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ORIGINAL ARTICLE

Addition of rituximab to the CHOP regimen has no benefit in patients with primary extranodal diffuse large B-cell lymphoma

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Background
The addition of rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy (R-CHOP) has significantly improved clinical outcomes for patients with diffuse large B-cell lymphoma (DLBCL). However, new predictors of patient response to R-CHOP have not been established. We aimed to evaluate the impact of R-CHOP compared with CHOP in patients with DLBCL and to establish clinical predictors of better outcomes in these patients.

Methods
We retrospectively identified 177 patients diagnosed with CD20-positive DLBCL and treated with CHOP (N=82) or R-CHOP (N=95). The response rate, event-free survival (EFS), and overall survival (OS) rates were compared between the 2 treatment groups. All patients were classified into primary extranodal lymphoma (PENL) or nodal lymphoma (NL) subgroups, and the clinical parameters of each subgroup were analyzed.

Results
The overall response rate was higher in R-CHOP group (95% vs. 84%, P=0.07). The 3-year EFS rate was significantly higher in R-CHOP group (71% vs. 52%, P=0.013), but the OS rate was comparable between the 2 groups (79% vs. 69%, P=0.23). A significant survival benefit was seen with R-CHOP compared to CHOP therapy in NL patients (P=0.002 for EFS and 0.04 for OS). Multivariate analyses confirmed that R-CHOP therapy is an independent prognostic factor for EFS (hazard ratio of 0.32 [0.17-0.62], P=0.001) and OS (hazard ratio of 0.4 [0.18-0.87], P=0.02) in NL patients.

Conclusion
Patients in the PENL group did not benefit from R-CHOP chemotherapy.

Key Words CHOP, Diffuse large B-cell lymphoma, Rituximab, Primary extranodal lymphoma

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin's lymphoma (NHL), accounting for approximately 30-40% of lymphoma cases [1, 2]. For several decades, the cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy regimen has been considered the gold standard for treatment of DLBCL, on the basis of serial clinical investigations in which other second- and third-generation chemotherapy regimens failed to demonstrate an advantage [3, 4]. The recent introduction of rituximab, a chimeric IgG1 monoclonal antibody targeting CD20, has led to alterations in treatment strategies for these patients. Rituximab, originally investigated for utility in patients with relapsed and refractory follicular and low-grade NHL, showed promising efficacy for DLBCL, both alone and in combination with CHOP (R-CHOP) chemotherapy, in phase II studies [5, 6]. Recent studies comparing the R-CHOP and CHOP regimens demonstrated the superiority of R-CHOP therapy, which led to significantly higher complete response (CR) rates and survival benefits in both elderly and young DLBCL patients. Accordingly, R-CHOP has replaced CHOP as a new standard treatment [7-10].

Although most patients exhibit improved outcomes with rituximab, some patients fail to respond to R-CHOP therapy. There is currently an urgent need to identify new prognostic factors in the R-CHOP era. To date, the International Prognostic Index (IPI) has been used as a powerful clinical tool to predict outcomes for patients with aggressive NHL [11]. However, the issue of whether the traditional IPI is relevant for patients subjected to R-CHOP chemotherapy remains to be established. In a recent study on patients treated with R-CHOP, IPI could not be effectively used to distinguish 4 discrete risk groups, although it remained partially predictive, and a revised IPI to identify 3 risk groups proved a better predictor [12]. Other studies have attempted to evaluate molecular prognostic markers, such as Bcl-2 and Bcl-6, in DLBCL patients treated with R-CHOP [13, 14].

Approximately 25-40% of NHLs arise from tissues other than lymph nodes. These lymphomas are often referred to as primary extranodal lymphomas (PENLs), although the exact definition is not established and currently a subject of controversy [15-17]. The incidence of PENL is higher in areas of Asia, including Korea, than in Western countries [18-20]. Several studies have attempted to elucidate the differences between PENL and nodal lymphoma (NL) in terms of etiology, clinical behavior, response to treatment, and outcome. A number of investigators have identified significant molecular differences between extranodal and nodal lymphoma, suggesting distinct genetic origins [21-24]. However, the clinical and prognostic differences between these 2 types of NHL are unclear at present. To date, few studies have been carried out to establish a correlation, if any, between rituximab treatment and both NHL types.

In this study, we conducted a retrospective analysis to evaluate the impact of the R-CHOP regimen and sought to identify clinical prognostic factors of DLBCL, particularly in PENL and NL patients treated with R-CHOP or CHOP alone.

MATERIALS AND METHODS

1. Patients

Using prospectively designed Asan Medical Center (AMC) registry data for NHL, 489 patients newly diagnosed with DLBCL from January 2001 to November 2005 were selected for this study. All patients with biopsy-proven DLBCL at any age, stage, and performance status, and treated with CHOP or R-CHOP as first-line chemotherapy, were eligible. Patients with primary central nervous system (CNS) lymphoma or CD20-negative DLBCL were excluded. In total, we identified 177 eligible patients, of whom 82 were treated with the CHOP regimen (CHOP group) between January 2001 and October 2005, and 95 with the R-CHOP regimen (R-CHOP group) between June 2003 and November 2005. All enrolled patients were subclassified as either PENL or NL, according to the main origin of disease. PENL was defined as lymphoma with either no or minor nodal involvement, along with a clinically dominant extranodal component after routine staging procedures [15].

2. Treatment

The CHOP group received a standard regimen consisting of cyclophosphamide (750 mg/m^2 intravenously), doxorubicin (50 mg/m^2 intravenously), and vincristine (1.4 mg/m^2, maximum total 2 mg intravenously) for 1 day, and prednisone (100 mg orally) was given for 5 days every 3 weeks. In R-CHOP group, rituximab was administered at a dose of 375 mg/m^2 along with the standard CHOP regimen every 3 weeks. For patients with stage I or II DLBCL, 3 or 4 cycles of chemotherapy were performed, followed by radiotherapy with curative intent. For stage III or IV patients, 5 or 6 cycles of chemotherapy were administered. A number of patients received up to 9 cycles of chemotherapy or additional radiotherapy at the physician's discretion. Second- and third-line chemotherapy or high-dose chemotherapy with stem cell rescue were administered to patients who displayed relapse of disease or failure to respond to first-line chemotherapy.

3. Statistical analysis and definitions

Patient characteristics and therapeutic outcomes were compared between CHOP and R-CHOP groups and between PENL and NL groups. The basic patient characteristics of the 2 groups were compared using Fisher's exact test. Response criteria were defined according to the Revised Response Criteria for Malignant Lymphoma [25]. Overall survival (OS) was defined as the time from the beginning of first-line chemotherapy to the date of death as a result of any cause. Event-free survival (EFS) was defined as the time from the beginning of first-line chemotherapy to appearance of any symptom of treatment failure, including disease progression or discontinuation of treatment for any reason (toxicity, patient preference, initiation of new treatment without documented progression, or death). The Kaplan-Meier method was employed to assess the OS and EFS rates of patients in each group. Survival was compared between the 2 groups with the 2-sided log-rank test. For the subgroup analysis, multivariate analysis was performed using the Cox proportional hazards model. We analyzed the data with the Statistical Software Package for the Social Sciences (SPSS version 12.0 for Windows; SPSS, Chicago, IL, USA).

RESULTS

1. Basic patient characteristics

The median age of all 177 patients, including 96 men (54%), was 56 years (range, 15-81). CHOP group consisted of 82 patients, while 95 patients were in R-CHOP group. The characteristics of the patients from both groups are summarized in Table 1. There was no statistically significant difference between the 2 groups in terms of clinical parameters. Among the 177 patients, 72 (41%) were in PENL group and 105 (59%) were in NL group. Clinical parameters were similar between the PENL and NL groups, except for

performance status and number of extranodal sites. NL group contained more patients with a good performance score (0-1) than PENL group (96% vs. 88%, P=0.04). The most common primary site of PENL was stomach (18/72 patients, 25%), followed by small bowel (14, 20%), head and neck (18%), large bowel (8%), and genitourinary tract (6%).

Table 1. Baseline patient characteristics in CHOP and R-CHOP groups.

Characteristics	CHOP (%) N=82	R-CHOP (%) N=95	P
Median age, years (range)	58 (15-79)	56 (16-81)	0.76
≤60	49 (59.8)	59 (62.1)	
>60	33 (40.2)	36 (37.9)	
Sex			0.76
Male	43 (52.4)	53 (55.8)	
Female	39 (47.6)	42 (44.2)	
ECOG PS			0.27
0-1	78 (95.1)	86 (90.5)	
≥2	4 (4.9)	9 (9.5)	
Stage			0.37
I-II	41 (50.0)	41 (43.2)	
III-IV	41 (50.0)	54 (56.8)	
No. of extranodal sites			0.49
0	35 (42.7)	34 (35.8)	
1	37 (45.1)	44 (46.3)	
>1	10 (12.2)	17 (17.9)	
LDH			0.21
Normal	27 (34.2)	41 (43.2)	
Elevated	52 (65.8)	52 (54.7)	
B symptoms	25 (30.5)	27 (28.4)	0.87
Bulky tumor (≥9 cm)	2 (2.4)	5 (5.3)	0.45
BM involvement	7 (8.5)	15 (15.8)	0.17
IPI			0.36
Low	38 (46.3)	46 (48.4)	
Low-intermediate	22 (26.8)	17 (17.9)	
High-intermediate	20 (24.4)	26 (27.4)	
High	2 (2.4)	6 (6.3)	
PENL vs. NL			0.76
PENL	32 (39.0)	40 (42.1)	
NL	50 (61.0)	55 (57.9)	

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP, rituximab-CHOP; ECOG PS, Eastern Clinical Oncology Group performance scale; LDH, lactate dehydrogenase; BM, bone marrow; IPI, international prognostic index; PENL, primary extranodal lymphoma; NL, nodal lymphoma.

2. Treatment and responses

Patients in both CHOP and R-CHOP groups received a median of 5 cycles (range, 1-9) of first-line chemotherapy. The CR rate was higher in R-CHOP than in CHOP group, but the difference was not significant (77% vs. 65%, P=0.16). The overall response rate (ORR) was also higher in R-CHOP group, but not to a significant extent (95% vs. 84%, P=0.07). Comparison analyses revealed no differences between the PENL and NL groups in CR rates (71% vs. 71%, P=0.86) and ORRs (88% vs. 91%, P=0.76). In addition, subgroup analysis of the response to each treatment regimen was carried out. In NL group, patients administered R-CHOP regimen displayed a significantly higher CR rate (84% vs. 58%, P=0.01) and ORR (100% vs. 82%, P=0.008) than those treated with CHOP. In contrast, in PENL group, no differences were evident in terms of CR rate (68% vs. 75%, P=0.57) or ORR (88% vs. 88%, P=1.00) between the R-CHOP and CHOP regimens. These results are presented in Table 2.

Patients who experienced disease recurrence and progression after first-line CHOP or R-CHOP therapy were treated with a variety of salvage regimens, including high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (ASCT). In CHOP group, 25 of 82 patients received second-line chemotherapy, of which 12 patients received rituximab-containing salvage regimens. In R-CHOP group, 23 of 95 patients received second-line treatment, of which 7 patients received rituximab-containing salvage chemotherapy. High-dose chemotherapy with ASCT was administered to 14 patients in CHOP group and 4 patients in R-CHOP group.

3. Survival outcomes

At a median follow-up duration of 52 months (range, 34-92 months), the average 3-year EFS and OS rates in all 177 patients were 62% and 74%, respectively. A comparison of survival outcomes according to treatment regimen revealed 3-year EFS and OS rates of 52% and 69%, respectively, in the CHOP group at a median follow-up duration of 66 months, and 3-year EFS and OS rates of 71% and 79%, respectively, in R-CHOP group at a median follow-up duration of 45 months. Overall, R-CHOP group displayed higher 3-year EFS and OS rates, with a significant difference in EFS (P=0.01 using log-rank test). Kaplan-Meier curves for

Table 2. Comparison of treatment responses of PENL and NL groups according to the treatment regimen.

	PENL (N=72)			NL (N=105)		
	CHOP (%) N=32	R-CHOP (%) N=40	P[b]	CHOP (%) N=50	R-CHOP (%) N=55	P[b]
CR[a]	24 (75.0)	27 (67.5)	0.57	29 (58.0)	46 (83.6)	0.01
PR[a]	4 (12.5)	8 (20.0)		12 (24.0)	9 (16.4)	
OR[a]	28 (87.5)	35 (87.5)	1.00	41 (82.0)	55 (100)	0.01

[a]7 patients were not evaluated (4 in the PENL and 3 in the NL group), [b]Fisher's exact test.
Abbreviations: PENL, primary extranodal lymphoma; NL, nodal lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP, rituximab-CHOP; CR, complete response; PR, partial response; OR, overall response.

EFS and OS in the 2 groups are depicted in Fig. 1. Subgroup analyses for survival according to treatment regimen revealed that in terms of EFS, young age (≤60 years), female gender, good performance status (ECOG PS score of 0-1), advanced stages (stage III, V), lower number of extranodal sites (0 or 1), absence of B symptoms, bone marrow involvement,

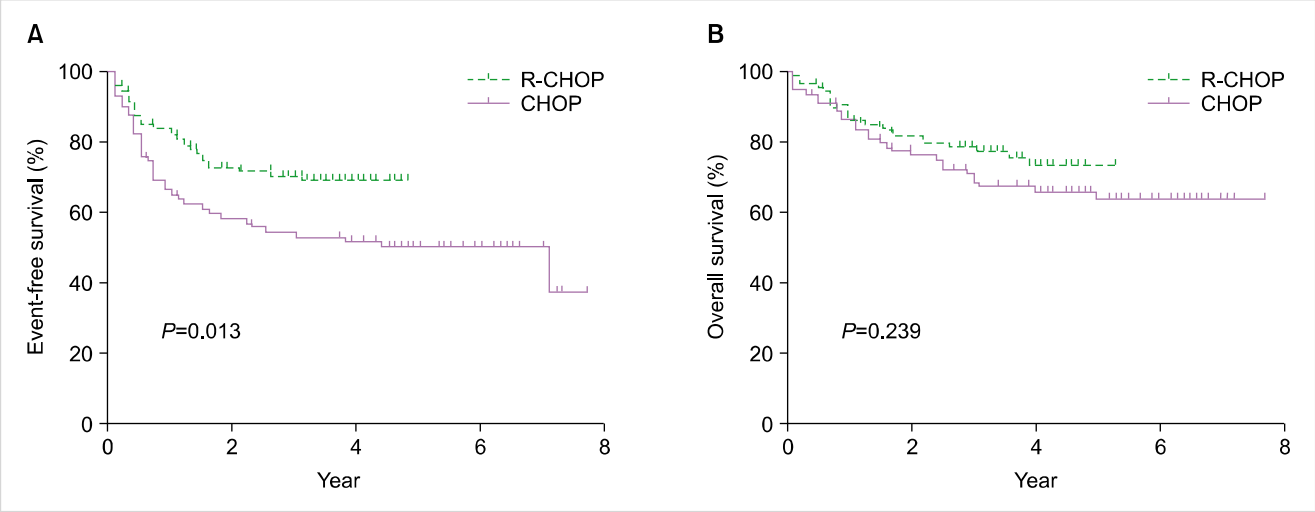

Fig. 1. Kaplan-Meier curves for **(A)** event-free survival and **(B)** overall survival in all 177 patients classified on the basis of the treatment regimen.

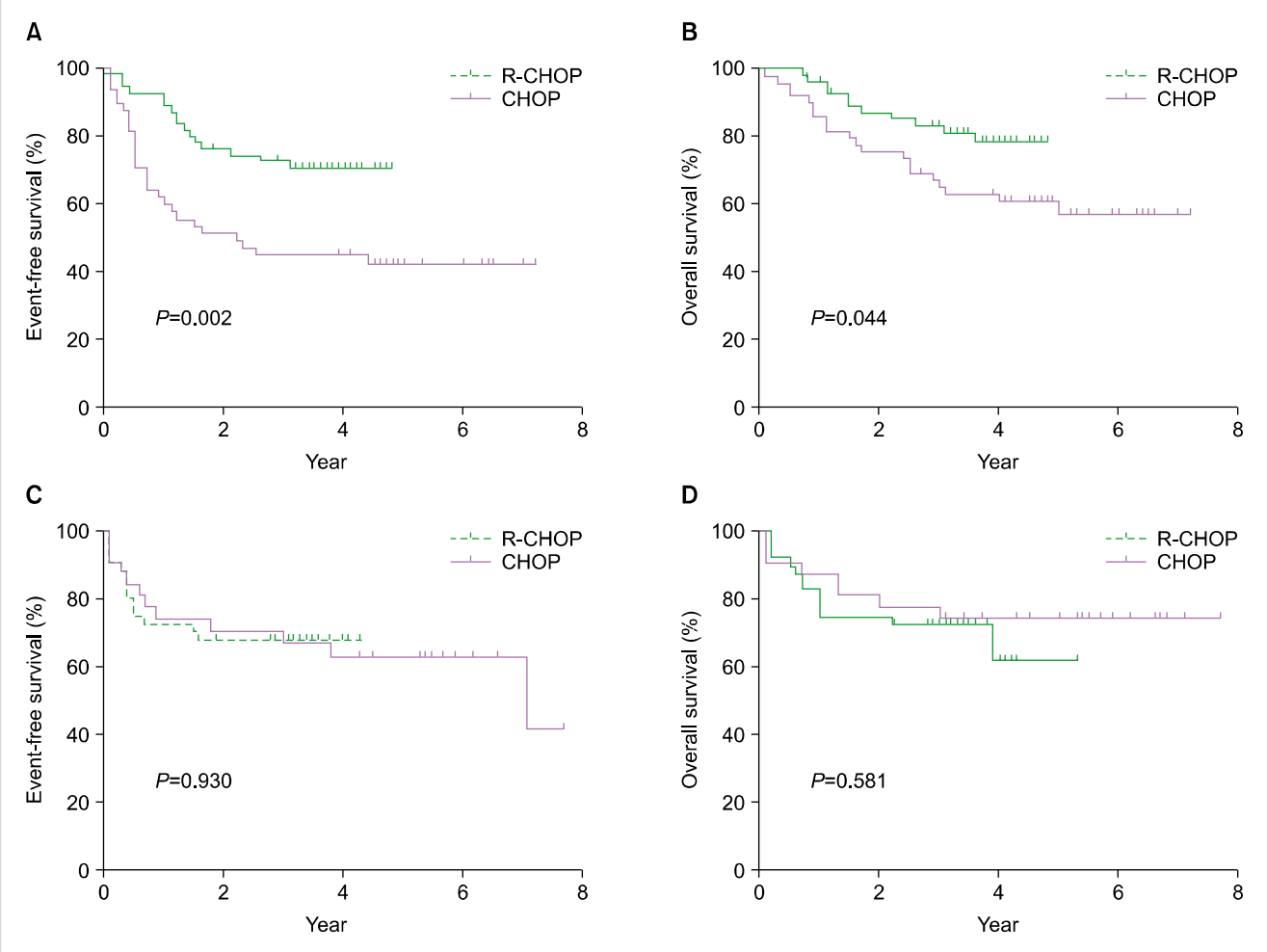

Fig. 2. Kaplan-Meier curves for **(A)** event-free survival and **(B)** overall survival in patients with nodal lymphoma; **(C)** event-free survival, and **(D)** overall survival in patients with primary extranodal lymphoma classified on the basis of the treatment regimen.

lower IPI score (low or low-intermediate), and NL (versus PENL) were all factors associated with significant survival benefits following R-CHOP therapy, while in terms of OS, only NL patients (versus PENL) showed significant survival benefits from R-CHOP therapy compared to CHOP therapy. In particular, patients in NL group treated with R-CHOP therapy exhibited significantly higher survival rates than those administered the CHOP regimen (3-year EFS, 73% vs. 45%, P=0.002; 3-year OS, 83% vs. 65%, P=0.044; Fig. 2A and 2B). In contrast, no survival benefit from R-CHOP therapy was evident in PENL patients (3-year EFS, 68% vs. 66%, P=0.93; 3-year OS, 73% vs. 74%, P=0.58; Fig. 2C and 2D).

In addition, survival outcomes were compared between the PENL and the NL groups. No significant differences in the 3-year EFS (67% vs. 59%) and OS (73% vs. 75%) rates were observed between the PENL and NL groups. Subgroup analysis was performed for each group. Univariate analysis in NL patients showed that the presence of earlier stages of the disease (stages I and II), normal lactate dehydrogenase (LDH) levels at diagnosis, and the use of the R-CHOP regimen were favorable prognostic factors for EFS, whereas R-CHOP therapy was the only favorable prognostic factor for OS. Multivariate analysis in the NL group further revealed that lower stage of the disease and R-CHOP therapy were independent prognostic factors for both EFS and OS (Table 3). On the other hand, in the PENL group, good performance status and normal LDH levels were favorable prognostic factors for EFS and OS in the univariate analysis, while good performance status was the only independent prognostic factor for both EFS and OS in the multivariate analysis (Table 4). These data clearly indicate that R-CHOP chemotherapy is not an effective prognostic factor to predict better survival of patients in the PENL group.

DISCUSSION

DLBCL is a heterogeneous disease entity in terms of clinical behavior, morphology, immunophenotype, and molecular characteristics. Several studies have attempted to identify differences in the clinical and molecular aspects of the

Table 3. Prognostic factor analysis in the NL group (N=105).

Variable	Univariate analysis				Multivariate analysis			
	EFS		OS		EFS		OS	
	$P^{a)}$	HR (95% CI)	$P^{a)}$	HR (95% CI)	$P^{b)}$	HR (95% CI)	$P^{b)}$	HR (95% CI)
Stage								
I, II vs. III, IV	0.01	0.46 (0.25-0.87)	0.07	0.50 (0.24-1.07)	0.01	0.38 (0.19-0.72)	0.03	0.42 (0.19-0.93)
LDH								
Normal vs. elevated	0.02	0.44 (0.21-0.89)	0.09	0.49 (0.21-1.15)	0.16	0.60 (0.28-1.26)	0.43	0.70 (0.28-1.72)
Treatment regimen								
R-CHOP vs. CHOP	0.01	0.39 (0.21-0.72)	0.04	0.47 (0.23-0.99)	0.01	0.32 (0.17-0.62)	0.02	0.40 (0.18-0.87)

[a)]Log-rank test, [b)]Cox proportional hazard model.
Abbreviations: NL, nodal lymphoma; EFS, event-free survival; OS, overall survival; HR, hazard ratio; CI, Confidence interval; LDH, lactate dehydrogenase; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP, rituximab-CHOP.

Table 4. Prognostic factor analysis in the PENL group (N=72).

Variable	Univariate analysis				Multivariate analysis			
	EFS		OS		EFS		OS	
	$P^{a)}$	HR (95% CI)	$P^{a)}$	HR (95% CI)	$P^{b)}$	HR (95% CI)	$P^{b)}$	HR (95% CI)
ECOG PS								
0-1 vs. ≥2	0.01	0.27 (0.11-0.68)	0.01	0.21 (0.08-0.54)	0.03	0.35 (0.13-0.91)	0.01	0.27 (0.10-0.74)
No. of extranodal sites								
0-1 vs. >1	0.10	0.49 (0.20-1.18)	0.03	0.37 (0.15-0.94)	0.60	0.76 (0.28-2.09)	0.49	0.68 (0.23-2.01)
LDH								
Normal vs. elevated	0.02	0.34 (0.13-0.86)	0.02	0.29 (0.09-0.86)	0.07	0.41 (0.16-1.07)	0.10	0.37 (0.12-1.19)
Treatment regimen								
R-CHOP vs. CHOP	0.93	0.96 (0.43-2.17)	0.58	1.29 (0.52-3.18)	–	–	–	–

[a)]Log-rank test, [b)]Cox proportional hazard model.
Abbreviations: PENL, primary extranodal lymphoma; EFS, event-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Clinical Oncology Group performance scale; LDH, lactate dehydrogenase; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP, rituximab-CHOP.

disease. With the advent of rituximab, new challenges have arisen in relation to rituximab treatment of DLBCL patients. In this retrospective study, we established that the addition of rituximab to CHOP leads to better response and survival rates in patients with DLBCL, which is in accordance with earlier data [7-10]. Moreover, we identified an interesting prognostic factor for the efficacy of R-CHOP therapy. In our experiments, NL patients displayed significantly better response and survival rates upon treatment with the R-CHOP regimen than with CHOP therapy alone. Multivariate analyses confirmed that R-CHOP therapy is an independent favorable prognostic factor for the survival of NL patients. On the other hand, PENL patients displayed no differences in response rates and survival duration upon treatment with the R-CHOP versus the CHOP regimens. In other words, patients with PENL did not benefit from the addition of rituximab to the CHOP regimen. Our findings suggest that the classification of DLBCL based on the major origin of the disease is important for predicting the response to rituximab therapy.

The superiority of the R-CHOP regimen to CHOP therapy has been confirmed in randomized prospective trials. In 2002, the Group d'Etudes des Lymphomes de l'Adulte (GELA) reported survival benefits of R-CHOP over CHOP therapy in elderly patients with DLBCL. This group further updated these results at a median 5-year follow-up in 2005 [7, 8]. In the MabThera International Trial (MInT), Pfreundschuh et al. [10] reported that rituximab added to 6 cycles of CHOP therapy was an effective treatment for young patients with good-prognosis DLBCL. In addition, Sehn and colleagues [9] showed improved outcomes using a combination of CHOP therapy and rituximab in DLBCL patients of all ages in a population-based study. Clearly, R-CHOP is the best choice of treatment for patients with DLBCL at present. However, the factors affecting prognosis in patients treated with rituximab remain to be established. The IPI or age-adjusted IPI score was reported as a useful factor to predict survival benefits in patients treated with R-CHOP in earlier trials. In the GELA LNH98-5 study, OS was markedly but selectively improved in patients with low-risk age-adjusted IPI score (0-1), but not in those with high-risk age-adjusted IPI score (2-3) [8]. In contrast, Park et al. [26] reported survival benefits of R-CHOP in patients with high-risk IPI score (3-5). In our study, patients with low-risk IPI score (0-2) displayed significant improvement in EFS following R-CHOP therapy. Sehn and co-workers [12] suggested a revised IPI scale as a better predictor of outcomes for patients with DLBCL. In their study, no differences in survival were observed between low and low-intermediate groups or between high and high-intermediate groups. Accordingly, IPI scores were classified into 3 prognostic groups (0, 1-2, and 3-5). However, our findings showed no survival differences between low-intermediate and high-intermediate groups. In our study, the IPI scores were, therefore, classified into the following 3 groups: 0-1, 2-3, and 4-5 risk factors (Fig. 3).

In addition to the IPI score, our NL patients displayed significantly better EFS and OS outcomes with the R-CHOP regimen than did patients with PENL. Basic patient characteristics between the NL and PENL subgroups were similar, except for the performance score. A higher number of patients in the NL subgroup had a good performance score (0-1) on the ECOG scale. To adjust for this difference between the 2 subgroups, we excluded several patients with poor performance scores (2-4) from each subgroup. The results were not different. Patients in NL group treated with R-CHOP regimen showed better outcomes in terms of EFS and OS rates (P=0.006 and P=0.06, respectively) than those treated with CHOP. In contrast, no survival benefits with R-CHOP regimen were observed in PENL group (P=0.48 and P=0.93, respectively). Multivariate analysis further confirmed that R-CHOP therapy is an independent prognostic factor for EFS and OS in NL group, but not in PENL group.

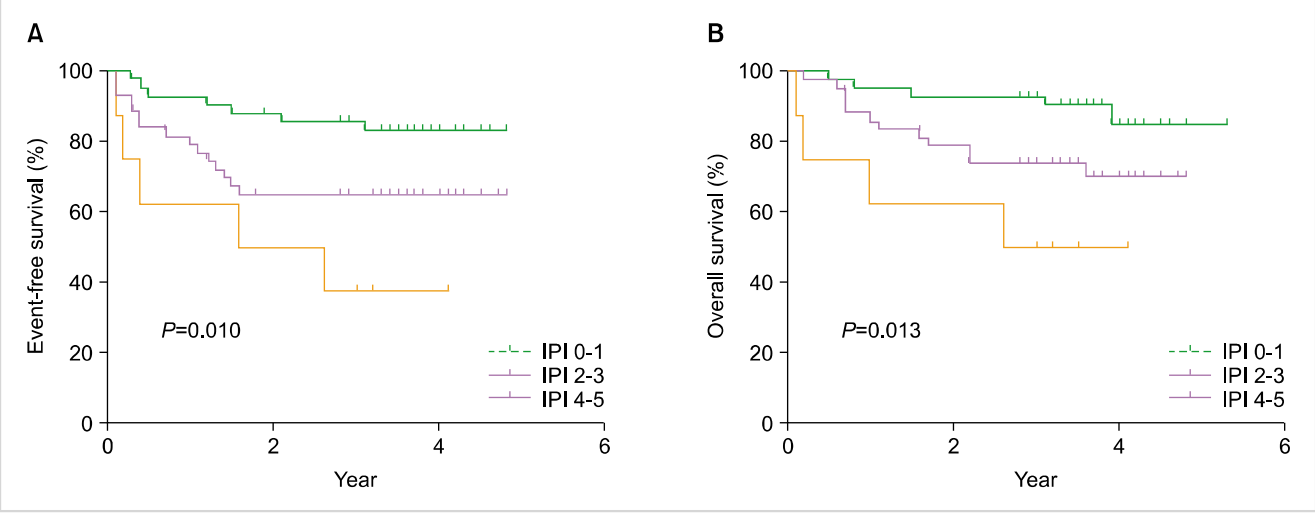

Fig. 3. Kaplan-Meier curves for **(A)** event-free survival and **(B)** overall survival in patients treated with R-CHOP classified on the basis of the redistributed International Prognostic Index score.

Our data suggest that PENL is distinct from NL with regard to clinicopathologic behavior and response to R-CHOP therapy. A number of studies suggested that the primary site of the lymphoma (either the lymph node or different extranodal territories) is a criterion that may be applied to separate the 2 different groups of DLBCL and attempted to identify differences in prognostic factors between PENL and NL for R-CHOP therapy. Kramer et al. [27] previously reported on the prognostic significance of Bcl-2 as a negative factor for disease-free survival with a high frequency in patients with NL. Mounier and colleagues [13] suggested a benefit of R-CHOP therapy in elderly Bcl-2-positive patients with DLBCL from the GELA LNH98-5 study. In their report, Bcl-2-positive patients treated with R-CHOP showed higher response rates and better 2-year OS than those treated with CHOP. In contrast, Bcl-2-negative patients displayed no significant differences in response rates and survival between the 2 treatment regimens. Patients with PENL presented more frequently with Bcl-6 expression than those with NL, as reported by Lopez-Guillermo and co-workers [28]. Winter et al. [14] reported that patients with Bcl-6-positive DLBCL did not benefit from the addition of rituximab to the CHOP regimen, while Bcl-6 protein expression was a powerful predictor of outcomes in DLBCL patients subjected to CHOP chemotherapy. In this study, we did not investigate molecular markers, such as Bcl-2 and Bcl-6 and thus, could not determine whether there is a correlation between the expression of molecular markers and the outcomes of the 2 treatment regimens in PENL and NL patients. Further studies are required to address this issue.

The current study has several limitations, because it is a retrospective investigation based on cancer registry data with a relatively small sample size. Nevertheless, continuing efforts to identify patients who do not benefit from rituximab and identification of other treatment strategies for such patients, are essential in this rituximab era.

In conclusion, the rituximab plus CHOP regimen improved outcomes in patients with newly diagnosed CD20-positive DLBCL compared with CHOP treatment alone. However, the addition of rituximab to CHOP chemotherapy was not beneficial for patients with PENL. Thus, other treatment strategies need to be developed for this patient group.

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