

## Primary mediastinal large B-cell lymphoma with sclerosis: a clinical study of 89 patients treated with MACOP-B chemotherapy and radiation therapy

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**Background and Objectives.** Primary mediastinal large B-cell lymphoma (PMLBCL) with sclerosis has recently been recognized as a specific clinical and pathologic entity for which the best therapeutic approach seems to be a combination of chemotherapy and radiotherapy.

**Design and Methods.** Between 1989 and 1998, 89 previously untreated patients with PMLBCL with sclerosis were treated with a combination of a third-generation chemotherapy regimen (MACOP-B) and mediastinal radiation therapy. The response evaluations were examined after chemotherapy and at the end of radiotherapy.

**Results.** Twenty-three (26%) patients achieved a complete response (CR) and 59 (66%) obtained a partial response (PR) after the MACOP-B regimen. After radiation therapy, 55/59 (93%) of the patients in PR achieved CR. The CR rate at the end of the treatment was 88% (78/89). Only 7 (8%) patients were non-responders. Among the 78 patients who obtained a CR there were 7 (9%) relapses in a median follow-up of 5 months (all relapses occurred within 9 months); the other 71 patients are currently in continuous CR with a median follow-up of 45 months (range, 4-110 months). Projected overall survival was 86% at 9 years; the relapse-free survival curve of the 78 patients who achieved CR was 91% at 9 years.

**Interpretation and Conclusions.** In patients with PMLBCL with sclerosis, combined modality treatment using the MACOP-B chemotherapy regimen and radiation therapy induces a good remission rate with the patients having a greater than 90% chance of surviving disease-free at 9 years. Radiotherapy often plays a pivotal role in obtaining CR status.

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Key words: PMLBCL with sclerosis, MACOP-B regimen, radiation therapy, relapse-free survival

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New biological and molecular knowledge has increasingly allowed application of differentiated therapeutic approaches for recently recognized histologic subtypes of aggressive non-Hodgkin's lymphoma (NHL) in line with their individual clinical features. Primary mediastinal large B-cell lymphoma (PMLBCL) with sclerosis is already considered to be a distinct clinical and pathologic entity and has been included in the R.E.A.L. classification<sup>1</sup> among the aggressive NHL. It has peculiar clinical features such as developing in young median age, a predilection for women, and the presence of a bulky mediastinal mass invading adjacent organs and structures.<sup>2,3</sup>

In terms of chemotherapeutic approaches, some studies using CHOP or CHOP-like regimens have produced good results,<sup>4-7</sup> but others have been disappointing.<sup>8-10</sup> However, good results have also been obtained with MACOP-B or MACOP-B-like regimens.<sup>11-16</sup> The role of high-dose chemotherapy with rescue by autologous bone marrow transplantation or peripheral blood stem cells in first-line treatment or in first remission is uncertain.<sup>17,18</sup> The ability of radiation therapy after chemotherapy to increase the complete remission rate and relapse-free survival is also controversial.

In this study, we report the clinical findings and response to the MACOP-B regimen and radiation therapy in 89 patients with PMLBCL with sclerosis.

### Design and Methods

Between January 1989 and 1998, 89 consecutive patients with PMLBCL with sclerosis completed treatment in 8 Italian institutions with a standardized MACOP-B third-line chemotherapy regimen and mediastinal radiotherapy. Criteria for entry into the study included: histologic diagnosis of PMLBCL with sclerosis according to the R.E.A.L. classification;<sup>1</sup> stage I with bulky disease and stage II-IV, as outlined by the Ann

Arbor staging system;<sup>19</sup> and no prior therapy. Staging evaluation included hematologic and clinical survey, in addition to a chest radiogram, abdominal ultrasonography, and computerized tomography (CT) scans of the chest and abdomen. A bone marrow biopsy was taken from all patients. Liver biopsy was performed when appropriate; no patient underwent staging laparotomy. Diagnostic material was obtained by transthoracic lymph node biopsy, thoracotomy or mediastinoscopy.

#### Patients' characteristics

All 89 patients were previously untreated (Table 1). Their median age was 32 years (range, 14 to 58 years); 61 were females and 28 males. Ten patients had stage I, 63 stage II, 6 stage III, and 10 stage IV disease. Three of the patients in stage IV had bone marrow involvement, and the other 7 had lung involvement. One or more systemic B-symptoms were present only in 28 (32%) patients. At diagnosis, 32 (36%) patients had clinical features of superior vena cava syndrome while 25 (28%) and 11 (12%) had pleural or pericardial effusions, respectively. Bulky mediastinal involvement was present in 59 (66%) patients. The extent of mediastinal disease was defined as a mediastinal mass ratio (MMR), which was calculated by measuring the maximum single horizontal width of the mediastinal mass on a standing PA chest radiograph, and dividing it by the maximum intrathoracic diameter. An MMR that exceeded one third or a mass measuring  $\geq 10$  cm in its largest single diameter, as measured by CT, was considered as bulky. Lactate dehydrogenase (LDH) levels were elevated in 54 (61%) patients.

#### Treatment protocol

All patients were treated with the MACOP-B protocol. The MACOP-B regimen was given as previously described by Klimo *et al.*<sup>20</sup> Four to six weeks after the completion of the chemotherapy regimen, all patients received radiation therapy to the mediastinum with a tumor dose ranging from 30 to 36 Gy over 4 to 5 weeks at a schedule of 180 cGy/day for 5 days per week. Radiologic and clinical staging with evaluation of tumor size included a CT scan at diagnosis (before therapy), at the end of chemotherapy, and 2 months after radiotherapy.

#### Response

Patients were assigned a response category based on standard criteria: complete response (CR) was defined as a complete regression of all assessable disease or a response  $\geq 80\%$  of residual mediastinal mass in the size of clinically apparent disease without any evidence of regrowth on completion of induction therapy. The mediastinal mass was always measured in terms of the product of the largest two perpendicular diameters. A partial response (PR) was defined as a reduction of  $\geq 50\%$  of known disease with disappearance of the systemic manifestations. No response was defined as  $< 50\%$  reduction of the measurable tumor, or progression.

Survival was calculated from the beginning of treatment until death or last follow-up. Relapse-free sur-

vival was estimated from the date of documented CR to the last follow-up or relapse. The overall survival and relapse-free survival curves were calculated according to the method of Kaplan and Meier.<sup>21</sup>

#### Results

The treatment outcome according to the different therapeutic outcomes is summarized in Table 2. After the MACOP-B regimen, 23 (26%) patients achieved a CR and 59 (66%) obtained a PR, giving an overall response rate of 92% (82/89). The remaining 7 (8%) patients showed progression of disease during the treatment. After the radiation therapy, 55/59 (93%) patients who had already achieved a PR obtained CR status. So, at the end of the combination treatment, 78/89 (88%) patients achieved a CR. <sup>67</sup>GaSPECT was performed on the 4 patients who remained in PR even after radiation therapy. Three turned out to be gallium negative and 1 positive. This last was given high-dose therapy as second-line treatment but died 25 months after diagnosis. The

**Table 1. Clinical characteristics of 89 consecutive patients with PMLBCL with sclerosis.**

Age		
Median		32 yrs
Range		14-58 yrs
Sex		
Male		28
Female		61
B-Symptoms		
No		61
Yes		28
Stage		
I-II		73 (82%)
III-IV		16 (18%)
Bulky mediastinal involvement		59 (66%)
Superior vena cava syndrome		32 (36%)
Pleural effusion		25 (28%)
Pericardial effusion		11 (12%)
Bone marrow involvement		3 (3%)
LDH abnormal		54 (61%)

**Table 2. The treatment outcomes of 89 patients with PMLBCL with sclerosis after MACOP-B chemotherapy followed by mediastinal radiation therapy. (CR, complete response; PR, partial response; NR, no response).**

	CR (%)	PR (%)	NR (%)	CR+PR(%)
After chemotherapy	23 (26)	59 (66)	7 (8)	82 (92)
After radiation therapy	78 (88)	4 (4)	7 (8)	82 (92)

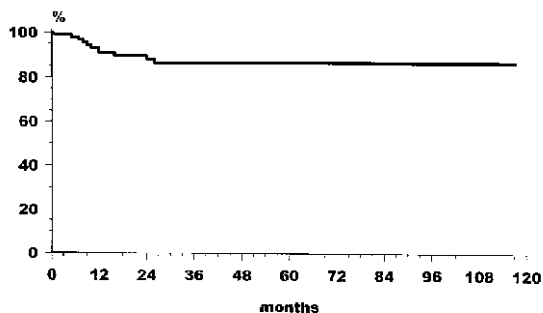


Figure 1. Overall survival curve of 89 patients with PMLBCL with sclerosis treated with MACOP-B plus mediastinal radiation therapy.

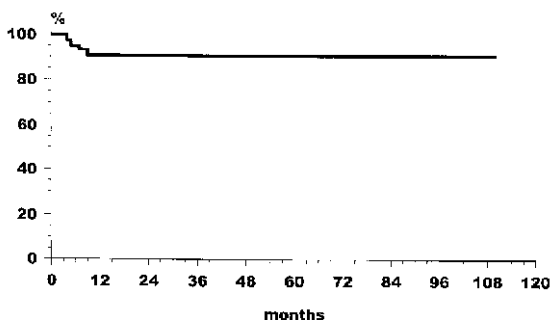


Figure 2. Relapse-free survival curve of 78 CR patients treated with MACOP-B plus mediastinal radiation therapy.

3 gallium-negative patients have received no further treatment and are still alive after 25, 29, and 34 months. All patients who showed disease progression died (median follow-up, 9 months; range, 1 to 22 months).

At the time of writing, 71/78 (91%) of the patients who achieved a CR are still in continuous CR with a median follow-up of 45 months (range, 4 to 110 months). There were 7 relapses (after a median follow-up of 5 months, range, 4 to 9 months). All but one of the relapsed patients died from disease progression. The remaining patient was submitted to high-dose therapy, and obtained a second CR which lasted only 5 months. She has now achieved a PR after 8 administrations of rituximab treatment.

As shown in Figure 1, the projected overall survival is 86% at 9 years. The relapse-free survival curve of the 78 patients who achieved CR was 91% at 9 years (Figure 2). According to the age-adjusted International Prognostic Index (IPI),<sup>22</sup> 70 (79%) patients presented with a score of 0-1 and 19 (21%) patients had a score  $\geq 2$ . Figures 3 and 4 show the overall survival and the relapse-free survival curves according to the different IPI sub-

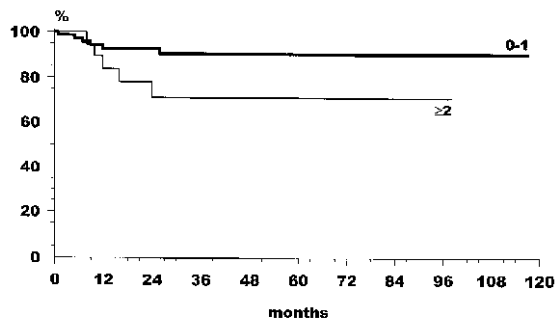


Figure 3. Overall survival curves of 89 patients with PMLBCL with sclerosis with respect to IPI score (score 0-1 vs.  $\geq 2$ ;  $p = 0.044$ ).

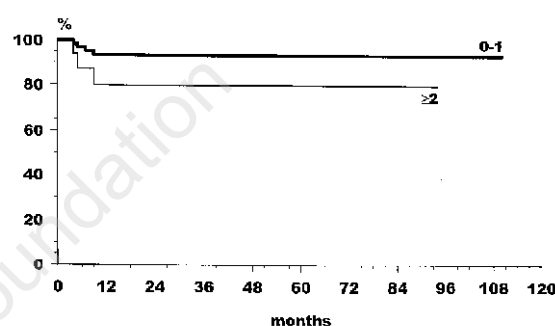


Figure 4. Relapse-free survival curves of 78 patients with PMLBCL with sclerosis with respect to IPI score (score 0-1 vs.  $\geq 2$ ;  $p = 0.11$ ).

sets (0-1 vs.  $\geq 2$ ;  $p = 0.044$  for overall survival and  $p = 0.11$  for relapse-free survival).

Specific evaluation of the clinical identikit of the 14 non-responder/relapsed patients revealed presence of bulky mediastinal disease in 10/14 (72%) patients, B-symptoms in 11/14 (79%), and superior vena cava syndrome in 6/14 (43%) (Table 3). These features were more frequent among the non-responder/relapsed patients than in the overall series (bulky disease: 72% vs 66%; B-symptoms: 79% vs. 69%; superior vena cava syndrome: 43% vs. 36%).

### Discussion

At the state of the art, PMLBCL with sclerosis must be considered a specific entity in the subset of aggressive NHL: it has particular clinical and histopathologic features and therefore requires specific treatment. Reported approaches to the treatment of this entity range from first-generation<sup>4-10</sup> to third-generation chemotherapy protocols.<sup>11-16</sup> The therapeutic choice is problematic and remains open, since it is very difficult to compare the different sets of data reported in the literature. In addi-

**Table 3. Specific clinical characteristics of patients who showed no response (NR) to therapy or relapsed.**

	NR (7) (%)	Relapsed (7) (%)	NR/relapsed (14) (%)
Bone marrow Involvement	1 (14)	0	1 (7)
Pleura effusion	2 (28)	0	2 (14)
Pericardial effusion	0	1 (14)	1 (7)
Superior vena cava syndrome	3 (43)	3 (43)	6 (43)
Bulky mediastinum	5 (72)	5 (72)	10 (72)
B-symptoms	6 (86)	5 (72)	11 (79)

tion, doubts exist as to whether radiation therapy increases the response rates that can be obtained with chemotherapy alone.

To our knowledge, the present report concerns the largest series of patients with PMLBCL with sclerosis to be prospectively treated with MACOP-B and local radiation therapy. It also evaluates the role of radiation therapy with stratification according to the IPI score. Among the 89 patients, we observed CR rates of 26% after the MACOP-B regimen, and of 88% after local mediastinal radiation therapy. The projected 9-year relapse-free survival is currently 91% (after a median follow-up of 45 months). Only 7 patients relapsed, all within the first year. As regards the IPI score, both the overall survival and relapse-free survival curves are better for the favorable prognostic subset (IPI 0-1); this difference reached significance in the overall survival ( $p = 0.044$ ). In addition, the patients who relapsed or did not respond to therapy had higher percentages of certain clinical features not included in the IPI score, such as the presence of B-symptoms, bulky mediastinal mass and superior vena cava syndrome.

On the basis of these data, our study indicates that the combination of the third-generation MACOP-B regimen with local mediastinal radiation therapy can cure a high percentage of patients with PMLBCL with sclerosis. Considering that the latest relapses appeared only 9 months after the CR and that most relapses in aggressive NHL occur within the first 2 years, after a median follow-up of 45 months there is reason to believe that the majority of patients in our series are probably cured.

Our findings also indicate that the addition of radiation therapy after chemotherapy is of pivotal importance for the eradication of PMLBCL with sclerosis. Indeed, radiation therapy boosted the CR rate from 26% to 88%. As regards the prognostic factors, the IPI score stratifies the patients into two well-defined subsets. Other clinical factors, such as B-symptoms, bulky mediastinum mass and superior vena cava syndrome, can probably also be considered specific, poor prognostic factors for this entity.

Prospective studies would be needed to compare the efficacy of CHOP and MACOP-B, with radiotherapy being used in both arms. This should help to determine the best treatment for PMLBCL with sclerosis. Howev-

er, on the basis of the reported non-randomized trials, the best results in terms of CR and relapse-free survival rates seem to have come from the combination of MACOP-B plus radiation therapy. In particular, in our institution, we have decided to keep treating all patients affected by PMLBCL with this combined modality treatment. New protocols should also take into account the pivotal role of  $^{67}\text{GaSPECT}^{16,23,24}$  in post-treatment imaging re-evaluation.

#### Contributions and Acknowledgments

PLZ designed the study and wrote the paper. MM and MB helped PLZ with the data analysis interpretation. ADR, AZ, EP, MB, BF, MG, FG, VS, MT were involved in clinical assessment of the patients. ST critically revised the paper and gave the final approval for its submission.

#### Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

#### Manuscript processing

This manuscript was peer-reviewed by two external referees and by Prof. Mario Lazzarino, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Prof. Lazzarino and the Editors. Manuscript received October 10, 2000; accepted December 20, 2000.

#### Potential implications for clinical practice

The combined modality treatment using MACOP-B chemotherapy regimen and radiation therapy induces a good remission rate with a greater than 90% chance of surviving disease-free. Radiotherapy can play an important role in obtaining CR status.

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