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【 ORIGINAL ARTICLE 】

3A Comparison between R-THP-COP and R-CHOP Regimens for the Treatment of Diffuse Large B-cell Lymphoma in Old Patients: A Single-institution Analysis

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Abstract:

Objective We retrospectively compared the clinical efficacy and toxicity of rituximab (R)-THP-COP (pirarubicin, cyclophosphamide, vincristine, and prednisolone) with that of R-CHOP (rituximab, adriamicin, cyclophosphamide, vincristine, and prednisolone) in previously untreated old patients with diffuse large B-cell lymphoma (DLBCL).

Patients and Methods Patients admitted to our institution between 2004 and 2013 were examined. The patients received either R(375 mg/m^2, day 1)-THP-COP (pirarubicin 50 mg/m^2 day 1, cyclophosphamide 750 mg/m^2 day 1, vincristine 1.4 mg/m^2 day 1, and prednisolone 100 mg day 1-5) or R-CHOP (adriamicin 50 mg/m^2 day 1, cyclophosphamide 750 mg/m^2 day 1, vincristine 1.4 mg/m^2 day 1, and prednisolone 100 mg day 1-5). The doses of chemotherapeutic agents were adjusted depending on the patient's age and associated complications. The treatment was performed for 6 to 8 cycles.

Results Among 74 patients with DLBCL (median 76, range 65-90 years; male 39, female 35), 29 received R-THP-COP, while 45 received R-CHOP. The overall response rates were 94.6% (complete response 86.4%, partial response 8.1%). The 2-year overall and progression-free survival rates were 77.6% and 68.5% for the R-THP-COP regimen and 79.2% and 78.9% for R-CHOP, respectively. No significant differences were found between these two regimens regarding the clinical efficacies. The most frequent adverse event was neutropenia (72.4% for the R-THP-COP regimen, 88.9% for the R-CHOP regimen). The cardiac function as evaluated by ejection fraction values was not impaired in either regimen.

Conclusion R-THP-COP was effective and safe as an alternative to R-CHOP.

Key words: diffuse large B cell lymphoma, R-CHOP, R-THP-COP, pirarubicin, old patients

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common form of non-Hodgkin's lymphoma (NHL) and accounts for one-third of newly diagnosed lymphoma cases (1). The standard chemotherapy regimen is rituximab combined with adriamicin, cyclophosphamide, vincristine, and prednisolone (R-CHOP). The R-CHOP regimen provides initial response rates of 70-80% with a 3-year overall survival of nearly 60% (2-5). However, the efficacy worsens in elderly patients (6, 7). The difficulty in treating elderly lymphoma patients is mainly attributable to the high incidence of adverse events and high mortality rates associated with the administration of chemotherapeutic agents (7, 8).

Tetrahydropyranyladriamycin (pirarubicin, THP) was iden-

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tified while searching for new anthracycline antibiotics among 4'-O-substituted compounds having fewer toxicities than other anthracycline anticancer drugs in 1979 (9). THP has been proven to have less cardiac toxicity than adriamicin (9-12). Accordingly, elderly patients with NHL have been treated with a combination of THP, cyclophosphamide, vincristine, and prednisolone (THP-COP) (13-16). Tsurumi et al. compared biweekly CHOP versus THP-COP regimens in a prospective, randomized phase II study for patients younger than 70 years with previously untreated aggressive NHL (15). The complete remission (CR) rate was 72.5% for CHOP and 72.5% for THP-COP, and the 5-year overall survival rate was 43.7% for CHOP and 54.0% for THP-COP. Tsurumi et al. also conducted a phase II study of THP-COP therapy for elderly DLBCL patients aged 70 years or older. They observed a CR rate of 72.1% and a 5-year survival rate of 38.1% without any therapy-related deaths (17). The therapeutic effectiveness was thus shown to be similar between the THP-COP and CHOP regimens before the clinical introduction of rituximab (R).

The present study retrospectively compared the clinical efficacy and adverse effects of R-THP-COP with those of R-CHOP in previously untreated old patients with DLBCL in our institution.

Patients and Methods

Patients

The present study was approved by the ethics committee of the University of Fukui (Fukui, Japan, No. 20150142). Patients ≥65 years of age who had been admitted to the University of Fukui Hospital (Fukui, Japan) between 2004 and 2013 were included in the study. All patients had been newly diagnosed with DLBCL. The diagnosis was based on the pathological findings of biopsy specimens and radiographic determination using computed tomography (CT) and positron emission tomography (18). The Ebstein-Bar virus status and cancer cell origin were not evaluated in detail. The ejection fraction was calculated via echocardiogram in patients before the initiation of chemotherapy and after the completion of treatment.

Treatment

All patients received 6-8 cycles every 21 days of either R-CHOP (375 mg/m^2 rituximab on day 1, 50 mg/m^2 doxorubicin on day 1, 750 mg/m^2 cyclophosphamide on day 1, 1.4 mg/m^2 vincristine on day 1, and 100 mg prednisolone on days 1-5) or R-THP-COP (375 mg/m^2 rituximab on day 1, 50 mg/m^2 THP on day 1, 750 mg/m^2 cyclophosphamide on day 1, 1.4 mg/m^2 vincristine on day 1, and 100 mg prednisolone on days 1-5). The doses of chemotherapeutic agents were adjusted depending on the patient's age and associated complications. A 5-HT$_3$ receptor antagonist was used for prevention of nausea and vomiting. Granulocyte colony-stimulating factor was administered subcutaneously if the peripheral neutrophil count was <500/μL. The exclusion criteria for this treatment were performance status 4 not related to the disease progression, uncontrollable severe infection, or severe dementia.

End points

The primary end point was the response rate after chemotherapy. The secondary endpoints were the two-year overall survival (OS), two-year progression-free survival (PFS), and adverse events. The patient's response to treatment and the incidence of relapse were defined according to the International Workshop criteria for non-Hodgkin's lymphoma (19, 20). Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria ver. 4.0. Following the completion of chemotherapy and the confirmation of the achievement of CR, the patients returned periodically for physical examinations, blood tests, and CT to monitor their disease status.

Statistical analyses

The OS was calculated from the date of the diagnosis until mortality due to any cause or the last follow-up. The PFS was calculated from the date of the diagnosis to disease progression or death. The OS time and the PFS time were estimated by the Kaplan-Meier method, and the differences were compared using a log-rank test. Graph generation and statistical analyses were performed using the Microsoft Excel 2013 (Microsoft, Redmond, USA) and GraphPad Prism (version 6.0; GraphPad Software, San Diego, USA) software programs. Values of $p<0.05$ were considered statistically significant.

Results

Patient characteristics

Ninety-eight elderly patients with DLBCL were admitted to our institution between 2004 and 2013. Among them, 74 patients (75.5%) with DLBCL (39 men, 35 women; median age 76 years, range 65-90 years) were conventionally treated (Table 1). Twenty-nine patients received R-THP-COP, while 45 received R-CHOP. Old patients often have comorbid disorders, including cardiac dysfunction; as such, THP is preferentially selected for these patients, because THP has less cardiotoxicity than adriamicin. The comorbidities observed in the patients are shown in Table 2. Cardiac dysfunction appeared to be more prevalent in the patients receiving R-THP-COP than in those receiving R-CHOP.

The performance status (PS) grade was compared between the two regimens. The mean PS value (1.5) in the patients treated with R-THP-COP appeared to be higher than that (1.1) in those treated with R-CHOP ($p=0.31$, unpaired t test) (Fig. 1A). The ages and Charlson Comorbidity Index values were also compared between the two regimen groups (Fig. 1B, C). The R-THP-COP regimen was used for older patients than the R-CHOP regimen ($p=0.01$, unpaired t test),

Table 1. Patient Characteristics.

No. of patients (%)	Total	R-THP-COP	R-CHOP
Number	74 (100)	29 (39.9)	45 (60.1)
Sex			
Male	32 (43.2)	13 (44.8)	19 (42.2)
Female	42 (56.7)	16 (55.2)	26 (57.8)
Age			
Median	75	77	74
Range	65-90	68-88	65-90
PS			
0, 1	39 (52.7)	14 (48.3)	25 (55.6)
2, 3, 4	22 (29.8)	10 (34.5)	12 (26.7)
NA	13 (17.5)	5 (17.2)	8 (17.8)
Clinical stage			
I/II	35 (47.3)	12 (41.4)	23 (51)
III/IV	39 (52.7)	17 (58.6)	22 (49)
IPI			
Low/Low-Int	25 (33.8)	7 (24.1)	18 (40)
High-Int/High	38 (51.3)	18 (62.1)	20 (44.4)
NA	11 (14.9)	4 (13.8)	7 (15.6)
sIL2R			
<2,000	41 (55.4)	15 (51.7)	26 (56.5)
≥2,000	33 (44.6)	14 (48.3)	19 (42.2)

NA: not assessed, PS: performance stage, IPI: international prognostic index, sIL2R: soluble interleukin 2 receptor

Table 2. Comorbidities in the Patients Receiving R-CHOP and R-THP-COP.

	R-CHOP	R-THP-COP
	Number	
Moderate or severe liver disease	2	0
Cardiac dysfunction/arrhythmia	0	3
Dementia	1	2
Cerebral infarction	0	3
Hypertension	19	4
Diabetes mellitus	5	5
Parkinson's syndrome	0	2
Deep venous thrombosis	0	1
Rheumatoid arthritis	3	1

although the Charlson Comorbidity Index values were comparable between the two regimens (p=0.48, unpaired t test). The median number of administration cycles was six for both regimens. The mean relative dose intensity (RDI) values were comparable between the R-THP-COP regimen (70.8%) and R-CHOP regimen (74.8%) (p=0.50, unpaired t test) (Fig. 2).

Response to therapy

The overall response rates were 94.6%, with a CR rate of 86.4% and a partial response (PR) rate of 8.1%. The CR/PR rates were 79.3%/13.8% for the R-THP-COP regimen, and 91.1%/4.4% for R-CHOP regimen. No significant difference in the overall response rates was found between the two regimens (p=0.64, chi-squared test).

Survival

The median follow-up time was 38.5 months. The 2-year OS rates were 77.6% in the R-THP-COP regimen group and 79.2% in the R-CHOP regimen group (Fig. 3A). The 2-year PFS rates were 68.5% in the R-THP-COP regimen group and 78.9% in the R-CHOP regimen group (Fig. 3B). No significant differences were found in either the OS (p=0.629) or PFS (p=0.433) between the two regimen groups. Of note, the OS was evaluated according to the RDI of the chemotherapy. The survival of the patients treated with R-CHOP or R-THP-COP with an RDI≥70% (2-year OS 87.0%) was significantly better than that with an RDI<70% (2-year OS 58.2%) (p=0.027) (Fig. 4A). Furthermore, the 2-year OS (93.3%) of the patients treated with R-THP-COP with an RDI≥70% was better than that (43.8%) with an RDI <70% (p<0.01) (Fig. 4B). This suggested the importance of maintaining the RDI, even in old patients with DLBCL. A univariate analysis demonstrated that the PS, clinical stage, IPI, LDH, and soluble interleukin 2 receptor level were prognostic factors for the OS. In a multivariate analysis of these factors, only PS remained an independent prognostic factor for the OS (hazard ratio 3.9, 95% confidence interval 1.4-10.8, p<0.001).

Toxicity

The most frequent adverse event was neutropenia (72.4% for R-THP-COP, 88.9% for R-CHOP, p=0.07, chi-squared test) (Table 3). Febrile neutropenia occurred in 31.0% of patients receiving the R-THP-COP regimen and 44.4% of those receiving the R-CHOP regimen. There were no significant differences in the frequency of adverse events between the two regimens. G-CSF was administered to 16 of 29 patients (55.2%) receiving the R-THP-COP regimen and 32 of 45 patients (71.1%) receiving the R-CHOP regimen (p=0.16, chi-squared test). However, the mean neutropenia grade was higher for the R-CHOP regimen (3.6) than for the R-THP-COP regimen (3.3) (p=0.08, unpaired t test) (Fig. 5). No treatment-related deaths occurred with either regimen.

Cardiac function

The cardiac function was evaluated by the ejection fraction values. The ejection fraction values at baseline did not differ markedly between the R-THP-COP group (70.5%) and the R-CHOP group (70.1%) (p=0.86, unpaired t test) (Fig. 6A). Furthermore, the values remained unchanged after the completion of chemotherapy in both groups (p=0.78 for R-THP-COP, p=0.50 for R-CHOP, paired t tests) (Fig. 6B). Three patients in the R-THP-COP group and 9 patients in the R-CHOP group showed an early filling-atrial filling ratio (E/A)<1 as measured by echocardiogram, which was used as a criterion of left ventricular diastolic dysfunction.

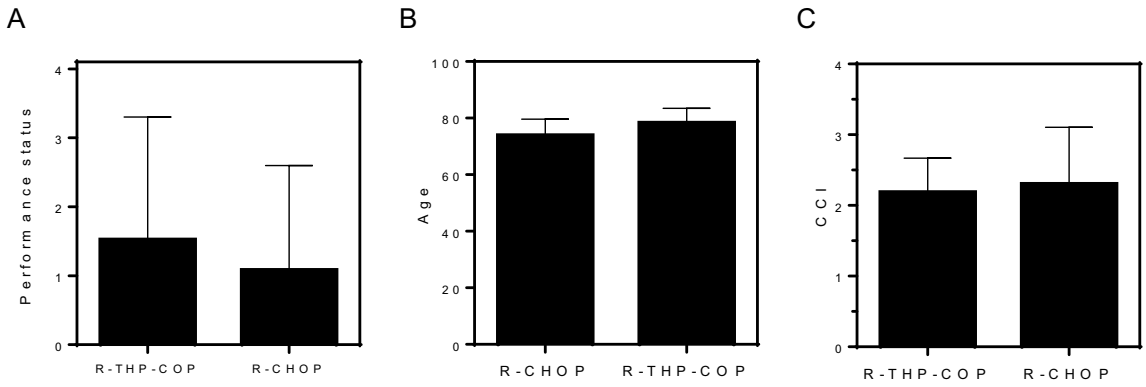

Figure 1. **The mean values of the performance status (A), age (B), and Charlson Comorbidity Index (CCI) (C) with each regimen.**

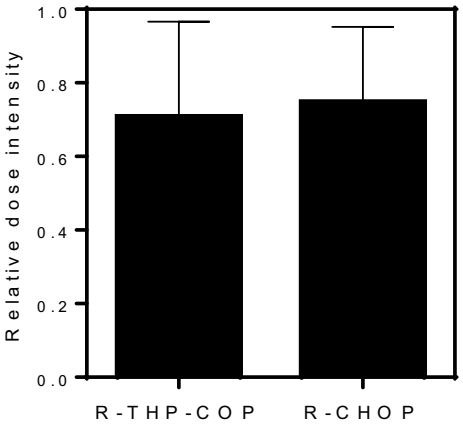

Figure 2. **The relative dose intensity of each regimen.**

Discussion

The present study retrospectively analyzed the clinical efficacy and tolerability of the R-THP-COP regimen in elderly patients with DLBCL at our institution. The results were compared with those of the R-CHOP regimen. We found that the R-THP-COP tended to be selected for older patients with worse PS and more comorbidities (Tables 1 and 2, Fig. 1A). The R-CHOP regimen appeared to provide a higher CR rate but with more severe neutropenia than the R-THP-COP regimen. However, the relative dose intensity values were roughly equivalent, and the number of treatment cycles was comparable between the two regimens (Table 1, Fig. 2). Accordingly, R-THP-COP provided a remission rate and 2-year OS and PFS equal to those achieved with R-CHOP (Fig. 3). Furthermore, the maintenance of the RDI was closely associated with the OS (Fig. 4). The substitution of THP for adriamicin did not increase the severity of any adverse events, including bone marrow suppression (Table 3, Fig. 5) and cardiac dysfunction (Fig. 6).

Chemotherapy using anticancer agents at strictly designated doses has resulted in a good response rate but increased rates of early death in elderly patients with lymphoma (6, 21). Although anthracycline is one of the most potent anticancer agents for NHL, its use is limited because of the risk of cardiotoxicity, especially in elderly patients. THP is a derivative of adriamycin designed from the structure of baumycins (9). It has shown stronger effects than adriamycin in inhibiting many mouse tumors, such as L1210 and P388 leukemia, B16 melanoma, and colon 38 adenocarcinoma (22, 23). Furthermore, THP was found to have lower cardiac and skin toxicity in hamsters than either adriamicin or aclacinomycin. THP has therefore been investigated for its clinical efficacy in elderly patients with NHL.

Several studies reported the clinical efficacy of THP in comparison with adriamicin for the treatment of NHL, including DLBCL (13, 16, 17, 25). Mori et al. compared the therapeutic outcomes among THP-COP, CHOP, and THP-COP plus etoposide in elderly patients (16). The subjects were 486 previously untreated patients ≥65 years of age with NHL. The response and eight-year survival rates were assessed. The remission rates for the THP-COP, CHOP, and THP-COPE groups were 45.3%, 44.9%, and 48.0%, respectively, for aggressive lymphoma. There was no marked difference in the OS or PFS among these three groups. Because adverse cardiac events were reported only in CHOP, the cardiotoxicity might have been low in the THP group. In that study, the doses of anticancer agents (THP 30 mg/m^2, cyclophosphamide 500 mg/m^2, vincristine 1 mg/m^2, prednisolone 30 mg/body) in the THP-COP regimen were lower than those used at our institution. The low administered doses and the absence of rituximab may therefore have contributed to the low CR rate in their study.

Kasahara et al. conducted a phase II study of the R-THP-COP regimen for treating elderly patients with DLBCL (26). The subjects were 52 patients between 70 and 80 years of age with newly diagnosed DLBCL. They reported that the CR and the 3-year overall survival rates were 63% and 53%, respectively, and no deaths related to the regimen occurred. Hara et al. conducted a phase II study to determine the effectiveness of the R-THP-COP regimen for patients (18-70 years) with DLBCL (27). The R-THP-COP regimen comprised 375 mg/m^2 rituximab on day 1, 750 mg/m^2 cyclophosphamide on day 3, 50 mg/m^2 THP on day 3, 1.4 mg/m^2 vincristine on day 3, and 100 mg prednisolone on days 3-7.

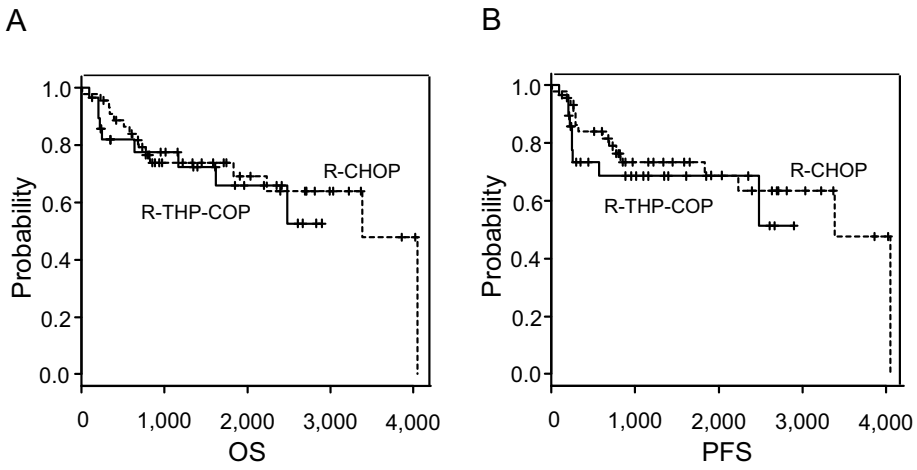

Figure 3. **The overall survival (OS) was calculated from the day of the diagnosis until death or last follow-up. The progression-free survival (PFS) was calculated from the day of the diagnosis until the disease progression or death. The survival durations were estimated by the Kaplan-Meier method. (A) The OS curve. (B) The PFS curve.**

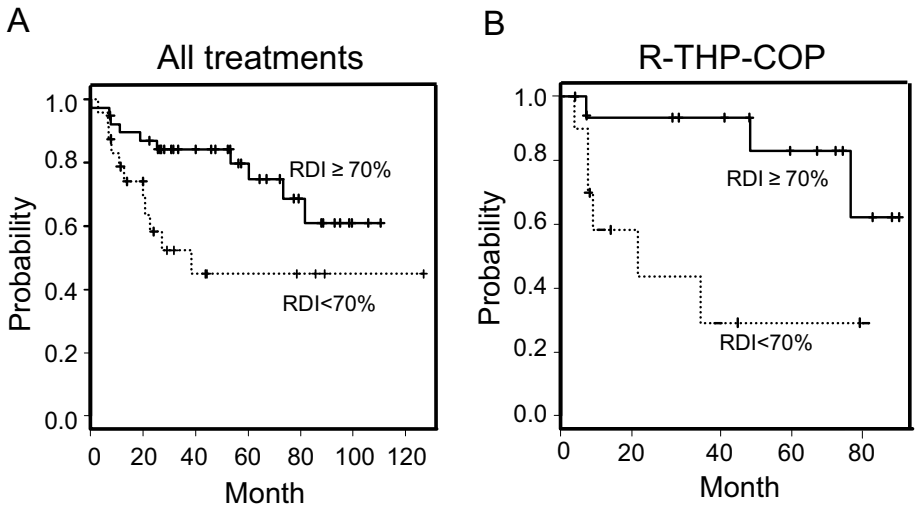

Figure 4. **The overall survival (OS) was calculated from the day of the diagnosis until death or last follow-up. The survival durations were estimated by the Kaplan-Meier method. (A) RDI≥70%, the patients who received R-CHOP or R-THP-COP with RDI≥70%; RDI<70%, the patients who received R-CHOP or R-THP-COP with RDI<70%. (B) RDI≥70%, the patients who received R-THP-COP with RDI≥70%; RDI<70%, the patients who received R-THP-COP with RDI<70%.**

Table 3. **Adverse Events.**

	R-THP-COP	R-CHOP
	Number (%)	
Febrile neutropenia	9 (31.0)	20 (44.4)
Neutropenia (Grade 3 or 4)	21 (72.4)	40 (88.9)
Anemia (Grade 3 or 4)	4 (13.8)	10 (22.2)
Thrombocytopenia (Grade 3 or 4)	3 (10.3)	4 (8.9)
Neuropathy (Grade 3 or 4)	0	2 (4.4)

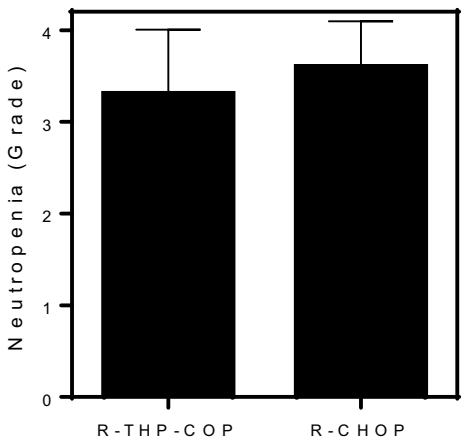

Figure 5. **The mean neutropenia grades for the R-THP-COP and R-CHOP regimens.**

Six to eight courses of the regimen were administered every two weeks. The CR rate was 92%, and the 3-year OS rate was 83%, and the 3-year PFS rate was 74%. No deaths associated with the treatment regimen occurred. Thus, the pre-

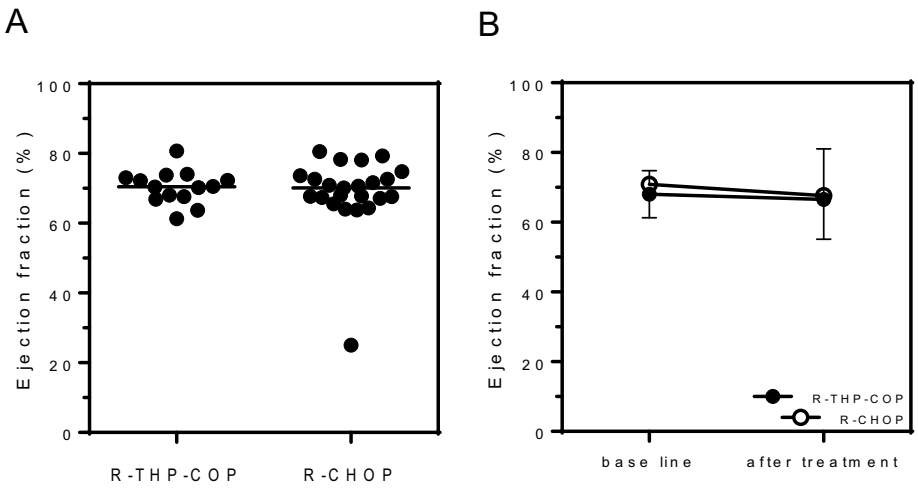

Figure 6. **The ejection fraction values determined in patients before the initiation of chemotherapy and after the completion of treatment. (A) The ejection fraction values at baseline in 14 patients treated with R-THP-COP and 23 patients treated with R-CHOP. (B) The ejection fraction values (median, range) at baseline and after treatment.**

sent study showed that the clinical efficacy of the R-THP-COP regimen for elderly patients with DLBCL was equal to or greater than the efficacies reported in the previous studies.

With regard to adverse events, Mori et al. reported that no patients died from adverse events due to chemotherapy (16). A decrease in the ejection fraction to less than 40% was reported in 5% of patients who received R-CHOP, but not in the patients, who received R-THP-COP. In the present study, there were no significant difference in the frequency of adverse events between the R-THP-COP and R-CHOP regimens. However, neutropenia tended to be more severe in the patients receiving the R-CHOP regimen than in those receiving the R-THP-COP regimen. No specific reason for this difference was found. The ejection fraction did not decrease after chemotherapy with either regimen, although not all patients were evaluated. The ejection fraction is not a sufficient parameter to fully evaluate the cardiac function in patients treated with anthracyclines. Several studies have suggested more severe cardiotoxicity in patients treated with adriacimin than in those treated with THP (13, 15, 16, 27). These results therefore suggest an advantage when using R-THP-COP for elderly patients.

Regarding factors that predict the survival, Tsurumi et al. reported the comparison of CHOP and THP-COP regimens in the treatment of newly diagnosed aggressive NHL (15). A univariate analysis demonstrated that the PS, clinical stage, LDH, soluble interleukin 2 receptor level, C reactive protein level, and the extent of extranodal involvement were prognostic factors for the OS. In a multivariate analysis, only the PS remained an independent prognostic factor for the OS ($p<0.01$, risk ratio 3.3, 95% confidence interval 1.56-6.81). Mori et al. showed that the clinical stage, sex, and IPI were associated with a reduced likelihood of CR (16). The predictive factors for the OS were sex, age, PS, stage, Working Formulation category, LDH, serum albumin level, and IPI. A multivariate analysis showed that a poor PS (PS≥2), patients' age, and clinical stages III and IV were the factors that contributed most to a poor prognosis. The present study extracted PS as the single independent prognostic factor for the OS in our multivariate analysis, which was in accordance with the results reported in these previous studies.

Zhai et al. found that the long-term outcomes of aggressive NHL patients receiving the THP-COP regimen were similar to those of patients receiving the CHOP regimen (28). Furthermore, the THP-COP regimen has been recently shown to be effective for treating not only patients with DLBCL but also those with peripheral T-cell lymphoma (29).

Hirakawa et al. demonstrated the importance of maintaining the RDI of CHOP-like regimens combined with rituximab in DLBCL patients (30). However, they found that maintaining the RDI was difficult in the patients treated with R-THP-COP, because it tended to be used to treat older patients (age over 70 years). Nevertheless, the RDI was maintained equally well in both regimen groups in the present study (31).

The present study found that the R-THP-COP regimen provided clinical efficacy equivalent to that of R-CHOP, with ostensibly less-severe toxicities than R-CHOP. In conclusion, the switching of adriamicin to THP may effectively and safely maintain the RDI, thereby improving the clinical efficacy, even in old patients with DLBCL.

The authors state that they have no Conflict of Interest (COI).

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