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ORIGINAL ARTICLE

Improved treatment outcome of primary mediastinal large B-cell lymphoma after introduction of rituximab in Korean patients

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Abstract The addition of rituximab to cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) improved the outcome of patients with diffuse large B-cell lymphoma (DLBCL). However, the impact of rituximab (R-CHOP) is still not determined in primary mediastinal large B-cell lymphoma (PMBCL), a subtype of DLBCL, especially in Asian patients. Thus, we analyzed the treatment outcome of PMBCL patients ($n = 21$) treated with R-CHOP and compared it with the historical group treated with CHOP ($n = 14$). The rate of complete response for R-CHOP was higher than that of CHOP (17/21, 81.0% vs. 8/14, 57.2%), although the difference was not statistically significant ($P = 0.151$). The number of patients with disease progression or relapse was higher in the CHOP group (6/14, 42.9%) than the R-CHOP group (2/21, 9.5%). Thus, patients treated with R-CHOP had higher 2-year progression-free survival (79.0%) than those treated with CHOP (50.0%, $P = 0.043$). Although the 2-year overall survival of the R-CHOP was also superior to that of the CHOP group (82.7% vs. 57.1%), this survival benefit did not reach statistical significance ($P = 0.081$). In conclusion, our comparison suggests that R-CHOP may increase response and reduce relapse resulting in prolongation of progression-free survival of patients with PMBCL.

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1 Introduction

Primary mediastinal large B-cell lymphoma (PMBCL) is a subtype of diffuse large B-cell lymphoma (DLBCL) that accounts for less than 3% of all cases of non-Hodgkin lymphomas [1]. PMBCL usually presents in the anterior mediastinum as a bulky mass larger than 10 cm and often invades adjacent structures. Thus, it may produce local compressive effects such as dyspnea and superior vena cava obstruction [2]. PMBCL is thought to arise from thymic B cells [3]. Early studies suggested that PMBCL might have an unusually poor prognosis with respect to other large B-cell lymphomas after CHOP chemotherapy [2, 4, 5]. However, molecular profiling has identified PMBCL as a distinct and more favorable subtype of DLBCL [6, 7]. Consistent with this finding, several reports with third generation regimens such as MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine and bleomycin) have shown improved response rate and survival [4, 8–10]. However, these dose-dense regimens generally require prolonged treatment duration and induce more severe hematologic and non-hematologic toxicities.

Since the introduction of rituximab, a monoclonal antibody targeting CD20, the combined treatment of R-CHOP has been widely used for the management of DLBCL, because rituximab does not have overlapping toxicity with other chemotherapeutic agents such as hematological toxicities [11]. Thus, the addition of rituximab to CHOP may increase the efficacy of CHOP without adding significant toxicity in PMBCL. However, there is little clear evidence regarding the impact of rituximab on PMBCL in the

R-CHOP paradigm, especially in Asian patients, because of its rarity in Asia. Therefore, we compared the treatment outcome of R-CHOP with that of the historical group treated with CHOP in Korean patients with PMBCL.

2 Materials and methods

2.1 Patients

Forty-two patients were consecutively diagnosed with PMBCL according to Revised European American Lymphoma (REAL) or World Health Organization (WHO) classifications between 1995 and 2009 in the Samsung Medical Center. The pathology was reviewed by an expert pathologist for lymphoma (Y. H. K.). Among them, seven patients were excluded from the analysis because they were enrolled and treated with experimental drugs in ongoing clinical trials. Thus, we analyzed 35 patients with PMBCL and compared them according to the type of primary treatment, R-CHOP or CHOP. Staging workups included complete blood count, serum lactate dehydrogenase (LDH), chest and abdomino-pelvic CT scan and bone marrow examination. PMBCL stage was determined according to the Ann Arbor staging system. Contiguous spread within the thorax (e.g., chest wall, lung, pleural or pericardial involvement) was considered to be stage II. Only non-contiguous spread to extranodal sites was assessed as stage IV. Bulky disease was defined as a lesion showing more than 10 cm in the longest diameter or occupying more than one-third of the mediastinal width of the thorax. This retrospective study was approved by the Institutional Review Board of Samsung Medical Center for the release of case information that was rendered anonymous.

2.2 Treatment and response evaluation

From 1995 to 2004, CHOP (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2 and vincristine 1.4 mg/m^2 (maximum 2 mg) were intravenously (IV) infused on day 1; prednisolone 100 mg was orally administered on days 1–5) chemotherapy was used as a primary treatment. After the health insurance of Korea began to cover rituximab, it was incorporated into CHOP chemotherapy (R-CHOP). Thus, 375 mg/m^2 of rituximab was intravenously infused on day 1 with the other drugs. Chemotherapy was repeated every 3 weeks and, originally, 6–8 cycles of chemotherapy with or without radiotherapy was planned. However, six patients could not receive more than three cycles because of early treatment-related deaths ($n = 2$), disease progression ($n = 3$) and poor performance status ($n = 1$). The majority of patients ($n = 24$) received six cycles of chemotherapy and among them 17 patients received radiotherapy. Five patients received eight cycles of chemotherapy including three patients receiving additional radiotherapy. Following completion of chemotherapy, radiotherapy was performed at the physicians' discretion. Thus, adjuvant radiotherapy was considered for patients having remnant lesions after chemotherapy or initially bulky disease.

Because PET scan was not available before 2005, treatment response was assessed according to the International Working Group (IWG) criteria published in 1999 [12]. Therefore, we used the CRu (unconfirmed complete response) classification from the IWG criteria. A CR was defined as disappearance of all previously measurable lesions and absence of any new tumor lesions. CRu was defined as the reduction of lesions $\geq$75% on CT scan without any radiologic or clinical evidence of new lesions. Partial response (PR) was defined as a decrease of at least 50% in the product of two perpendicular diameters of each measurable lesion. Stable disease (SD) was defined as a decrease of <50% or an increase of <25% in tumor size. Lastly, progressive disease (PD) was defined as a >25% increase in the product of the two diameters of at least one tumor or the presence of a newly developed lesion.

2.3 Statistical analysis

Overall survival (OS) was calculated from the date of diagnosis to the date of last follow-up or death from any cause. Progression-free survival (PFS) was evaluated from the date of diagnosis to the date of disease progression or relapse or death from any cause. Survival was estimated from Kaplan–Meier curves and compared using the log-rank test. The Cox proportional hazards regression model was used for the multivariate analysis to compare the factors proven significant in the univariate analysis. The Chi-square test and log-rank test were used to determine the significance of prognostic factors on treatment response and survival, respectively. The follow-up duration was calculated by the method of Kaplan–Meier estimate of potential follow-up as previously reported [13]. A two-sided p value of less than 0.05 was considered to be significant.

3 Results

3.1 Characteristics of patients

A total of 35 patients were analyzed, and their baseline characteristics are summarized in Table 1. The median patient age was 30 years (range, 17–79), and three of the 35 patients were over 60 years (8.6%). The male to female ratio was approximately 1:1. Most patients had localized

Table 1 Patient characteristics

Characteristics	$N = 35$ (%)	CHOP ($N = 14$)	R-CHOP ($N = 21$)	P-value
Sex				
Male	17 (48.6)	8	9	0.500
Female	18 (51.4)	6	12	
Age (median 30, range 17–79)				
Age $\leq$ 60	32 (91.4)	13	19	>0.999
Age > 60	3 (8.6)	1	2	
Extranodal involvement				
0/1	31 (88.6)	14	17	0.133
$\geq$2	4 (11.4)	0	4	
Performance status				
ECOG 0.1	31 (88.6)	13	18	0.635
ECOG $\geq$ 2	4 (11.4)	1	3	
Ann Arbor stage				
I/II	4/18 (11.4/51.4)	2/9	2/9	0.290
III/IV	9/4 (25.7/11.4)	3/0	6/4	
Serum lactate dehydrogenase				
Normal	3 (8.6)	1	2	>0.999
Increased	32 (91.4)	13	19	
International Prognostic Index (IPI)				
Low/low-intermediate	19 (54.3)/10 (28.6)	10/4	9/6	0.154
High-intermediate/high	4 (11.4)/2 (5.7)	0/0	4/2	
B symptoms				
Absent	24 (68.6)	9	15	0.721
Present	11 (31.4)	5	6	
Pleural effusion				
Absent	18 (51.4)	7	11	>0.999
Present	17 (48.6)	7	10	
Pericardial effusion				
Absent	18 (51.4)	5	13	0.176
Present	17 (48.6)	9	8	
Bulky disease				
Absent	9 (25.7)	3	6	0.712
Present	26 (74.3)	11	15	
Superior vena cava syndrome				
Absent	28 (80.0)	10	18	0.401
Present	7 (20.0)	4	3	
Local invasion to adjacent structures				
Absent	20 (57.1)	9	11	0.728
Present	15 (42.9)	5	10	
Bone marrow involvement				
Absent	34 (97.1)	14	20	>0.999
Present	1 (2.9)	0	1	
Splenomegaly/spleen involvement				
Absent	28 (80.0)	11	17	>0.999
Present	7 (20.0)	3	4	
Age-adjusted IPI for patients $\leq$60 years				
Low/low-intermediate	2 (6.3)/20 (62.5)	0/10	2/10	0.395
High-intermediate/High	9 (28.1)/1 (3.1)	3/0	6/1	

Table 1 continued

Characteristics	$N = 35$ (%)	CHOP ($N = 14$)	R-CHOP ($N = 21$)	P-value
Radiotherapy				
Not done (planned)	8 (22.9)	2	6	>0.999
Done	20 (57.1)	7	13	
Not done due to other causes	7 (20.0)	5	2	

disease confined to the mediastinum and adjacent structures (65.7%), and good performance status (88.6%). Thus, the risk according to the International Prognostic Index (IPI) was dominantly low or low-intermediate (85.7%), although most patients presented with increased LDH levels (91.4%). Approximately, half of the patients (48.6%) had pleural or pericardial effusions, although only a limited number were analyzed (13 patients). Among them, only two patients showed the presence of tumor cells in their effusion. Patients with stage IV had non-contiguous extranodal organ involvements including kidney, ovary, bone, lung, pancreas, etc. Superior vena cava (SVC) syndrome was observed in seven patients (20.0%), and bone marrow involvement was extremely rare (2.9%).

3.2 Treatment response and relapse

Twenty-one patients were treated with R-CHOP and 14 were initially treated with CHOP. When we dichotomized patients according to treatment type, baseline characteristics were balanced between patients treated with CHOP and R-CHOP (Table 1). However, more patients with stage IV and high/high-intermediate IPI risk were included in the R-CHOP group. The final response of patients was based on the response after the completion of scheduled chemotherapy. If patients showed clinical or radiological evidence of progression, their disease status was documented as PD.

The application of radiotherapy was balanced between the CHOP and R-CHOP groups (Table 1). Eight patients did not receive radiotherapy because their response to chemotherapy was CR ($n = 2$) or the initial disease was not bulky ($n = 6$). However, six patients achieving CR after chemotherapy received additional radiotherapy because their initial diseases were bulky diseases. Twelve patients with CRu and two with PR received radiotherapy as an adjunct to chemotherapy. Among the 12 patients with CRu, 8 patients achieved CR after the completion of radiotherapy, but 3 patients still had remnant lesions with undetermined significance and one patient progressed after radiotherapy. Among two partial responders who received radiotherapy, one relapsed after radiotherapy and died due to disease relapse and the other was alive without the evidence of disease progression at the time of data cutoff. In six patients who progressed during CHOP or R-CHOP chemotherapy and one patient died due to septic shock during R-CHOP treatment, radiotherapy could not be performed.

Table 2 Treatment outcome

Outcomes	Number (%)	CHOP (%)	R-CHOP	P value
Response				
CR/CRu	8/17 (71.4)	4/4 (57.2)	4/13 (81.0)	0.151
PR	4 (11.4)	2 (14.3)	2 (9.5)	
PD	5 (14.3)	4 (28.6)	1 (4.8)	
Not evaluated	1 (2.9)	0	1 (4.8)	
Relapse or progression				
Yes	8 (22.9)	6 (42.9)	2 (9.5)	0.039
No	27 (77.1)	8 (57.1)	19 (90.5)	
Survival				
Living	24 (68.6)	6 (42.9)	18 (85.7)	0.011
Dead	11 (31.4)	8 (57.1)	3 (14.3)	
Disease related	7	6	1	
Non-disease related	4	2	2	

Among 35 patients, 24 showed CR (including CRu); thus, the overall CR rate was 71.4% (Table 2). However, the CR rate of R-CHOP was higher than that of the historical group treated with CHOP (81.0% vs. 57.2%), although this difference was not statistically significant ($P = 0.283$). One partial responder (male, 61 years old) died due to treatment-related mortality (survival duration: 3.57 months) and the other patient (male, 21 years old) with PR died due to disease progression (survival duration: 25.3 months). The number of patients with disease progression during treatment or relapse after treatment was higher in the CHOP group (6/14, 42.9%) than the R-CHOP (2/21, 9.5%). All patients who progressed or relapsed during or after CHOP or R-CHOP did not show response to the salvage treatment, including DHAP and IMVP-16. Rituximab was added to salvage treatment for patients who were previously treated with CHOP but failed to achieve a response. Because the response to salvage chemotherapy of all patients was poor, only two patients received high-dose chemotherapy followed by autologous stem cell transplantation. However, they finally progressed after autologous stem cell transplantation.

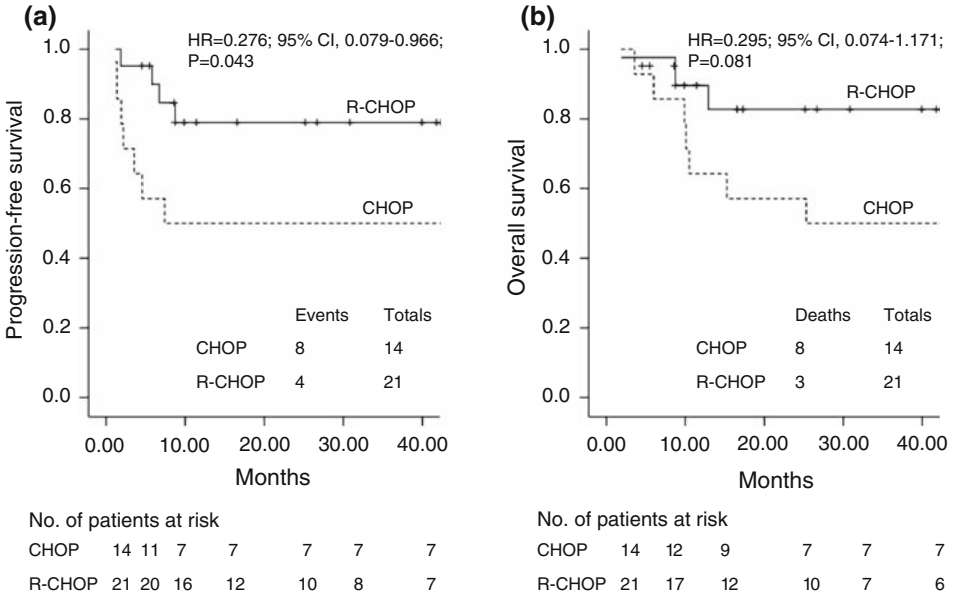

Fig. 1 The survival curves of patients treated with R-CHOP (*solid line*) were compared to those of the historical group treated with CHOP (*dotted line*). **a** Progression-free survival of R-CHOP group was significantly better than that of CHOP. **b** Overall survival was not significantly different between the two groups, although the R-CHOP group showed a trend toward better overall survival than the CHOP group. In both figures, the survival curves beyond 40 months were omitted to magnify the difference between the two groups. The number of patients at risk until 40 months of follow-up was added in a table at the bottom of each figure. *HR* hazard ratio, *CI* confidence interval, *No* number

3.3 Survival analysis

During follow-up, 11 deaths were observed and a higher number of deaths were recorded for the CHOP group than the R-CHOP (Table 2). While seven deaths were disease related, four patients died due to non-disease-related causes. One patient died due to hepatic failure because of liver cirrhosis, while another patient died due to a non-disease-related cause during the long-term follow-up. Treatment-related mortality was observed in two patients, one in each treatment group; both patients died of septic shock during chemotherapy. Thus, a 61-year-old male patient died after he achieved a PR, and a 79 year-old male died before his response was evaluated (Table 2). The estimated 2-year OS and PFS from a total of 35 patients were 70.9 and 67.5%, respectively. When the survival outcomes of the two groups were compared at a Kaplan–Meier estimate of potential median follow-up of 91.6 months (CHOP group, range 3.57–123.6 months) and 26.7 months (R-CHOP group, range 1.87–54.7 months), the estimated 2-year PFS of patients treated with R-CHOP was better than CHOP (79.0% vs. 50.0%, $P = 0.043$, Fig. 1a). The estimated 2-year OS of the R-CHOP group (82.7%) was also superior to that of the CHOP (57.1%), although this difference was not statistically significant ($P = 0.081$, Fig. 1b).

3.4 Prognostic factor analysis

The patients in this study who were older than 60 years of age had a median OS of 3.57 months, while those less than 60 years did not reach the median survival. Thus, elderly patients had worse survival outcomes, which may be explained by treatment-related mortalities, because two patients died early on in the treatment schedule. Considering that PMBCL primarily affects younger patients, we analyzed the prognostic factors among patients $\leq$60 years old. When we performed univariate analysis, there were no pretreatment prognostic factors for OS and PFS, including age-adjusted international prognostic index, superior vena cava syndrome and pleural and pericardial effusions ($P > 0.05$). However, the achievement of CR (including CRu) was significantly associated with better OS and PFS ($P < 0.001$). The addition of rituximab to CHOP showed a tendency of better OS and PFS in patients $\leq$60 years old, because it showed a marginal statistical significance ($P = 0.081$ and 0.048, respectively). Radiotherapy as a consolidation treatment failed to show an additive survival benefit in terms of OS and PFS. However, these parameters failed to show an independent prognostic significance in the multivariate analysis: the achievement of CR and the addition of rituximab ($P > 0.05$).

Table 3 Comparison with previous treatment outcomes of regimens without rituximab

Authors	Number	Treatment (number)	Patients with stage I/II (%)	CR rate (%)	Survival outcome
Bieri et al. [8].	27	CHOP (11)	70.4	55.6	
		Intensive regimen (12)			10-Year OS 50%
		Others (4)			10-Year TTP 44%
Abou-Elella et al. [20].	43	4 Cytoxan-based regimens	58	63	5-Year OS 46%
		Plus radiotherapy (11)			5-Year FFS 38%
Zinzani et al. [22].	89	MACOP-B + Radiotherapy (CR rate 26% after MACOP-B)	82	88	9-Year OS 86%
					9-Year RFS 91%
Todeschini et al. [4].	138	CHOP (43)	67.4	51.1	5-Year EFS 39.5%
		MACOP-B/VACOP-B (95)	69.4	80	5-Year EFS 75.7%
Hamlin et al. [5]	141	CHOP-like (56)	59	59	15-Year OS 50%
		NHL-15 (68)	65	88	15-Year OS 83%
Current study	35	CHOP (14)	78.6	57.2	5-Year PFS 55.5%
		R-CHOP (21)	52.4	81	5-Year PFS 88.9%

4 Discussion

A recent meeting abstract from a subgroup analysis of the Mabthera International Trial group (MInT) study comparing CHOP-like chemotherapy regimens with and without rituximab suggested that rituximab added to six cycles of CHOP-like chemotherapy increased the response rate and PFS to the same extent as in other DLBCL [14]. They showed 80.0% of CR rate, including CR and CRu in 87 patients with PMBCL, and 88.0% of estimated 3-year PFS with a median observation time of 37 months. The 3-year OS (89.0%) of those patients treated with rituximab was also better than CHOP-like chemotherapy alone, but did not reach statistical significance [14]. Our study compared the outcome of R-CHOP with our historical group treated with CHOP. The comparison with the historical group is vulnerable to biases, because the quality of supportive care might be worse in the historical group. Thus, the survival difference between CHOP and R-CHOP group might be affected by the historical group-related bias rather than the effect of rituximab. However, the estimated 2-year PFS (50.0%) of CHOP group in our study was comparable to the survival (51.0–52.0%) in previous reports, including prospective MInT study [5, 14]. Thus, our historical group could be a control group for comparison with the R-CHOP group. In our study, R-CHOP showed a CR rate (81.0%) similar to the MInT results, and it was higher than that of patients treated with CHOP (57.1%). Although it failed to show statistical significance, it might be related to a relatively small number of patients. Disease progression during treatment or relapse after treatment was also less frequent in the R-CHOP group (Table 2), which translated into a significant difference in PFS between R-CHOP and CHOP (Fig. 1a). As in a report from the MInT study, the OS benefit observed with R-CHOP did not reach statistical significance, though the 2-year OS of R-CHOP (82.7%) was higher than CHOP (57.1%). This might be related to the relatively shorter duration of follow-up in the R-CHOP group than in CHOP (26.7 months vs. 91.6 months). Considering that most relapses and deaths occurred early in the course of disease, OS benefit of R-CHOP would be prominent if patients had a longer follow-up duration.

The addition of rituximab has also been tried in intensive regimens. Thus, the combination of rituximab with VACOP-B or dose-adjusted EPOCH produced better event-free or progression-free survival than chemotherapy alone [15, 16]. However, the comparison of R-VACOP-B with R-CHOP showed no difference in 5-year PFS [15]. Furthermore, the survival outcome of patients treated with R-CHOP in our study was comparable to previous reports with dose-dense regimens without rituximab (Table 3) [4, 8–10]. Together, these results support that the positive impact of rituximab demonstrated previously for DLBCL is relevant to the management of PMBCL and that R-CHOP may become an effective front-line treatment regimen for PMBCL.

The role of consolidation radiotherapy in treating PMBCL also remains a matter of debate. Previous studies incorporating mediastinal consolidation radiotherapy on completion of chemotherapy reported the best treatment outcomes and the conversion of PR to CR [4, 10, 17, 18]. Thus, a recent report from the Italian group recommended the association of chemotherapy and radiotherapy as the first-line treatment for PMBCL [19]. However, excellent long-term results have been achieved with chemotherapy alone based on a study of 141 patients performed at the Memorial Sloan Kettering Cancer Center [5]. A report from British Columbia also showed no difference in PFS or

OS based on the use of radiotherapy [9]. In our study, radiotherapy was performed in more than half of the patients (20/35, 57.1%). Although radiotherapy did not produce a survival difference in terms of OS and PFS regardless of CHOP or R-CHOP, nine patients including eight CRu and one PR showed conversion into CR. Therefore, the role of radiotherapy could not be determined with our results. However, given the young median age and concerns about the long-term toxicity of radiation, the decision about consolidation radiotherapy should be cautious.

Primary mediastinal large B-cell lymphoma predominantly affects young adults, with a peak incidence in the third and fourth decades of life, and mainly presents as localized disease. As a result, most patients have low or low-intermediate risk according to the IPI. Thus, the prognostic value of the IPI is limited with respect to PMBCL [4, 5, 9, 20]. Consistent with these studies, IPI and age-adjusted IPI failed to show prognostic value. Furthermore, PMBCL-specific clinical features such as pleural/pericardial effusion and superior vena cava syndrome were not prognostic for survival. Although two of the three patients who were over 60 years died from treatment-related mortality, the prognostic value of age might not be clinically relevant because most patients were younger than 60 years. Consistent with those of previous reports [4, 9], the CR achievement after the first-line chemotherapy was significantly associated with OS and PFS. In our study, the male to female ratio was approximately 1:1 unlike the reports from Western countries [21, 22]. This pattern is consistent with a previous Japanese study reporting 16 male and 12 female patients [23]. Thus, the female preponderance of PMBCL might not exist in Asian patients, and this tendency should be confirmed by a larger study population-based study in the future.

In conclusion, our comparison suggests that the addition of rituximab to CHOP may increase response and reduce relapse, and so it may result in prolongation of PFS of Korean patients with PMBCL. Therefore, the addition of rituximab may eliminate the outcome disadvantage of PMBCL observed with CHOP chemotherapy alone.

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