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Original Article

A multicenter, phase II study of full-dose THP-COP therapy for elderly patients with newly diagnosed, advanced-stage, aggressive non-Hodgkin lymphoma

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The cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) regimen, containing doxorubicin (DXR), which is a key drug for aggressive non-Hodgkin lymphoma (NHL), is a standard chemotherapeutic regimen; however, its administration in elderly patients is often intolerable. Pirarubicin (tetrahydropyranyl adriamycin [THP]) is an anthracycline developed in Japan. We have conducted a phase II trial of a full-dose THP-COP (modified CHOP regimen with DXR replaced by THP) regimen for elderly patients with newly diagnosed, advanced-stage, aggressive NHL. Patients aged 70–79 years old with previously untreated NHL according to the Working Formulation (D through H and J), disease stage I with a bulky mass or stage II–IV, and performance status of 0–1 were eligible. The THP-COP regimen, which consisted of 750-mg/m^2 cyclophosphamide, 50-mg/m^2 THP, 1.4-mg/m^2 vincristine (capped at 2.0 mg) on day 1, and 100-mg prednisolone daily on days 1 to 5, was delivered every 3 weeks for 6 cycles. The primary endpoint was complete response (CR) rate. Twenty-nine patients were enrolled in the study. The CR rate was 65.5% (95% confidence interval, 45.7–82.1%). The 3-year failure-free and overall survival rates were 54.1% and 53.9%, respectively. The most frequent observed grade 3 or 4 toxicity was neutropenia, which occurred in 80% of the patients. Grade 3 cardiac dysfunction was observed in one patient. The full-dose THP-COP regimen exhibited similar efficacy and safety, and a tendency for less cardiac toxicity, when compared with the standard CHOP regimen in elderly Japanese patients with newly diagnosed, advanced-stage, aggressive NHL.

Keywords: aggressive non-Hodgkin lymphoma, elderly Japanese, pirarubicin

INTRODUCTION

In recent years, the prevalence of non-Hodgkin lymphoma (NHL) in Japan has been estimated to exceed 20 per 100,000 people. The total number of patients in 2018 has increased about twofold from that in 2000.[1] The peak NHL incidence occurs in individuals between 70 and 80 years old, and more than half of patients with NHL are aged 60 years old and above.[2] Japan's population is aging, and increasing numbers of elderly patients with NHL are emerging. Therefore, the therapeutics for elderly patients with NHL are increasingly important.

The CHOP (cyclophosphamide [CPA], doxorubicin [DXR], vincristine [VCR], and prednisolone [PDN]) regimen, which is a first-generation multidrug combination chemotherapy, was developed in the 1970s for aggressive NHL treatment in the United States of America (USA). In 1993, a large-scale randomized USA intergroup trial demonstrated that CHOP is a standard chemotherapeutic regimen in patients with newly diagnosed, advanced-stage, aggressive NHL.[3] However, it has been relatively difficult to administer a full-dose CHOP regimen to elderly patients due to its chemotherapeutic toxicity. In general, anticancer drug metabolism worsens with age due to organ function deterioration, and elderly patients often present with various underlying complications such as cardiovascular disease. Under these circumstances, the administration of certain drugs is restricted. Therefore, elderly patients with aggressive NHL treated with chemotherapy have a poor prognosis because of the difficulty in maintaining an adequate dose intensity of

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chemotherapeutic drugs.[4] Well tolerated regimens with fewer adverse effects in elderly patients have been investigated; however, they were less effective and not more beneficial compared with the CHOP regimen.[5,6]

Pirarubicin (tetrahydropyranyl adriamycin [THP]), a 4′-*o*-substituted derivative of DXR, is an anthracycline that was developed in Japan by Umezawa *et al*.[7] It exhibited a 10-fold higher cytotoxic effect than DXR in a DXR-resistant mouse lymphoblastoma cell line.[8,9] In a study on hamsters, electrocardiography and myocardial electron microscopy revealed lower cardiac muscle impairment with THP than with DXR.[10] The reported congestive heart failure frequency was low and good cardiac tolerability was confirmed in several phase I and II trials of THP for various advanced cancers.[11,12] Therefore, THP is considered to have equivalent antitumor effects as those of DXR in addition to cardiac toxicity reduction.

We conducted a phase II trial of full-dose THP-COP regimen, which is the same as the CHOP regimen except that DXR is replaced by THP at the same dose, to investigate the efficacy and safety of THP in elderly patients with newly diagnosed, advanced-stage, aggressive NHL.

PATIENTS AND METHODS

Eligibility criteria

Six centers participated in this trial. The eligibility criteria were as follows: 70–79 years of age, previously untreated with intermediate-grade or high-grade NHL according to the Working Formulation (D through H and J),[13] disease stage I with a bulky mass or stage II–IV according to the Ann Arbor classification,[14] Eastern Cooperative Oncology Group performance status (PS) of 0–1, absolute neutrophil count (ANC) $\geq 1.2 \times 10^9$/L, platelet count $\geq 50 \times 10^9$/L, aspartate aminotransferase and alanine aminotransferase (ALT) levels ≤ 5 times the upper limit of the normal range, total bilirubin levels ≤ 2.0 mg/dL, serum creatinine levels ≤ 2.0 mg/dL, left ventricular ejection fraction > 50%, and $PaO_2 > 60$ torr.

Patients with any other malignancies, mental illness, myocardial infarction or angina history, central nervous system infiltration, uncontrollable diabetes, human immunodeficiency virus infection, hepatitis B virus surface antigen, and/or hepatitis C virus antibody positivity were excluded. Written informed consent was obtained from all patients. The study protocol was approved by the Institutional Review Board of each participating center.

Treatment

For THP-COP therapy, 50-mg/m^2 THP, 750 mg/m^2 CPA, and 1.4-mg/m^2 VCR (max 2.0 mg) were administered on day 1, and 100-mg PDN was administered on days 1–5 in accordance with the CHOP regimen regulations. This regimen was administered every 3 weeks for up to six courses. If the THP dose was decreased due to toxicity, up to two courses of additional treatment were administered to permit the cumulative dose of THP to reach 300 mg/m^2. The treatment protocol was discontinued if disease progression was identified during the treatment. If complete remission was achieved after six courses, additional treatments were not administered. If bone marrow suppression was observed, treatment was postponed until the ANC was $\geq 1.2 \times 10^9$/μL and the platelet count was $\geq 75 \times 10^9$/L. If the ANC and platelet count did not recover after 2 weeks, THP and CPA doses were reduced by 50%, and treatment was reinitiated. When grade 4 neutropenia or > grade 3 thrombocytopenia, according to the World Health Organization (WHO) toxicity criteria,[15] persisted for more than 5 days, THP and CPA doses were reduced for the next course to 75% of the original dose. Patients received G-CSF and blood transfusions if necessary. When ≥ grade 2 bilirubinemia was observed, THP was omitted for the next course. When > grade 2 stomatitis was observed, the THP dose was reduced to 75% of the original dose. When > grade 2 arrhythmias, > grade 3 cardiac dysfunction, treatment delay of > 4 weeks, or no improvement to below grade 1 toxicity were observed, the treatment protocol was discontinued.

Response assessment

Tumor responses were classified as complete response (CR), unconfirmed CR (CRu), partial response (PR), no response, and progressive disease (PD). Responses were assessed by clinical examination and computed tomography after the completion of six chemotherapy courses, according to the criteria by the WHO.[16]

Statistical methods

All analyses were conducted on the basis of the intent-to-treat principle. The primary endpoint was the CR rate and the secondary endpoints were failure-free survival (FFS), overall survival (OS), and the adverse event incidence. The FFS was calculated from the enrollment date until the progression date, any other treatment administration, relapse, or death from any causes. If the patients survived without any adverse event incidences, FFS was censored at the latest date when no event was confirmed. The OS was calculated from the enrollment date until the date of death from any cause.

The sample size was calculated on the basis of the expected and threshold CR rates of 70% and 40%, respectively. The required sample size was estimated at 27 patients. The CR rate was calculated as the proportion of treated patients who achieved CR or CRu.

The OS and FFS were estimated using the Kaplan-Meier method. All statistical analyses were performed with EZR software version 1.55.[17]

The planned enrollment period of this study was 1 year and the planned follow-up period was 5 years.

RESULTS

Patient characteristics

A total of 30 patients (19 males and 11 females) from 6 hospitals belonging to the Hematological Malignancy

Clinical Study Group (HMCSG) were registered between January 1999 and June 2000. After registration, one patient was ineligible because his diagnosis changed from NHL to Hodgkin lymphoma, and the remaining 29 eligible patients were enrolled (Table 1). The age of the registered patients ranged from 70 to 79 years old, with a median of 72 years old. Out of the 30 patients, 20 (65.5%) patients were 70–74 years of age, and 10 (34.5%) were 75–79 years of age. Fourteen patients (46.7%) were PS 0, and 16 patients (53.3%) were PS 1. Regarding histopathological type, 19 patients (63.3%) had diffuse, large B-cell lymphoma (DLBCL). Regarding the clinical stage, 16 (53.3%) patients had stage II disease, 14 (46.7%) had stage III–IV disease, and three patients (10.0%) had a bulky mass. When the 29 eligible patients were stratified into four groups using the International Prognostic Index (IPI),[18] 8 patients (26.7%) were in the low-risk group, 10 patients (33.3%) were in the low-intermediate-risk group, 12 patients (40.0%) were in the high-intermediate-risk group, and no patients were in the high-risk group.

Feasibility of the planned treatment

Of the 29 eligible patients, 21 patients (72.4%) completed the planned treatment course. Of the eight patients that could not complete the course, five patients (17.2%) had PD, one developed congestive heart failure, one refused to continue treatment, and one developed mental depression. The physicians decided not to continue their treatment. The median number of treatment courses was 6 (range: 2-8), and the median treatment interval was 3.1 (range, 2.9-4.2) weeks.

Table 1. Patient characteristics

Sex		
	Male/female	19/11
Performance status (ECOG)		
	0/1	14/16
Age	(years)	
	70–74	20
	74–79	10
	Min–max (median)	70–79 (72)
Histology		
	Follicular large	1
	Follicular mixed	1
	Diffuse mixed	3
	Diffuse large	19
	Diffuse medium	2
	Immunoblastic	1
	Unknown	3
Ann Arbor stage		
	I bulky–II	16
	III–IV	14
Immunologic phenotype		
	B-cell	24
	T-cell	3
	Unknown	3
IPI risk		
	Low, low–int/high–int, high	18/12

One patient was judged ineligible after enrollment because his final diagnosis was Hodgkin lymphoma.
IPI: International Prognostic Index, ECOG: Eastern Cooperative Oncology Group

Relative dose intensity

The overall THP and CPA treatment dose of all eligible patients was calculated as the relative dose intensity (RDI). The RDI was calculated as the total administered dose divided by the total planned dose for all given courses. The median RDI of THP was 0.900 (range, 0.584–1.016) and that of CPA was 0.906 (range, 0.500–1.033).

Response and survival

Reponses were assessed for all 29 eligible patients. Nineteen patients achieved CR or CRu, and the CR rate was 65.5% (95% confidence interval [CI], 45.7–82.1%). The overall response rate was 82.8% (95% CI, 64.2–94.2%). This result met the statistical hypothesis.

The data cutoff date was December 31, 2005. The 3-year FFS rate was 54.1% (95% CI, 34.3–70.2%), and the OS rate was 53.9% (95%CI, 34.1–70.1%) (Figure 1). Patients whose disease progressed or relapsed in the early phase died of lymphoma without attaining remission. However, most of the patients with CR achieved long-term survival without relapse. Therefore, FFS was equivalent to OS at 3 years.

Toxicity

Toxicity was assessed on the basis of the Japan Clinical Oncology Group Toxicity Criteria, which is an expanded and modified version of the National Cancer Institute Common Toxicity Criteria version 1.0.[19] The adverse event evaluation was performed for all registered patients (30 patients) who received at least one course of treatment. The adverse event incidence is shown in Table 2. The most common hematologic toxicity was grade 4 neutropenia, which occurred in 24 patients (80%), followed by grade 4 thrombocytopenia, which occurred in two patients (6.6%). The most common grade 3 or higher non-hematologic toxicities were febrile neutropenia in three patients and grade 4 infection in one patient; grade 3 ALT increase, bilirubinemia, ileus, phlebitis, and dyspnea were observed in one patient each. Regarding cardiotoxicity, grade 3 cardiac dysfunction was observed in one patient after 5 courses, but this adverse event was ameliorated by appropriate supportive care and study treatment termination. Regarding treatment-related death, one patient died of infection-related complications.

DISCUSSION

We conducted a phase II clinical trial for elderly Japanese patients with newly diagnosed, advanced-stage, aggressive NHL to investigate the efficacy and safety of a full-dose THP-COP regimen using the same doses as the CHOP regimen that is recognized as the standard therapy for elderly

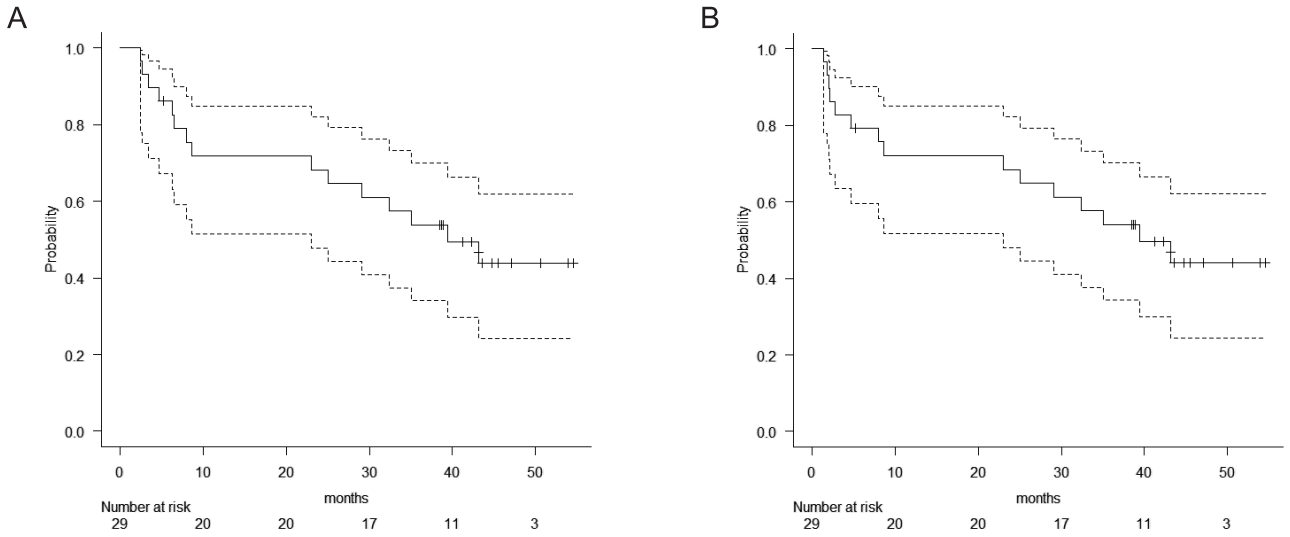

Fig. 1. ***A***: Failure-free survival curves for all eligible patients, ***B***: Overall survival curves for all eligible patients

Table 2. Grade 3/4 treatment-related toxicity (N = 30)

Toxicity	Grade 3 Number of patients (%)		Grade 4 Number of patients (%)	
Hematologic				
Leukocytes	9	(30)	18	(60)
Neutrophils	3	(10)	24	(80)
Hemoglobin	14	(47)	4	(13)
Platelets	4	(13)	2	(7)
Nonhematologic				
Infection	2	(7)	1	(3)
Elevation of ALT	3	(10)		
Total bilirubin	1	(3)		
Ejection fraction	1	(3)		
Ileus	1	(3)		
Phlebitis	1	(3)		
Dyspnea	1	(3)		

Western patients with aggressive NHL. In our trial, the THP-COP regimen showed a CR of 65.5%, a 3-year FFS rate of 54.1%, and a 3-year OS rate of 53.9%. Regarding the standard CHOP regimen, the long-term survival possibility in the elderly is approximately 35–40% with this regimen in Western countries,[20] and our results were comparable. The RDI of THP was 0.900 and that of CPA was 0.906, indicating that it is possible to maintain sufficient dose intensities during treatment. Regarding toxicities, > grade 3 neutropenia was most frequent; however, this toxicity was substantially managed by administering G-CSF when necessary. At that time, G-CSF was used on demand when neutropenia occurred due to medical insurance in Japan. Today, G-CSF prophylactic use has become common because most hematologists have wide knowledge of the guidelines and peg G-CSF use is approved. Therefore, this adverse effect is more manageable. The cardiac toxicity frequency, which is usually a concern with anthracyclines, was low. In addition, one grade 3 cardiac dysfunction was observed during the study period, which was managed by supportive care. Although this was a small scale study, the early cardiac toxicity frequency caused by THP-COP was lower than that of the CHOP.[21]

Aging is an independent prognostic factor in IPI, and the prognosis of elderly patients with aggressive NHL is usually poor. Generally, patients in their 60s can tolerate chemotherapy to a similar extent to younger adults, but the same is difficult for many patients over 70 years old. Therefore, serious dose reduction of important chemotherapeutic drugs in these patients often becomes mandatory. As a result, adequate treatment cannot be administered, and prognosis is subsequently affected. Treatment methods with alternative drugs have also been considered; however, it has been demonstrated that anthracycline drugs should be used for the elderly and that CHOP-based regimens that maintain dose intensity were the most beneficial.[5,6] Ultimately, the CHOP combination is recommended as the standard chemotherapeutic regimen. Although it was reported that the CHOP regimen combined with routine use of G-CSF brought equivalent efficacy to young patients,[22] a full-dose CHOP regimen for Japanese elderly patients was not established as a standard therapy, and patients over 70 years old were excluded in clinical trials using the standard CHOP regimen for aggressive NHL.[23,24] In 1990s, reduced-dose CHOP was commonly utilized in clinical practice for patients aged 70 years old or over without evidence. In a Japanese clinical trial conducted by Mori *et al.* prior to this study, in which three groups received reduced-dose CHOP, reduced-dose THP-COP (500-mg/m^2 CPA, 30 mg/m^2 THP, and 1 mg/m^2 VCR), or reduced-dose THP-COP with etoposide regimen, the authors reported that the overall efficacies were approximately equivalent for elderly patients over 65 years old in all three treatment groups.[25] Tsurumi *et al.* reported a phase II trial of the reduced-dose THP-COP regimen for elderly patients with DLBCL, the 2-year progression-free survival rate was 48.9%, and the 2-year OS rate was 52.9% in patients aged 70–79 years old.[26] Compared to the results of these reports, our

full-dose THP-COP regimen yielded sufficient outcomes without increased intolerable toxicity.

However, approximately half of all patients experienced recurrence and required salvage chemotherapy. The cumulative dose of anthracycline is limited due to the cardiotoxicity risk. When the cumulative dose of DXR exceeds 550 mg/m^2, the risk of congestive heart failure increases; therefore, 550 mg/m^2 is recommended as the maximum cumulative dose. In addition, in patients over 65 years old, when the total administered dose of DXR reaches 400 mg/m^2, the incidence congestive heart failure increases, compared to that in adults less than 65 years old.[27] In contrast, the maximum practical cumulative dose of THP is estimated to be 1000 mg/m^2.[28] Even if the maximum regulated dose of THP is administered in the initial THP-COP therapy, it can again be administered in the subsequent salvage therapy. Zhai *et al.* performed a retrospective analysis of patients who were treated with CHOP or THP-COP and found equivalent efficacies of the two regimens. In addition, the cardiotoxicity incidence was lower for the THP-COP regimen.[29] Another method to reduce the cardiac toxicity caused by DXR is continuous intravenous infusion.[30] The EPOCH (etoposide, PDN, VCR, CPA, and DXR) regimen is a combination chemotherapy for aggressive NHL using continuous intravenous infusion of DXR. It was developed for relapsed or refractory aggressive NHL,[31] but it also showed equivalent efficacy to the CHOP regimen for untreated patients with aggressive NHL in a small-scale clinical trial.[32] Although it is unclear which regimen, THP or continuous infusion of DXR, greater reduces cardiac toxicity, the THP-COP regimen has the advantage of improving the patient's quality of life because the EPOCH regimen can not be administered in outpatient care. By virtue of its substantial therapeutic efficacy and safety in initial therapy, as well as its possible utility in secondary therapy, THP may be an attractive alternative drug that is potentially equivalent to DXR.

There are several limitations of the current study. First, this study was conducted before the advent of rituximab, which is an essential key drug for the treatment of aggressive B-cell NHL. Although the use of rituximab in addition to THP-COP seems to be useful, similar to the R-CHOP regimen, there is currently no clinical trial evidence of R-THP-COP in elderly patients with newly diagnosed, advanced-stage, aggressive NHL. Second, the histopathological classifications used in this study are outdated. Although the histopathologies of the enrolled patients were heterogeneous, we did not perform a central pathological review. The number of patients enrolled in this study is relatively small, therefore, it is unclear whether this result applies to the current classification of aggressive lymphoma. Third, this study was conducted from 1999 to 2000 and lacked a long-term follow-up. Consequently, the true prognosis and late cardiac toxicity of elderly Japanese patients with NHL treated with the THP-COP regimen are unclear. However, achieving 2-year event-free survival in patients with DLBCL treated with immunochemotherapy is shown to lead to a good prognosis.[33] The results of this study are comparable with past clinical trials investigating the efficacy of the CHOP regimen, and thus appear to be reliable. Due to advances in supportive care, such as the use prophylactic G-CSF, elderly patients are now included in clinical trials using standard the CHOP-like regimen. Under such circumstances, the results of this study may not have sufficient value. However, the majority of reports about the outcome, the RDI and the feasibility of CHOP-like regimens for Japanese elderly patients are retrospective, and few clinical trials have been conducted prospectively. Therefore, the findings of this prospective study which demonstrated the feasibility of the full-dose CHOP-like regimen for Japanese elderly patients are beneficial and provide a rationale for the use this regimen as a standard chemotherapeutic regimen for elderly patients in Japan with aggressive NHL.

CONCLUSION

The full-dose THP-COP regimen exhibited similar efficacy and safety, as well as less cardiac toxicity, to that of the standard CHOP regimen in elderly Japanese patients with newly diagnosed, advanced-stage, aggressive NHL.

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CONFLICT OF INTEREST

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