase was thought to be within the range of measurement error, these two lesions were identified as PD using RECIST version 1.1 criteria. In some cases, this event might be caused by an increase in the necrotic tumor size secondary to chemoembolization. Therefore, the inter-criteria reproducibility between RECIST version 1.1 and mRECIST criteria for loco-regional therapy achieving complete tumor necrosis may have a low concordance.

The differences in the CR rate and the response rate between RECIST version 1.1 and mRECIST criteria indicate that the researchers should ascertain the presence or absence of 'm' (mRECIST? or RECIST?).

Table IV. Inter-observer reproducibility.

	Kappa	Proportion of agreement (%)
Inter-observer reproducibility		
RECIST	0.628 (95% CI 0.571–0.684)	78.8
mRECIST	0.829 (95% CI 0.792–0.866)	90.0

Inter- and intra-observer reproducibility

Standardized tumor response evaluation systems are considered to be reliable in clinical trials when they are reproducible among different observers. The importance of inter-observer reproducibility for any

Table V. Intra-observer reproducibility.

	Kappa	Proportion of agreement (%)
Intra-observer reproducibility		
RECIST	0.643 (95% CI 0.565–0.722)	79.4
mRECIST	0.900 (95% CI 0.858–0.942)	94.2

classification scheme has been discussed previously for other grading systems (10-14). Clinical investigators must take into account inter-observer reproducibility in tumor response evaluations, which can greatly affect the results of clinical trials.

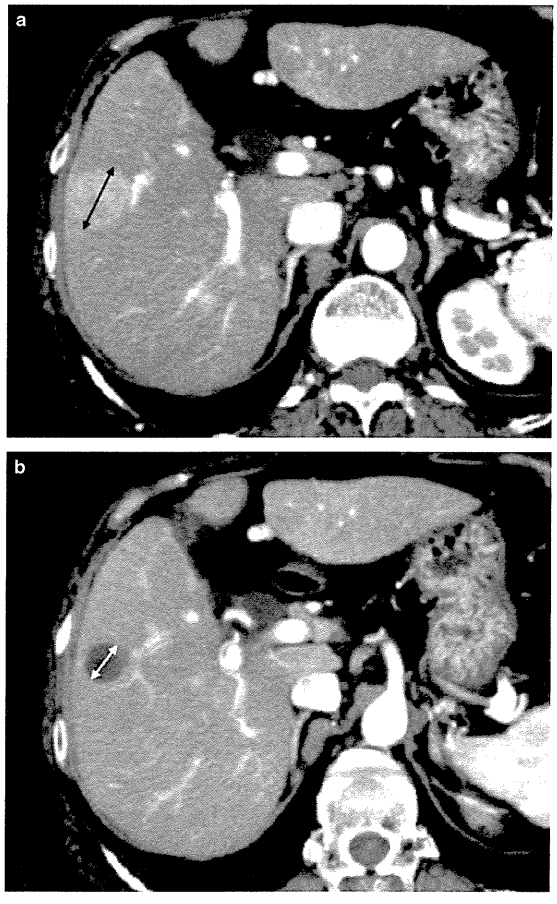

Figure 2. A: CT before TACE: Both criteria (RECIST version 1.1 and mRECIST) measured the longest diameter of the tumor. B: CT after TACE: The tumor had become entirely necrotic. The tumor response was evaluated as CR using mRECIST criteria (i.e. no measurement) and as non-CR using RECIST version 1.1 criteria (i.e. the measurement of the longest diameter of the entire tumor).

In our inter- and intra-observer reproducibility study, the kappa value and the proportion of agreement using mRECIST criteria ('almost perfect agreement') were higher than those for RECIST version 1.1 criteria ('substantial agreement'). In consideration of the high inter- and intra-observer reproducibility, mRECIST can be more recommended for use as tumor response criteria in clinical trials of TACE for HCC.

The present study had several limitations. The number of patients was relatively small, and the analyses were performed not on a per-patient basis, but on a per-lesion basis. To investigate which set of criteria was superior as tumor response criteria in clinical trials of TACE for HCC, the observer consistency study (inter- and intra-observer reproducibility between the two updated sets of criteria) were investigated in this study. A validation study comparing the updated criteria to the gold standard (i.e. overall survival) should be encouraged in future studies.

In conclusion, considering the differences in the CR rate and the response rate between RECIST version 1.1 and mRECIST criteria, close attention must be paid to the criteria used for a precise interpretation of the tumor response outcome. Furthermore, mRECIST criteria may be more suitable for tumor response criteria in clinical trials of TACE for HCC, compared with RECIST version 1.1 criteria, from the viewpoint of the high inter- and intra-observer reproducibility.

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References

1. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000;92: 205–16.