Radiotherapy after immunochemotherapy improves outcomes in patients with primary mediastinal large B-cell lymphoma

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Abstract
Objective: Primary mediastinal B-cell lymphoma is a rare and unique type of non-Hodgkin's lymphoma that develops more frequently in younger patients and women. The combination of immunochemotherapy and radiotherapy (RT) has been suggested as the primary treatment choice. However, no consensus has been reached. Thus, we carried out an open-label clinical trial. Patients with complete response after six cycles of immunochemotherapy were randomized to receive or not receive RT (control group).

Methods: From July 2004 to December 2012, 324 patients with primary mediastinal B-cell lymphoma were enrolled and randomized at 1:1, with 164 and 160 patients in the RT and control groups, respectively.

Results: The 5-year progression-free survival was 84% (95% confidence interval [CI] 77–89%) in the RT group and 67% (95% CI 60–76%) in the control group (P < 0.01). The 5-year overall survival was 86% (95% CI 79–96%) in the RT group and 68% (95% CI 60–74%) in the control group (P < 0.01). Toxicity was minimal and well controlled. No late toxicities were observed.

Conclusion: RT as adjuvant treatment in patients with complete response after six cycles of immunochemotherapy improved the progression-free survival and overall survival with minimal toxicities.

KEYWORDS
diffuse large B-cell lymphoma, immunochemotherapy, primary mediastinal lymphoma, radiotherapy

1 | INTRODUCTION

Primary mediastinal large B-cell lymphoma (PMBCL) has specific pathological features and clinical presentation. It develops more frequently in younger patients (age <40 years) and women, and generally involves bulky disease (tumor mass >10 cm) in the mediastinum. Although there are multiple therapeutic approaches, to date, there has been no clear consensus regarding the best treatment.¹ ³ Initial studies with standard regimens for diffuse large B-cell lymphoma used an anthracycline-based regimen: cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), but overall survival (OS) was extremely poor. Treatment for PMBCL also uses CHOP; however, in most studies, OS was again extremely poor.⁴ ⁵ A recent series with dose-intense regimens obtained positive outcomes in these groups of patients; however, most studies included a small sample size and short follow-up period.⁶ ¹³ Additionally, some reports showed that the addition of rituximab (RCHOP) can improve the results; however, these were retrospective analyses or had a small number of patients, precluding definitive conclusions.¹⁴ ¹⁵ The efficacy of radiotherapy (RT) in PMBCL with bulky disease is controversial, and some studies have shown no clear advantage on OS.¹ ³ ¹³ ¹⁴ However, these studies were carried out in the pre-rituximab era, and no controlled studies have been performed. Thus, no consensus has been reached so far on the best treatment for this group of patients.⁸ ¹⁶

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Recently, Dunleavy et al. used dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin (EPOCH) chemotherapy and reported improved OS; but subsequent studies did not confirm these results. Furthermore, severe acute toxicities, in some cases grade 4, often requiring hospitalization that increase the cost of treatment, without improving the outcomes, were observed. At our institution, we previously showed, in a small controlled clinical trial, that the use of RT as adjuvant treatment in patients with complete response (CR) after chemotherapy improves progression-free survival (PFS) and OS; however, the trial was carried out before the introduction of rituximab. Thus, we carried out an open-label clinical trial to examine the effects of adjuvant RT in patients with CR after receiving immunochemotherapy.

2 | METHODS

Between July 2004 and December 2012, patients diagnosed with PMBCL according to the World Health Organization were considered candidates for receiving adjuvant RT for mediastinal bulky disease (tumor mass >7 cm) if they met the following criteria: age >18 years; no sex difference; no previous treatment; no severe associated disease; negative results for HIV, hepatitis B and C infections; performance status <3 according to the Eastern Cooperative Oncology Group criteria; and normal hepatic, renal, pulmonary, and cardiac functions, and B-cell immunophenotype and CD20+. Patients with stage III and IV PMBCL, including those with central nervous system infiltration, were excluded.

Baseline staging procedures included the following: complete physical examination; complete blood counts including platelet, renal, and hepatic tests; serum determination of lactic dehydrogenase and beta-2 microglobulin levels; HIV, hepatitis B and C virus tests; and computed tomography of the neck, thorax, abdomen, and pelvis. Positron emission tomography could not be carried out, as it is not available at our institution. Cardiac function was evaluated with 2-D echocardiography, and bone marrow aspiration and biopsy were also carried out.

All patients received the planned RCHOP chemotherapy: cyclophosphamide 750 mg/m², intravenous (iv), on day 1; doxorubicin 50 mg/m², i.v., on day 1; vincristine 2 mg, standard dose, i.v., on day 1; and rituximab 375 mg/m², i.v., on day 1; and prednisone 60 mg/m², oral, days 1–5. Each cycle was administered every 21 days, if hematological tests showed a granulocyte count >1.5 × 10⁹ and a platelet count >100 × 10⁹. After six cycles, patients were carefully evaluated, which included computed tomography of the thorax.

Response criteria were assessed according to international standard criteria at the initiation of the study. Patients who achieved CR were randomized in a sequential and consecutive proportion 1:1 to receive or not receive RT (control group). The mean time to RT after initial treatment was 2–6 weeks (median 4.9 weeks). RT comprises 30 Gy in 20 fractions, in 4 weeks, delivered to the middle plane of the mediastinum, using megavoltage parallel-oppose field to the involved regions, with an adequate safety margin. The study was carried out in compliance with the Declaration of Helsinki, and approved by our institutional review board (HO-2004/2). All patients provided written informed consent to participate in the study.

2.1 | Statistical analysis

Clinical parameters at the time of each patient’s entry into the trial were prospectively recorded. Differences in baseline characteristics between patients treated with adjuvant RT and those in the control group were evaluated using Fisher’s exact test for categorical variables. PFS was calculated from the date of diagnosis to the date of relapse, disease progression, or death from toxicity. OS was defined in all patients as the time from the date of diagnosis to the date of death; survivors were censored at the date of last follow up (December 2017). Prognostic factors associated with PFS and OS were analyzed using a Cox model: age, sex, stage, International Prognostic Index, and tumor size.

3 | RESULTS

A total of 463 patients were initially treated with RCHOP; all received the planned six cycles. Given that the hematological toxicities were grade I or II, no reduction in doses was necessary. A total of 324 patients (69%; 95% confidence interval [CI] 59–74%) achieved CR. Of these, 164 received RT and 160 did not.

Table 1 shows the clinical and laboratory characteristics of the enrolled patients. No statistical differences were observed between the two groups. The median follow-up duration in the study was 98.8 months (range 69–138 months). The pattern of relapse is presented in Table 2. Relapse occurred statistically more often in patients who did not receive RT compared with those who did receive RT.

The 5-year PFS in the actuarial curves was 84% (95% CI 77–90%) in the RT group, which was statistically greater than that in the control group (67%, 95% CI 60–76%; P < 0.01). OS was also statistically higher in the RT group (86%, 95% CI 79–96%) than in the control group (68%, 95% CI 60–74%; P < 0.001). Toxicity secondary to RT was minimal and well controlled. A total of 17 patients developed cutaneous grade I lesions, and three patients had dysphagia for 2 weeks, but they continued to eat. To date, no evidence of cardiac toxicity or second neoplasm and acute leukemia has been observed. The univariate analysis showed that age, sex, and tumor size were not significantly different, and only RT showed a statistically significant difference (data not shown).

4 | DISCUSSION

In this group of patients with newly diagnosed PMBCL and adverse prognostic factors, such as bulky disease, we assessed the effect of consolidative RT on the outcome of patients who were initially treated with RCHOP and achieved CR after six cycles of immunochemotherapy. We observed improvements in the outcomes, with longer PFS.
TABLE 1  Main clinical and laboratory characteristics

| Radiotherapy | Yes | No (% | P |
|--------------|-----|-------|---|
| n            | 164 (100) | 160 (100) | |
| Age (years) median | 34.6 | 36.0 | 0.88 |
| Range | 26–49 | 23–50 | |
| Sex | | | |
| Male | 80 (48.7) | 76 (47.5) | 0.75 |
| Female | 84 (51.2) | 84 (52.5) | 0.666 |
| Stage I | 69 (42.0) | 70 (43.7) | 0.80 |
| Stage II | 95 (57.9) | 90 (56.2) | 0.60 |
| IPI* | | | |
| 0,1 | 61 (37.1) | 56 (35.0) | |
| 2 | 76 (46.3) | 80 (50) | |
| 3 | 27 (16.4) | 24 (15) | 0.489 |
| LDH** | | | |
| Normal | 84 (51.2) | 76 (47.5) | |
| High (>2 N) | 80 (48.7) | 84 (52.4) | 0.213 |
| Tumor mass (cm) | | | |
| 7–10 | 45 (27.4) | 70 (43.5) | 0.08 |
| >10 | 119 (72.5) | 90 (56.2) | 0.05 |
| Performance status | | | |
| 0,1 | 38 (23.1) | 45 (25.6) | 0.90 |
| 2 | 82 (50.0) | 77 (48.6) | 0.88 |
| 3 | 44 (26.8) | 42 (26.5) | 0.90 |

IPI, International Prognostic Index; LDH, lactic dehydrogenase.

TABLE 2  Relapse pattern

| Radiotherapy | Yes (%) | No (%) | P |
|--------------|---------|--------|---|
| Mediastinal  | 1 (0.6) | 36 (21.4) | <0.001 |
| Lung | 4 (2.3) | 5 (3.1) | 0.33 |
| Extrathoracic | 20 (11.5) | 18 (11.8) | 0.55 |
| Total | 25 (15.2) | 59 (36.8) | <0.001 |

and OS in patients who received adjuvant RT. To date, no standard treatment has been defined in this patient group.\(^{7-15}\) RCHOP therapy has been considered the gold standard in nodal diffuse large B-cell lymphoma, but its usefulness has not been confirmed.

Recently, Dunleavy et al., who reported the results on the use of adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin (R-EPOCH), suggested that this regimen could be considered the best treatment for PMBCL.\(^{16}\) However, their study showed an excessive number of acute toxicities, such as granulocytopenia grades III–IV, infection-related granulocytopenia, and death, prolonged hospitalization, and increased costs. Furthermore, the number of patients was small, and the follow-up duration (2 years) was extremely short to draw a definitive conclusion. Woesman et al. in an editorial letter considered that their results were not conclusive.\(^{17}\) Shah et al. carried out a multi-analysis that compared RCHOP with dose-adjusted R-EPOCH. They found no differences in OS at 2 years, 89% in patients treated with RCHOP versus 91% in those treated with R-EPOCH. They suggested that these findings highlight the significant influence that journal reports have on the clinical practice of providers, even in the setting of a non-randomized, single-arm study.\(^{18}\) RT in PMBCL has been controversial because, in small non-controlled studies, adjuvant RT did not improve the outcomes.\(^{11,13-15}\) Recently, Giri et al. and Jackson et al. reviewed the use of RT and observed that RT improved the outcomes.\(^{20-22}\) However, no controlled studies were found. The reluctance to use RT is also based on the risk of cardiac and lung toxicities. However, Pugh et al. have reported the results of a surveillance study from which they concluded that only increased anthracycline doses were associated with an increase in cardiac deaths.\(^{23}\) Furthermore, in the present study, we did not observe any evidence of late cardiac or lung toxicities.

In the present study, which to our knowledge is the first controlled clinical trial of RT, we observed that RT is important in the treatment of PMBCL because, given that relapse occurs more frequently in bulky disease, we showed better PFS and OS in patients who received RT compared with those in patients who did not receive RT, without severe toxicities. Furthermore, the use of rituximab did not preclude the use of RT in this patient setting. In a recent retrospective study, it was proposed that stem cell transplant could be beneficial, but the number of patients was small, and the follow-up period was extremely short to draw definitive conclusions.\(^{24}\)

5 CONCLUSION

Adjuvant RT is useful, and leads to increased PFS and OS compared with RCHOP therapy alone. We suggest that RT should be considered in the initial treatment of these patients.

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CONFLICT OF INTEREST

The authors declare that they had read the article and there are no competing interests.

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