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The Effect of Adding Rituximab to CHOP-based Therapy on Clinical Outcomes for Taiwanese Patients with Diffuse Large B-cell Lymphoma: A Retrospective Analysis in the Tri-Service General Hospital

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Objective: Diffuse large B-cell lymphoma (DLBCL), as defined by 2008 World Health Organization (WHO) classification, is the most common subtype. Rituximab (R), a chimerical monoclonal antibody against the CD20 B-cell antigen, has shown improved outcomes in patients with newly diagnosed DLBCL. Based on clinical results, a retrospective analysis was performed of treatment outcome, using rituximab, in patients with DLBCL. **Materials & Methods:** Two hundred and twenty newly diagnosed patients with non-Hodgkin's lymphoma (NHL), between June 2001 and December 2006, were evaluated for histological subtypes and clinical characteristics. Ninety-nine patients with DLBCL were investigated further for clinical results after CHOP-like chemotherapy with or without rituximab. **Results:** Among 220 patients with NHL, 172 (78.2%) patients had B-cell lineage and 35 (15.9%) T/NK-cell lineage. Ninety-nine patients were diagnosed with DLBCL, which was the most common B-cell lineage subtype and accounted for 45% of the patients with NHL. Among the 99 patients with DLBCL, 43 received R-CHOP like chemotherapy (R-CHOP group), 29 received CHOP-like chemotherapy alone (CHOP group), 13 had other chemotherapy regimens, and 14 received supportive care only. The response rate was significantly higher in the R-CHOP group compared to the CHOP group (86% vs. 58.6%, p=0.012). The progression free survival was significantly higher in the R-CHOP group (p=0.05, HR=0.524, CI, 95%, 0.255-1.075). The survival benefit was also more favorable in the R-CHOP group (p=0.06, HR=0.520, CI, 95%, 0.253-1.067). **Conclusions:** DLBCL is the most common subtype of NHL. The addition of rituximab to CHOP-like chemotherapy increased the response rate and improved the therapeutic outcome with regard to the progression free survival. A longer follow-up duration is necessary to evaluate overall survival.

Key words: rituximab, CHOP, diffuse large B cell lymphoma

INTRODUCTION

The World Health Organization (WHO) classification of lymphoid neoplasms is well established; the clinical and pathological features of malignant lymphoma (ML) have been analyzed since 2008. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype; it accounts for about 33.1 to 47.2% of patients with non-Hodgkin's lymphoma (NHL) reported at different hospitals in Taiwan. The CHOP regimen, which includes cyclophosphamide, doxorubicin, vincristine, and prednisone, has been the standard therapy for patients with high-grade NHL for more than two decades.[1-2] Rituximab (R), a chimeric murine/human monoclonal antibody against the CD20 B-cell antigen, has been shown to improve the outcome of patients with newly diagnosed DLBCL. R plus CHOP-based chemotherapy has generally been used for patients with DLBCL. However, no randomized controlled trial has been conducted in Taiwan.[3-7] To clarify the impact of this treatment regimen on Taiwanese patients, adding R to CHOP-based therapy, a retrospective analysis was performed, comparing the clinical outcomes of R plus CHOP-based chemotherapy to CHOP-based chemotherapy in Taiwanese patients with DLBCL at the Tri-Service General Hospital.

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Table 1 Extranodal Sites Involved in Diffuse Large B Cell Lymphoma (N=56)

Site	Number	%
Liver	8	8.1
Bone	8	8.1
Pleural effusion	7	7.1
Stomach	6	6.1
Lung	5	5.1
Tonsil	4	4
Nasopharynx	3	3
Pancreas	3	3
Breast	2	2
Ascites	2	2
Thyroid	1	1
Testis	1	1
Adrenal gland	1	1
Penis	1	1
Uterine cervix	1	1
Bladder	1	1
Duodenum	1	1
Anus	1	1

Table 2 The distribution of 220 patients with Non-Hodgkin's lymphoma according to the 2008 WHO classification

Subtype	Number (N=220)	%
B cell	172	78.2
Diffuse large cell lymphoma	99	45
Follicular lymphoma	21	9.5
Extranodal MALT lymphoma	7	3.2
Mantle cell lymphoma	13	5.9
Nodal marginal zone lymphoma	5	2.3
Burkitt	5	2.3
CLL/SLL	21	9.5
T cell rich B cell lymphoma	1	0.5
T cell	35	15.9
T cell lymphoma-unspecified	20	9.1
Panniculitis	1	0.5
Anaplastic	4	1.8
Angioimmunoblastic	5	2.3
NK/T	3	1.4
Mycosis fungodies	1	0.5
Sezary syndrome	1	0.5
Unknown	13	5.9

MATERIALS AND METHODS

The WHO classification was used to assess the clinical results, in this retrospective analysis of treatment outcome. A total of 248 patients with newly diagnosed ML were identified between June 2001 and December 2006; the histological subtypes and clinical characteristics of these patients were assessed at the Tri-Service General Hospital. Two hundred and twenty patients (88.7%) had NHL and 28 (11.3%) Hodgkin's lymphoma. A total of 99 patients with DLBCL were investigated for the clinical outcomes after chemotherapy with or without R. For the 99 DLBCL patients, there were 43 nodal and 56 extranodal sites identified (Table 1).

The clinical data collected included: age at diagnosis, Ann Arbor stage, Eastern Cooperative Oncology Group (ECOG) performance status, lactate dehydrogenase (LDH) level, extra-nodal sites, and International Prognostic Index (IPI). Initial staging included a history and physical examination, standard blood tests (including LDH and other biochemical markers), chest X-ray, computed tomography of the neck, chest, abdomen, and pelvis, and unilateral bone marrow aspiration and biopsies.

CHOP chemotherapy includes: cyclophosphamide, 750 mg/m2 as intravenous (i.v.) infusion on day 1, doxorubicin, 50 mg/m2 i.v. on day 1, vincristine, 1.4 mg/m2 (maximum dose; 2 mg/body) i.v. on day 1, and prednisone 60 mg/m2 per orally (p.o.) on days 1–5 (CHOP) or cyclophosphamide, 750 mg/m2 i.v. on day 1, epirubicin, 80 mg/m2 i.v. on day 1, vincristine, 1.4 mg/m2 (maximum dose; 2 mg/body) i.v. on day 1, and prednisone 60 mg/m2 p.o. on days 1 to 5 (CHOP). R-CHOP or CHOP was given for three or four courses following radiotherapy for bulky disease, and for six to eight courses for advanced disease. The CEOP regimen was given to patients with cardiac dysfunction or who were older than 70 years of age. The dosage and schedule of rituximab in the present study was 375 mg/m2 every three weeks with chemotherapy.

Complete remission (CR) and partial remission (PR) in response to the chemotherapy were assessed according to the Japan 327123 International Working Group criteria.[8] Stable disease (SD) was defined as less than a PR but not progressive disease (PD). PD was defined as the occurrence of new lesions or an increase of the C25% in the sum of the products of the cross-sectional diameters of all previously detected lesions. The final

Table 3 Compression of clinical characteristics in two groups of patients receiving CHOP with or without Rituximab

Variables	CHOP-like (N=29)	R-CHOP-like (N=43)	P value
Median age	57	57	
<60	12 (41.4%)	16 (37.2%)	0.48
≧60	17 (58.6%)	27 (62.8%)	0.34
Sex			
Male	17 (58.6%)	26 (60.5%)	0.37
Female	12 (41.4%)	17 (39.5%)	0.28
B symptoms (%)	7 (24.1%)	13 (30.2%)	0.25
Stage			
I-II	9 (31.0%)	17 (39.5%)	0.18
III-IV	20 (69.0%)	26 (60.5%)	0.53
IPI			
L/LI	17 (58.6%)	26 (60.5%)	0.35
H/HI	12 (41.4%)	17 (39.5%)	0.67
BM involvement	5 (17.2%)	8 (18.6%)	0.34
Splenomegaly	3 (10.3%)	7 (16.3%)	0.16
Hepatomegaly	3 (10.3%)	5 (11.6%)	0.54
ECOG			
0-1	18 (62.1%)	33 (76.7%)	0.10
≧2	11 (37.9%)	10 (23.3%)	0.27
LDH			
Normal	14 (48.3%)	24 (55.8%)	0.42
High	15 (51.7%)	19 (44.2%)	0.32
Hepatitis B,C carrier	12 (41.4%)	13 (30.2%)	0.32
RT addition	8 (27.6%)	11 (25.6%)	0.65
Treatment			
CHOP ± R	26 (89.7%)	34 (79.1%)	0.25
COP ± R	3 (10.3%)	9 (20.9%)	0.12

date for the progression-free survival (PFS) was defined as the last day before documented disease progression or relapse or the day the patient was last known to be alive without disease progression. The final date for the overall survival (OS) was defined as the day of death from any cause or the last day the patient was known to be alive. The PFS and OS were assessed using the Kaplan–Meier method and compared between groups using the log-rank test.[9-10] All the survival analyses were conducted with the STATA; a P<0.05 was considered statistically significant.

RESULTS

1. Patient characteristics

Among the 220 patients with NHL, 172 (78.2%) patients had a B-cell lineage and 35 (15.9%) T/NK-cell lineage (Table 2). Ninety-nine patients were diagnosed

Table 4 The clinical response in the two groups of patients

Response	CHOP (n=29)	R-CHOP (n=43)	P value
Overall response rate (%)	17 (58.6%)	37 (86.0%)	0.012
Complete response, n (%)	11 (37.9%)	23 (53.5%)	
Partial response, n (%)	4 (13.8%)	12 (27.9%)	
Stable disease, n (%)	2 (6.9%)	2 (4.7%)	
2-year overall survival, n (%)	14 (48.3%)	29 (67.4%)	0.10

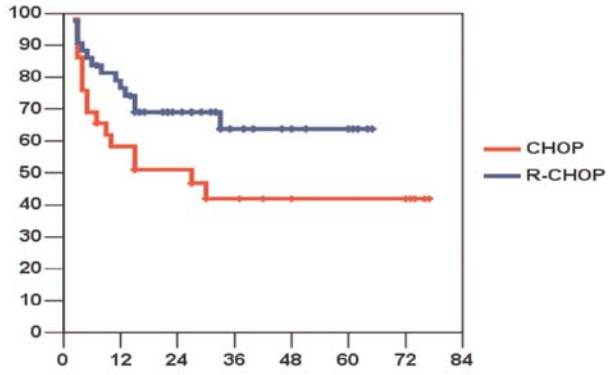

Fig 1a Overall Survival of Patients with DLBCL that Received CHOP (N=29) and R-CHOP (N=43) (HR=0.520, 95%CI 0.253-1.067, P:0.06)

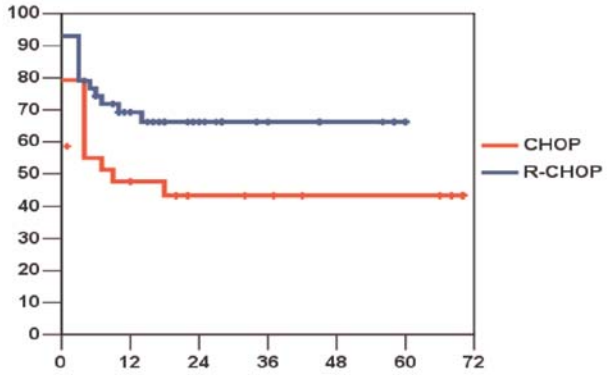

Fig 1b Progression-Free Survival of Patients with DLBCL that Received CHOP (N=29) and R-CHOP (N=43) (HR=0.524, 95% CI 0.255-1.075, P:0.04)

with DLBCL, the most common B-cell lineage subtype that accounted for 45% of the patients with NHL. Among the 99 patients with DLBCL, 43 received R-CHOP like chemotherapy (R-CHOP group), 29 CHOP-like chemotherapy alone (CHOP group), 13 other chemotherapy regimens, and 14 supportive care alone. The clinical characteristics of the R-CHOP group and CHOP group are summarized in Table 3.

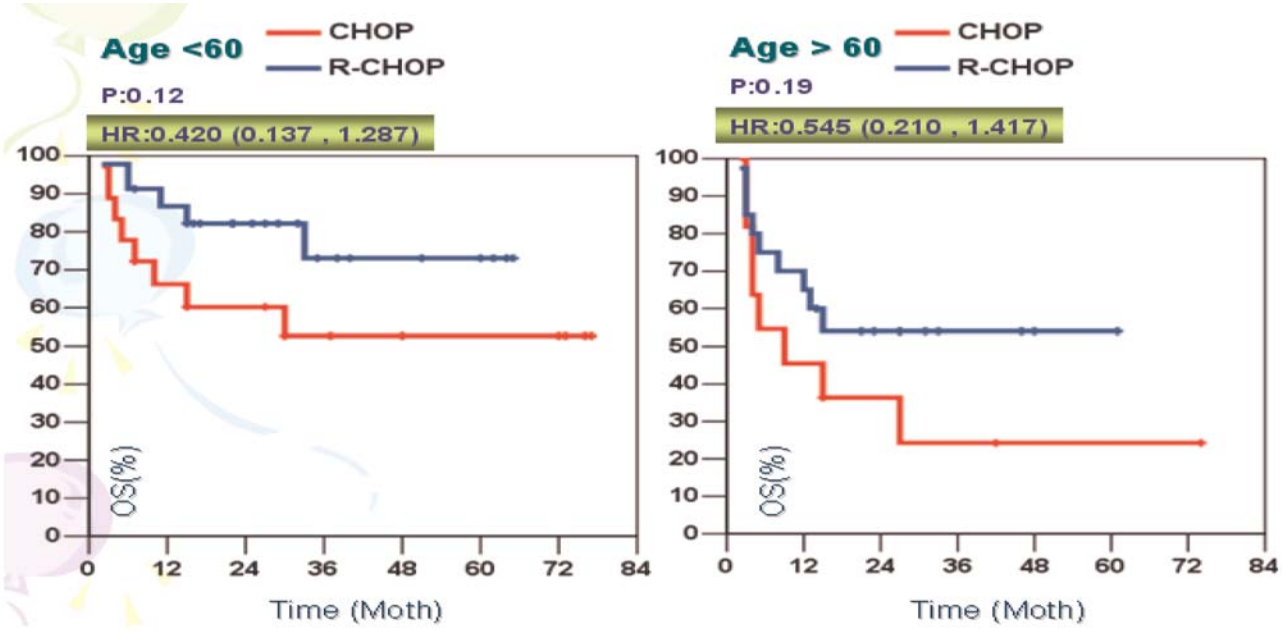

Fig 2a Overall Survival of patients treated with R-CHOP or CHOP divided between patients 60 years or older and patients younger than 60 years

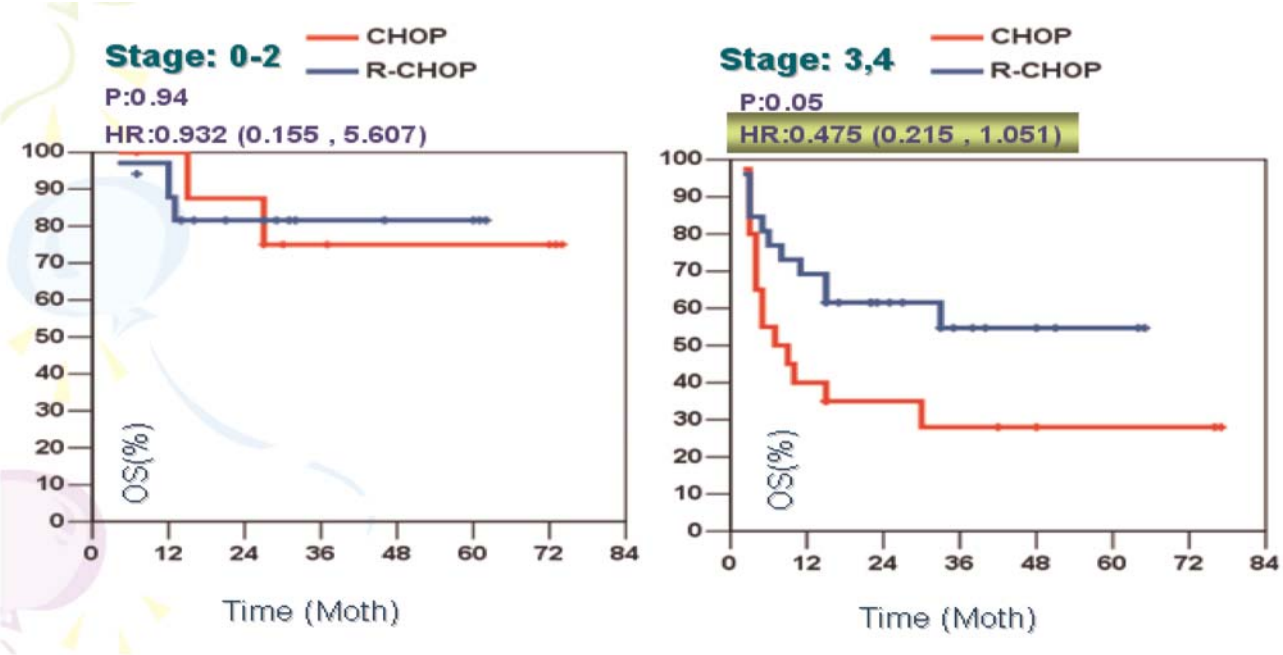

Fig. 2b Overall Survival of patients treated by R-CHOP or CHOP divided between stage 0-2 and stage 3-4

2. Outcomes

The overall response rate was significantly higher in the R-CHOP group compared to the CHOP group (86% vs. 58.6%, p=0.012, Table 4). The 2-year overall survival was 67.4% for the R-CHOP group and 48.3% for the R- group (p=0.1). The OS of the patients with DLBCL that received R-CHOP was better than the patients that received CHOP (HR=0.520, 95%CI 0.253-1.067, P:0.06, Fig 1a). The PFS of the patients with DLBCL that received R-CHOP was better compared to the patients that received CHOP (HR=0.524, 95% CI 0.255-1.075, P:0.04, Fig 1b).

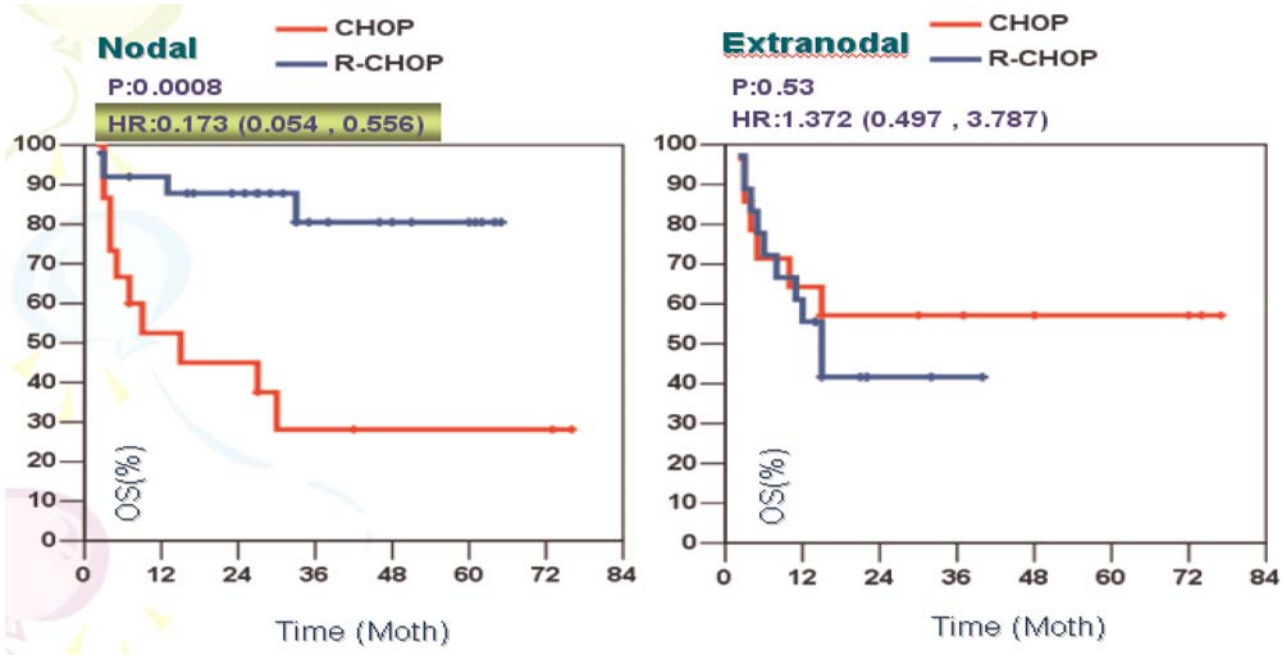

Fig. 2c Overall Survival of patients treated with R-CHOP or CHOP divided between patients with nodal and extra-nodal sites

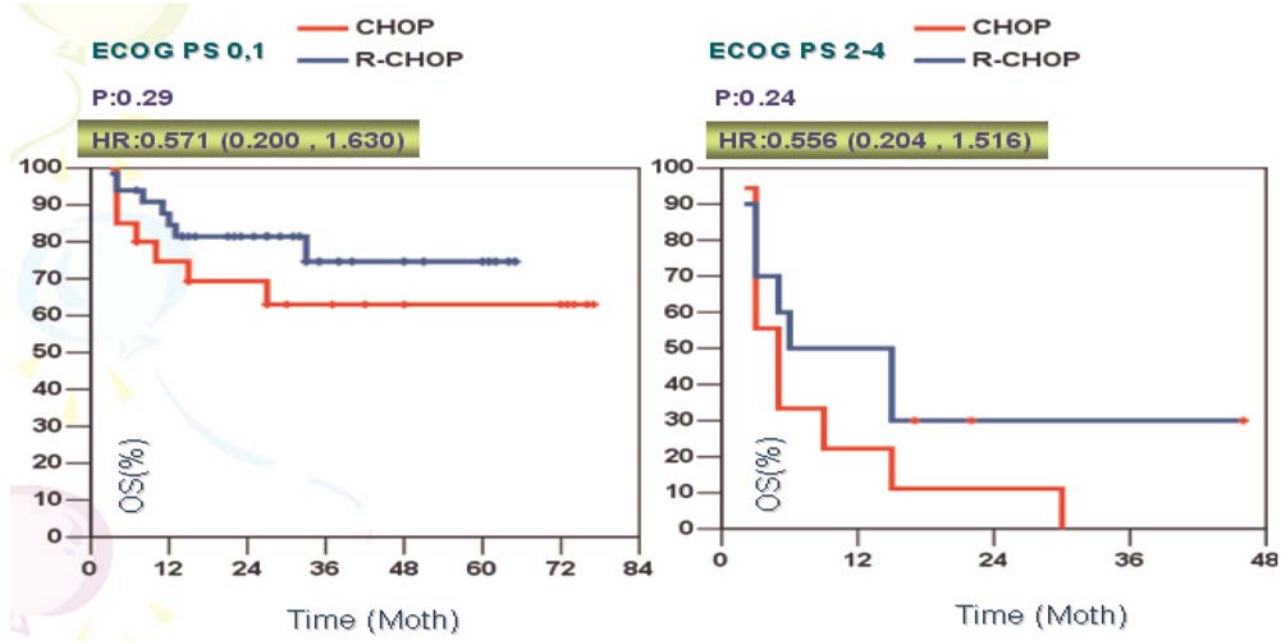

Fig. 2d Overall Survival of patients treated with R-CHOP or CHOP divided between patients with a low (PS:0-1) ECOG and patients with a high (PS:2-4) ECOG

A subgroup analysis was performed based on the age at diagnosis between < 60 years > 60 years (Fig. 2a). For age, the impact of R-CHOP becomes less clear (P>0.05). A secondary subgroup analysis by stage (early: 0-2 and late: 3-4) is presented in Figure 2b. The late stage patients significantly benefited from R-CHOP (HR= 0.475, 95% CI 0.215 -1.051, P:0.05), although the statistical significance was marginal. For the patients with early stage disease, the impact of R-CHOP was less clear (HR = 0.932, 95% CI 0.155-5.607, P:0.94)

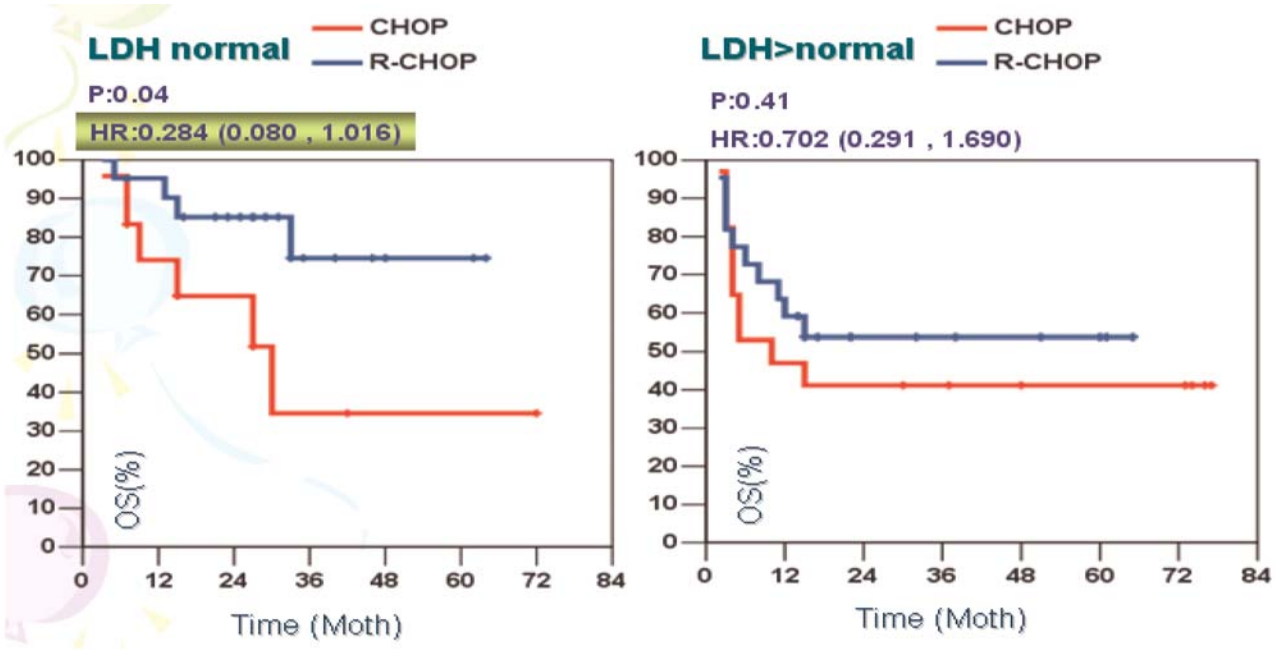

Fig 2e Overall Survival of patients treated with R-CHOP or CHOP divided between patients with a normal LDH and patients with a high LDH.

The third subgroup analysis assessed the nodal sites (nodal and extra-nodal), Figure 2c. The patients with nodal sites significantly benefited from R-CHOP (HR=0.173, 95% CI 0.054-0.556, P:0.0008), although the statistical significance was marginal. For extra-nodal sites, the impact of R-CHOP was less clear (HR =1.372, 95% CI 0.497-3.787, P:0.53). The fourth subgroup analysis was of the ECOG performance status (low:0-1 and high:2,3,4), Figure 2d; the impact of R-CHOP was less clear (P>0.05). For the fifth subgroup analysis of LDH (normal and high LDH) Figure 2e, the patients significantly benefited from R-CHOP with normal LDH (HR=0.284, 95% CI 0.080-1.016, P:0.04), although the statistical significance was marginal. For the patients with a high LDH, the impact of R-CHOP was less clear (HR =0.702, 95% CI 0.291, 1.690, P:0.41).

DISCUSSION

In this study, B-cell lineage accounted for 78.2% patients with NHL, and DLBCL accounted for 45%. The R-CHOP group significantly benefited with regard to the overall response rate. The OS and PFS of patients with DLBCL that received R-CHOP did better than those that received CHOP. The subgroup analysis showed that late stage disease, nodal sites and a normal LDH were factors associated with a greater benefit associated with rituximab therapy. However, a recent study demonstrated that the addition of rituximab to chemotherapy provided a benefit with respect to outcome at any IPI status and any age in Japanese patients with DLBCL.[20] Furthermore, a large study for further evaluation is necessary to clarify the findings of patients with late stage, nodal sites, normal LDH and advanced stage disease resulting in a better survival.

The recent study showed improved outcomes after R-CHOP therapy; the addition of rituximab tended to improve the OS and was a strong independent prognostic factor for the PFS, which is a good replacement marker for OS given the limited duration of follow-up.[11] There are no reports in the Medical Literature of a randomized controlled trial conducted in Taiwan. Lin TY et al showed that the addition of Rituximab to CHOP regimens reduced the risk of treatment failure and disease progressive rates in patients with DLBCL, and did not increase the occurrence of chemotherapy- related adverse events, in China.[19] Park YH et al showed that the CR and event-free survival rates were higher in (p=0.001 and 0.0194) in a Korean cohort. This survival benefit in the R-CHOP group was maintained in high-risk patients according to the IPI (p=0.0039).[19] Seki R et al reported the results of a large-scale, multicenter study in Japan that showed that

rituximab plus CHOP provided a greater survival benefit than CHOP alone.[20] These studies and the study reported here provide evidence that the addition of rituximab to chemotherapy provides a benefit with respect to outcome in Asian patients with DLBCL.

Localized disease is defined as Ann Arbor stage I and non-bulky stage II.[12] Three cycles of R-CHOP with subsequent involved-field radiotherapy (IFRT) has been shown to be effective treatment in a phase II study.[13] However, the survival benefit of the addition of IFRT to chemotherapy remains controversial. Although the current National Comprehensive Cancer Network Clinical Practice Guidelines for NHL recommends both three cycles of R-CHOP plus IFRT, and six to eight cycles of R-CHOP with or without subsequent IFRT, this is based on data from the pre-rituximab era. For prolonged chemotherapy, the risk of toxicity should be considered according to the patient's condition.

Junshik Hong et al reported in a recent study that the difference in outcomes between the three to four cycles of R-CHOP followed by IFRT (N=22) and the six to eight cycles of R-CHOP (N=14) was not significant. In the current study, among 345 patients that received localized radiation therapy in Japan, the addition of rituximab to CHOP reduced the survival difference between the CHOP and R-CHOP groups ($P = 0.104$), compared to the group with no radiation ($P < 0.001$).[20] Receiving radiotherapy showed less of a benefit with the addition of rituximab to chemotherapy compared to patients without radiotherapy, with respect to the OS. The effect of IFRT and the optimal treatment should be clarified in prospective clinical trials of treatment with rituximab.[13-15]

Bulky DLBCL disease, stage II, generally includes patients regarded as having advanced disease, such as stage III or IV disease.[16] Previous studies have suggested that eradicating microscopic tumors with localized lymphomas might not be achieved with three cycles of CHOP alone and that the role of IFRT is limited to reducing the local relapse rate.[17] Thus, subsequent IFRT is important for reducing the local relapse rate in bulky DLBCL.

LIMITATIONS

The limitations of this study include the following. This was not a randomized trial. The characteristics and historical backgrounds of the two groups differed. The small number of patients, in the severe mismatch group, restricts drawing any firm conclusions. Furthermore, the number of patients included and duration of follow-up were limited. A longer follow-up might confirm and clarify the results.

CONCLUSIONS

DLBCL is the most common subtype of NHL. The addition of Rituximab to CHOP-like chemotherapy increased the response rate and improved the therapeutic outcome of the overall survival. The subgroup analysis showed that late stage disease, nodal sites and a normal LDH were factors associated with a greater benefit from Rituximab therapy. A longer follow up duration is necessary to evaluate the significance of the overall survival.

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DISCLOSURE

The author declares that this study has no conflict of interest.

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