Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone with or Without Radiotherapy in Primary Mediastinal Large B-Cell Lymphoma: The Emerging Standard of Care

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the effect of the addition of rituximab to standard CHOP chemotherapy on the outcome of patients with primary mediastinal large B-cell lymphoma.
2. Explain potential changes in the use of radiotherapy and aggressive chemotherapy in the rituximab era.

CME

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ABSTRACT

More aggressive treatment approaches (methotrexate, cytarabine, cyclophosphamide, vincristine, prednisone, and bleomycin [the MACOP-B regimen] or consolidation with high-dose therapy and autologous stem cell transplantation) have been considered to be superior to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in patients with primary mediastinal large B-cell lymphoma (PMLBCL). Rituximab-CHOP (R-CHOP) is the standard of care for diffuse large B-cell lymphoma, whereas efficacy in PMLBCL has not been adequately confirmed.

Patient and Methods. Seventy-six consecutive PMLBCL patients who received R-CHOP with or without radiotherapy (RT) were compared with 45 consecutive historical controls treated with CHOP with or without RT. Baseline characteristics of the two groups were balanced.

Results. The rate of early treatment failure was much

lower with R-CHOP with or without RT (9% versus 30%; $p = .004$). The 5-year freedom from progression rate after R-CHOP with or without RT was 81%, versus 48% for CHOP with or without RT ($p < .0001$). The 5-year event-free survival rates were 80% and 47% ($p < .0001$) and the 5-year overall and lymphoma-specific survival rates were 89% and 69% ($p = .003$) and 91% and 69% ($p = .001$), respectively, with only seven of 76 lymphoma-related deaths. Among R-CHOP responders, 52 of 68 received RT.

Conclusions. Based on these results, most patients with PMLBCL appear to be cured by R-CHOP in 21-day cycles with or without RT, which could be the current standard of care. Therefore, the need for more aggressive treatment strategies is questionable unless high-risk patients are adequately defined. Further studies are required to establish the precise role of RT. *The Oncologist* 2012;17:239–249

INTRODUCTION

Primary mediastinal (thymic) large B-cell lymphoma (PMLBCL) was recognized as a subtype of diffuse large B-cell lymphoma (DLBCL) in the Revised European American Lymphoma (REAL) Classification in 1994 [1]. It was classified as a separate entity in the 2001 World Health Organization (WHO) classification [2]. In contrast to DLBCL, which accounts for 30% of all cases of non-Hodgkin's lymphoma, PMLBCL is rare, representing only 2.5% of cases [2].

PMLBCL is characterized by distinctive morphologic, demographic, and clinical features [1–4]. It affects mainly young patients (median age, 30–35 years), with a female predominance, and is very rare in patients aged >60 years. PMLBCL presents, by definition, with a mediastinal mass, which is usually bulky, causing cough, shortness of breath on exertion and, frequently, superior vena cava syndrome. Pleural and/or pericardial effusions are also frequently observed at presentation.

The optimal treatment for PMLBCL patients has been a matter of debate [3]. Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) with or without radiotherapy (RT) is not sufficient, because cure rates do not exceed 50%–60% [5–8]. Some groups have suggested that more aggressive regimens, such as methotrexate, cytarabine, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B), may be more effective [5–7, 9, 10]. Retrospective studies have also suggested a potential benefit of high-dose therapy (HDT) and autologous stem cell transplantation (ASCT), when used as consolidation of response to first-line chemotherapy [6, 8]. Other investigators have reported results that compare favorably with those of CHOP, using various intensive regimens [8, 11, 12]. However, the use of any particular approach is not supported by randomized trials.

Rituximab has revolutionized the treatment of aggressive B-cell lymphomas [13, 14]. The combination of rituximab with CHOP (R-CHOP) is superior to CHOP in patients with DLBCL aged >60 years [13, 15, 16] and in younger patients falling into the low or low-intermediate risk group according

to the age-adjusted International Prognostic Index (aaIPI) [17]. R-CHOP also provides satisfactory results in younger patients with higher risk DLBCL [18]. Although the intensified R-CHOP plus etoposide (R-CHOEP-14) regimen was not inferior to an HDT approach [19], there is no direct randomized comparison to evaluate whether or not standard R-CHOP-21 is equally effective to these strategies in the subgroup of young, higher risk DLBCL patients. On the other hand, a recent randomized trial demonstrated significantly better progression-free survival (PFS) and overall survival (OS) outcomes in younger DLBCL patients with an aaIPI score of 1 when treated with more intensive chemoimmunotherapy (rituximab plus doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone) versus R-CHOP-21 [20].

Patients with PMLBCL have been included in trials of DLBCL. However, the majority of these young patients have elevated serum lactate dehydrogenase (LDH) levels and bulky disease, which is a recognized adverse prognostic factor with R-CHOP [21]. They may also present with a poor performance status and/or stage IV disease. As a result, almost all patients with PMLBCL have unfavorable features and an aaIPI score ≥ 1 , falling into the low-intermediate, high-intermediate, or high risk group [7, 8, 21], for which the optimal treatment has not been exactly defined [19, 20]. Therefore, the combination of rituximab with more intensive treatment, such as MACOP-B [5–7, 9, 10], consolidation with HDT and ASCT [6, 8, 22], high-dose methotrexate-based and dose-dense regimens [8, 11, 20, 23, 24], CHOEP, or time-intensified CHO(E)P-14 [19, 25], could be a potential option in patients with this particular subtype of aggressive lymphoma.

Because R-CHOP is a low-toxicity regimen compared with the above-mentioned treatment approaches, these considerations render its evaluation in PMLBCL an issue of high priority. The results presented here show that R-CHOP, an easily administered regimen without significant hematological toxicity or the need for hospitalization, can cure the majority of patients with PMLBCL.

MATERIALS AND METHODS

Patients and Staging

Seventy-six consecutive patients with PMLBCL were treated with R-CHOP with or without RT in the participating centers, whereas such patients had been treated with CHOP with or without RT in the prirituximab era. The transition from CHOP to R-CHOP was made at a certain point in each center, with R-CHOP becoming the standard practice based on recent knowledge of the high efficacy of rituximab in the treatment of DLBCL [13]. Patients were eligible for inclusion if they had presented with a clinical picture (dominated by a prominent mediastinal mass) and a histology report consistent with PMLBCL according to the WHO or REAL Classification [1, 2, 7]. Patients with minimal mediastinal involvement as part of more extensive lymphoma elsewhere were excluded [7]. Patients were also excluded if they had any concomitant extramediastinal mass greater in size than the primary mediastinal lesion [8, 24]. The analysis was restricted to patients aged <80 years, thus resulting in the exclusion of two patients, in order to ensure the inclusion of optimally treated patients, because patients aged ≥ 80 years may actually receive reduced-dose regimens or no anthracycline at all.

We compared the outcome of 45 consecutive historical control patients treated with CHOP with or without RT (including five patients treated with the equivalent intensified cyclophosphamide, mitoxantrone, vincristine, and prednisone [CNOP] with or without RT [26], four who received standard dose epirubicin instead of doxorubicin, and a single patient treated with MACOP-B) with the outcome of patients treated with R-CHOP with or without RT. Among the latter 76 patients, we included six patients, who received standard dose R-CNOP ($n = 4$) or R-CHOP-14 ($n = 2$), that is, regimens known to be inferior to and equivalent to R-CHOP, respectively [27, 28]. Patients treated with (R)-CHOP variants were incorporated in order to include all consecutive patients and avoid a major source of selection bias. Furthermore, their inclusion could only lead to underestimation (and not to overestimation) of the potential superiority of R-CHOP over CHOP.

All patients were retrospectively evaluated with respect to their demographic characteristics and clinical and laboratory findings. Patients were clinically staged using standard procedures with a conservative interpretation of the Ann-Arbor definitions [7]. Stage IV was assigned only if noncontiguous extensive spread of lymphoma to extranodal sites was documented. Contiguous spread within the thorax was considered stage II even in the presence of radiologic chest wall, osseous, lung, pleural, or pericardial involvement [7]. Patients with solitary lung lesions that were adjacent (proximal) but not contiguous to the mediastinal mass were also considered “E” and not stage IV [29, 30]. Patients with multiple lung lesions were assigned as stage IV. Risk stratification was based on the aaIPI [31], because the vast majority of patients were aged <60 years (116 of 121, or 96%) (Table 1).

Treatment Strategies and Criteria of Response

Standard CHOP and R-CHOP as well as their variants and MACOP-B were administered as originally described [9, 13,

14, 16]. The treatment plan included six to eight cycles of CHOP-based chemotherapy. The precise number of chemotherapy cycles was determined by the treating physician. Patients with stable or progressive disease were withdrawn earlier at the discretion of the treating physician. G-CSF support was also used at the discretion of the treating physician.

We did not analyze separately the rates of complete remission (CR), unconfirmed CR, and partial remission (PR) because of the potential heterogeneity of these definitions in a multicenter retrospective setting. Patients with <50% reduction in the sum of the products of two perpendicular diameters of all measurable lesions were considered to have stable disease (SD). Progressive disease (PD) was defined as an increase $\geq 25\%$ of any measurable lesion or the appearance of a new one. Early treatment failure was defined as PD or relapse within 6 months from treatment initiation or within 4 weeks from the end of chemotherapy (prior to or at postchemotherapy restaging). Premature treatment withdrawal as a result of SD and switch to salvage therapy was also defined as early treatment failure. Relapsed and refractory patients were treated according to the policy of each participating center.

The addition of involved-field RT to the treatment strategy of responding patients was a decision of the treating physician. However, following the introduction of positron emission tomography (PET) scanning in routine clinical practice, this decision was affected by PET results. Postchemotherapy PET scans were evaluated according to the Revised Response Criteria for Malignant Lymphoma [32, 33].

Endpoints

The main endpoint was freedom from progression (FFP). Other endpoints were the early treatment failure, event-free survival (EFS), OS, and lymphoma-specific survival (LSS) rates. The FFP interval was defined as the time interval between treatment initiation and treatment failure or last follow-up. PD while on treatment, SD, switching to another chemotherapy program or HDT because of an inadequate response, and relapse after CR were considered treatment failures. Two responders to R-CHOP who were forwarded to HDT because of the suspicion of persistent disease were also considered as treatment failures (see below). Patients with toxic deaths while responding were censored at the time of death. The EFS interval was defined as the time interval between treatment initiation and treatment failure, death resulting from any cause, or last follow-up. The OS time was defined as the time interval between treatment initiation and death resulting from any cause or last follow-up. The LSS interval was defined as the time interval between treatment initiation and death resulting from disease-related causes, including toxic death, or last follow-up.

Statistical Analysis

Comparison of the baseline patient characteristics and early progression rates between the two treatment groups was performed by the Fisher's exact test. Survival curves were plotted according to the Kaplan–Meier method [34] and were compared using the log-rank test [35]. The multivariate survival

Table 1. Baseline demographic, clinical, laboratory, and treatment characteristics of patients treated with CHOP with or without RT versus R-CHOP with or without RT

	R-CHOP with or without RT		CHOP with or without RT	
	<i>n</i>	%	<i>n</i>	%
Median age (range), yrs	31.5 (17–73)		32 (18–63)	
Age >60 yrs	4/76	5	1/45	2
Female	49/76	65	32/45	71
Stage III or IV	9/76	12	6/45	13
B-symptoms	25/76	33	15/45	33
Performance status score ≥ 2	13/73	18	13/43	30
Bulky mass (≥ 10 cm)	43/71	61	24/36	67
Elevated lactate dehydrogenase	60/74	81	30/42	71
Anemia	30/76	40	16/41	39
Leukocytosis ($\geq 10 \times 10^9/L$)	17/76	22	12/42	29
Albumin <4 g/dL	26/68	38	15/34	44
Age-adjusted International Prognostic Index score high or high-intermediate risk	16/74	22	12/41	29

All *p*-values were nonsignificant (*p* > .15).
Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP, rituximab plus CHOP; RT, radiotherapy.

analysis was based on Cox's proportional hazards model [36]. Two-sided *p*-values <.05 were considered significant. Statistical analyses were performed using the Statistical Package for Social Sciences (version 11.5 for Windows, SPSS Inc., Chicago, IL).

RESULTS

Patient and Treatment Characteristics

The baseline characteristics of patients treated with R-CHOP with or without RT or CHOP with or without RT were similar (Table 1). Among patients presenting to center #1 (where a DLBCL database was available) in 2002–2009, PMLBCL cases accounted for 8.3% of the total DLBCL and PMLBCL patient population (versus 7.3% reported in the WHO classification [2] and 10.7% reported in the Vancouver series [7]), thus supporting the validity of the PMLBCL diagnosis.

Among the 76 patients in the R-CHOP group, one (1%) died during chemotherapy because of a cerebrovascular event while responding and seven of 75 patients (9%) experienced early treatment failure (Table 2). Notably, one patient with early progression received only the first cycle of R-CHOP; subsequently, she was treated with rituximab plus cyclophosphamide, vincristine, and prednisone (five cycles), omitting doxorubicin because of concerns regarding cardiac toxicity. Sixty-eight patients completed the immunochemotherapy schedule and responded. Among them, 52 (76%) received additional RT at a median dose of 3,600 cGy (range, 2,000–4,625 cGy) and 16 (24%) were followed without further treatment upon decision of the treating physician. In nine of 16 patients, RT was omitted on the basis of a negative PET scan at the completion of R-CHOP (see below).

Among 45 patients included in the CHOP group, one (2%) died as a result of treatment complications while responding and 13 of 44 (30%) experienced early treatment failure (Table 2). In two patients, the definition of early treatment failure was not fulfilled but response status could not be accurately assessed (both progressed later on). Twenty-nine patients completed the chemotherapy schedule and responded. Among them, 14 (48%) received additional RT at a median dose of 3,800 cGy (range, 2,320–5,000 cGy) and 15 (52%) were followed without further treatment upon the treating physician's decision. Finally eight of 29 responders relapsed, for a total of 23 treatment failures.

The median follow-up times of currently alive patients are 48 months (range, 19–122 months) for patients treated with R-CHOP with or without RT and 114 months (range, 41–174 months) for those treated with CHOP with or without RT.

Outcome

The rate of early treatment failure was significantly lower with R-CHOP with or without RT than with CHOP with or without RT (seven of 75, or 9%, versus 13 of 44, or 30%; *p* = .004) (Table 2).

Patients treated with R-CHOP with or without RT had a significantly superior 5-year FFP rate of 81%, versus 48% for those treated with CHOP with or without RT (*p* < .0001) (Fig. 1A). Over the long term, a total of 14 patients failed R-CHOP with or without RT, excluding a single early death resulting from a cerebrovascular event. Seven patients experienced early treatment failure with documented resistant disease or PD and two patients progressed soon after RT (six of them died and three were alive after ASCT). Two patients relapsed after having achieved a neg-

Table 2. Early failures, early deaths, and use of RT in patients with primary mediastinal large B-cell lymphoma treated with CHOP with or without RT versus R-CHOP with or without RT

	R-CHOP with or without RT		CHOP with or without RT	
	<i>n</i>	%	<i>n</i>	%
All patients (<i>n</i>)	76	100	45 ^a	100
Early deaths	1/76	1	1/45 ^a	2
Early treatment failures	7/75	9	13/44 ^a	30
Completed (immuno)chemo and responded	68		29 ^a	
Received RT	52/68	76	14/29	48
Median RT dose (range), Gy	36 (20–46)		38 (23–50)	

Use of RT is reported only for responders to (immuno)chemotherapy (salvage RT excluded).

^aIn two patients, the definition of early treatment failure was not fulfilled but response status could not be accurately assessed (both progressed later on).

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP, rituximab plus CHOP; RT, radiotherapy.

active PET status with chemoimmunotherapy with and without RT (both alive after ASCT). A single patient, who died as a result of surgical complications during a biopsy of a large residual mass that was positive on PET after R-CHOP plus RT, was considered as a failure. As mentioned in **Methods**, two responders who were forwarded to HDT plus ASCT because of suspected resistant disease, but without radiological or clinical PD, were considered as failures. The suspicion of active disease was based on a positive PET scan in one patient and on the presence of a computed tomography (CT) scan–detected residual adrenal lesion in the other. Both those patients remained in long-term remission after ASCT. Of note, both patients treated with R-CHOP-14 experienced treatment failure. All treatment failures occurred within 18 months from treatment initiation.

Among 45 patients treated with CHOP with or without RT, 23 failed primary therapy; all treatment failures occurred within 22 months from treatment initiation. One patient died as a result of treatment complications after three cycles of chemotherapy, while responding.

Among the 37 patients who failed primary therapy, the median times to treatment failure were 5.7 months (range, 3.5–17.7 months) for the 14 patients treated with R-CHOP with or without RT and 4.8 months (range, 2.1–22.0 months) for the 23 patients treated with CHOP with or without RT.

The EFS outcome was also superior with R-CHOP with or without RT than with CHOP with or without RT, with 5-year EFS rates of 80% and 47%, respectively ($p < .0001$) (Fig. 1B).

Patients treated with R-CHOP with or without RT had a 91% 5-year LSS rate, versus a 69% LSS rate for those treated with CHOP with or without RT ($p = .001$) (Fig. 1C). Only seven patients died as a result of disease or treatment-related causes in the R-CHOP with or without RT group, compared with 15 deaths recorded among the 45 patients treated with CHOP with or without RT. The OS outcome was also superior with R-CHOP with or without RT than with CHOP with or without RT, with 5-year OS rates of 89% and 69% ($p = .003$) (Fig. 1D).

Although relatively high, the efficacy of R-CHOP with or

without RT in subgroups of patients with a potentially adverse prognosis was inferior to the already reported results for the whole patient population. In the 16 patients (22% of the total population) with an aaIPI score of two or three, the 5-year FFP and OS rates were 63% and 75%, respectively. In the subgroup of 43 patients (61% of the total population) with bulky masses, that is, ≥ 10 cm, the 5-year FFP and OS rates were 74% and 84%, respectively.

Multivariate Analysis

In order to exclude a potential effect of the distribution of other parameters between the two treatment groups, we performed a multivariate analysis including treatment group, the aaIPI score (2 or 3 versus 0 or 1) and the presence of bulky disease. After adjustment for these factors, the use of CHOP with or without RT was the only strong independent adverse prognostic factor for FFP, with a hazard ratio of 3.4 (95% confidence interval, 1.6–7.2; $p = .001$) in comparison with R-CHOP with or without RT. When performance status and LDH level were included in the model instead of the aaIPI score, CHOP with or without RT remained as an independent adverse prognostic factor for FFP, with a hazard ratio of similar magnitude (data not shown).

Effect of RT

As already mentioned, RT was not equally used among responders to R-CHOP and CHOP (76% versus 48% of patients) (Table 2). However, there was no meaningful or statistically significant difference in the use of RT among patients with and without bulky disease either in the whole patient population or in the two subgroups separately (Table 3). If the analysis was restricted to responders (and the two patients who were not irradiated but were forwarded to salvage chemotherapy and ASCT without having progressed after R-CHOP were excluded), RT administration was not associated with any FFP or OS benefit. As shown in Table 3, the 5-year FFP and OS rates were 93% and 100%, respec-

Figure 1. Comparative outcomes of 76 patients with primary mediastinal large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) with or without radiotherapy and 45 historical controls treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) with or without radiotherapy. (A): Freedom from progression (FFP). (B): Event-free survival (EFS). (C): Lymphoma-specific survival (LSS). (D): Overall survival (OS).

tively, for the 14 R-CHOP responders who were not irradiated, compared with 92% and 96%, respectively, for the 52 R-CHOP responders who received RT (differences not statistically significant). After response to CHOP alone, RT tended to lead to a longer FFP interval but the difference did not reach statistical significance (5-year rate, 79% versus 67%). The OS duration was also not affected.

In order to exclude the possibility that the better outcome of patients treated with R-CHOP than with CHOP could be attributed to the variable use of RT in the two

groups, we performed a separate analysis. Among 15 patients who did not receive RT after response to CHOP, only those who remained in long-term remission ($n = 10$) were included, whereas five patients (those who relapsed) were excluded. In contrast, all 16 patients who did not receive RT after response to R-CHOP were included, so that this analysis included all patients treated with R-CHOP irrespective of RT administration in order to minimize any bias in favor of R-CHOP resulting from the variable use of RT. In this “worst scenario” R-CHOP was again proven to be more ef-

Table 3. Effect of RT in patients with primary mediastinal large B-cell lymphoma responding to immunochemotherapy

	Bulky, <i>n</i> (%)	Progressed, <i>n</i>	5-yr FFP (%)	Died, <i>n</i>	5-year OS (%)
R-CHOP responders (<i>n</i> = 66) ^a	36/62 (58)	5/66		2/66	
Radiotherapy (<i>n</i> = 52)	29/48 (60)	4/52	92	2/52	96
No radiotherapy (<i>n</i> = 14) ^a	7/14 (50)	1/14	93	0/14	100
<i>p</i> -value	>.20		>.20		>.20
CHOP responders (<i>n</i> = 29)	13/22 (59)	8/29		4/30	
Radiotherapy (<i>n</i> = 14)	6/9 (67)	3/14	79	3/14	86
No radiotherapy (<i>n</i> = 15)	7/13 (54)	5/15	67	1/15	93
<i>p</i> -value	>.20		>.20		>.20

^aFigures do not sum to 68 and 16, respectively. As stated in the text, two patients, who were forwarded to salvage chemotherapy and ASCT without prior RT and had not experienced documented disease progression, were excluded from this analysis. Both were cured by ASCT and were counted as failures in the whole analysis, but could not be considered as failures resulting from omission of RT, because RT was omitted because of a medical decision.

Abbreviations: ASCT, autologous stem cell transplantation; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; FFP, freedom from progression; OS, overall survival; R-CHOP, rituximab plus CHOP; RT, radiotherapy.

fective than CHOP, with highly significant differences. The 5-year FFP rates were 81% and 54% ($p = 0.0006$), the 5-year EFS rates were 80% and 53% ($p = .0005$), the 5-year LSS rates were 91% and 68% ($p = .0007$), and the 5-year OS rates were 89% and 68% ($p = .002$), respectively.

The Role of PET Scan

Only patients more recently treated with R-CHOP underwent PET-CT scan evaluation following chemoimmunotherapy and prior to potential subsequent RT. Excluding patients with primary refractory disease, 33 patients who responded to R-CHOP using conventional restaging procedures were evaluated using PET-CT scanning: 18 (55%) achieved a negative PET-CT status and 15 (45%) remained PET positive. Among the 18 patients with a negative PET-CT status, nine received RT (no relapses) and nine were simply followed without further treatment (one of nine, or 11%, relapsed). Among 15 patients with positive PET-CT scans, 13 received RT, one was forwarded to HDT and ASCT, and one was followed without further treatment. Three of 13 patients who received RT (23%) subsequently relapsed and one died as a result of surgical complications, for a total of four failures (31%). Both patients who did not receive RT remained in prolonged remission. The majority of PET-CT scans were performed in a single center, whereas three centers were involved in total. However, it should be noted that PET-CT scanning had not been centrally reviewed at the time of the analysis.

DISCUSSION

Although derived from a very limited number of cases (series of 10–18 patients), preliminary clinical observations from our, as well as other, centers suggested the superiority of R-CHOP with or without RT over CHOP with or without RT, with cure rates $\geq 82\%$ (Table 4) [7, 37, 38]. Those initial findings deserved confirmation in larger series, because the impressive results might have been a result of patient selection, publication bias, or merely chance. The present study demonstrated that

R-CHOP with RT, or even alone, may indeed cure the vast majority of patients with PMLBCL, based on the analysis of 76 patients with adequate follow-up, demonstrating a 5-year FFP rate of 81% and long-term OS rate of 89%. The superiority of R-CHOP with or without RT could not be attributed to RT strategies different from those used in the CHOP with or without RT group.

Apart from the documentation of the benefit of rituximab for PMLBCL, which now appears to be undisputable, the present study focused on patient outcomes using R-CHOP with or without RT per se for this entity, because the published experience with R-CHOP (or rituximab plus chemotherapy) in PMLBCL patients still remains limited, being mainly derived from small patient series (Table 4). In a review of the Vancouver series [7], 18 patients aged <65 years were treated with R-CHOP and RT, achieving a 3-year OS rate of 82%, which is slightly (but not significantly) inferior to those seen with MACOP-B or etoposide, cytarabine, cyclophosphamide, vincristine, prednisone, and bleomycin (VACOP-B). Another study, reported at the 2004 American Society of Hematology (ASH) Meeting (subsequently published in 2007), suggested excellent efficacy using R-CHOP with or without RT (with rituximab administered in various schedules) in 10 patients, with no failures after a 20-month median follow-up [37]. Results, which were similar to those of the Vancouver series, were recently published by a Korean group, reporting 3-year PFS and OS rates of 79% and 83%, respectively, in 21 patients [39]. Attempted comparison with CHOP-treated historical controls failed to show significant differences or was only marginally significant with respect to OS outcomes [7, 39].

In the context of the MabThera International Trial (MINT) [17], 87 patients with good-prognosis PMLBCL (bulky stage I or stage II–IV and aaIPI score of 0 or 1) aged <60 years received six cycles of chemotherapy versus rituximab plus the same chemotherapy (Table 4) [40, 41]. More than 90% of patients received R-CHOP or R-CHOEP; etoposide (R-CHOEP) was used in 45% of these patients

Table 4. Rituximab-based immunochemotherapy in the treatment of primary mediastinal large B-cell lymphoma

Regimen. study	n of patients	RT ^b	3-yr FFP/EFS ^a	3 yr OS ^a
R-CHOP-21				
R-CHOP, Novoselac et al. (2007) [37] (initial abstract, 2004)	10	++	100%	100%
R-CHOP, Vassilakopoulos et al. (2005) [38] (abstract, initial report)	15	+++	100%	93%
R-CHOP, Savage et al. (2006) [7]	18	++	NG	82%
R-CHOP, Ahn et al. (2010) [39]	21	++	79%	83%
R-CHO(E)P, Trneny et al. (2008) [40] and Rieger et al. (2011) [41], aaIPI ≤1; R-CHO(E)P, 43%; R-MACOP-B, 7%	44	++	78%	89%
R-CHOP, Vassilakopoulos et al. (2010) (present study)	76	++	81%	89%
More aggressive regimens				
da-EPOCH-R, Dunleavy et al. (2005) [48] and Dunleavy et al. (2008) [49] (abstract)	40	-/+	93%	100%
R-C ₁₀₀₀ HOP-14 × 4 plus ICE × 3, Moskowitz et al. (2010) [46] (abstract)	54	no	78% ^c	88% ^c
R-CHOP-14, Schneider et al. (2010) [47] (abstract)	23	+++	91%	96%
R-VACOP-B, Avigdor et al. (2007) [44] (abstract)	21	no	84%	~96%
R-MACOP-B, Zinzani et al. (2009) [43]	45	++	84%	80%

Shown are results of published studies (abstracts or full papers) with R-CHOP or more intensive regimens and variable use of RT.

^aSurvival curves generally reach a plateau phase within 2 years.

^bRT given to: -/+, <10%; +, 10%–50%; ++, 50%–75%; +++, >75% of patients.

^cAt 4 years.

Abbreviations: aaIPI, age-adjusted International Prognostic Index; CHOEP, cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone; da-EPOCH-R, dose-adjusted etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone plus rituximab; EFS, event-free survival; FFP, freedom from progression; ICE, ifosfamide, carboplatin, and etoposide; MACOP-B, methotrexate, cytarabine, cyclophosphamide, vincristine, prednisone, and bleomycin; NG, not given; OS, overall survival; R-CHOEP, rituximab plus CHOEP; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-MACOP-B, rituximab plus MACOP-B; RT, radiotherapy; R-VACOP-B, rituximab plus etoposide, cytarabine, cyclophosphamide, vincristine, prednisone, and bleomycin.

[41]. RT was routinely administered to patients with bulky disease, so that 71% of the patients actually received 30–40 Gy mediastinal RT. Similar to our results, the addition of rituximab to chemotherapy minimized the development of primary refractory disease (3% versus 24%; $p = .006$) and resulted in higher 3-year PFS (88% versus 64%; $p = .006$) and EFS (78% versus 52%; $p = .012$) rates, but the OS rate was only slightly greater (89% versus 78%; $p = .16$). Although derived from an unplanned subgroup analysis, these data provide the strongest evidence to date for the superiority of R-CHO(E)P over CHO(E)P in the treatment of PMLBCL patients [41]. However, a significant number of patients with PMLBCL (22%–59% in various studies) actually have a high–intermediate or high risk aaIPI score and do not fall into the patient population examined in MInT.

The present study is the largest one reporting the results of R-CHOP with or without RT in unselected PMLBCL patients. The incidence of primary refractory disease was minimized and >80% of the patients were cured. The results reported herein apply to the whole population of patients with PMLBCL, irrespective of aaIPI score. Some patients were suc-

cessfully salvaged, so that the 5-year OS and LSS rates were 89% and 91%, respectively, significantly higher than those achieved with CHOP with or without RT. Thus, this is the first study to show a superior OS outcome with the addition of rituximab in PMLBCL treatment. This might be simply a result of the much larger patient number included in the present study. Specifically, in the MInT subgroup analysis, the addition of rituximab had only a modest effect on the OS outcome [41]. In addition to patient number, this might be a result of easier salvage of rituximab-naïve patients with rituximab-based salvage therapy, or the potentially superior outcome of patients treated with CHOEP but not rituximab versus CHOP [17, 21, 25], which may have led to a higher OS rate in the chemotherapy-only arm.

Prior to the introduction of rituximab, several groups treated patients with PMLBCL using more intensive regimens, such as MACOP-B, dose-dense regimens, or even front-line consolidation HDT and ASCT [4–12, 23, 24, 42]. Most of those studies showed long-term failure-free survival (FFS) and OS rates of 65%–85% and 70%–88% (usually around 80% and 85%), respectively, which appear much better than the re-

sults obtained with CHOP. However, none of these intensified approaches is now expected to provide results superior to those seen with R-CHOP.

A reasonable question arising from these observations is whether or not rituximab combined with more intensive chemotherapy would further improve the already impressive results achieved using R-CHOP. In a recent study, R-MACOP-B provided very good results, which, however, did not appear to be better than expected with MACOP-B alone [5–7, 9] when both were combined with RT [43]. In another report, wherein R-VACOP-B appeared to be superior to VACOP-B alone, both without RT, the long-term FFS rate for the former was 84% [44]. Furthermore, the Memorial Sloan-Kettering Cancer Center group reported a 78% FFS rate and 88% OS rate following four cycles of high dose R-CHOP-14 and three cycles of ifosfamide, carboplatin, and etoposide without RT [45, 46]. The results of those three studies are absolutely comparable with those achieved using R-CHOP-21 with or without RT, as reported here. Cure rates >90% were also reported at the 2010 ASH Meeting in 23 patients using R-CHOP-14 and RT; however, the favorable patient profile may have played a role in that study [47]. Interestingly, the National Cancer Institute group has presented very encouraging data regarding 40 patients with PMLBCL, who were treated with six to eight cycles of infusional dose-adjusted etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone (EPOCH) plus rituximab (da-EPOCH-R), without routine use of RT [48, 49]. Thirty-nine of the 40 patients did not receive RT. At a median follow-up of 3.3 years the FFS and OS rates were 93% and 100%, respectively, significantly higher than in da-EPOCH-treated historical controls [49]. However, given that R-CHOP-21 with or without RT is associated with an 81% FFS rate and an 89% OS rate, it will be difficult to demonstrate any benefit of intensified chemoimmunotherapy regimens in this rare lymphoma subtype in the context of a randomized trial.

Although there are no data for PMLBCL, the long-term consequences of thoracic RT in Hodgkin's lymphoma patients are well documented. Future studies in PMLBCL patients should probably focus on minimization of the use of RT with the optimal integration of PET scanning in the treatment schedule. Whether more intensive chemotherapy [44, 46, 49] without RT is equivalent or even superior to R-CHOP-21 with PET-CT-guided minimization of RT use should be investigated. In more recent years, we have omitted RT in 16 patients, nine of whom had a negative PET-CT status and had an adequate radiographic response after chemotherapy. Only one of those patients actually relapsed. RT did not appear to improve the outcome of patients responding to R-CHOP over that of nonirradiated responders (Table 3). However the present study cannot adequately address the question regarding the need for RT in the treatment of PMLBCL patients. Limitations include the relatively small number of patients and failure events among responders to R-CHOP as well as the fact that PET-CT scanning was not available during the whole study period and was used to guide RT at the discretion of the treating physician without a prespecified protocol.

CONCLUSION

The present study demonstrated that the original R-CHOP-21 regimen with its low toxicity is much more effective than CHOP and provided results comparable with those of more intensive regimens in a series of 76 unselected patients with PMLBCL. In 24% of responders, RT was omitted without an apparent loss in efficacy, preferably based on a negative PET-CT scan. Thus, we consider R-CHOP for six to eight cycles plus RT as a justified current standard therapy for PMLBCL patients. If patients with a truly adverse prognosis could be identified at diagnosis or early during treatment, more intensive chemoimmunotherapy could be further investigated. However, reproducible prognostic factors will be difficult to demonstrate as treatment becomes more successful. Finally, whether or not RT can be safely omitted either in selected patients based on a negative postchemotherapy PET-CT scan or through the use of more intensive chemoimmunotherapy needs to be investigated.

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