Available online at www.sciencedirect.com

ScienceDirect

Journal of the Chinese Medical Association 78 (2015) 400–407

www.jcma-online.com

Original Article

Rituximab induction therapy, survival benefits, and the increasing selection of radiotherapy as the postinduction treatment in patients with primary mediastinal large B-cell lymphoma

Sheng-Hsiang Yang [a,b,c], Liang-Tsai Hsiao [a,b,*], Tzeon-Jye Chiou [b,d], Ching-Fen Yang [b,e], Yuan-Bin Yu [a,b], Chun-Yu Liu [a,b], Jyh-Pyng Gau [a,b], Jin-Hwang Liu [a,b], Po-Min Chen [a,b], Cheng-Hwai Tzeng [a,b]

[a] *Division of Hematology and Oncology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*
[b] *National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC*
[c] *Department of Medicine, National Yang-Ming University Hospital, Ilan, Taiwan, ROC*
[d] *Division of Transfusion Medicine, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*
[e] *Department of Pathology and Laboratory Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*

Received August 15, 2014; accepted December 6, 2014

Abstract

Background: Primary mediastinal large B-cell lymphoma (PMBCL) is a rare malignancy that has been reported in young individuals, especially young women. Patients with PMBCL commonly receive rituximab induction. This single-institution study was designed to analyze the clinical benefits of rituximab induction and its impact on postinduction treatments (PITs), especially radiotherapy.

Methods: The benefits of rituximab induction were evaluated by complete response (CR), early treatment failure, relapse, and overall survival (OS) rates. The impact of the induction therapy on the adoption of PIT was evaluated by the proportion of patients who had received at the last follow up any PIT modality [i.e., radiotherapy or hematopoietic stem cell transplantation (HSCT)], radiotherapy alone, HSCT alone, or both modalities.

Results: Between 1999 and 2012, 48 PMBCL patients (29 men, 60%) were identified; they had a median age of 31 years. Twenty-eight patients received rituximab induction; of these, 23 (82%) patients also underwent fludeoxyglucose-positron emission tomography (FDG-PET) evaluation. Rituximab induction was significantly associated with higher rates of CR and OS, and lower rates of early treatment failure and relapse. Regarding PIT, patients with rituximab induction were more likely to receive radiotherapy alone [with rituximab induction (25%) vs. without rituximab induction (5%)], and patients with FDG-PET evaluation were similarly more likely to receive radiotherapy alone [with FDG-PET evaluation (28.6%) vs. without FDG-PET evaluation (0%)]. In multivariate analysis, age older than 60 years [hazard ratio (HR), 16.697; 95% confidence interval (CI), 1.106–252.022; $p = 0.042$] and rituximab induction (HR, 0.089; 95% CI, 0.012–0.653; $p = 0.017$) were significantly associated with OS.

Conclusion: Rituximab improved the CR and OS rates of patients with PMBCL, but these improvements may be attributable to the increased use of radiotherapy (which may have also resulted from FDG-PET evaluation).

Keywords: overall survival; positron emission tomography; primary mediastinal large B-cell lymphoma; radiotherapy; rituximab

Conflicts of interest: The authors have no conflicts of interest to declare in relation to the subject matter or materials discussed in this article.

* Corresponding author. Dr. Liang-Tsai Hsiao, Division of Hematology and Oncology, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, ROC.
E-mail address: lthsiao@vghtpe.gov.tw (L.-T. Hsiao).

http://dx.doi.org/10.1016/j.jcma.2015.02.005

1. Introduction

Primary mediastinal large B-cell lymphoma (PMBCL) is a relatively rare malignancy, and accounts for only 2% of all cases of non-Hodgkin's lymphoma (NHL).[1] In comparison to patients who have diffuse large B-cell lymphoma, not otherwise specified (abbreviated as DLBCL hereafter), patients with PMBCL are reportedly younger at diagnosis and predominantly female.[1] Regarding chemotherapy induction therapy, several large-scale analyses in Western countries have shown that the third-generation chemotherapy regimen methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B) is associated with a higher response rate[2]; however, cyclophosphamide, doxorubicin or epirubicin, vincristine, and prednisone every 21 days (CHOP-21) is commonly used in Asian countries.[3–6] In addition, the disease may be controlled further by postinduction treatments (PIT) such as radiotherapy[7] and/or high-dose therapy plus autologous hematopoietic stem cell transplantation (HSCT).[8,9]

Since the 2000s, rituximab and fludeoxyglucose-positron emission tomography (FDG-PET) have been commonly used in the management of B-cell NHL, which includes PMBCL. Several recent reports have demonstrated that the addition of rituximab in induction therapy (hereafter referred to as rituximab induction) is associated with improved rates of response and progression-free survival.[10,11] Fludeoxyglucose-positron emission tomography is usually employed to decide whether these patients should receive additional radiotherapy, especially for patients who have possible residual or recurrent lesions in the mediastinum.[12,13] However, Dunleavy et al[14] demonstrated in their Phase II trial of the combination of dose-adjusted etoposide, prednisone, Oncovin (vincristine), cyclophosphamide, and hydroxydaunorubicin (doxorubicin) (EPOCH) and rituximab (DA-EPOCH-R) that end-of-treatment FDG-PET evaluation of PMBCL patients had a relatively low positive predictive rate (17%), based on the pathological findings of PET-positive lesions.[14] In a nontrial setting, the rate of biopsy for this malignancy is low, and it is therefore anticipated that the use of radiotherapy will increase for PMBCL, especially after rituximab-containing immunochemotherapy. In the current study, we capitalized on our experience of patients with PMBCL and performed a single-institution investigation of rituximab's clinical benefits, as evaluated by treatment response, relapse, and survival. Furthermore, we sought to illustrate the evolution of PIT after the adoption of rituximab induction.

2. Methods

2.1. Patients

We reviewed the records of patients who had B-cell NHL and had been admitted to our hospital between 1999 and 2012. All patients with the mediastinum as the primary site of the neoplastic growth, as detected on computed tomography (CT), and a pathological diagnosis of DLBCL for the mediastinal mass were identified and reclassified as having PMBCL, according to the 2008 World Health Organization (WHO) classification.[1] After excluding two identified patients who did not receive treatment at our hospital, 48 patients were enrolled in the present study. Information was collected regarding clinical features at diagnosis, treatments, and outcomes at the latest follow up (as of November 2013). This retrospective study was approved by the Institutional Review Board of our hospital.

The clinical features that were analyzed included age, sex, performance status [according to the Eastern Cooperative Oncology Group (ECOG) scale], specific symptoms, serum lactate dehydrogenase (LDH) levels, involvement of extranodal sites (e.g., bone marrow), and clinical stage. In regard to specific symptoms at diagnosis, superior vena cava (SVC) syndrome was defined by imaging evidence of the SVC encased by neoplastic growth plus the presence of clinical symptoms such as facial swelling, chest discomfort, or superficial vein engorgement over the anterior chest wall. Patients in which the greatest dimension of the mediastinal tumor measured >10 cm were defined as having bulky disease. Disease stages were defined according to the Ann Arbor system, and patients who had lesions that were limited to above the diaphragm with pleural effusion or pericardial effusion were defined as having stage IIE disease, if no lymphoma cells were found in the effusion. In addition, International Prognostic Index (IPI) scores were calculated according to the published criteria.[15]

2.2. Treatments

Induction treatment consisted of chemotherapy with 6–8 cycles of the CHOP-21 regimen and (since 2005) CHOP-21 and rituximab (R-CHOP-21).

Postinduction treatment was defined as radiotherapy and HSCT in the consolidation or salvage setting. Consolidation PIT was administered if the response to treatment was less than a complete response (CR) or was an unconfirmed complete response (CRu) after induction and/or if negative prognostic factors that indicated an elevated risk of relapse (e.g., bulky disease or poor IPI score) had been identified at diagnosis, as determined at the discretion of the physicians involved. Salvage PIT was usually administered for relapsed or refractory disease.

Radiotherapy was generally administered whenever any questionable or definite residual lesion was found in the mediastinum after the induction or salvage therapy. The mobilization of peripheral blood stem cells was performed after chemotherapy with second-line regimens [e.g., etoposide, methylprednisolone, high-dose cytarabine, and cisplatin (ESHAP)]. The main preparative regimens of HSCT were busulfan, etoposide, cytarabine, and cyclophosphamide (BEAC) and busulfan, etoposide, cytarabine, and melphalan (BEAM). Autologous HSCT was usually performed as consolidation or salvage therapy for patients with a response to chemotherapy using second-line regimens, and allogeneic HSCT was only considered for patients with refractory disease after chemotherapy using second-line regimens.

2.3. Response evaluation

Treatment responses were evaluated using CT or FDG-PET after every 3−4 cycles of induction therapy and after 2−3 cycles of salvage chemotherapy, prior to and after radiotherapy and HSCT, and/or whenever there was clinical evidence of poor response or relapse. Complete response, CRu, partial response (PR), and progressive disease (PD) were defined according to previously reported criteria,[16,17] and were adjusted according to whether FDG-PET had been used, which was determined at the discretion of the physicians involved.

2.4. End points

The primary end point of the present study was the clinical benefit of rituximab induction, which was evaluated by the differences between the response, early treatment failure (ETF), relapse, and overall survival (OS) rates of patients who had and had not received rituximab induction. Patients with PMBCL were classified as having ETF if they had experienced a slow or inadequate response to 2−3 cycles of induction therapy (determined according to the discretion of the physicians) and had received chemotherapy with second-line regimens earlier. Hence, the definition of ETF was modified from previous definitions,[11] which include (1) early death during induction chemotherapy, (2) premature treatment withdrawal as a result of stable disease (SD) and switch to salvage therapy, and (3) PD or relapse within 6 months from treatment initiation or within 4 weeks from the end of chemotherapy (prior to or at postchemotherapy restaging). The OS was measured from the time of diagnosis to the date of death from any cause or the time of the last follow up.

The secondary end point of the study was the relevance of rituximab induction to the evolution of PIT in patients with PMBCL. The evolution of PIT was evaluated by the proportions of patients who had received any PIT modality by the time of the last follow up. The PIT modalities were classified as either radiotherapy alone, HSCT alone, or the combination of both modalities. In addition, because rituximab and FDG-PET were applied at fairly similar times during the clinical care of patients with PMBCL, we also examined the impact of FDG-PET on the evolution of PIT. We analyzed the associations of PIT with rituximab induction and FDG-PET evaluation separately because patients receiving rituximab did not always undergo FDG-PET. We assumed that the decision to administer PIT could only have depended on FDG-PET findings in the patients who received FDG-PET during the treatment and during the follow-up period. For conciseness, the term "FDG-PET evaluation" is employed in this manuscript to describe patients with FDG-PET evaluations during treatment and during follow up.

2.5. Statistical analysis

All statistical analyses were performed using SPSS for Windows v. 17.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were compared using the Pearson χ^2 test or the Fisher's exact test, whereas continuous variables were compared using the *t* test or the Mann−Whitney rank-sum test. The Kaplan−Meier method was used to estimate the OS, and the log-rank test was used to compare the survival of patients with different prognostic factors and treatments. Multivariate Cox proportional hazards regression analysis was used to identify factors that were independently associated with OS

Table 1
The clinical features of 48 patients with primary mediastinal large B-cell lymphoma, according to rituximab induction.

Parameters		No. of cases (%)	Without rituximab, *n* (%)	With rituximab, *n* (%)	*p*
Total		48 (100)	20 (100)	28 (100)	
Sex	Male/female	29 (60)/19 (40)	13 (65)/7 (35)	17 (61)/11 (39)	>0.99
Age (y)	Median (range)	31 (16−85)	30 (17−84)	31 (16−85)	>0.99[a]
	>60 y	8 (17)	4 (20)	4 (14)	
ECOG PS					0.16[b]
	0−2	38 (79)	18 (90)	20 (71)	
	3−4	10 (21)	2 (10)	8 (29)	
B symptoms	Yes	12/47 (26)	4/19 (21)	8 (29)	0.414
SVC syndrome	Yes	21/47 (45)	8/19 (42)	13 (46)	0.469
Pleural/pericardial/effusion	Yes	30/46 (65)	13/19 (68)	17/27 (63)	0.902
Bulky disease	Yes	23/45 (51)	10/17 (59)	13 (46)	0.542
Marrow involvement	Yes	3 (6)	3 (15)	0	0.066
Ann Arbor stage					0.110
	I and II	35 (73)	12 (60)	23 (82)	
	III and IV	13 (27)	8 (40)	5 (18)	
Serum LDH	>ULN	38/45 (84)	15/17 (88)	23 (82)	0.693
IPI score					0.410
	0−1	20/45 (45)	6/17 (35)	14 (50)	
	2−3	24/45 (53)	11/17 (65)	13 (46)	
	4−5	1/45 (2)	0/17 (0)	1 (4)	

ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index; LDH = lactate dehydrogenase; PS = performance status; SVC = superior vena cava; ULN = upper limit of normal.

[a] Mann−Whitney *U* test.

[b] Fisher's exact test.

Table 2
The responses, postinduction treatments, and outcomes of 48 patients with primary mediastinal large B-cell lymphoma, according to rituximab induction.

Parameters		Total, *n* (%)	Without rituximab, *n* (%)	With rituximab, *n* (%)	*p*
Total		48 (100)	20 (100)	28 (100)	
FDG-PET evaluation		28 (58)	5 (25)	23 (82)	<0.001
Response rates to first induction	CR/CRu	34 (71)	10 (50)	24 (86)	0.024
	PR, SD, PD	9 (19)	6 (30)	3 (11)	
	Not evaluable	5 (10)	4 (20)	1 (4)	
Early treatment failure		16 (33)	13 (65)	3 (11)	<0.001
	Early death	4 (8)	3 (15)	1 (4)	
	Premature treatment withdrawal	4 (8)	4 (20)	0	
	Early PD or relapse	8 (17)	6 (30)	2 (7)	
Radiotherapy	Consolidation	12 (25)	1 (5)	11 (39)	0.001
	Salvage	9 (19)	8 (40)	1 (4)	
HSCT	Consolidation	9 (19)	2 (10)	7 (25)	0.004
	Salvage	16 (33)	12 (60)	4 (14)	
Relapse		7/34 (21)	5/10 (50)	2/24 (8)	0.014
Alive at last follow-up		36 (75)	11 (55)	25 (89)	
Mean OS (mo)[a]		113.9	88.5	90.9	0.011
Cause of death		12	9	3	
	Lymphoma	3	2	1	
	Infection	9	7	2	

CR = complete response; CRu = unconfirmed complete response; FDG-PET = fludeoxyglucose-positron emission tomography; HSCT = hematopoietic stem cell transplantation; OS = overall survival; PD = progressive disease; PR = partial response; SD = stable disease.
[a] The median OS was not achieved for either subgroup.

[with 95% confidence intervals (CIs)], after adjusting for the factors that had $p < 0.1$ in univariate analyses. For all analyses, $p < 0.05$ was considered statistically significant.

3. Results

3.1. Clinical characteristics at diagnosis, according to rituximab induction therapy

Forty-eight patients were included in our analysis [29 (60%) males; median age, 31 years; range, 16–85 years; Table 1]. Eight (17%) patients were older than 60 years. At diagnosis, symptoms of SVC syndrome and a bulky mass were present in 21 (45%) of 47 patients and in 27 (60%) of 45 patients, respectively. Thirty-eight (84%) of 45 patients had elevated serum LDH levels. Thirteen (27%) patients had advanced stages (III or IV) of disease, 25 (55%) of 45 patients had an intermediate-to-high IPI score (i.e., ≥2) at diagnosis, and 28 (58%) patients received rituximab induction. Patients with and without rituximab induction had similar demographics (Table 1).

3.2. Postinduction treatment and outcomes, according to rituximab induction therapy

In comparison to their counterparts, patients with rituximab induction were more likely to have undergone FDG-PET for response evaluations (25% vs. 82%, respectively; $p < 0.001$; Table 2). In addition, rituximab induction was associated with significantly higher CR/CRu rates [86% (with rituximab) vs. 50% (without rituximab), $p = 0.024$] and lower ETF rates [11% (with rituximab) vs. 65% (without rituximab), $p < 0.001$]. The lower ETF rate in patients with rituximab induction reflected the combination of differences in early death rates [with vs. without rituximab induction (4% vs. 15%, respectively)], premature treatment withdrawal rates (0% vs. 20%, respectively), and early PD or relapse rates (7% vs. 30%, respectively).

With regard to PIT modalities (Table 2), the proportion of cases that included radiotherapy was similar in patients with and without rituximab induction (43% vs. 45%, respectively), whereas patients with rituximab induction were more likely to have received radiotherapy as a consolidation therapy because

Table 3
Distribution of postinduction treatments, according to the classification of rituximab induction or FDG-PET evaluation.

No. of patients		Rituximab induction			FDG-PET evaluation		
		No (%)	Yes (%)	*p*	No (%)	Yes (%)	*p*
Total		20 (100)	28 (100)		20 (100)	28 (100)	
Any PIT	Yes	15 (75)	18 (64.3)	0.535[a]	11 (55)	22 (78.6)	0.117[a]
PIT modality				0.128			0.03
	Radiotherapy alone	1 (5)	7 (25)		0 (0)	8 (28.6)	
	HSCT alone	6 (30)	6 (21.4)		4 (20)	8 (28.6)	
	Both	8 (40)	5 (17.9)		7 (35)	6 (21.4)	

FDG-PET = fludeoxyglucose-positron emission tomography; HSCT = hematopoietic stem cell transplantation; PIT = postinduction treatment.
[a] Fisher's exact test.

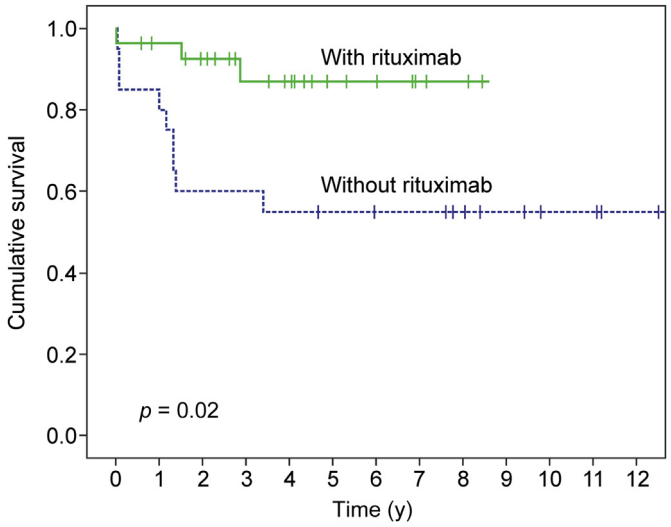

Fig. 1. The overall survival of patients with primary mediastinal large B-cell lymphoma, according to the use of rituximab induction.

CT or FDG-PET revealed residual lesions in the mediastinum (39% vs. 5%, $p < 0.001$). In addition, patients with rituximab were less likely to have received HSCT (43% vs. 70%, $p = 0.014$), and HSCT was used as a consolidation therapy in a higher proportion of these patients. Of the 25 patients who received HSCT once, seven (28%) patients received allogeneic HSCT as salvage therapy, which included three patients who received autologous HSCT.

3.3. Distribution of PIT, according to classification of rituximab induction or FDG-PET evaluation

Because many patients who received rituximab induction also underwent FDG-PET for the evaluation of PMBCL, we further investigated the use of PIT according to rituximab induction and the FDG-PET evaluation status. As Table 3 shows, we found that FDG-PET evaluation was significantly associated with the distribution of PIT ($p = 0.03$). In comparison to patients who did not undergo FDG-PET evaluation, a higher proportion of the patients who underwent FDG-PET evaluation received radiotherapy alone, whereas a lower proportion received both radiotherapy and HSCT. A similar trend was observed for rituximab induction (Table 3).

3.4. Survival and prognostic factors

The median duration of follow up was 67.2 months (range, 7.1–150 months). At last follow up, 36 (75%) patients were alive and disease-free. The 3-year OS rate was 73%. Patients with rituximab induction had a better mean duration of OS than patients without rituximab induction (90.9 months vs. 88.5 months, respectively, $p = 0.011$; Table 2 and Fig. 1). The causes of death included uncontrolled lymphoma in three patients, and treatment-related neutropenia and infection in nine patients (Table 2).

As Table 4 shows, we evaluated the univariate relationships between several factors and OS. Factors that were associated with poor OS included age older than 60 years, the presence of SVC syndrome, in a high IPI risk group at diagnosis, the absence of rituximab induction, and the absence of any PIT. When all factors with $p < 0.1$ (except for the IPI risk group) were included in the multivariate Cox regression analysis, age older than 60 years [hazard ratio (HR), 16.697; 95% CI, 1.106–252.022; $p = 0.042$] and rituximab induction (HR, 0.089; 95% CI, 0.012–0.653; $p = 0.017$) were independent prognostic factors for OS. Furthermore, SVC syndrome at diagnosis tended to be associated with poor OS.

4. Discussion

Based on clinical experiences at a single institution, this study's findings demonstrated the clinical benefits of rituximab

Table 4
Prognostic factors for overall survival in 48 patients with primary mediastinal large B-cell lymphoma.

		Univariate			Multivariate		
Parameters		HR	95% CI	*p*	HR	95% CI	*p*
Sex	Male vs. female	1.707	0.462–6.315	0.423	—	—	—
Age (y)	>60 vs. ≤60	6.840	2.187–21.388	0.001	16.697	1.106–252.022	0.042
ECOG PS	2–4 vs. 0–1	3.414	0.747–15.613	0.113	—	—	—
B symptoms	Yes vs. no	1.912	0.999–3.661	0.05	0.268	0.015–4.883	0.374
SVC syndrome	Yes vs. no	4.359	1.153–16.488	0.03	3.867	0.431–34.665	0.227
Pericardial/pleural effusion	Yes vs. no	1.405	0.685–2.884	0.345	—	—	—
Bulky disease	Yes vs. no	1.681	0.947–2.983	0.076	4.844	0.378–62.077	0.225
Marrow involvement	Yes vs. no	4.230	0.910–19.666	0.066	1.179	0.087–16.034	0.901
Ann Arbor stage	III/IV vs. I/II	1.384	0.416–4.602	0.596	—	—	—
LDH	>ULN vs. ≤ULN	1.841	0.931–3.642	0.079	0.806	0.057–11.318	0.873
IPI (score)	High (4–5) vs. intermediate (2–3) vs. low (0–1)	4.641	1.495–14.413	0.008	—	—	—
Rituximab induction	Yes vs. no	0.213	0.057–0.787	0.020	0.089	0.012–0.653	0.017
Any PIT	Yes vs. no	0.218	0.061–0.785	0.020	0.172	0.017–1.687	0.131
Radiotherapy	Yes vs. no	0.796	0.253–2.511	0.697	—	—	—
HSCT	Yes vs. no	0.553	0.175–1.746	0.313	—	—	—

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; HSCT = hematopoietic stem cell transplantation; IPI = International Prognostic Index; LDH = lactate dehydrogenase; PIT = postinduction treatments; PS = performance status; SVC = superior vena cava; ULN = upper limit of normal.

induction in patients with PMBCL, and illustrated the associations between rituximab induction and PIT; rituximab induction was particularly associated with the increased use of radiotherapy alone. When administered to patients with PMBCL, rituximab induction improved the CR/CRu and OS rates, and reduced the ETF and relapse rates. These findings are similar to the results of several recent studies.[5,10,11,18] Furthermore, rituximab induction was associated with greater use of radiotherapy as a consolidation therapy rather than as salvage therapy (Table 3), although the proportion of PMBCL patients who finally received radiotherapy was similar with and without rituximab induction (45% vs. 43%, respectively; Table 2). In fact, the proportion of our patients who received radiotherapy may have been reduced because of the early adoption of front-line HSCT. Several recent studies have demonstrated trends of increased radiotherapy use in PMBCL patients who received rituximab induction. Among German patients with PMBCL, radiotherapy was slightly more common in patients with rituximab (73%) than in patients without rituximab (67%).[10] The proportion of Greek patients undergoing radiotherapy was similarly greater among patients with rituximab (70%) than among patients without rituximab (48%).[11] The proportion of patients undergoing radiotherapy further increased to 89% in a report by the International Extranodal Lymphoma Study Group (IELSG).[19]

Our present results, and those of the aforementioned studies, showed that most patients with PMBCL experienced a good treatment response after induction therapy with R-CHOP-21 and received radiotherapy because CT or FDG-PET scans showed an avid residual lesion in the mediastinum. These findings have positive and negative implications. First, R-CHOP-21 alone is insufficient as a means of fully controlling PMBCL.[20] It is possible that FDG-PET improves the detection of small residual lesions in the mediastinum, which could explain the greater administration of radiotherapy in the patients with PMBCL who underwent FDG-PET. However, radiotherapy may be unnecessary in some patients with PMBCL, as shown in the study of DA-EPOCH-R by Dunleavy et al.[14] Furthermore, radiotherapy did not confer a benefit in the OS of PMBCL patients with or without rituximab in our study or in several previous studies.[10,11]

Rituximab induction and subsequent FDG-PET evaluation have probably contributed to the increased use of radiotherapy in patients with PMBCL. Our attempts to weigh the individual influences of rituximab induction and FDG-PET evaluation were limited by their fairly similar application times and the relatively small number of patients in this study. The findings of several recent studies have nonetheless supported this theory. Han et al[21] and Avivi et al[22] report that rituximab induction in DLBCL patients is associated with higher false-positive rates by FDG-PET, compared to the false-positive rates of FDG-PET in DLBCL patients without rituximab induction. This is possibly a consequence of immune-mediated inflammation. Pregno et al[23] showed that interim FDG-PET failed to predict the outcomes of DLBCL in patients treated with R-CHOP, and Avigdor et al[24] showed that interim FDG-PET failed to predict the outcomes of PMBCL in patients after R-VACOP-B and R-CHOP-21. Most importantly, Dunleavy et al[14] clearly demonstrated by aggressively performing biopsies that end-of-treatment FDG-PET had a relatively high false-positive rate after DA-EPOCH-R therapy. Because patients with PMBCL are usually relatively young, radiotherapy of the mediastinum is potentially associated with long-term sequelae, as seen in patients with Hodgkin disease.[25,26] The Deauville 5-point criteria has increasingly been used to interpret FDG-PET−positive residual lesions in the mediastinum after rituximab induction.[27] This approach will provide a basis for using PET/CT to define the role of radiotherapy in PMBCL.[19]

Another interesting finding of our study was the predominance of male patients in our study cohort. This finding contrasts with most studies from Western countries,[12,28] whereas several reports from China,[29] Japan,[3] Canada,[30] and from other hospitals in Taiwan[31,32] show findings that are similar to our own (Table 5).[3,4,12,28,30]

This retrospective study is subject to several limitations. Our institution is a veterans' hospital; however, this was not a confounding factor in our study because the median age of our PMBCL patients was relatively low. It is possible that we enrolled patients with the disease known as “mediastinal gray-zone lymphoma”. Mediastinal gray-zone lymphoma usually presents with the pathological features of DLBCL and Hodgkin disease,[33] and predominantly occurs among men.[34] Additional staining for PMBCL-specific transcription factors (e.g., cREL, MAL, and FIG-1) might be used to resolve any accidental inclusion of mediastinal gray-zone lymphoma.[1] However, such staining was not performed in the present study because of the limited number of available specimens. Because the IELSG study has suggested that male sex is an independent poor prognostic factor for patients with PMBCL,[12] geographic and racial differences in the sex distribution of PMBCL may be informative and warrant additional molecular studies to clarify the underlying pathogenesis. Furthermore, in comparison with other reports,[10,11,19]

Table 5
Comparison of reported sex distributions for patients with primary mediastinal large B-cell lymphoma

Study, author (year)	Country/region	Calendar period	Total no. of patients	No. of males	% male
Zinzani (2002)[12]	Europe	1981–1999	426	165	39
Savage (2006)[30]	Canada	1980–2003	153	86	56
Hamlin (2005)[28]	United States of America	1980–1999	141	76	54
Sekiguchi (2004)[3]	Japan	1982–2002	28	16	57
Ahn (2010)[4]	Korea	1995–2009	35	17	49
Current study (2014)	Taiwan	1999–2012	48	29	60

the present study included a higher proportion of patients who received front-line HSCT, and a lower proportion of patients who received radiotherapy. Thus, it is possible that the benefits from front-line HSCT with CHOP-21 as the induction chemotherapy in select patients may resemble the benefits of induction therapy with higher-intensity chemotherapies such as MACOP-B[2] and DA-EPOCH.[14] Our investigation's ability to clearly demonstrate the benefits of radiotherapy and HSCT may have been limited by the heterogeneity of PIT in our patient cohort, and by the relatively small number of patients. However, in the subset of our patients who did not receive rituximab induction, the CR/CRu rate was relatively low, which suggests that the prognosis of PMBCL patients was indeed improved by radiotherapy and/or HSCT as the consolidation or salvage therapy. In our study, one patient was chemoresistant to salvage chemotherapy and received radiotherapy and subsequent allogeneic HSCT; this patient remained disease-free at the latest follow up (5 years post-transplant), which is similar to the findings of a previously reported study.[35]

In conclusion, the findings of our study demonstrate the clinical benefits of rituximab induction in patients with PMBCL who are treated with CHOP-21, which is the conventional chemotherapy regimen. In addition, our findings illustrate the changes to PIT that accompany rituximab induction, which are characterized by an increased use of radiotherapy. However, these changes may be partially attributable to the use of FDG-PET evaluation. Because of the potential for long-term sequelae, treating physicians should carefully evaluate FDG-PET scan-positive lesions in patients with PMBCL whenever radiotherapy is planned after rituximab induction.

Acknowledgments

We thank Dr. M. Y. Lee of the Koo Foundation Sun Yat-Sen Cancer Center (Taipei, Taiwan) for prompt communication about the sex distribution in her report.[31] The present study was supported by grants from the Taiwan Clinical Oncology Research Foundation (Taipei, Taiwan), Taipei Veterans General Hospital (Taipei, Taiwan; grant number V100E2-001), and the National Science Council (Taipei, Taiwan; grant numbers NSC99-2314-B-075-017-MY2, NSC101-2325-B-075-008, and NSC102-2325-B-075-005).

References

1. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. *WHO classification of tumours of haematopoietic and lymphoid tissues*. 4th ed. Lyon, France: International Agency for Research on Cancer; 2008.
2. Zinzani PL, Martelli M, Magagnoli M, Pescarmona E, Scaramucci L, Palombi F, et al. Treatment and clinical management of primary mediastinal large B-cell lymphoma with sclerosis: MACOP-B regimen and mediastinal radiotherapy monitored by (67) gallium scan in 50 patients. *Blood* 1999;**94**:3289–93.
3. Sekiguchi N, Nishimoto J, Tanimoto K, Kusumoto S, Onishi Y, Watanabe T, et al. Primary mediastinal large B-cell lymphoma: a single-institution clinical study in Japan. *Int J Hematol* 2004;**79**:465–71.
4. Ahn HK, Kim SJ, Yun J, Yi JH, Kim JH, Won YW, et al. Improved treatment outcome of primary mediastinal large B-cell lymphoma after introduction of rituximab in Korean patients. *Int J Hematol* 2010;**91**:456–63.
5. Tai WM, Quah D, Yap SP, Tan SH, Tang T, Tay KW, et al. Primary mediastinal large B-cell lymphoma: optimal therapy and prognostic factors in 41 consecutive Asian patients. *Leuk Lymphoma* 2011;**52**:604–12.
6. Zhu YJ, Huang JJ, Xia Y, Zhao W, Jiang WQ, Lin TY, et al. Primary mediastinal large B-cell lymphoma (PMLBCL) in Chinese patients: clinical characteristics and prognostic factors. *Int J Hematol* 2011;**94**:178–84.
7. Nguyen LN, Ha CS, Hess M, Romaguera JE, Manning JT, Cabanillas F, et al. The outcome of combined-modality treatments for stage I and II primary large B-cell lymphoma of the mediastinum. *Int J Radiat Oncol Biol Phys* 2000;**47**:1281–5.
8. Sehn LH, Antin JH, Shulman LN, Mauch P, Elias A, Kadin ME, et al. Primary diffuse large B-cell lymphoma of the mediastinum: outcome following high-dose chemotherapy and autologous hematopoietic cell transplantation. *Blood* 1998;**91**:717–23.
9. Popat U, Przepiork D, Champlin R, Pugh W, Amin K, Mehra R, et al. High-dose chemotherapy for relapsed and refractory diffuse large B-cell lymphoma: mediastinal localization predicts for a favorable outcome. *J Clin Oncol* 1998;**16**:63–9.
10. Rieger M, Osterborg A, Pettengell R, White D, Gill D, Walewski J, et al. Primary mediastinal B-cell lymphoma treated with CHOP-like chemotherapy with or without rituximab: results of the Mabthera International Trial Group study. *Ann Oncol* 2011;**22**:664–70.
11. Vassilakopoulos TP, Pangalis GA, Katsigiannis A, Papageorgiou SG, Constantinou N, Terpos E, et al. Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone with or without radiotherapy in primary mediastinal large B-cell lymphoma: the emerging standard of care. *Oncologist* 2012;**17**:239–49.
12. Zinzani PL, Martelli M, Bertini M, Gianni AM, Devizzi L, Federico M, et al. Induction chemotherapy strategies for primary mediastinal large B-cell lymphoma with sclerosis: a retrospective multinational study on 426 previously untreated patients. *Haematologica* 2002;**87**:1258–64.
13. Johnson PW, Davies AJ. Primary mediastinal B-cell lymphoma. *Hematology Am Soc Hematol Educ Program* 2008;**2008**:349–58.
14. Dunleavy K, Pittaluga S, Maeda LS, Advani R, Chen CC, Hessler J, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. *N Engl J Med* 2013;**368**:1408–16.
15. Anon. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med* 1993;**329**:987–94.
16. Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol* 1999;**17**:1244.
17. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007;**25**:579–86.
18. Xu LM, Fang H, Wang WH, Jin J, Wang SL, Liu YP, et al. Prognostic significance of rituximab and radiotherapy for patients with primary mediastinal large B-cell lymphoma receiving doxorubicin-containing chemotherapy. *Leuk Lymphoma* 2013;**54**:1684–90.
19. Martelli M, Ceriani L, Zucca E, Zinzani PL, Ferreri AJ, Vitolo U, et al. [18F]Fluorodeoxyglucose positron emission tomography predicts survival after chemoimmunotherapy for primary mediastinal large B-cell lymphoma: results of the International Extranodal Lymphoma Study Group IELSG-26 Study. *J Clin Oncol* 2014;**32**:1769–75.
20. Soumerai JD, Hellmann MD, Feng Y, Sohani AR, Toomey CE, Barnes JA, et al. Treatment of primary mediastinal B-cell lymphoma with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone is associated with a high rate of primary refractory disease. *Leuk Lymphoma* 2014;**55**:538–43.
21. Han HS, Escalón MP, Hsiao B, Serafini A, Lossos IS. High incidence of false-positive PET scans in patients with aggressive non-Hodgkin's

lymphoma treated with rituximab-containing regimens. *Ann Oncol* 2009;**20**:309−18.
22. Avivi I, Zilberlicht A, Dann EJ, Leiba R, Faibish T, Rowe JM, et al. Strikingly high false positivity of surveillance FDG-PET/CT scanning among patients with diffuse large cell lymphoma in the rituximab era. *Am J Hematol* 2013;**88**:400−5.
23. Pregno P, Chiappella A, Bellò M, Botto B, Ferrero S, Franceschetti S, et al. Interim 18-FDG-PET/CT failed to predict the outcome in diffuse large B-cell lymphoma patients treated at the diagnosis with rituximab-CHOP. *Blood* 2012;**119**:2066−73.
24. Avigdor A, Sirotkin T, Kedmi M, Ribakovsy E, Berkowicz M, Davidovitz Y, et al. The impact of R-VACOP-B and interim FDG-PET/CT on outcome in primary mediastinal large B cell lymphoma. *Ann Hematol* 2014;**93**:1297−304.
25. Adams MJ, Lipsitz SR, Colan SD, Tarbell NJ, Treves ST, Diller L, et al. Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. *J Clin Oncol* 2004;**22**:3139−48.
26. Galper SL, Yu JB, Mauch PM, Strasser JF, Silver B, Lacasce A, et al. Clinically significant cardiac disease in patients with Hodgkin lymphoma treated with mediastinal irradiation. *Blood* 2011;**117**:412−8.
27. Meignan M, Gallamini A, Meignan M, Gallamini A, Haioun C. Report on the First International Workshop on Interim-PET-Scan in Lymphoma. *Leuk Lymphoma* 2009;**50**:1257−60.
28. Hamlin PA, Portlock CS, Straus DJ, Noy A, Singer A, Horwitz SM, et al. Primary mediastinal large B-cell lymphoma: optimal therapy and prognostic factor analysis in 141 consecutive patients treated at Memorial Sloan Kettering from 1980 to 1999. *Br J Haematol* 2005;**130**:691−9.
29. Chen DG, Yang Y, Pan CZ. Primary mediastinal large B-cell lymphoma: a report of 24 cases with literature review. *Ai Zheng* 2008;**27**:187−90 [In Chinese, English abstract].
30. Savage KJ, Al Rajhi N, Voss N, Paltiel C, Klasa R, Gascoyne RD, et al. Favorable outcome of primary mediastinal large B-cell lymphoma in a single institution: the British Columbia experience. *Ann Oncol* 2006;**17**:123−30.
31. Lee MY, Tan TD, Feng AC, Liu MC. Clinicopathological analysis of 598 malignant lymphomas in Taiwan: seven-year experience in a single institution. *Am J Hematol* 2006;**81**:568−75.
32. Chen WL, Tsai WC, Chao TY, Sheu LF, Chou JM, Kao WY, et al. The clinicopathological analysis of 303 cases with malignant lymphoma classified according to the World Health Organization classification system in a single institute of Taiwan. *Ann Hematol* 2010;**89**:553−62.
33. Rüdiger T, Jaffe ES, Delsol G, deWolf-Peeters C, Gascoyne RD, Georgii A, et al. Workshop report on Hodgkin's disease and related diseases (“grey zone” lymphoma). *Ann Oncol* 1998;**9**(Suppl 5): S31−8.
34. Traverse-Glehen A, Pittaluga S, Gaulard P, Sorbara L, Alonso MA, Raffeld M, et al. Mediastinal gray zone lymphoma: the missing link between classic Hodgkin's lymphoma and mediastinal large B-cell lymphoma. *Am J Surg Pathol* 2005;**29**:1411−21.
35. Nath SV, Seymour JF. Cure of a patient with profoundly chemotherapy-refractory primary mediastinal large B-cell lymphoma: role of rituximab, high-dose therapy, and allogeneic stem cell transplantation. *Leuk Lymphoma* 2005;**46**:1075−9.