Prognostic significance of pleural or pericardial effusion and the implication of optimal treatment in primary mediastinal large B-cell lymphoma: a multicenter retrospective study in Japan

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ABSTRACT

The prognosis of patients with primary mediastinal large B-cell lymphoma has improved over recent years. However, the optimal treatment strategy including the role of radiotherapy remains unknown. We retrospectively analyzed the clinical outcomes of 345 patients with newly diagnosed primary mediastinal large B-cell lymphoma in Japan. With a median follow up of 48 months, the overall survival at four years for patients treated with R-CHOP (n=187), CHOP (n=44), DA-EPOCH-R (n=9), 2nd- or 3rd-generation regimens, and chemotherapy followed by autologous stem cell transplantation were 90%, 67%, 100%, 91% and 92%, respectively. Focusing on patients treated with R-CHOP, a higher International Prognostic Index score and the presence of pleural or pericardial effusion were identified as adverse prognostic factors for overall survival in patients treated with R-CHOP without consolidative radiotherapy (IPI: hazard ratio 4.23, 95% confidence interval 1.48-12.13, *P*=0.007; effusion: hazard ratio 4.93, 95% confidence interval 1.37-17.69, *P*=0.015). Combined with the International Prognostic Index score and the presence of pleural or pericardial effusion for the stratification of patients treated with R-CHOP without radiotherapy, patients with lower International Prognostic Index score and the absence of effusion comprised approximately one-half of these patients and could be identified as curable patients (95% overall survival at 4 years). The DA-EPOCH-R regimen might overcome the effect of these adverse prognostic factors. Our simple indicators of International Prognostic Index score and the presence of pleural or pericardial effusion could stratify patients with primary mediastinal large B-cell lymphoma and help guide selection of treatment.

Introduction

Primary mediastinal large B-cell lymphoma (PMBL) is characterized by distinct clinical, pathological and genetic features and comprises a subtype of diffuse large B-cell lymphoma (DLBCL) according to the current World Health Organization (WHO) classification.[1] The disease is more common in younger females and often presents with bulky mediastinal mass without extrathoracic spread and pleural or pericardial effusion.[2-5]

Prior to the introduction of rituximab, the outcomes of patients treated with anthracycline-containing chemotherapies, including cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP), had a suboptimal progression-free survival (PFS) of 38%-52%.[5,6] Several retrospective analyses revealed that the outcomes of the 2nd- and 3rd-generation chemotherapeutic regimens, such as methotrexate, leucovorin, doxorubicin, cyclophosphamide, vincristine, bleomycin and prednisolone (MACOP-B), might be superior to those of CHOP regimens.[5,7-10] High-dose chemotherapy followed by autologous stem cell transplantation (HDT/ASCT) was also associated with encouraging results (PFS >75% for newly diagnosed PMBL patients).[3,11,12] These reports indicate that intensive regimens might be beneficial in a certain proportion of PMBL patients.

In the rituximab era, the combination of rituximab and

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chemotherapy has improved outcomes in various subtypes of B-cell lymphoma.[13-22] In the literature, more than 80% of patients with PMBL receiving immunochemotherapy with or without radiotherapy (RT) also achieved long-term overall survival (OS).[17-22] Despite the outstanding advances with R-CHOP, 20%-30% of patients still experience progression or relapse and have poor outcomes. Moreover, approximately 80% of long-term survivors treated with R-CHOP required consolidative RT for residual mediastinal disease.[20-23] Considering late adverse events induced by the mediastinal RT, namely the increased risk of secondary breast cancer and cardiac toxicity, the risk of RT should be minimized, especially for younger patients.[24-26]

Recently, Dunleavy *et al*. reported excellent outcomes for dose-adjusted etoposide, cyclophosphamide, doxorubicin, vincristine, prednisolone and rituximab (DA-EPOCH-R) when restricting candidates for RT according to the results of positron-emission tomography/computed tomography (PET/CT).[27] Although outcomes were reported from a phase II trial, the regimen might be a promising treatment strategy to reduce the risk of RT. Meanwhile, the DA-EPOCH-R regimen is somewhat complicated and expensive, requiring continuous infusion for 96 h in each cycle and frequent evaluation of complete blood counts. Considering R-CHOP-based regimens without RT could provide curative potential for a significant proportion of PMBL patients without hospitalization,[19,21] it would, therefore, be beneficial to identify the subset of patients that could be cured with this treatment strategy.

The goal of the present multicenter co-operative retrospective study in Japan was to investigate the optimal treatment strategy for PMBL patients by evaluating the clinical outcomes in response to various treatments and to assess a risk-stratified treatment strategy to minimize the risk of late adverse events in PMBL patients.

Methods

Patients

A total of 363 patients with PMBL newly diagnosed between May 1986 and September 2012 at one of any of the 65 participating hospitals in Japan were retrospectively analyzed. We registered consecutive patients who were diagnosed with PMBL at each institution in accordance with the WHO classification.[1] The time period during which we could collect the clinical data from each institution varied due to the differences in the length of time medical records are kept there. Medical record data since the 1980s were collected from three institutions, while data since the 1990s and 2000s were available from 10 and 65 institutions, respectively. In this study, PMBL was defined as patients with a dominant mass within the anterior mediastinum, irrespective of the tumor size. In addition, a central pathological review was performed by a hematopathologist (SN) for 196 patients for whom histological paraffin-embedded tissue materials could be provided. Eighteen of the 363 patients were excluded from analysis due to disease other than PMBL (n=10) by central pathological review or due to the absence of important clinical information (n=8). For the remaining patients who were not available for the central review, the histological diagnosis of PMBL was re-confirmed by a pathologist at each institution, according to the current WHO classification. Therefore, 345 patients were finally analyzed for the present study. Patients were treated according to each institution's treatment standards. The study protocol was approved by the institutional review boards of Nagoya Daini Red Cross Hospital where this study was organized and of each participating hospital. The study complied with all the provisions of the Declaration of Helsinki.

Immunohistochemistry

Immunohistochemistry was performed using formalin-fixed, paraffin-embedded tissue sections using the avidin-biotin peroxidase complex method. Monoclonal antibodies targeting the following proteins were used: CD20, CD30, CD3, CD10, BCL6, MUM1 and CD15 (Dako). In addition, programmed cell death ligand-1 (PDL1) was evaluated, as previously described.[28] To evaluate PDL1, we used a polyclonal rabbit antibody for CD274 (ab82059; Abcam) according to the manufacturer's instructions. The cut-off values for these markers were 20% for CD30, and 30% for Bcl-6, MUM1 and PDL1.[29-31]

Treatment

Initial treatments were performed based on the physicians' decisions at each institution, as there had been no uniform treatment guidelines for PMBL in Japan. Patients who received CHOP or a CHOP-like regimen, with or without rituximab, were categorized and analyzed as the R-CHOP or CHOP group, respectively. Patients who received 2nd-/3rd-generation treatments were categorized and analyzed as the 2nd-/3rd-generation regimen group, irrespective of the use of rituximab. Patients who received the DA-EPOCH-R regimen[27] were analyzed as the DA-EPOCH-R group. Patients who underwent consolidative HDT/ASCT after initial therapy were analyzed as the HDT/ASCT group, irrespective of the use of rituximab. CHOP- or R-CHOP-based regimens were mainly selected in 46 institutions. Physicians at six institutions selected 2nd-/3rd-generation chemotherapeutic regimens other than CHOP- or R-CHOP-based regimens as the first-line treatment. HDT/ASCT as the first-line treatment was performed at 13 institutions. Consolidative RT was performed according to the treatment strategy used at each institution.

Response assessment

Clinical data were collected from case report forms. In principle, an effusion was evaluated by CT and/or echocardiography, as per the usual pre-treatment evaluation. Responses were evaluated by each investigator in accordance with the 1999 International Workshop Criteria.[32]

Statistical analysis

Overall survival was defined as the period from diagnosis to death or last follow up. Progression-free survival (PFS) was defined as the period from diagnosis to disease progression, relapse, death from any cause, or last date of follow up. Patients who did not achieve a complete remission (CR) or partial response (PR) were considered to have primary refractory disease. Early relapse was defined as relapse occurring less than 12 months after diagnosis. PFS and OS were analyzed using Kaplan-Meier methods and results were compared using the log rank test. Univariate and multivariate Cox regression analyses were performed to assess the effects of prognostic factors. Multivariate analysis was built with a forward/backward, step-wise method using threshold values for removal from and addition to the model of P=0.20 and P=0.05, respectively. The individual factors of IPI were entered into the model in multivariate analysis. All probability values were two-sided and had an overall significance level of 0.05. Statistical analyses were performed with Stata SE 12 software (StataCorp LP, College Station, TX, USA).

Results

Patients' characteristics

Patients' characteristics are summarized in Table 1. Median age was 32 years (range 17-83 years) and females were predominant (58%). The median diameter of mediastinal mass was 10 cm (range 3-32 cm). Stage I/II disease, low-risk disease according to the International Prognostic Index (IPI), and performance status (PS) 0/1 were also predominant (67%, 52% and 75%, respectively). The presence of pleural or pericardial effusion, elevated lactate dehydrogenase (LDH) level and more than one extranodal lesion were observed in 46%, 80% and 9% of patients, respectively. For the patients who had extra-nodal involvement, major extra-nodal sites were lung (n=44), effusion (n=49) and cardiac (n=28). Pathological features are listed in Table 1. Lymphoma cells in all patients expressed CD20. Further, CD30, BCL6, and MUM1 expression was detected in 71%, 61%, and 96%, respectively. PDL1 was expressed in 62% of 110 evaluable patients.

Table 1. Patients' characteristics.

Characteristic	All		CHOP		R-CHOP		DA-EPOCH-R		2nd/3rd generation		HDT/ASCT	
	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%
Median follow up (months)	48		118		36		19		48		101	
Patient number	345		44		187		9		45		57	
Age at diagnosis (years)												
Median	32		31.5		33.5		30		31		27	
Range	17-83		17-77		17-83		24-64		18-76		17-63	
>60 years	47	14	10	23	30	16	1	11	3	7	3	5
Gender, male	146	42	18	41	85	45	4	44	12	27	27	47
PS, ≥2	84/338	25	12/42	29	40/182	22	3	33	8	18	20	3
Extranodal sites, >1	64/334	19	7/40	17	31/181	18	0	0	11	24	15/56	27
Stage, I/II	230/342	67	27	61	133/184	72	7	78	31	69	31	54
LDH at diagnosis, ≥ULN	270/337	80	35/41	85	134/183	73	8	89	37	82	54/56	96
B symptoms, present	90/337	27	15/42	36	40/183	22	2	22	11	24	22/55	40
IPI												
Low	175/334	52	19/40	48	103/181	57	5	56	26	58	21/56	38
Low-intermediate	84/334	25	11/40	28	44/181	24	3	33	9	20	16/56	29
High-intermediate	43/334	13	4/ 40	10	21/181	12	0	0	5	11	12/56	21
High	32/334	10	6/40	15	13/181	7	1	11	5	11	7/56	13
Bulky tumor size												
Median	10		10		9.2		12.6		10.5		10	
≥10 cm	166/324	51	20/36	56	84/180	47	6	67	26	59	30/56	58
s-IL2R after first-line therapy, ≥1000 U/mL	141/305	46	20/30	67	91/175	52	2/8	25	17/40	43	33/49	67
Presence of pleural or pericardial effusion	159/343	46	15/43	35	83/186	43	5	56	23	51	31	54
WBC, >10×10⁹/L	23/339	7	2/42	5	12/184	7	0	0	5	11	3/56	5
Hemoglobin, ≤12 g/dL	119/329	36	16/39	41	57/81	31	3	33	21	47	19/52	37
Platelet count, <150×10⁹/L	20/331	6	2/40	5	16/182	9	0	0	0	0	2/52	4
ALC at diagnosis, <0.5×10⁹/L	62/321	19	2/33	6	29/180	16	5	56	12	27	13/52	25
IHC staining, positive												
CD20	152/152	100	15/15	100	99/99	100	5/5	100	8/8	100	25/25	100
CD10	4/129	3	1/11	9	2/85	2	0/5	0	0/7	0	1/21	5
CD30	100/140	71	9/13	69	62/85	70	5/5	100	5/8	63	18/25	72
BCL6	72/116	61	8/11	73	46/75	61	2/5	40	4/6	67	12/19	63
MUM1	105/109	96	10/11	91	67/68	99	4/5	80	6/6	100	18/19	95
PDL-1	68/110	62	7/11	64	44/68	65	2/5	40	1/5	20	14/21	67
Treatment												
Administration of rituximab	267	77	0	0	187	100	9	100	28	62	43	75
Consolidation RT	145	42	21	48	64	34	4	44	30	67	24	42
Late adverse event												
Secondary cancer	7	2	1	2	4	2	0	0	0	0	2	4
Cardiac toxicity	10	3	0	0	9	5	0	0	0	0	1	2

CHOP: cyclophosphamide, adriamycin, vincristine and prednisone; R: rituximab; DA-EPOCH-R: dose-adjusted etoposide, cyclophosphosphamide, doxorubicin, vincristine, prednisolone and rituximab; HDT/ASCT: high-dose chemotherapy followed by autologous stem cell transplantation; PS: performance status; LDH: lactate dehydrogenase; ULN: upper limit of normal; IPI: international prognostic index; s-IL2R: soluble interleukin-2 receptor; WBC: white blood cell count; ALC: absolute lymphocyte count; IHC: immunohistochemical staining; RT: radiation therapy.

Treatment regimen

In all, 267 patients received rituximab-containing chemotherapy. CHOP and R-CHOP chemotherapy groups consisted of 44 and 187 patients, respectively. DA-EPOCH-R chemotherapy was administered to 9 patients. In the 2nd-/3rd-generation regimen group (n=45), 28 patients received MACOP-B with (n=18) or without (n=10) rituximab, 15 patients received cyclophosphamide, vincristine, bleomycin, etoposide, doxorubicin and prednisolone (CyclOBEAP)[33] with (n=12) or without (n=3) rituximab, and 2 patients received vincristine, cyclophosphamide, doxorubicin, ranimustine, vindesine, etoposide carboplatin and prednisone (JCOG-LSG15 study regimen).[34] In the HDT/ASCT group (n=57), 43 patients received rituximab-containing chemotherapy as the initial chemotherapy. Consolidative RT was given to 42% of all patients. After approval of the use of rituximab for DLBCL in Japan in 2003, the use of rituximab-containing regimens rapidly increased, as shown in *Online Supplementary Table S1*. There was a moderate decrease in the use of HDT/ASCT and radiation therapy after initial treatment. The DA-EPOCH-R regimen was selected in the latest period.

Clinical outcomes

With a median follow up of 48 months in surviving patients, the OS and PFS at four years were 87% and 70%, respectively (Figure 1A and B). The OS and PFS of patients treated with rituximab-containing chemotherapy were superior to those of patients receiving chemotherapy without rituximab (4-year OS: 91% *vs.* 77%, $P<0.001$; 4-year PFS: 75% *vs.* 54%, respectively, $P<0.001$). There was no difference in the risk of central nervous system (CNS) relapse between patients treated with and patients treated without rituximab as first-line treatment (3.8% *vs.* 1.3%; $P=0.251$). The OS at four years for patients treated with CHOP, R-CHOP, DA-EPOCH-R, the 2nd-/3rd-generation regimens, and HDT/ASCT was 67%, 90%, 100%, 91% and 92%, respectively, with median follow-up durations of 118 months, 36 months, 19 months, 48 months and 101 months, respectively ($P<0.001$) (Figure 1C); PFS at four years was 40%, 71%, 100%, 83% and 76%, respectively ($P<0.001$) (Figure 1D).

Secondary malignancies and cardiac toxicity developed after treatment in 7 and 10 patients, respectively. The median age of these 17 patients was 62 years. Seven of 17

Table 2. Risk factors for overall survival, progression-free survival and early relapse for patients treated with R-CHOP without consolidative radium therapy.

	OS				PFS					Early relapse					
	univariate analysis			multivariate analysis			univariate analysis			multivariate analysis					
Variables	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Effusion present	4.93	1.37-17.69	0.015	4.67	2.28-9.57	<0.001	3.53	1.69-7.40	0.001	6.45	2.45-16.98	<0.001	6.11	2.30-16.24	<0.001
Age > 60 years	2.23	0.75-6.68	0.150	0.62	0.26-1.48	0.282	–	–	–	0.14	0.019-1.05	0.056	–	–	–
Sex Male	1.35	0.47-3.89	0.584	0.93	0.50-1.73	0.821	–	–	–	0.67	0.31-1.43	0.299	–	–	–
PS	> 1	4.50	1.56-12.97	0.005	2.85	1.49-5.47	0.002	–	–	–	2.68	1.25-5.73	0.011	–	–
Extranodal sites > 1	2.47	0.83-7.37	0.106	2.28	1.16-4.51	0.017	–	–	–	2.38	1.08-5.27	0.032	1.75	0.79-3.91	0.169
Stage III/IV	1.75	0.61-5.06	0.300	2.76	1.47-5.18	0.002	2.16	1.14-4.11	0.018	2.89	1.37-6.09	0.005	–	–	–
LDH > ULN	1.80	0.50-6.46	0.369	3.72	1.45-9.53	0.006	2.28	0.86-6.00	0.096	3.02	1.05-8.71	0.041	–	–	–
B symptoms present	0.74	0.17-3.32	0.697	1.08	0.49-2.35	0.853	–	–	–	1.55	0.68-3.53	0.292	–	–	–
IPI ≥ 3	4.23	1.48-12.13	0.007	2.94	1.55-5.57	0.001	–	–	–	2.95	1.40-6.25	0.005	–	–	–
Tumor diameter ≥ 10 cm	1.31	0.44-3.90	0.150	2.40	1.26-4.60	0.088	–	–	–	3.69	1.61-8.43	0.002	–	–	–
s-IL2R > 1000 U/L	1.88	0.57-6.25	0.302	2.40	1.18-4.90	0.016	–	–	–	1.93	0.85-4.37	0.115	–	–	–
Serum albumin < 3.5 g/dL	1.82	0.56-5.89	0.322	1.46	0.69-3.10	0.321	–	–	–	1.80	0.79-4.10	0.159	–	–	–
ALC < 0.5×10^9/L	1.15	0.26-5.15	0.855	1.17	0.49-2.79	0.728	–	–	–	1.33	0.50-3.50	0.566	–	–	–
Hemoglobin <12 g/dL	1.86	0.64-5.37	0.253	1.17	0.60-2.29	0.643	–	–	–	1.20	0.55-2.59	0.651	–	–	–
Platelet count <150×10^9/L	2.15	0.48-9.65	0.316	1.82	0.71-4.67	0.316	–	–	–	0.93	0.22-3.91	0.919	–	–	–

OS: overall survival; PFS: progression-free survival; R-CHOP: rituximab, cyclophosphamide, adriamycin, vincristine and prednisone; RT: radiation therapy; HR: hazard ratio; CI: confidence interval; Effusion: pleural or pericardial effusion; PS: performance status; LDH: lactate dehydrogenase; ULN: upper limit of normal; IPI: international prognostic index; s-IL2R: soluble interleukin-2 receptor; ALC: absolute lymphocyte count.

patients received RT or ASCT as first-line treatment. In addition, 3 of 7 patients who developed secondary malignancies received RT during the initial series of treatment. Among the secondary malignancies, myelodysplastic syndrome (MDS) or acute myeloblastic leukemia (AML) was reported in 2 patients. The patient who developed MDS received HDT/ASCT as a first-line treatment. The patient who developed AML received CHOP as a first-line treatment and ICE as a salvage treatment. Among the 187 patients treated with R-CHOP, 9 experienced cardiac toxicity, and 4 developed a secondary cancer. The median time to development of a secondary malignancy was 40.5 months (range 9-200 months).

Patients' characteristics and clinical outcomes in the R-CHOP group

Detailed characteristics of patients in the R-CHOP group are shown in *Online Supplementary Table S2*. We divided this group into four subgroups according to the disease status after R-CHOP or R-CHOP-like regimen and the presence or absence of consolidative RT: namely, R-CHOP+RT with residual mass, R-CHOP+RT in CR, R-CHOP with residual mass and R-CHOP in CR. Among the 187 patients in the R-CHOP group, 64 patients received consolidative RT after R-CHOP (*Online Supplementary Table S3*). Elderly age and higher IPI score were less common in those who received consolidative RT. Thirty-three of 64 patients received consolidative RT with residual mass after R-CHOP, while 31 of 64 patients received RT in CR after R-CHOP. Among the remaining 123 patients without consolidative RT, 34 patients did not achieve CR after R-CHOP, and 89 patients were in CR after R-CHOP, respectively. Among 34 patients with residual mass who were treated with R-CHOP, 16 patients developed progressive disease (PD), and 4 patients received follow up without RT based on the negative findings on PET/CT after the initial series of treatment. Of 89 patients who achieved a CR after R-CHOP but did not receive RT, 14 patients experienced relapse. Among these 14 patients, 9 developed the relapsed disease in their mediastinum, while the remaining 5 relapsed in other sites. The OS and PFS at four years of patients receiving consolidative RT were 100% and 85%, respectively, in the group with residual mass, and 96% and 90%, respectively, in the

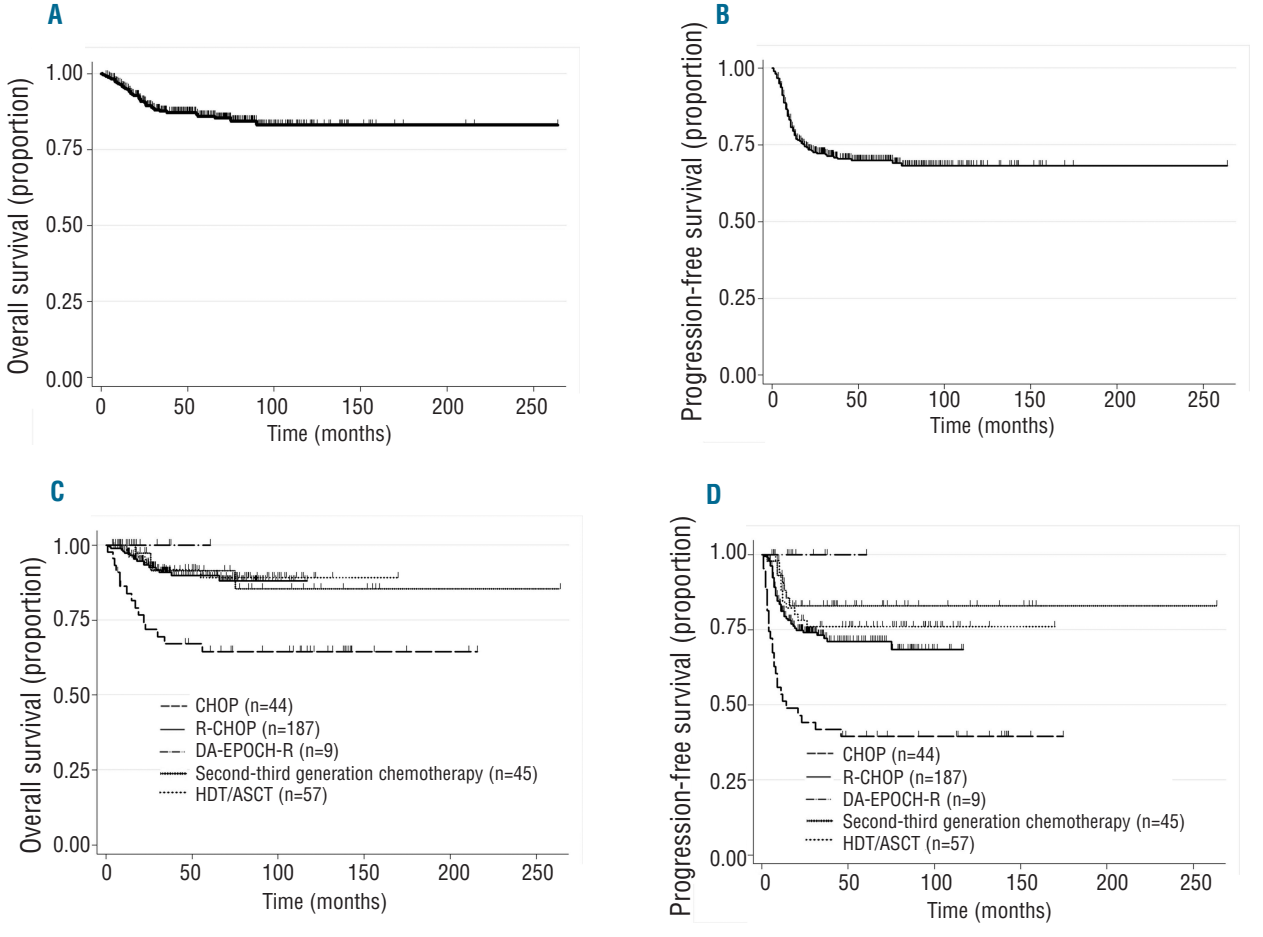

Figure 1. Survival of patients with primary mediastinal large B-cell lymphoma. (A) Overall survival (OS) of all patients with primary mediastinal large B-cell lymphoma (PMBL). (B) Progression-free survival (PFS) of all patients with PMBL. (C) OS of patients with PMBL treated with CHOP (n=44), R-CHOP (n=188), DA-EPOCH-R (n=9), 2nd- or 3rd-generation regimens (n=45), and HDT/ASCT (n=57). (D) PFS of patients with PMBL treated with CHOP (n=44), R-CHOP (n=188), DA-EPOCH-R (n=9), 2nd- or 3rd-generation regimens (n=45), and HDT/ASCT (n=57). CHOP: cyclophosphamide, adriamycin, vincristine and prednisone; R: rituximab; DA-EPOCH-R: dose-adjusted etoposide, cyclophosphosphamide, doxorubicin, vincristine, prednisolone and rituximab; HDT/ASCT: high-dose chemotherapy followed by autologous stem cell transplantation.

group in CR (OS: *P*=0.15; PFS: *P*=0.80) (*Online Supplementary Figures S1 and S2*). Meanwhile, the OS and PFS at four years of patients who did not receive consolidative RT were 64% and 35%, respectively, in the group with residual mass without disease progression, and 95% and 77%, respectively, in the group in CR (OS: *P*<0.001; PFS: *P*<0.001). Taken together, these data indicate that a significant proportion of patients achieving CR after R-CHOP can be cured without consolidative RT.

Prognostic factors and survival for patients treated with R-CHOP and without consolidative radiotherapy

One hundred and twenty-three patients receiving R-CHOP without consolidative RT were analyzed. The analysis of potential prognostic factors is shown in Table 2. On univariate analysis, the presence of pleural or pericardial effusion, performance status (PS) over 1 and higher IPI were adverse prognostic factors for OS, and the presence of pleural or pericardial effusion, advanced stage, extranodal involvement, PS, LDH, soluble interleukin-2 receptor (sIL-2R), and higher IPI were adverse prognostic factors for PFS. On multivariate analysis, we could not identify significant prognostic factors for OS. The presence of pleural or pericardial effusion [hazard ratio (HR), 3.53; 95% confidence interval (CI), 1.69-7.40; *P*=0.001] and advanced stage (stage III/IV; HR, 2.16; 95%CI: 1.14-4.11; *P*=0.018) were identified as adverse prognostic factors for PFS. As almost all the patients with progression after R-CHOP developed disease within 12 months after diagnosis, we performed Cox regression analyses to determine the predictive factors for primary refractory or early relapse within 12 months after diagnosis. On multivariate analysis, only the presence of pleural or pericardial effusion was predictive of primary refractory or early relapse within 12 months (HR, 6.11; 95%CI: 2.30-16.24; *P*<0.001). In this cohort, only 5 (8%) of 65 patients without pleural or pericardial effusion experienced primary refractory or early relapse within 12 months; meanwhile, 25 (43%) of 58 patients with pleural or pericardial effusion (*P*<0.001) had refractory or early relapsed disease.

As IPI and the presence of pleural or pericardial effusion were prognostic factors for OS on univariate analysis, and these were not related (correlation coefficient = 0.39), the OS and PFS in patients receiving R-CHOP without RT were analyzed according to these prognostic factors. The OS and PFS in patients receiving R-CHOP without RT were analyzed according to the presence of pleural or pericardial effusion and IPI. As expected (Figure 2A and B), the best OS and PFS were observed in patients with low IPI and without pleural or pericardial effusion. The OS and

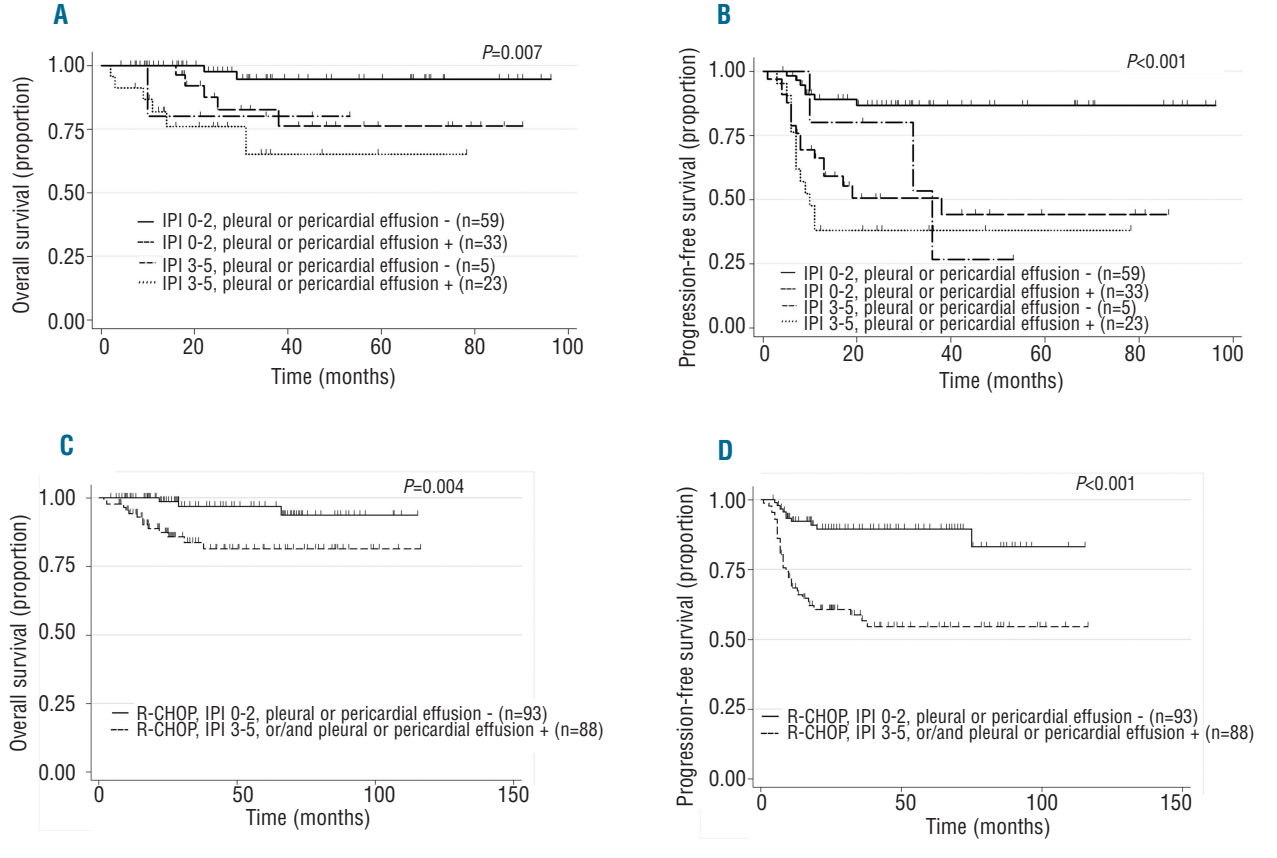

Figure 2. Survival of patients with primary mediastinal large B-cell lymphoma according to the International Prognostic Index and the presence pleural or pericardial effusion. (A) Overall survival (OS) of patients with primary mediastinal large B-cell lymphoma (PMBL) treated with R-CHOP without radiation therapy (RT) according to the international prognostic index (IPI) and the presence pleural or pericardial effusion. (B) Progression-free survival (PFS) of patients with PMBL treated with R-CHOP without RT according to the IPI and the presence pleural or pericardial effusion. (C) OS of patients with PMBL treated with R-CHOP according to the IPI and the presence pleural or pericardial effusion. (D) PFS of patients with PMBL treated with R-CHOP according to the IPI and the presence pleural or pericardial effusion. R-CHOP: rituximab, cyclophosphamide, adriamycin, vincristine and prednisone; RT: radiation therapy.

PFS at four years of these 58 patients were 95% and 87%, respectively. Meanwhile, based on individual factors of LDH, B symptom, and pleural or pericardial effusion identified on multivariate analysis for PFS, the OS and PFS were also analyzed (*Online Supplementary Figures S3 and S4*). Although the OS and PFS could be well stratified, the number of patients categorized into the well stratified low-risk category was lower than that of patients under the stratification using IPI and effusion. Taken together, these data indicate that a significant proportion of patients with low IPI and without pleural or pericardial effusion at the time of diagnosis can be potentially cured by the R-CHOP regimen without consolidative RT.

Meanwhile, the treatment should be considered for patients with higher IPI and the presence of pleural or pericardial effusion. As shown in Figure 2C and D, the outcomes of R-CHOP were not satisfactory in patients with higher IPI and/or the presence of pleural or pericardial effusion (4-year OS: 97% *vs.* 81%, P=0.004; 4-year PFS: 89% *vs.* 54%, P<0.001, respectively).

Discussion

It is important to establish a more effective and less toxic standard treatment for PMBL, as affected patients tended to be young and can be cured when properly treated. The present study investigated a larger cohort than other studies and indicated that almost all PMBL patients with lower IPI and the absence of the pleural or pericardial effusion could be cured by the R-CHOP regimen without consolidative RT. Considering the excellent outcomes of the recent promising regimen DA-EPOCH-R, reported by Dunleavy *et al.*,[27] the initial treatment regimen for PMBL could be stratified according to our simple indicators of IPI score and the presence of pleural or pericardial effusion; DA-EPOCH-R or R-CHOP could be selected for high- or low-risk PMBL patients, respectively.

Consistent with other studies, patients who received rituximab-containing chemotherapies showed better outcomes.[17-22,27,35] HDT/ASCT and 2nd-/3rd-generation regimens that were more intensive and that have been historically used as first-line treatment for PMBL resulted in better outcomes than those seen in response to CHOP chemotherapy.[11,17,18,36] In the present study, similar OS and PFS was observed among patients treated with a 2nd-/3rd-generation regimen, HDT/ASCT, and R-CHOP. This suggests that R-CHOP regimen might have curative potential in a significant proportion of PMBL patients without utilizing 2nd-/3rd-generation regimen or HDT/ASCT and thereby avoiding their associated toxicities.

Late toxicities are another important issue to consider when weighing the benefits of different curative regimens. In the current study, 17 patients had late adverse events (secondary cancer, n=7; cardiac toxicity, n=10). Previous reports indicated that RT to the mediastinum significantly increased the risk of breast cancer and cardiac toxicity.[24-26,37] Although longer follow up is required to evaluate for late toxicities, we investigated whether we could omit the consolidative RT from the current treatment strategies. We analyzed the outcomes of patients treated with R-CHOP without consolidative RT, and identified higher IPI and the presence of pleural or pericardial effusion as adverse risk factors for OS. Moreover, the presence of the effusion was identified as an adverse risk factor for early relapse. Considering that previous studies had reported that the presence of pleural effusion was associated with poor outcomes in patients with PMBL and Hodgkin lymphoma,[21,38] our results might be universal. Our simple indicators could identify patients who could be cured in response to R-CHOP without consolidative RT; however, patients with these factors comprised only approximately one-half of patients receiving R-CHOP. This means the remaining patients should be treated with an alternative regimen. The fact that excellent outcomes were seen in patients with higher IPI and the presence of the effusion receiving DA-EPOCH-R regimen in this study, as well as in another recent report,[27] suggests that it may be reasonable to use this approach in high-risk PMBL patients. A prospective trial of this strategy is warranted.

Another approach to stratify PMBL patients is currently being investigated in Europe. The prospective IELSG-37 trial is investigating whether consolidative RT could be omitted according to the presence or absence of FDG-PET or PET/CT findings after the initial series of treatments. In clinical practice, we frequently encounter patients in whom it is difficult to judge FDG-PET positivity.[39,40] Unfortunately, we could not evaluate the role of PET/CT in this study because of retrospective settings. Meanwhile, the very recent report from the IELSG-26 study clarified the role of PET/CT after treatment in PMBL patients.[41] Considering the difficulty of re-biopsy of the suspected mediastinal mass after treatment, using the optimal cut-off value on PET/CT after treatment reported by IELSG could be an important tool to assess the risk of treatment failure.

This study has several limitations. First, its retrospective nature might have unrecognized biases and the results should be interpreted with care. Regarding evaluation of response, evaluation of the residual mass might have been heterogeneous at each institution because of the retrospective setting. Therefore, the CR rate in our study could be over-estimated. Second, patients received various treatment regimens and consolidative RT according to each institution's preferred strategy; thus, treatment outcomes might have been over-estimated or under-estimated. In particular, patients who did not receive consolidative RT might have had clinical indicators that physicians considered favorable, resulting in an overestimation of the clinical outcomes in response to R-CHOP without consolidative RT. However, in the present analysis, the proportion of patients with higher IPI and with the presence of effusion was not low in patients who did not receive consolidative RT compared with that in patients who did receive RT. This suggests that the base-line characteristics and outcomes of patients without consolidative RT were not necessarily favorable and that they might not have been over-estimated. Finally, we carried out a central pathological review for only 196 patients. We tried to collect as much pathological histological paraffin-embedded tissue materials as possible. However, in some cases, sufficient materials were not available because they were too old. In addition, the period during which data could be submitted differed because clinical data were kept for different lengths of time at the different institutions. Therefore, the number of institutions who could submit clinical data in the 1980s and 1990s was smaller than in the 2000s: 10 and 65 institutions before and after the year 2000, respectively. Furthermore, although gene expression or methylation profiling can help to diagnose PMBL correctly, for the moment we cannot use these tools in routine clinical prac-

tice. Further study of the utility of these biological tools is necessary to improve diagnosis and management of this disease.

In conclusion, the present study demonstrated that IPI and the presence of pleural or pericardial effusion were adverse prognostic factors for risk stratification of PMBL patients treated with R-CHOP. R-CHOP without consolidative RT can achieve a high rate of cure for approximately one-half of PMBL patients, while alternative regimens, including DA-EPOCH-R, should be offered to the remaining patients. Prospective studies to validate these prognostic factors and a risk-adopted treatment strategy are warranted.

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Authorship and Disclosures

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