# The role of immunotherapy in the treatment of primary mediastinal non-Hodgkin lymphoma

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**ABSTRACT**

*Based on its clinical, histopathology, molecular, and genetics features, primary mediastinal large B cell lymphoma was selected from the large group of malignant non-Hodgkin large B cell lymphomas, representing about 3% of all B cell lymphomas. Its optimal treatment is evaluated in various studies. It is very important to assign an appropriate protocol, because it has been found that where there is complete remission after first line therapy, late relapse is rarely observed and also because in cases where a relapse or disease progression does occur, salvage therapy has limited effectiveness. It should be noted that with the introduction of immunotherapy the superiority of third generation regimens (VACOP -B) versus CHOP disappeared. Currently, standard treatment in the U.S. is CHOP-like polichemotherapy, in combination with Rituximab, while in Europe most commonly used regime is R-MACOP-B. Other regimes that have been used successfully are EPOCH-R and NHL87.*

**Key words:** primary mediastinal non-Hodgkin lymphoma, Rituximab

## BACKGROUND

Described in 1980 by Lichtenstein and colleagues (1), primary mediastinal non-Hodgkin large B cell lymphoma (PMBCL) is now recognized and described as a distinct entity in both the REAL and WHO classifications (2). Based on its clinical histopathology, molecular, and genetics features it was selected from the large group of malignant nonhodgkin large B cell lymphomas, representing about 3% of all B cell lymphomas. (2)

It occurs mainly in young women, in the third or fourth decade of life, as a tumor in the anterior mediastinum (3). It is characterized by large sizes, over 7-10 cm, rapid expansion and local invasion in the lung, pleura, pericardium and chest wall (4). For this reason, the onset is often noisy, with dyspnea, cough, dysphagia, hoarseness, superior vena cava syndrome, leading to early diagnosis when it is limited to the supradiaphragmatic region (5). At presentation marrow damage is rare. Extranodal damage is common in the event of a relapse of the disease, often affecting the kidneys, adrenal glands, central nervous system, liver, ovaries.

Onset occurs in the thymic medullary B lymphocytes. Tumor cells are medium-sized cells with pale, abundant cytoplasm, with round-oval nuclei and a diffuse growth pattern. They can be divided by bands of fibrosis. Immunophenotyping of B lymphocytes identify B cell antigens, like CD19, CD20, CD22, CD79a. Bcl-2 is expressed in 80% of cases. CD10 is inconsistently expressed; CD30 is weak and non-homogeneously expressed, unlike intense and uniform expression in Hodgkin's disease, the classical form, and

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anaplastic large cell lymphoma. CD21 and surface immunoglobulins are not expressed (2, 6). Distinct chromosomal abnormalities have been reported, among them most frequently gains at 9p and 2p chromosomes, corresponding to JAK2 loci and cREL. (7, 8)

Optimal treatment for primary mediastinal large B cell lymphoma is evaluated in various studies. It is very important to assign an appropriate protocol, because it has been found that where there is complete remission after first line therapy, late relapse is rarely observed and also because in cases where a relapse or disease progression does occur, salvage therapy has limited effectiveness. (9, 10)

Over time, some studies have compared the effectiveness of conventional CHOP protocols with more aggressive regimes such as MACOP / VACOP and the impact of adding immunotherapy to chemotherapy. (4, 9, 10, 11, 12, 13)

In 1993 Lazzarino and colleagues reported a series of 29 patients diagnosed with PMBCL. Out of these 55% (16 patients) achieved complete remission of which 36% (4 of 14 patients treated) achieved complete remission after CHOP chemotherapy and 73% (11 of 15 patients treated) after MACOP-B/VACOP-B chemotherapy. Complete remission was not obtained for the other 13 patients and they did not have any rescue therapy. (14) In 1997 106 patients were reported as diagnosed with PMBCL, of which 99 followed protocols with doxorubicin. 35 patients were not sensitive to chemotherapy.

Out of the 64 patients who presented sensitivity to chemotherapy, 23 achieved complete remission, the others showing a residual mediastinal mass. None of the patients who achieved complete remission showed early relapse. (15)

In 2002, Zinzani and collaborators published the results of a multinational retrospective study, analyzing the responses obtained from patients diagnosed with PMBCL, treated with either conventional chemotherapy (CHOP and CHOP-like) or with the third generation (MACOP B, VACOP B, ProMACECytaBOM) or high dose regimes (autologous bone marrow transplant). (12) The study enrolled 426 patients between August 1981 – December 1999, from 20 institutions. Complete response was obtained when using the CHOP/CHOP like protocol in 49% of patients (50/105), in 51% of patients (142/277 patients) in the case of MACOP B protocol, and 53% of patients respectively (24/44 patients) in high dose protocols. Partial response was obtained in 32%, 36% and respectively 35% of patients. All patients who achieved complete response and 84% (124/142) of those who achieved partial response received radiotherapy at mediastinal level. Reevaluation performed later showed complete response in 61% of patients treated with protocol CHOP/CHOP like, 79% for patients receiving third-generation protocols, and 75% for patients receiving high dose protocols. Relapse after achieving complete response was described in 23% (15/64) of patients receiving chemotherapy CHOP/CHOP - like at 48.5 months, in 12% (27/218 patients) of patients at 51.7 months for those who followed the third generation protocol of and in 0% of patients (0/33 patients) at 32,4 months for those who followed high dose protocol, suggesting that third-generation protocols associated with radiotherapy would be a better option for treatment of primary mediastinal large B cell lymphoma. (12)

The superiority of third generation regimens MACOP B/B-VACOP came to an end with the association of immunotherapy-Rituximab - to CHOP-like chemotherapy.

This has been analyzed in several studies. One of the most recent articles is “Primary mediastinal B-Cell Lymphoma Treated with CHOP-like chemotherapy with or without rituximab: results of the MabThera International Trial Group Study”, published in Annals of Oncology 22, 2011.

This was the first time a prospective study demonstrated that immunotherapy has a substantial role for PMBCL. Patients considered eligible for this study were those aged between 18 and 60 years with aggressive untreated B cell lymphoma with a maximum one risk factor according to aaIPI (Age - Adjusted International Prognostic Index), stage II-IV of disease or stage I with “bulky disease”. Patients received either six cycles of CHOP -like chemotherapy (CHOP-21, CHOEP -21, MACOP-B, and PMitCEBO) and rituximab or CHOP-like chemotherapy alone. Some of the patients with “bulky” disease and with extramedullary disease also underwent radiotherapy (30-40 Gy). The main objective was EFS and the secondary endpoint was the observation of complete responses (CR), unconfirmed complete responses (CRu), progression disease and overall survival. From the 824 patients enrolled in the study, only 714 could be analyzed, because the others had not been confirmed with a large B cell kind of lymphoma. PMBCL was diagnosed in 87 patients, and 44 (51%) of them received chemo-immunotherapy. Of the 627 patients diagnosed with DLBCL, 315 (50%) received chemo-immunotherapy. (Table 1) (16)

*TABLE 1. Distribution of the different treatment regimens (16)*

| | CHOP patients (%) | CHOEP patients (%) | MACOP-B patients (%) | PMitCEBO patients (%) |
|---|---|---|---|---|
| **PMBCL** | | | | |
| All (*n* = 87) | 41 (47.1) | 39 (44.8) | 6 (6.9) | 1 (1.1) |
| Without rituximab | 19 (21.8) | 20 (23.0) | 3 (3.4) | 1 (1.1) |
| With rituximab | 22 (25.3) | 19 (21.8) | 3 (3.4) | 0 |
| **DLBCL** | | | | |
| All (*n* = 627) | 316 (50.4) | 261 (41.6) | 27 (4.3) | 23 (3.7) |
| Without rituximab | 158 (25.2) | 128 (20.4) | 13 (2.1) | 13 (2.1) |
| With rituximab | 158 (25.2) | 133 (21.2) | 14 (2.2) | 10 (1.6) |

*DLBCL: diffuse large B-cell lymphoma; PMBCL: primary mediastinal B-cell lymphoma.*

Of the patients with PMBCL, 31 (72%) achieved complete or partial remission in the CHOP-like arm and 37 (84%) in the R CHOP-like arm. Progression of the disease was observed only for 7 patients in the CHOP-like arm.

Radiation therapy was recommended for 76 (87%) of patients with PMBCL, due to the presence of „bulky disease". In 30% (18/61) of patients who received radiotherapy, there was an improvement in their response. Only 4 patients (7%) experienced disease progression after radiotherapy.

*TABLE 2. Response after chemo (immuno) therapy and before intended radiotherapy. (16)*

| **PMBCL** | **CHOP-like *n* = 43** | **CHOP-like + rituximab *n* = 44** |
|---|---|---|
| Remission status after chemo (immuno)therapy | | |
| CR/Cru | 14 (32.6%) | 23 (52.3%) |
| PR | 17 (39.5%) | 14 (31.8%) |
| NC | 2 (4.7%) | 4 (9.1%) |
| PD | 7 (16.3%) | 0 |
| Death | 0 | 1 (2.3%) |
| Unknown | 3 (7.0%) | 2 (4.5%) |
| RT intended | 39 (90.7%) | 37 (84.1%) |
| RT intended and given | 29 (67.4%) | 31 (70.5%) |
| RT intended and not given | 10 (23.3%) | 6 (13.6%) |
| RT not intended | 4 (9.3%) | 6 (13.6%) |
| RT not intended and given | 0 | 1 (2.3%) |
| RT not intended and not given | 4 (9.3%) | 6 (13.6%) |

*CR/Cru – complete response/complete response unconfirmed; NC – no change; PD – progressive disease; PMBCL – primary mediastinal B-cell lymphoma; PR – partial remission; RT – radiotherapy*.

After chemo (immuno) therapy, followed or not by radiation therapy, CR/UCR was obtained in 52 of the 77 patients with PMBCL (68%) and 442 of the 557 patients with DLBCL (79%). Patients with DLBCL achieved CR/UCR in a higher percentage than patients with PMBCL if Rituximab was not associated (72% vs 54% p = 0.029). Association of immunotherapy led to the disappearance of the differences between the two groups in terms of CR/UCR (80% vs 87%, p = 0.24). It was also observed that addition of rituximab to chemotherapy resulted in a dramatic decrease in the frequency of disease progression in PMBCL (2.5% vs 24%, p = 0.006) and DLBCL (4% vs 10%, p = 0.006). In the absence of immunotherapy, PD was more common in patients with PMBCL (24% vs 10%, p = 0.0095), while its association wiped out any difference between the rate of PD between the two forms of lymphoma (2.5 % vs. 3.9% p = 0.66).

Similar results have been presented by other study groups A. Avigdor presented a single centre experience, based on a retrospective analysis, regarding disappearance of the superiority of the VACOP-B regime to the CHOP-21 regime, once immunotherapy was added to the treatment. (17) The clinical characteristics and evolution of 95 patients treated between 1995 and 2009 in Sheba Medical Center were analyzed. Of these, 52 patients were treated with CHOP-type regimens (5) and VACOP-B (47), in the pre-rituximab and 43 patients associated also Rituximab R-VACOP -B (30) and R-CHOP (13).

Radiotherapy was not associated. After an average 65 months follow-up of all patients, overall survival (OS) and survival without progression of disease (PFS) at 5 years was 92% for VACOP-B, and 65% for CHOP. In the patients who received chemo-immunotherapy, PFS at 5 years was 79% (vs. 58% from patients who did not receive immunotherapy, p = 0.06) and overall survival (OS) at 5 years 97% (vs. 88%, p = 0.2). PFS in patients treated with R-VACOP-B, R-CHOP, VACOP-B, CHOP was 83%, 69%, 62% and 20%. Direct comparison of survival demonstrated no statistically significant difference in terms of PFS between patients treated with R-MACOP and R-CHOP- B (p = 0.3) . It should be noted that with the introduction of immunotherapy the superiority of third generation regimens (VACOP -B) versus CHOP disappeared. (17)

Currently, standard treatment in the U.S. is CHOP-like polichemotherapy, in combination with Rituximab, while in Europe most commonly used regime is R-MACOP -B Other regimes that have been used successfully are EPOCH-R and NHL87

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