

Original Article

A multicenter, phase II study of R-THP-COP therapy for elderly patients with newly diagnosed, advanced-stage, indolent B-cell lymphoma

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The optimal combined chemotherapy regimen with rituximab has yet to be established for elderly patients with advanced-stage indolent B-cell lymphoma (B-NHL). A multicenter study was performed to evaluate the efficacy and toxicity of R-THP-COP therapy in elderly patients (aged 70–79 years) with newly diagnosed advanced-stage indolent B-NHL using the complete response rate (%CR) as the primary endpoint. Patients with newly diagnosed, clinical stage III/IV, indolent B-NHL, aged 70–79 years, with a performance status of 0–2 were eligible for this study. R-THP-COP consists of 375 mg/m² of rituximab, 50 mg/m² of pirarubicin, 750 mg/m² of cyclophosphamide, 1.4 mg/m² of vincristine, and 100 mg/day of oral prednisolone for 5 days. This study was discontinued due to poor accrual after the enrollment of 18 patients, although the planned sample size was 40 patients. The numbers of patients with follicular lymphoma, mucosa-associated lymphoid tissue lymphoma, and mantle cell lymphoma were 16, 1, and 1, respectively. The median age was 73 (range, 70 to 79) years. The %CR including unconfirmed CR was 45% (95% confidence interval: 25-66%) and the overall response rate was 72%. The estimated 5-year overall survival and progression-free survival rates were 55% and 28%, respectively. The major toxicity observed was grade 4 neutropenia (94%). Grade 4 non-hematological toxicities were not observed and no patients developed grade 3/4 cardiac toxicities. This phase II study provides useful information regarding the efficacy and toxicity of R-THP-COP therapy for patients aged 70 years or older with newly diagnosed, advanced-stage, indolent B-NHL, although the sample size was small.

Keywords: Indolent B-cell lymphoma, elderly patients, R-THP-COP

INTRODUCTION

Indolent B-cell lymphoma accounts for 10% to 20% of all non-Hodgkin lymphoma (NHL) cases in Japan, and the prevalence of follicular lymphoma (FL) in particular has been increasing in recent years.¹ Currently, combination chemotherapy containing rituximab is the standard treatment

strategy for patients with newly diagnosed advanced-stage FL with a high tumor burden. Chemotherapy regimens, such as CHOP (cyclophosphamide, doxorubicin (DXR), vincristine, and prednisolone), CVP (cyclophosphamide, vincristine, and prednisolone), and bendamustine, are commonly combined with rituximab.² However, no current consensus on the choice of chemotherapy that should be combined with


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rituximab has been established,²⁻⁵ and evidence has mostly been obtained from studies that included younger patients.² Notably, the incidence rates of FL peak between 60 and 70 years of age in Taiwan,⁶ and the number of elderly patients with FL has also increased in Japan.¹

The present phase II study (R-THP-COP regimen, THP-2 study) was planned to evaluate combination chemotherapy with rituximab in elderly patients aged 70–79 years with advanced-stage, indolent B-NHL in 2003. In this THP-2 study, pirarubicin (THP) was expected to have the same or better antitumor effects and fewer toxicities, especially for cardiotoxicity, than DXR used in CHOP therapy.⁷ We report the results of this phase II study of R-THP-COP therapy for elderly patients aged 70 to 79 years with indolent B-NHL.

PATIENTS AND METHODS

This study was performed on elderly patients aged 70 to 79 years with previously untreated CD20-positive, low-grade, B-cell lymphoma that was diagnosed according to the 2001 WHO classification.⁸ Eligibility criteria included clinical stage III or IV, sufficient liver function (serum bilirubin level ≤ 2.0 mg/dL and serum liver aminotransferase ≤ 5 times the upper limit of normal), kidney function (serum creatinine ≤ 2.0 mg/dL), and cardiac function (left ventricular ejection fraction $\geq 50\%$ and no severe abnormalities on electrocardiography), and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) between 0 and 2. Written informed consent was received from all patients before enrollment. The protocol was reviewed and approved by the institutional review boards of all participating centers, and the study was conducted in accordance with the Declaration of Helsinki.

Study design

This was a prospective, multicenter, phase II study on elderly patients with newly diagnosed, advanced-stage, indolent B-NHL. R-THP-COP consists of 750 mg/m² of cyclophosphamide, 50 mg/m² of THP, and 1.4 mg/m² of vincristine (capped at 2.0 mg) administered intravenously on day 3, and 100 mg of oral prednisolone daily on days 3 to 7. Rituximab at 375 mg/m² was administered on day 1. R-THP-COP was delivered every 3 weeks for up to 6 cycles. Granulocyte colony-stimulating factor (G-CSF) was administered subcutaneously if needed for neutropenic fever or grade 4 neutropenia. The doses of chemotherapeutic agents were adjusted depending on defined toxicities.

Study end points

The primary end point was the complete response rate (%CR) including unconfirmed CR (CRu). The secondary endpoints included the overall response rate (ORR), overall survival (OS), progression-free survival (PFS), and toxicities. OS was calculated from the date of registration to the date of death from any cause and was censored at the last follow-up time point. PFS was calculated from the date of registration to the date of relapse, progression, or death from any cause

and was censored at the last verifiable progression-free date. Adverse events (AEs) were graded according to the National Cancer Institute–Common Toxicity Criteria (NCI-CTC) version 2.0. The planned sample size was 40 patients, which provided at least 80% power with the expected CR rate of 55%, threshold of 35%, and a one-sided α of 5%.⁹ This study was registered at <http://umin.ac.jp/ctr/index/htm> as UMIN000002287.

Assessment

Tumor assessments were performed for all target regions at baseline by computed tomography (CT) after completion of 6 cycles of R-THP-COP. Tumor response was assessed according to the International Workshop Criteria.¹⁰

Statistical analysis

OS and PFS were estimated using the Kaplan-Meier method. All statistical analyses were performed with JMP software (SAS Institute Inc., Cary, NC).

RESULTS

Patient characteristics

Eighteen patients from 14 hospitals belonging to the Hematological Malignancy Clinical Study Group (HMCSG) were enrolled in this THP-2 study between May 2005 and July 2014 in Japan. The enrollment period was initially planned as 3 years, but the protocol was revised to 9 years due to slow enrollment. The study was terminated prematurely after the registration of 18 patients, although the planned sample size was 40 patients.

The characteristics of the patients at enrollment are listed in Table 1. The median age was 73 years (range, 70 to 79 years) and all patients had advanced-stage disease (stage III or IV). According to the WHO classification system,⁸ 16 patients (89%) were diagnosed with follicular lymphoma (FL), 1 patient (6%) was diagnosed with mucosa-associated lymphoid tissue (MALT) lymphoma, and 1 patient (6%) was diagnosed with mantle cell lymphoma (MCL). MCL, which is now treated as aggressive NHL, was included because MCL was considered to be indolent B-NHL at the time this study was designed. According to the follicular lymphoma international prognostic index (FLIPI),¹¹ of the 16 patients with FL, 3 (19%) had intermediate-risk disease and 13 (81%) had high-risk disease. All patients had a good PS (grade 0 to 2). The following comorbidities were observed in 6 patients: hypertension in 3 patients (19%), diabetes mellitus in 2 patients (11%), and old tuberculosis in 1 patient (5.6%).

Response and efficacy

Thirteen patients (72%) completed the planned 6 cycles of therapy. The number of treatment cycles was 6 in 13 patients, 3 in 1 patient, 2 in 1 patient, and 1 in 3 patients. The median number of delivered cycles was 6 (range, 1–6 cycles).

The %CR including CRu was 45% (8/18) [95%

Table 1. Patient characteristics

		No. of patients	(%)
Total No.		18	
Age (years)	Median (Range)	73 (70-79)	
Sex	Male/Female	7/11	(39/61)
PS (ECOG)	0/1/2	11/5/3	(61/28/11)
Clinical Stage (Ann Arbor)	III/IV	7/11	(39/61)
Bone marrow involvement		10	(56)
B symptoms		3	(17)
Histology (WHO classification)			
Follicular lymphoma		16	(89)
MALT lymphoma		1	(6)
Mantle cell lymphoma		1	(6)
FLIPI			
Intermediate		3	(19)
High		13	(81)
Hb (g/dL)	<12 g/dL	7	(44)
LDH	Elevated	6	(38)
Lymph node involvement	>4	10	(63)

Abbreviations: PS, performance status; FLIPI, Follicular Lymphoma International Prognostic Index

confidence interval (CI): 25-66%] and the PR rate was 28% (5/18) (95% CI: 13-51%). The ORR was 72% (95% CI: 49-88%)(Table 2). The stable disease rate was 11% (2/18) and progressive disease was observed in 6% (1/18). After the completion of R-THP-COP therapy, 4 patients relapsed or progressed, and 3 patients received salvage chemotherapy at a median follow-up time of 59 months (range, 5–162 months). The estimated 5-year OS was 55% (95% CI: 32-76%), whereas the estimated 5-year PFS was 28% (95% CI: 12-52%) in all enrolled patients. The median OS was 138 months and the median PFS was 23.5 months (Figure 1). At the time of data cutoff (September 2019), 9 patients had died; 7 patients died of lymphoma, 1 patient died of bile duct cancer, and 1 patient died of interstitial pneumonitis.

Toxicities

The AEs observed in this study are listed in Table 3. The most frequently observed grade 4 AE was neutropenia (94%) and 16 patients (89%) received G-CSF. Five patients (28%) developed febrile neutropenia. Red blood cell transfusions were administered to 4 of 18 patients (22%), and 3 of them had a low hemoglobin level of less than 10 g/dL at the time of enrollment. One patient received platelet transfusion. No patients developed grade 3 or 4 cardiac toxicities. The ejection fraction (EF) was measured in 9 patients before treatment and ranged from 60% to 79% (median, 72%); the EF was also measured after 6 cycles of therapy and ranged from 65% to 88% (median, 69%). In 3 patients, the EF decreased by 7% to 15% after treatment, but those patients had a sufficient EF of greater than 50%. Five patients (28%) developed grade 2 sensory peripheral neuropathy, but no patients had grade 3 or 4 peripheral neuropathy.

Five patients discontinued treatment prematurely after 3

Table 2. Response to treatment

	No. (N=18)	(%)
Complete response (CR)*	5	(28)
Unconfirmed complete response (CRu)*	3	(17)
Partial response (PR)**	5	(28)
Stable disease (SD)	2	(11)
Progressive disease (PD)	1	(6)
Overall response rate (ORR)***	13	(72)
Could not be assessed****	2	(11)

* CR including CRu: 44% (95% CI: 25-66%)

** PR: 28% (95% CI: 13-51%)

*** ORR: 72% (95% CI: 49-88%)

**** Treatment was stopped because of toxic effects, patient's decision or the investigator's decision before evaluation of tumor [1: vomiting (grade 3), 1: hepatic dysfunction (grade 3)].

or fewer cycles, and of these, 4 discontinued treatment due to toxicities [liver dysfunction (grade 3), interstitial pneumonitis (grade 1), and vomiting (grade 3) or chest pain (grade 2)], whereas 1 patient discontinued treatment after 2 courses due to the development of dementia. The doses of cyclophosphamide and THP were reduced in 4 patients, and those of vincristine and prednisolone were reduced in 3 patients. The cycles were prolonged in 7 patients.

DISCUSSION

Age is one of the most important prognostic factors in patients with lymphoma;¹¹ however, there are few studies confined to elderly patients with indolent B-NHL.

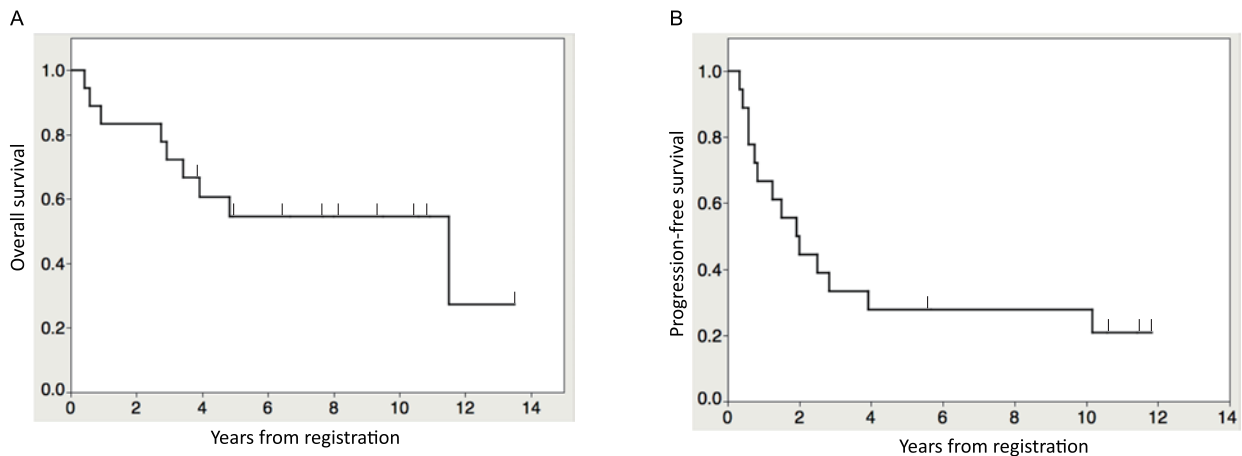


Fig. 1. Kaplan-Meier curves of overall survival and progression-free survival of patients treated by R-THP-COP therapy.

A. Overall survival in 18 patients with advanced-stage indolent B-cell lymphoma.

The estimated 5-year OS: 55% (95% CI: 32-76%).

B. Progression-free survival in 18 patients with advanced-stage indolent B-cell lymphoma.

The estimated 5-year PFS: 28% (95% CI: 12-52%).

Table 3. Adverse events in patients treated with R-THP-COP

Adverse event*	Grade	No. of patients (N=18)	(%)
Hematologic			
Anemia	3	5	(28)
Leucopenia	3/4	1 / 16	(6/89)
Neutropenia	3/4	1 / 17	(6/94)
Lymphocytopenia	3/4	5 / 1	(28/6)
Thrombocytopenia	3/4	5 / 1	(28/6)
Nonhematologic			
ALT	3	2	(11)
AST	3	2	(11)
FBS	3	1	(6)
Infection	2	2	(11)
Nausea	2	4	(22)
Vomiting	2/3	2 / 1	(11/6)
Ileus	2	1	(6)
Peripheral neuropathy	2	5	(28)
Motor neuropathy	2	1	(6)
Sensory neuropathy	2	5	(28)
Febrile neutropenia	2/3	1 / 4	(6/22)
Infusion related reaction	2/3	1 / 1	(6/6)

* Adverse events were evaluated according to the National Cancer Institute-Common Toxicity Criteria version 2.0.

Therefore, the present THP-2 study of elderly patients aged 70–79 years with advanced-stage, indolent B-NHL was conducted. However, only 18 patients, 45% of the planned number, were registered and this study was discontinued. Insufficient enrollment may have been due in part to limiting the eligible patients to those between the ages 70 and 79 years. Furthermore, major facilities were participating in development trials of new drugs for newly diagnosed FL at that time. Therefore, no definite conclusions were able to be made. However, considering that the age of the patients

ranged from 70 to 79 years, this study of the R-THP-COP regimen provides useful information on elderly patients with advanced-stage, indolent B-NHL, although it was a small study.

Combination chemotherapy with rituximab has been established as the standard of care for patients with newly diagnosed advanced-stage FL with a high tumor burden, and consequently, R-CHOP or R-bendamustine^{4,5} is widely used. However, there is currently no consensus on which chemotherapy agent should be combined with rituximab.³⁻⁵ Tetrahydropyranil adriamycin (pirarubicin, THP) is a tetrahydropyranil derivative that exerts stronger therapeutic effects than DXR.¹² THP is effective and associated with relatively low rates of cardiac toxicities compared with DXR.¹³ Therefore, it is expected to have comparable or greater antitumor effects and lower toxicities, such as cardiotoxicity, than DXR.^{7,14-16} In Japan, Mori *et al.* reported that the efficacy of THP-COP is almost the same as that of CHOP in patients with NHL over 65 years of age, and that the 5-year survival rate of patients aged 65 years or older with low-grade lymphoma is 48.2% after THP-COP therapy.⁷ Ogura *et al.* investigated whether THP-COP therapy is equivalent to CHOP for high-grade NHL in patients aged 70 years or older.¹⁵ They also reported that the CR rate is 62% and that adverse drug reactions are primarily hemotoxic.

For patients with newly diagnosed advanced-stage FL, Hiddemann *et al.* reported the results of a randomized, phase III study to compare R-CHOP with CHOP.¹⁷ In that study, registered patients ranged in age from 29 to 82 years, and the R-CHOP arm contained 62 patients (37%) aged 60 to 82 years. After a median follow-up of 18 months, the estimated time to treatment failure after R-CHOP in patients aged 60 years or older was 29 months. In Japan, a phase II/III study of R-CHOP-21 versus R-CHOP-14 for patients aged 20-69 years with untreated, indolent B-NHL was conducted by the Japan Clinical Oncology Group (JCOG).¹⁸ The %CR including CRu was 78% and the ORR was 97%. The 6-year

PFS of patients with FL treated by R-CHOP-21 was 41%.

In the present study, THP was used as the chemotherapeutic agent combined with rituximab. In patients aged 70-79 years treated by R-THP-COP therapy, the %CR including CRu and the ORR were 45% and 72%, respectively, and the estimated 5-year OS and PFS rates at the median follow-up time of 4.9 years were 55% and 28%, respectively. The majority of published studies on patients with FL included results obtained in the young and elderly.^{3-5,17,18} However, it is clear that the results of those clinical trials cannot be extended to all elderly patients. Compared with these results, the present study demonstrated comparable outcomes in elderly patients with advanced-stage, indolent B-NHL, considering that patients older than 70 years and those with poor prognostic factors (FLIPI high-risk) were enrolled. In terms of toxicities, the EF was not significantly lower in all patients examined after chemotherapy in the present study. Grade 2 sensory neuropathy developed in 28% patients, and the frequency of neuropathy in the present study was comparable with that in elderly patients aged 60 to 80 years with diffuse large B-cell lymphoma treated by CHOP versus R-CHOP reported by Coiffier *et al.*¹⁹ Therefore, elderly patients may develop peripheral neuropathy more frequently than younger patients. Thus, the R-THP-COP regimen resulted in AEs, but they were considered to be manageable toxicities among patients aged 70 years and older. Recently, treatments that may have greater efficacy and avoid toxicity have been investigated, and an approach using agents, such as a newer anti-CD20 monoclonal antibody (obinutuzumab) and lenalidomide, may aid in the treatment of elderly patients with low-grade lymphoma.^{2,20}

In conclusion, this phase II study may provide useful information regarding the efficacy and tolerability of full-dose R-THP-COP in elderly patients aged 70 to 79 years with newly diagnosed, indolent B-NHL, mainly FL, although the present study had a small sample size. Further large-scale studies or randomized studies should be conducted to confirm these findings.

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CONFLICTS OF INTEREST

Dr. Yamamoto has received research funding from Celgene, Chugai, Eisai, SymBio, Yakult, and Zenyaku; and has received honoraria from Chugai and Eisai. All remaining authors declared no conflicts of interest.

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