Retracted article: Adjuvant radiotherapy in patients with diffuse large B-cell lymphoma in advanced stage (III/IV) improves the outcome in the rituximab era

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ABSTRACT

Objectives: To assess the efficacy and toxicity of adjuvant radiotherapy (RT) in patients with diffuse large B-cell lymphoma (DLBCL) and nodal bulky disease, on complete response, after six cycles of RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone), we began to evaluate high-dose chemotherapy in a large cohort with longer follow-up to evaluate the outcome measured from progression-free survival (PFS) and overall survival (OS).

Patients and methods: Between 2006 and 2010, 258 consecutive patients with DLBCL and nodal bulky disease (tumor mass >10 cm) were randomly assigned to receive either RT (involved field, 30 Gy) (127 patients) or no (control group) (131 patients).

Results: The actuarial curves at 5 years of PFS were 87% (95% confidence interval (CI): 72–97%) in the RT group, which was significantly different from the control group value of 45% (95% CI: 34–60%) (p < 0.001); also OS in the RT group was significantly better than that in the control group: 91% (95% CI: 84–99%) and 59% (95% CI: 52–66%), respectively (p < 0.001). RT was well tolerated, acute toxicity was mild and until now late toxicity did not appear.

Conclusions: The use of adjuvant RT in patients with DLBCL and nodal bulky disease improves the outcome with PFS and OS, with minimal toxicity; thus, we felt that adjuvant RT will be considered as a part of the initial treatment in this setting of patients, even in the rituximab era.

KEYWORDS

Diffuse large B-cell lymphoma; diffuse large B-cell lymphoma treatment; radiotherapy; rituximab

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma, modern treatment with chemoimmunotherapy: CHOP-R (cyclophosphamide, doxorubicin, vincristine and prednisone) can be curative about 60% of patients, but relapse is frequent; and these patients require aggressive salvage chemotherapy, including stem cell transplant.

Although bulky disease was not considered to be an adverse prognostic factor in the International Project Index (IPI) actually, data continue to emerge in the treatment of patients with DLBCL, which suggested that the benefit of consolidative RT in improving local control, progression-free survival (PFS) and potentially overall survival (OS) [1–18]. We previously evaluated the efficacy of RT in patients with DLBCL, at higher clinical risks and additionally the presence of bulky nodal disease (nodal tumor mass >10 cm), and show that RT improves PFS and OS; however, these studies were performed in the pre-rituximab era [19,20]. In the present study, we examined the effects of consolidative RT in patients who were in complete response (CR) after receiving six cycles of CHOP-R.

Patients and methods

The study included data of patients who were diagnosed with DLBCL, in advanced stages III and IV, and with nodal bulky disease, treated with RCHOP between 2006 and 2010. The primary endpoints were to assess the PFS and OS, and the secondary endpoints were to assess late toxicity secondary to radiotherapy (RT). All patients provided written, informed consent in accordance with the Declaration of Helsinki. The study was approved by our institutional review board.

The criteria to be included in the study include: aged between >18 and <60 years, have untreated DLBCL, advanced disease stage according to the Ann Arbor Classification (III/IV), an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0–2, nodal bulky disease (tumor mass >10 cm), high or high–intermediate clinical risk according to the IPI, and adequate organ function. Patients that were pregnant or breast-feeding, or if they had evidence of central nervous system were excluded.

Patients with partial response (PR) were not considered candidates because when the study was performed, Positron-emission tomography (PET) was not available in our study, and the presence of minimal residual disease was very difficult to evaluate if these
changes were residual tumor or fibrosis, biopsy could be considered, but in most cases, it requires surgery, and we treated this setting of patients as residual disease, with more intensive RT; thus, we felt that it could be a bias.

Baseline staging procedures including: biopsy to be proven DLBCL, complete blood counts, serum chemistry, serum determinations of lactic dehydrogenase and beta 2 microglobulin, serologic test for immunodeficiency syndrome, hepatitis B and C virus, bone marrow aspiration and biopsy. Left ejection ventricular test (LEVT, normal values >50%), was performed before and after treatment, and repeated at 6, 12, 18, 24, 48 and 60 months to evaluate cardiac toxicity. Computed tomography of neck, thorax, abdomen and pelvis, and gallium scan was conducted.

**Treatment**

All patients received six cycles of RCHOP, which consisted of rituximab 375 mg/m², intravenously (IV) on Day 1; cyclophosphamide 750 mg/m², IV on Day 1; adriamycin, 50 mg/m², IV on Day 1; vincristine 1.4 mg/m², IV on Day 1 and prednisone 75 mg standard dose, orally on Days 1–5; each cycle was administered every 21 days, by 6 cycles. Granulocyte colony-stimulating factor was employed at 5 µg/kg/day on Days 5–15 to avoid the possibility of severe granulocytopenia. Before each cycle was started, the absolute granulocyte count and platelet count needed to recover to >1000× mm³ and 100,000× mm³, respectively. In addition, non-hematological toxicity will be <2 grade. If the toxicity grade is III or IV, reduced doses of cyclophosphamide and/or doxorubicin were considered.

**Toxicity and response evaluation**

Toxicity grades were based on Common Terminology Criteria for Adverse Events, and assessed from the initiation of the regimen until the end of chemotherapy. Response was evaluated upon either completion or termination of chemotherapy and was coddred as CR, PR, stable disease or progression disease, as determined by the International Working Group criteria. The time of each patient’s entry into the clinical trial was registered prospectively. Differences in baseline characteristics between patients treated with adjuvant RT and those in the control group were evaluated using Fisher’s exact test for variables in categorized forms. PFS was calculated from the date of diagnosis to the date of disease progression or death from toxicity. OS was measured from the date of the end of treatment to the last observation or death from any cause. The survival function was estimated using the Kaplan–Meier method and the comparison between survival curves was performed with Cox’s proportional univariate and multivariate analysis. The study was intended to observe a difference of 15% in OS and thus, we planned to recruit 182 patients in each group; however, an interim analysis (June 2008) showed that patients who did not receive RT have early relapse; the Ethical Committee of our institution suggested closing the study and the follow-up of the treated patients will be continued.

**Results**

Table 1 shows the diagram flow of the patients; 258 patients were registered: 127 in the RT arm and 131 in the control group. Table 2 shows the characteristics of the enrolled patients; no statistical differences were observed between the two groups.

**Treatment**

Four hundred and twenty-four patients with stages III or IV and nodal bulky disease were treated with the RCHOP regimen; CR was achieved in 258 cases (61%). All patients received the planned six cycles. Reduced doses were considered in 12 cycles (7 patients).

**Safety**

Granulocytopenia grade 3 was observed in five patients and thrombocytopenia grade 3 was observed in two cases. Three patients developed a decrease in LEVF, but until now, no clinical evidence of cardiac failure has been observed and LEVF returned to normal values between 7 and 14 months after treatment. So far, no acute leukemia or second neoplasm has been observed.

**Efficacy**

The median follow-up of the study was 56.8 months (range 63–98 months). Table 3 includes the PFS and OS experience of this cohort. Local, disseminated and
total recurrences were statistically worse in the patients who did not receive RT compared to the RT group. RT improves PFS because actuarial curves at 5 years were 87% (95% confidence interval (CI): 72–97%), which is statistically different from patients who did not receive RT: 45% (95% CI: 34–60%) \( (p < 0.001) \); OS was also statistically higher in the RT group (91% (95% CI: 84–99%)) than that in the control group (59% (95% CI: 52–66%) \( (p < 0.0001) \)).

The univariate and multivariate analysis of prognosis factors associated with OS showed that only the use of RT had a favorable impact on these aspects of patients (Table 4).

**Table 1.** Treatment diagram flow.

| DLBCL, STAGES III/IV: | 612 cases |
|-----------------------|-----------|
| Excluded: 188 cases   |           |
| No bulky: 184         |           |
| Refused treatment: 3  |           |
| Die, before treatment: 1 |         |

| Bulky disease: 424 cases |
|--------------------------|
| Treated: RCHOP: 424 |
| Complete response: 258 (61%) |
| Radiotherapy |
| Yes | 127 |
| Not | 131 |

**Table 2.** Baseline characteristics.

| RCHOP + RT | RCHOP |
|------------|-------|
| No. (%)    | p     |
|-------------|-------|
| Total       | 258 (100) | 131 (51) | 0.8 |
| Age, median (years) | 52.9 | 50.7 | 53.8 | 0.3 |
| Range       | 39–60 | 40–60 | 39–60 | 0.5 |
| Male sex    | 140 (54) | 65 (51) | 75 (57) | 0.6 |
| Stage III   | 68 (26) | 32 (25) | 36 (27) | 0.5 |
| IV          | 190 (73) | 95 (75) | 93 (73) | 0.6 |
| IPI         | High–intermediate | 82 (32) | 39 (30) | 43 (33) | 0.2 |
| High        | 176 (68) | 88 (69) | 88 (67) | 0.8 |
| Site of bulky disease | Neck | 46 (18) | 25 (19) | 21 (16) | 0.56 |
|            | Axilla | 11 (4) | 4 (3) | 7 (5) | 0.41 |
| Abdomen*   | 201 (78) | 98 (77) | 103 (77) | 0.8 |
| Performance statusb | 0.1 | 16 (6) | 7 (5) | 9 (7) | 0.75 |
| 2          | 242 (94) | 120 (94) | 122 (93) | 0.9 |
| Bone marrow involved | 76 (29) | 37 (20) | 39 (22) | 0.4 |

*Including retroperitoneum.

*According to the Eastern Cooperative Oncology Group.

**Table 3.** Outcome.

| RCHOP + RT | RCHOP |
|------------|-------|
| (95% confidence interval) | p     |
| Local recurrence | 0 | 18 (9–31%) | <0.001 |
| Distant recurrence | 7 (2–16%) | 5 (1–9%) | 0.66 |
| Local and distant recurrence | 9 (2–17%) | 36 (24–45%) | <0.001 |
| Total recurrences | 16 (6–29%) | 59 (43–69%) | <0.001 |
| PFS* | 87 (72–94%) | 45 (34–64%) | <0.001 |
| OS* | 91 (84–99%) | 59 (44–67%) | <0.001 |

Note: PFS: progression-free survival; OS: overall survival.

*Actuarial curves at 5 years.
Discussion

In this cohort of patients with newly diagnosed DLBCL with adverse prognostic factors such as high clinical risks and the presence of nodal bulky disease, we examined the impact of consolidative RT on the outcome among patients who were treated initially with RCHOP, and adding RT or not RT, as consolidation treatment. We observed improvement in the outcome with better PFS and OS, in patients who received adjuvant RT.

Recently, clinical reports indicated that adjuvant RT could improve the outcome in patients who were treated with RCHOP, but, in all instances, retrospective analysis and definitive conclusions were difficult to be drawn for different reasons [1–8]. Dabaja et al. performed a national review on the use of RT in the rituximab era and they mentioned several biases: RT was predominantly given to patients with limited-stage disease, the patients were treated across several institutions that compliance with intendent treatment might have been unaccounted, and the heterogeneity was also inherently difficult to control. This is because the indication of RT was based on the clinical decision of oncologist, and therefore varied among institutions. Moreover, not all studies were randomized, and all indicate the reason to employ RT [17].

To the best of our knowledge, there are no studies on patients with diagnosis of DLBCL who were in complete remission, after RCHOP, in the rituximab era. In the modern treatment of patients with DLBCL, there is an ongoing debate about the use of adjuvant RT, and its usage is actually diminished. Vargo et al. [21] reported a study with 59,255 patients demonstrated that the use of adjuvant RT declines from 47% in 2000 to 32% in 2012; in their study, in patients who received adjuvant RT, OS was significantly better in the combined modality arm compared to the chemotherapy arm alone.

Some of the risks of employing RT are the possible appearance of late complications such as acute leukemia or second neoplasm. In our cohort, neither of these complications has been observed. Three patients showed below-normal levels of LEVF, but, until now, no clinical evidence of cardiac failure has been observed.

One potential bias is that we did not employ modern techniques to evaluate response, and in some cases, the confirmation of CR was based on computed tomography, but as mentioned, Positron tomography was not available when we began the study. Recently, Valls et al. [22] mentioned that no data are currently available demonstrating that a Positron-tomography-guided change in treatment improves the patient’s outcome, and recommended biopsy confirmation of an abnormal study’s findings before changing therapy; obviously, taking a biopsy of the abnormal site is not possible. Rahman et al. [23] observed that the addition of RT improved PFS significantly independent of whether the PET is positive or negative. It appears that in the case of residual nodal disease in patients with bulky disease, the use of Positron tomography remains unsolved. Other points could be that our population was more younger than that in other reports, a scientific explanation we did not have; our Meztiso population is different; and we have more advanced stages, more higher clinical risks, probably the population in our country is more younger than Caucasian population, but it is a hypothesis. We decide to treat younger patients (<60 years) because they did not have experience with aggressive treatments, and employ a combined therapy that includes chemoimmunotherapy and RT, which could be dangerous to older patients.

Thus, we concluded that even in the rituximab era, the use of RT can be of benefit to patients with bulky disease because RT seems to reduce the risk of death or treatment failure. Rituximab minimized but did not eliminate the adverse prognostic effects of bulky disease on the outcome. Thus, we suggested that adjuvant RT should be a considered part of the total treatment in patients with advanced-stage DLBCL with nodal bulky disease because it is of benefit to these patients with and without minimal toxicity.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

[1] Phan J, Medeiro LJ, Zreik TG, et al. Benefit of consolidative radiation therapy in patients with diffuse large B-cell

Table 4. Univariate and multivariate analysis from overall survival.

| Comparison | Univariate | Multivariate |
|------------|------------|--------------|
|            | HR | 95% CI | p value | HR | 95% CI | p value |
| Stage: III vs. IV | 1.389 | 0.61–3.6 | 0.56 | 6.14 | 0.901–4.11 | 0.85 |
| Bone marrow Positive vs. negative | 1.111 | 0.48–3.18 | 0.69 | 0.776 | 0.417–1.87 | 0.57 |
| IPI: high vs. Intermediate | 0.940 | 0.51–1.814 | 0.80 | 0.486 | 0.160–1.600 | 0.42 |
| Sex: male vs. female | 0.776 | 0.417–1.871 | 0.57 | 5.83 | 0.61–34.8 | 0.173 |
| Tumor size | 10 cm vs. <10 cm | 0.486 | 0.160–1.600 | 0.42 | 1.173 | 0.901–4.11 | 0.85 |
| RT yes vs. not | 5.83 | 0.61–34.8 | 0.173 | 6.14 | 0.901–4.11 | 0.85 |

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lymphoma treated with RCHOP chemotherapy. J Clin Oncol. 2010;28:4170–4176.

[2] Dorth JA, Prosnitz LR, Broadwater G, et al. Impact of consolidation radiation therapy in stage III/IV diffuse large B-cell lymphoma with negative post-chemotherapy radiologic imagen. Int J Radiat Oncol Biol Phys. 2012;84:762–769.

[3] Held G, Murawski N, Zlepert M, et al. Role of radiotherapy to bulky disease in elderly patients with aggressive B-cell lymphoma. J Clin Oncol. 2014;32:1112–1118.

[4] Marcheselli L, Marschel R, Bari A, et al. Radiation therapy improved outcome in patients with diffuse large B-cell lymphoma. Leuk Lymphoma. 2011;52:1867–1872.

[5] Jagadeesh N, Rajpari R, Esiashvil N, et al. Predictors of local recurrence after rituximab based chemotherapy alone in stage III/IV DLBCL: Guided decision for consolidative radiation. Int J Radiat Oncol Biol Phys. 2015;92:107–112.

[6] Halasz LM, Jacene HA, Catalamo PJ, et al. Combined modality therapy for PET-positive non-Hodgkin’s lymphoma favorable outcome of combined modality treatment for patients with non-Hodgkin’s lymphoma with positive interim or postchemotherapy FGG-PET. Int J Radiol Oncol Biol Phys. 2012;83:e647–e654.

[7] Shi Z, Daz S, Okwan-Duodo V, et al. Patterns of failure in advanced stage diffuse large B-cell lymphoma after complete response to R-CHOP immunochemotherapy and the emerging role of consolidative radiation therapy. Int J Radiat Oncol Biol Phys. 2013;86:569–577.

[8] Cassady RJ, Jagadeesh S, Witchenno J, et al. The role of radiotherapy for patients over age 60 years with diffuse large B-cell lymphoma in the rituximab era. Leuk Lymphoma. 2016;57:1876–1881.

[9] Ng AK, Dabaja BS, Hoppe RT, et al. Re-examining the role of radiation therapy for diffuse large B-cell lymphoma in the modern era. J Clin Oncol. 2016;34:1443–1447.

[10] Shi Z, Esiash V, Flowers C, et al. Renewed interest in the role of consolidation radiotherapy in advanced stage diffuse large B-cell lymphoma. Leuk Lymphoma. 2013;54:2122–2130.

[11] Boyle JM, Beaven AW, Diez LF, et al. Improves outcome in advanced DLBCL. Systematic approaches. Oncology (Willistone-Park). 2014;28:1074–1081.

[12] Hodgson DC, Mikhaelis NT. Consolidation radiation in DLBCL. Evidence-based recommendations. Curr Oncol Rep. 2015;17:49.

[13] Ho C, Deng C, Zou W, et al. The role of consolidative radiotherapy after a complete response to chemotherapy in the treatment of diffuse large B-cell lymphoma in the rituximab era. Results from a systematic review with a meta-analysis. Acta Haematol. 2015;134:111–118.

[14] Flowers CR, Cohen JB, Khan MK. Rebirth of radiotherapy for elderly patients with diffuse large B-cell lymphoma in the rituximab era. Leuk Lymphoma. 2015;56:557–558.

[15] Yahalom J. Radiation therapy after RCHOP for diffuse large B-cell lymphoma. The gain remains. J Clin Oncol. 2016;34:4105–4107.

[16] Khan MS. Bulky aggressive B-cell lymphoma. To irradiate or not irradiate, that is the question. J Clin Oncol. 2014;32:1097–1098.

[17] Dabaja BS, Vanderplas AM, Crosby-Thompson AL, et al. Radiation for diffuse large B-cell lymphoma in the rituximab era. Analysis of the National Comprehensive Cancer Network lymphoma outcomes project. Cancer. 2015;121:1032–1039.

[18] Zimmermann M, Oehler C, Mey V, et al. Radiotherapy for non-Hodgkin’s lymphoma still standard practice and not an outdate treatment option. Radiat Oncol. 2016;11:110.

[19] Aviles A, Delgado S, Nambo MJ, et al. Adjuvant radiotherapy to sites of bulky disease in patients with stage IV diffuse large B-cell lymphoma. Int J Radiat Oncol Biol Phys. 1994;30:799–804.

[20] Aviles A, Fernandez R, Perez F, et al. Adjuvant radiotherapy in stage IV diffuse large B-cell lymphoma. Int J Radiat Oncol Biol Phys. 2004;60:1385–1389.

[21] Vargo JA, Gill BS, Balasubramani GK, et al. Treatment selection and survival outcomes in early-stage DLBCL. J Clin Oncol. 2015;33:3710–3717.

[22] Valls L, Badue L, Auric S, et al. FDG-PET imaging in hematological malignancies. Blood Rev. 2016;30:317–332.

[23] Rahman F, Brady JT, Dunn JT, et al. Consolidation radiation therapy improves outcome of diffuse large B-cell lymphoma independent of treatment prognosis or response to chemotherapy. Int J Radiat Oncol Biol Phys. 2016;96(Suppl 2): S39(abstract 88).