A retrospective analysis of outcomes for primary mediastinal large B-cell lymphoma treated with RCHOP followed by radiotherapy or front-line autologous stem cell transplantation

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ABSTRACT

Objectives: Our aim was to retrospectively investigate the data from our institute the response rate and outcome in patients with primary mediastinal B-cell lymphoma (PMBL) who received the rituximab in combination with CHOP (RCHOP) followed by autologous stem cell transplantation (ASCT) or RCHOP followed by involved field radiation therapy (IFRT).

Methods: Sixty five patients with PMBL received RCHOP as first-line chemotherapy between January 2005 and December 2010. Forty of the 65 patients completed the planned subsequent IFRT after initial chemotherapy. Thirteen of the 65 patients received the front-line ASCT after RCHOP. Twelve patients received RCHOP alone.

Results: Thirty two of the 40 patients who received the RCHOP followed by IFRT have complete remission (CR) or CRu (CR/unconfirmed). All patients have CR or CRu after the ASCT. The progression free survival (PFS) and the estimated overall survival (OS) rate at 5 years for 32 CR/CRu patients in the RCHOP followed by IFRT group were 57 and 65%, respectively, as compared to RCHOP/ASCT group who were 94 and 100%, respectively. For all 65 patients, the age-adjusted international prognostic index (aaIPI) score remained the only predictor of a worse outcome.

Conclusion: The PFS and OS rate of RCHOP/IFRT were found to be unsatisfied. RCHOP/ASCT showed a satisfactory PFS and OS rate.

KEYWORDS
Chemotherapy; mediastinal; lymphoma; radiation; front-line autologous stem-cell transplantation

Introduction

Primary mediastinal B-cell lymphoma (PMBL) is a subtype of diffuse large B-cell lymphoma (DLBCL). It is believed to have arisen from the thymus B-cells. It usually presents with a bulky tumor in the mediastinum that is rapidly progressive, causing local compressive symptoms. Although distant spread is infrequent at presentation, this lymphoma tends to spread to unusual sites such as the liver, kidneys and central nervous system [1].

Early retrospective analysis showed that the dose intensification such as MACOP-B (methotrexate, cytarabine, cyclophosphamide, vincristine, prednisone, and bleomycin) may be superior to CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) in the management of PMBL with regard to progression free survival (PFS) and overall survival (OS) rate [2,3].

Rituximab in combination with CHOP (RCHOP) followed by involved field radiation therapy (IFRT) portended a 3-year OS rate of 87%, which is comparable to survival rates with those more intensive chemotherapy regimens plus radiotherapy [4]. It seems highly likely that Rituximab may abrogate the differences between the intensive chemotherapy regimens and CHOP [5]. However, the choice of a chemotherapy regimen is difficult in the absence of randomized trials that compare different regimens.

RCHOP followed by IFRT is one of the induction treatment strategies for patients with PMBL. The issue of subsequent radiation therapy after RCHOP remains open in the Rituximab era [6]. A recent study reported that RCHOP followed by IFRT is associated with a high rate of primary refractory disease [7]. Treatment failure usually occurs in 10–30% of patients with PMBL, either during initial treatment or within the first 6–12 months
after completion of RCHOP followed by IFRT treatment [8]. Logically, the front-line autologous stem cell transplantation (ASCT) for PMBL needs to be considered.

Early studies show that front-line ASCT has no significant difference in PFS or OS as compared to conventional chemotherapy in aggressive non-Hodgkin lymphoma [9,10]. Recent report shows that RCHOP followed by ASCT may have a beneficial effect in chemosensitive high-risk DLBCL patients compared to RCHOP alone. Unfortunately, the different sub-entities of DLBCL were not performed in these early studies. During the Rituximab era, less data was presented in terms of the role of front-line ASCT in specified PMBL patients. A retrospective analysis of PMBL patients from MSKCC demonstrated the lack of OS, but showed improved PFS with the front-line ASCT [11]. Several other reports also show that the front-line ASCT in chemo-sensitive patients with PMBL were associated with an improved PFS [12]. However, the data related to the treatment strategy for PMBL is still scarce.

We retrospectively analyzed the data from our institute the response rate and outcome in 65 consecutive patients with PMBL who received the RCHOP followed by ASCT or RCHOP followed by IFRT. Further prospective randomized clinical trials are awaited.

**Patients and methods**

Chart reviews were done focusing on patients with PMBL between 2005 and 2010 in our institution. Sixty five consecutive Chinese patients with PMBL were entered this study. The pathological materials of these patients were re-reviewed by two expert pathologists in our institute for diagnostic confirmation and categorization according to the 2008 World Health Organization (WHO) classification [13]. Patients were staged clinically after establishment of diagnosis using the Ann Arbor staging system. Patients with minimal mediastinal involvement as part of a more extensive lymphoma elsewhere were not included in our analysis [14,15]. All the patients were previously untreated and received RCHOP regimen as initial chemotherapy. Frequent monitoring of electrolytes and aggressive correction was consistently done throughout the treatment in order to prevent the tumor lysis syndrome.

Forty of the 65 patients completed the IFRT after RCHOP. The dose ranged from 30.6 to 39.6 Gy (mean dose 36 Gy in 20 fractions). A total of 13 CR or PR patients after RCHOP received front-line ASCT by physician choice and patients consent. The source of stem cells was mobilized from peripheral blood. All received BEAM regimen (Carmustine at a dose of 300 mg/m² in D-6, etoposide at a dose of 200 mg/m²/day for 4 days in D-5 to D-2, Cytarabine at a dose of 400 mg/m²/day for 4 days in D-5 to D-2, Melphalan at a dose of 140 mg/m² in D-1). All of them had successful engraftment. One patient received IFRT 21 days after completion of ASCT (35 Gy in 20 fractions).

Radiological examination of CT for all patients was performed before RCHOP and after the completion of every two cycles of chemotherapy. The mediastinal mass was defined as a bulky disease if it was longer than 7.5 cm in major diameter or occupied more than one-third of the intra-thoracic in diameter measured at the level of T5–6. Early treatment failure was defined as progressive disease (PD) or relapse within 4 weeks from the end of chemotherapy. Because the PET-CT was not performed in all of the 65 patients, we used the standardize response criteria for NHL as Cheson described in 1999 [16]. Toxicity was assessed in each cycle according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

The international prognostic index (IPI) was determined in all patients. In most patients, tumors were measured every 3 months over the first 2 years of the study and every 6–12 months thereafter over the follow-up period in our institute. The survival analysis curves were plotted using Kaplan–Meier. The IPI characteristics of the patients were compared by means of the Wilcoxon rank-sum test. Cox regression analysis was performed to determine the independent contribution of the following variables: age, stage, performance status, stage, extranodal involvement, bulky disease, treatment strategies, B symptoms and aaIPI. Differences were considered significant if the two-

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**Table 1. Clinical characteristic of patients with primary mediastinal large B-cell lymphoma.**

| Characteristic                        | Eligible patients (n = 65) |
|---------------------------------------|---------------------------|
|                                       | n | %             |
| Gender                                |   |               |
| Male                                  | 38 | 58.5          |
| Female                                | 27 | 41.5          |
| Age (y)                                |   |               |
| Median                                | 30 | –             |
| Range 16–75                           | – | –             |
| Stage                                 |   |               |
| I                                     | 23 | 35.4          |
| II                                    | 32 | 49.2          |
| III                                   | 9  | 13.8          |
| IV                                    | 1  | 1.5           |
| Bulky disease                         | 54 | 83.1          |
| B symptoms                            | 36 | 55.4          |
| ECOG performance status               |   |               |
| 0–1                                   | 38 | 58.5          |
| 2–3                                   | 27 | 41.5          |
| Superior vena cava syndrome           | 8  | 12.3          |
| Pleural effusion                      | 10 | 15.4          |
| Pericardial effusion                  | 7  | 8.2           |
| Elevated serum LDH                    | 42 | 64.6          |
| IPI                                    |   |               |
| Low                                   | 39 | 60.0          |
| Low-intermediate                      | 14 | 21.5          |
| Intermediate-high                     | 8  | 12.3          |
| High                                  | 4  | 6.2           |
| aaIPI                                  |   |               |
| Low                                   | 17 | 26.2          |
| Low-intermediate                      | 25 | 38.5          |
| Intermediate-high                     | 17 | 26.2          |
| High                                  | 6  | 9.2           |
tained p-value was <0.05. All analysis was performed using the SPSS software program (SPSS Inc., Chicago, IL, U.S.A.).

Results

Sixty five patients with untreated PMBL from August 2005 to January 2010 in our institute were retrospectively analyzed in the study. The clinical characteristics of the 65 patients were summarized in Table 1. All patients were CD20+ and CD30+ expression. Patients who did not exhibit disease progression received at least four cycles of chemotherapy (4–6 cycles). The median number of cycles of RCHOP was 4.5.

For all patients, the CR, CRu and PR rate was 50 (76.9%), 4 (6.2%) and 8 (12.3%), respectively, adding up to an overall response rate (ORR) of 62 (95.3%) after RCHOP. 2 (3.1%) patients who received less than 4 cycles of chemotherapy had early treatment failure.

After completion of RCHOP, forty patients received subsequent IFRT, thirteen received ASCT and twelve entered the observation or second-line chemotherapy. Overall, for all 65 of the analyzed patients at the end of combined treatment, the median follow-up time was 50 months (range, 4–106 months), with PFS and OS rate at 5 years of 69 and 75%. The median PFS was 96 months (Figure 1a,b).

For 40 patients who were treated with RCHOP followed by IFRT, the CR, CRu, PR and OR rate were 24 (60%), 4 (10%), 10 (25%) and 38 (95%), respectively, after RCHOP and 31 (77.5%), 1 (7.7%), 6 (15.0%) and 38 (95.0%), respectively, after RCHOP followed by IFRT (Table 2). Overall, the median follow-up time of these 40 patients was 59 months (range, 4–116 months), with PFS and OS rate at 5 years of 65 and 67%, respectively. The median PFS was 71 months and median OS was 87 months. The PFS and OS rate did not show a statistically significant difference between the RCHOP followed by IFRT group and the RCHOP only group (5-year PFS: 65% vs. 62%, p = 0.068; 5-year OS: 67% vs. 57%, p = 0.053) (Figure 1c,d). The absolute difference between the OS of these two groups was 10%.

Thirteen of the 65 patients who received the front-line ASCT after completion of chemotherapy had a similar IPI score as the patients who were treated with RCHOP followed by IFRT (p = 0.056 for the IPI low risk, p = 0.077 for Low-intermediate and p = 0.33 for intermediate-high). At transplant, nine patients were in CR, one in CRu and three in PR. After the transplant, twelve patients achieved CR and one achieved CRu. The overall CR rates were 92.3% after such combined treatment. With a median follow-up of 52.5 months, the PFS rate at 5 years was 94% in CR patients, compared with 57% in 32 CR/CRu patients who received RCHOP followed by IFRT (p = 0.028). The median OS in front-line ASCT group was not reached (Figure 1e,f). The OS rate at 5 years for 32 CR/CRu patients in the RCHOP followed by IFRT group was 65%. Twelve patients in the front-line ASCT group remained no disease progression and one had disease progression but was alive at the time of the analysis. This case, at present, is receiving subsequent radiation.

By multivariate Cox regression analysis, the age-adjusted international prognostic index (aaIPI) score remained the only predictor of a worse outcome, statistically related to PFS (p < 0.001) and OS (p = 0.019). The 5-years actuarial PFS rate was 88.7, 69.4, 43.8 and 15.6% for low, low-intermediate, intermediate-high and high risk, respectively. And the 5-years OS rate was 84, 77, 55.5 and 26% for low, low-intermediate, intermediate-high and high risk, respectively (Figure 2).

Discussion

In this study, we retrospectively analyzed the outcomes of the 65 patients with PMBL treated with RCHOP followed by IFRT or by front-line ASCT. The CR rate further improved from 60.0 to 77.5% by the subsequent IFRT. The PFS rate is 65% in the group of RCHOP followed by IFRT compared to 62% in RCHOP alone. The improved overall response by subsequent radiation seemed not transfer to a better PFS and OS rates. RCHOP followed by the front-line ASCT has a satisfied PFS rate.

In the pre-Rituximab era, the intensive chemotherapy followed by IFRT improved the outcome in patients with PMBL compared to chemotherapy alone. However, some other reports show that intensive chemotherapy followed by IFRT did not improve the outcome in patients with PMBL as compared to chemotherapy alone. Lazzarino et al. reported similar rates of intra-thoracic recurrences among patients who did or did not receive radiation [17]. The excellent results obtained in the GELA (Groupe d’Etude des Lymphomes de l’Adulte) study without radiation therapy also raised doubts about IFRT’s necessity [18].

In Rituximab era, some studies show Rituximab plus CHOP followed by IFRT improved the 5-year PFS rates in patients with PMBL compared to those without subsequent IFRT after initial RCHOP induction chemotherapy [19]. RCHOP followed by IFRT was an acceptable protocol for patients with PMBL. On the other hand, some studies showed the opposite results. Research from Korea demonstrated subsequent radiation did not produce a survival difference in terms of OS and PFS regardless of CHOP or RCHOP [4]. Wang et al. did not conclude the positive significant role of subsequent IFRT after anthracycline-based chemotherapy in PMBL patients [20]. More recent single institution data showed good OS rate of 79% by prospective study of dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab (DA-EPOCH-R) without
subsequent IFRT [21]. The subgroup analysis of 40 patients with PMBL who received RCHOP followed by IFRT in our study also did not statistically show the improved PFS and OS rate as compared to the patients without subsequent IFRT. The absolute difference of the OS rate between the two subgroups is 10%. Given the low patient numbers, this finding only indicates the trend of improved OS rate in RCHOP followed by IFRT group. This trend requires further expansion of clinical studies and longer

**Figure 1.** PFS (a) and OS (b) curves of all 65 patients. PFS (c) and OS (d) by RCHOP followed by IFRT or RCHOP only (5-year PFS: 65 vs. 62%, \( p = 0.068 \); 5-year OS: 67% vs. 57%, \( p = 0.053 \)). PFS (e) and OS (f) by RCHOP followed ASCT or IFRT for CR patients from RCHOP induction chemotherapy (5-year PFS: 94 vs. 57%, \( p = 0.028 \); 5-year OS: 100 vs. 65%).

**Table 2.** Response rate by treatment approach.

| Treatment       | No. | CR (%) | CRu (%) | PR (%) | PD (%) | CR/CRu + PR (%) |
|-----------------|-----|--------|---------|--------|--------|-----------------|
| Total           | 65  | 50 (76.9%) | 4 (6.2%) | 8 (12.3%) | 3 (4.6%) | 62 (95.3%)      |
| Chemo + IFRT    | 40  | 31 (77.5%) | 1 (7.7%) | 6 (15.0%) | 2 (5.0%) | 38 (95.0%)      |
| Chemo + ASCT    | 13  | 12 (92.3%) | 1 (7.7%) | 0 (0.0%) | 0 (0.0%) | 13 (100.0%)     |
| Chemo only      | 12  | 7 (58.3%)  | 1 (8.3%) | 3 (25.0%) | 1 (8.3%) | 11 (91.6%)      |

CR, complete remission; CRu, CR/unconfirmed; PR, partial remission; PD, progressive disease. 
Chemo, chemotherapy; IFRT, involved field radiation therapy; ASCT, autologous stem cell transplantation.
follows to confirm. For some of the patients undergoing RCHOP, insufficient tumor mass reduction might have been over-treated by radiation. In fact, a residual mass by CT evaluation at the site of the often bulky primary disease is often the extensive sclerotic proliferation compared to other aggressive large B-cell lymphomas. Radiotherapy theoretically had the negative impacts to the PFS or OS rate in the PMBL patients who had only extensive sclerotic proliferation. Furthermore, patients with PMBL always occur in young people, and have long disease remission after comprehensive treatment. Therefore, the incidence of second malignancies and long-term cardiac disease after chest radiation should still be further investigated [2]. Conclusions about cardiac toxicity require a follow-up of 15 years or more [22]. In recent years, 3-dimensional conformal and image-guided intensity modulated RT gave excellent dose coverage and a favorable prognosis, with mild toxicity in patients with early stage mediastinal lymphoma [6]. But the data was still scarce, and the patients need a long follow-up period.

Relative worse PFS and OS rates compared with some of other related study [23,24] have some reasons. Firstly, our consecutively cases included in this study had stage III–IV patients (15.3%). Secondly, bulky disease accounted for 83.1%. Finally, the patients with ECOG performance status 2–3 accounted for 41.5% in our study. Although the role of IPI is important to predict the outcome in patients with DLBCL, in PMBL patients, it is not very clear because of the different clinical and pathological characteristics as compared to patients with DLBCL. In our study, the aaIPI score was the only predictor of a worse outcome.

Meanwhile, PET-CT seems very useful in the evaluation of the distant spread of PMBL [25]. The negative PET-CT is an excellent outcome predictor for patients with PMBL after treatment, but for active residual masses, it remains debatable [26]. In our retrospective analysis, only 10.7% patients with PMBL had base-line PET-CT results. Less than 15% of the patients had PET-CT results after first-line chemotherapy. In addition, biopsy for PET-CT positive patients was not done. Hence, in order to avoid the statistical bias, analysis in our study did not include the data of PET-CT information.

Although some groups [22] report excellent results with R-CHOP, recent prospective studies have suggested that patients with PMBL have improved outcomes by regimens of increased dose intensity, such as the DA-EPOCH-R regimen [21]. ASCT obviously allowed for the delivery of high dose chemorhapy with stem cell rescue and may result in the improved outcomes in PMBL. Recent reports indicate the ASCT was effective and could be curative after relapsed or refractory disease in patients with PMBL [27]. However, major studies were still lacking, and the role of front-line ASCT had not been well recognized in patients with PMBL. In pre-Rituximab era, there was no good evidence to recommend a front-line ASCT to be a consolidate treatment, even in poor risk patients with PMBL. Some retrospective reports reviewed that front-line ASCT should not be a choice in first CR patients [28]. On the other hand, some study showed the front-line ASCT was associated with improved PFS without an OS advantage in patients with PMBL [11]. The integrated chemotherapy, front-line ASCT and radiotherapy in poor prognosis PMBL result in a high incidence of durable remissions [29,30]. Rodriguez et al. published the excellent OS rates among patients with PMBL treated with intensive chemotherapy followed by ASCT [31]. In the Rituximab era, RCHOP improved the outcome of the patients with PMBL compared with CHOP alone. Rituximab may abrogate the differences between the intensive chemotherapy regimens and CHOP. In terms of subsequent radiation, the high response rate by consolidative IFRT had not brought

![Figure 2. Separate line of the aaIPI by Cox multivariate analysis: PFS (p < 0.001) (a) and OS (p = 0.019) (b).](image-url)
about a better PFS and OS in this entity. But a recent study demonstrated that front-line ASCT showed superior PFS and a trend towards favorable OS compared to R-CHOP alone [32].

Our analysis showed a definite statistically significant difference of prolonged PFS rate and a strong trend of prolonged OS rate by front-line ASCT in comparison with the patients who received the RCHOP followed by IFRT in patients with CR after initial chemotherapy. It is certainly an issue in our retrospective study about the selection bias of patients who received the ASCT. All patients with PMBL in our institution received RCHOP introduction chemotherapy. Most of them received subsequent IFRT based on our institutional protocol. In fact, bulky disease accounted for 83.1% in our cohort. We use the 32 CR/CRu patients in RCHOP followed by IFRT group as the control of ASCT group. However, it was still difficult to conclude that the front-line ASCT was better than non-ASCT patients because of small sample size in ASCT group. In fact, it was also difficult to enroll more patients in our study who have received the front-line ASCT because it is not an acceptable standard strategy at present in treating PMBL. Currently, to our knowledge, no other prospective randomized clinical trials were conducted to demonstrate which one is better in terms of chemotherapy plus radiation vs. chemotherapy plus ASCT. Random clinical trials to compare chemotherapy followed by IFRT vs. chemotherapy followed by the front-line ASCT are worth being conducted.

Our analysis showed that RCHOP chemotherapy followed by IFRT improved the ORR compared to those treated with RCHOP alone. But the additional IFRT had not transferred the favorable ORR to a better PFS rate. Front-line ASCT showed superior PFS, a strong trend towards favorable OS compared to RCHOP plus IFRT. A study with a longer follow-up period is required to better define the outcomes of RCHOP-based combined treatment of PMBL. In the future, prospective and multicenter studies are needed.

Disclosure statement
No potential conflict of interest was reported by the authors.

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