

Induction chemotherapy strategies for primary mediastinal large B-cell lymphoma with sclerosis: a retrospective multinational study on 426 previously untreated patients

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Background and Objectives. This multinational retrospective study compares the outcomes of patients with primary mediastinal large B-cell lymphoma (PMLBCL) with sclerosis after first-generation (dose-intensive regimens), third-generation (alternating regimens) and high-dose chemotherapy strategies, frequently with adjuvant radiation therapy.

Design and Methods. Between August 1981 and December 1999, a total of 426 previously untreated patients with confirmed diagnosis were enrolled in 20 institutions to receive combination chemotherapy with either first generation (CHOP or CHOP-like) regimens, third generation (MACOP-B, VACOP-B, ProMACE CytaBOM) regimens or high-dose chemotherapy (HDS/ABMT).

Results. With chemotherapy, complete response (CR) rates were 49% (50/105), 51% (142/277) and 53% (23/44) with first generation, third generation and high-dose chemotherapy strategies, respectively; partial response (PR) rates were 32%, 36% and 35%, respectively. All patients who achieved CR and 124/142 (84%) with PR had radiation therapy on the mediastinum. The final CR rates became 61% for CHOP/CHOP-like regimens, 79% for MACOP-B and other regimens, and 75% for HDS/ABMT. After median follow-ups from attaining CR of 48.5 months for CHOP/CHOP-like regimens, 51.7 months for MACOP-B type regimens and 32.4 months for HDS/ABMT, relapses occurred in 15/64 (23%), 27/218 (12%) and 0/33 (0%) patients, respectively. Projected 10-year progression-free survival rates were 35%, 67% and 78%, respectively ($p=0.0000$). Projected 10-year overall survival rates were 44%, 71% and 77%, respectively ($p=0.0000$), after median follow-ups from diagnosis of 52.3 months, 54.9 months and 35.8 months, respectively.

Interpretation and Conclusions. In patients with PMLBCL with sclerosis, MACOP-B plus radiation therapy may be a better strategy than other treatments; these retrospective data need to be confirmed by prospective studies. The

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encouraging survival results after high dose chemotherapy require confirmation in selected high-risk patients.
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Key words: PMLBCL, chemotherapy, radiotherapy, response rate, combined modality treatment.

In the new Revised European American Lymphoma (R.E.A.L.) classification,¹ primary mediastinal large B-cell lymphoma (PMLBCL) with sclerosis is listed as a specific clinical and pathologic entity. Histologically, this lymphoma is characterized by a diffuse proliferation of large B-cells with clear cytoplasm and by the presence of a variable degree of sclerosis, which causes the typical compartmentalization pattern.^{2,3,4} Clinically, there is a predominant female to male ratio, and patients are commonly in the 25- to 40-year age group. PMLBCL with sclerosis presents as a rapidly growing invasive tumor with contiguous spread within mediastinal masses. Chest pain, cough, and dyspnea are common. B symptoms are frequently present, and 30% to 40% of patients have superior vena cava obstruction. Pleural and pericardial invasion with effusion are common. The lesion is frequently bulky and often involves the thymus. Although PMLBCL with sclerosis was originally believed to have a particularly adverse prognosis, the outcome of patients who receive chemotherapy or combined modality treatment is now considered equivalent to that of patients with other large cell lymphomas of equivalent stage. Treatment with first-generation

chemotherapy regimens such as CHOP or CHOP-like protocols⁵⁻¹¹ and, more recently, third-generation regimens (alternating regimens) such as the MACOP-B protocol (dose-intensive regimens) has been reported.¹²⁻²⁰ The role of high-dose chemotherapy with rescue of peripheral blood stem cells or autologous bone marrow is uncertain.²¹⁻²³ Fisher *et al.*²⁴ have reported that CHOP and intensive third-generation regimens produce equivalent results. This observation may limit discussion about the use of more aggressive protocols for PMLBCL with sclerosis. However, the debate is still open, because it is difficult to compare the advantages of the different types of protocols and it is also difficult to explain the rather different complete response and survival rates reported by different institutions using similar regimens. Although the value of adjuvant radiation therapy after chemotherapy requires confirmation, it could play an important role in the achievement of long-term progression-free survival (PFS), especially in patients with bulky disease at presentation.²⁵⁻²⁷ In this retrospective multinational study, we report on 426 patients with a confirmed diagnosis of PMLBCL with sclerosis and their relative responses to three different induction strategies: first-generation, third-generation and high-dose chemotherapy.

Design and Methods

Patients

Between August 1981 and December 1999, a total of 426 patients with previously untreated PMLBCL with sclerosis were admitted to 20 institutions (17 in Italy, 2 in England, 2 in Switzerland and 1 in Greece) to receive combination chemotherapy with either first-generation (105 patients), third-generation (277 patients) or high-dose (44 patients) protocols. All the centers kept treating patients according to the chemotherapy regimen locally adopted at that time. As a consequence, all the 426 patients reported here were eligible for this retrospective analysis. Histologic preparations of more than 300 cases were preserved in the archives of the institutions involved. They were reviewed by local expert pathologists according to the criteria of the R.E.A.L. classification,¹ and were all found to fulfill the standards for the diagnosis of PMLBCL with sclerosis. On the basis of this confirmatory analysis, the cases without recorded pathologic material were also regarded as *bona fide* examples of the tumor. More than 280 cases were involved in a pathologic study with central review. In all cases, staging evaluation included initial hematologic and chemical survey, in addition to chest X-rays, computerized tomography

(CT) of the chest and abdomen, and bone marrow biopsy. Bulky disease was defined as a tumor mass ≥ 6 cm. Staging and definition of extranodal sites were based on the Ann Arbor classification.²⁸ The overall characteristics of the 426 patients with respect to the three treatment subsets are shown in Table 1, while Table 2 summarizes the patients' distribution with respect to the International Prognostic Index (IPI) score.²⁹

Treatment subsets

In the first-generation subgroup (105 cases), 90 were treated with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone)³⁰ and 15 with CHOP-B (cyclophosphamide, doxorubicin, vincristine, prednisolone, and bleomycin).³¹ In the third-generation subgroup (277 cases), 204 patients were treated with MACOP-B (methotrexate, adriamycin, cyclophosphamide, vincristine, prednisone, and bleomycin),³² 34 with VACOP-B (a MACOP-B-like regimen with etoposide instead of methotrexate),³³ and 39 with ProMACE CytaBOM (cyclophosphamide, doxorubicin, etoposide, prednisone, cytarabine, bleomycin, vincristine, and methotrexate).³⁴ In the high-dose treatment subgroup (44 cases), 27 patients received the high-dose sequential (HDS) regimen as reported by Gianni *et al.*³⁵ and 17 were submitted to autologous bone marrow transplantation (ABMT) (as front-line treatment). Radiation therapy was given to 339 (80%) patients including all those who achieved CR; it was always started four to six weeks after the last cycle of induction chemotherapy, and was limited to the original sites of involvement with a dose of radiation ranging from 30 to 40 Gy over four to five weeks.

Assessment of response

All patients were restaged with chest and abdomen CT two to four weeks after completion of chemotherapy. Thereafter, all patients submitted to radiation therapy were restaged with chest CT about one month after the completion of treatment. Complete response (CR) was defined as the complete disappearance of signs and symptoms due to disease, as well as the normalization of all previous abnormal investigations. Partial response (PR) was defined as at least 50% reduction of known disease with disappearance of the systemic manifestations. No response was defined as anything less than PR.

Statistical analysis

All survival data were censored at the closing date or the date of last contact when this preceded the closing date. Overall survival (OS) was calculated by the Kaplan-Meier method³⁶ from the date of diagnosis (starting time) until last contact or death from

Table 1. Characteristics of the 426 patients according to the three main induction chemotherapy strategies.

	First generation CHOP/ CHOP-B	Third generation MACOP-B/VACOP-B/ ProMACE CytaBOM	High-dose HDS/ABMT	Total
N. patients	105	277	44	426
Sex M/F	37/68	113/164	15/29	165/261
Age median	35	35	30	32
Age range	19-87	13-82	15-72	13-87
Patients over 60 years (%)	9	5	9	5
B Symptoms	40	120	22	182
LDH abnormal	70	178	32	280
Performance status (%)				
≤ 2	82	86	82	85
> 2	18	14	18	15
Mediastinal involvement	105	277	44	426
	(100%)	(100%)	(100%)	(100%)
Abdominal involvement	9 (9%)	38 (14%)	3 (7%)	50 (12%)
Bulky mass	86 (82%)	225 (81%)	40 (91%)	351 (83%)
Site:				
mediastinal	84	213	38	339
nodal	1	4	2	1
abdominal	1	6	–	1
other	–	2	–	2
Extranodal localization	38 (36%)	83 (30%)	15 (34%)	136 (32%)
Site:				
lung	16	37	9	58
kidney	3	6	2	11
other	19	40	4	63
Pleural effusion	31 (30%)	70 (25%)	16 (36%)	117 (27%)
Pericardial effusion	14 (13%)	37 (13%)	12 (27%)	63 (15%)
Superior vena cava syndr.	22 (21%)	68 (25%)	17 (39%)	107 (25%)
Stage				
I	25 (24%)	36 (13%)	2 (5%)	63 (15%)
II	49 (47%)	169 (61%)	33 (75%)	251 (59%)
III	6 (6%)	24 (9%)	3 (7%)	33 (8%)
IV	25 (24%)	48 (17%)	6 (14%)	79 (18%)
Bone marrow involvement	4 (4%)	14 (5%)	2 (5%)	20 (5%)

Table 2. Patients' distribution with respect to the IPI score in the three main chemotherapy subgroups.

Chemotherapy subgroup	No. of patients	IPI					
		0 (%)	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)
First-generation	105	17 (16)	43 (41)	16 (15)	21 (20)	8 (8)	–
Third-generation	277	57 (21)	113 (41)	56 (20)	37 (13)	11 (4)	3 (1)
High-dose	44	6 (14)	18 (41)	13 (30)	6 (14)	1 (2)	–
Overall	426	80 (19)	174 (40)	85 (20)	64 (15)	20 (5)	3 (1)

Table 3. The treatment outcome after induction chemotherapy according to the three main subgroups.

Chemotherapy subgroups	No. of pts.	CR	PR	ORR
First generation	105	50 (49%)	33 (32%)	83 (81%)
Third generation	277	142 (51%)	100 (36%)	242 (87%)
High-dose	44	23 (53%)	15 (35%)	38 (88%)
Overall	426	215 (51%)	148 (35%)	363 (85%)

ORR: overall response rate.

any cause (event). PFS was calculated for patients who achieved a response after the first-line therapy from the date of first response to the date of last contact, if alive and non-progressed, or to relapse or death (events), whichever came first. Univariate analysis was performed by the log-rank test³⁷ or Cox's proportional hazard regression model,³⁸ as appropriate. Multivariate analysis was performed by a Cox model using a stepwise selection method. The χ^2 test was used whenever appropriate for comparison of subgroups. Two-sided *p* values were used throughout.

Results

The treatment outcome according to the different therapeutic approaches is summarized in Table 3. After induction chemotherapy, the CR rate was 49% (50/105) for first-generation chemotherapy (CHOP/CHOP-like), 51% (142/277) for third-generation chemotherapy (MACOP-B etc) and 53% (23/44) for high-dose chemotherapy (HDS/ABMT); the overall CR rate was 51% (215/426). The PR rates were 32%, 36% and 35%, respectively (35%; 148/426 globally). The overall response rates were 81% (83/105), 87% (242/277) and 88% (38/44), respectively (85%; 363/426 globally). The remaining 63 (15%) patients showed progression of disease during treatment. All the 215 patients who achieved CR received radiation therapy to the mediastinum, as did 124/148 (84%) patients who had a PR. After the radiation therapy, 100/124 (81%) patients who had already achieved a PR obtained CR status; thus, the CR rates for the first-generation, third-generation and high-dose chemotherapy subgroups were 67% (14/21), 84% (76/90) and 77% (10/13), respectively. Table 4 summarizes the outcome after radiotherapy. Concerning the role of the combination of anthracyclines plus radiation therapy in inducing cardiac sequelae, it was impossible to have specific data because of the retrospective nature of this study. Relapses occurred in 15/64 (23%) patients treated with first-generation chemotherapy, 27/218 (12%) in the third-generation subgroups and 0/33 (0%) in the high-dose subgroup ($p=0.004$ among the three subgroups; $p=0.02$, first- vs. third-generation protocols). Globally, projected 10-year overall survival (OS) was 65% (Figure 1) and 10-year PFS was 62% (Figure 2). Projected 10-year OS of the first-generation, third-generation and high-dose chemotherapy subgroups was 44%, 71% and 77%, respectively (Figure 3) ($p=0.0000$ among the three subgroups; $p=0.0001$, first- vs. third-generation); projected 10-year PFS was 35%, 67% and 78%, respectively (Figure 4) ($p=0.0000$ among the three

Table 4. The therapeutic outcome with the inclusion of radiation therapy.

Chemotherapy subgroup	Patients who achieved CR after CHT	Conversions to CR among patients who received RT while in PR	Global CR after chemotherapy and RT
First-generation	50/105 (49%)	14/21 (67%)	64/105 (61%)
Third-generation	142/277 (51%)	76/90 (84%)	218/277 (79%)
High-dose	23/44 (53%)	10/13 (77%)	33/44 (75%)
Overall	215/426 (51%)	100/124 (81%)	315/426 (74%)

RT = radiation therapy; CHT = chemotherapy.

subgroups; $p=0.0003$, first- vs. third-generation). As regards OS, the median follow-up from diagnosis for the first-generation, third-generation and high-dose chemotherapy subgroups was 52.3 (range, 1-202), 54.9 (range, 1-184) and 35.8 (range, 3-143) months, respectively; as regards PFS, the median follow-up after achievement of initial CR was 48.5 (range, 3-198), 51.7 (range, 6-180) and 32.4 (range, 18-136) months, respectively.

Univariate analysis was performed to identify poor prognostic factors for OS and PFS. Male sex ($p=0.0032$), poor performance status ($p<0.00001$), increasing age ($p=0.00001$), stage III-IV disease ($p=0.00001$), and the different chemotherapy induction ($p=0.0001$ among the three chemotherapy subgroups; $p=0.00001$ first- vs. third-generation protocols) were statistically significant poor prognostic factors for OS. Increasing age ($p=0.0036$), poor performance status ($p=0.0334$), and the induction chemotherapy strategy ($p=0.0621$ among the three subgroups) were found to adversely influence PFS. Lactate dehydrogenase level was not significant for the outcome. At multivariate analysis, all factors remained significant for poor OS (Table 5), whereas the only factor that remained significant for poor PFS was increasing age ($p=0.0106$).

The fit of the IPI model to our set of patients was good. Figure 5 shows the impact of IPI risk factors (0-1 vs ≥ 2) on OS ($p=0.0000$).

Discussion

PMLBCL with sclerosis was first described as a distinct clinical-pathologic entity in the 1980s. It is recognized in both the R.E.A.L¹ and WHO³⁹ classifications. The disease originates in the thymus, and produces a large anterior mediastinal mass that can lead to airway compromise and superior vena cava syndrome. Although it resembles nodal large-cell lymphomas, PMLBCL with sclerosis has discrete morphologic, phenotypic and genetic features. It is derived from thymic B-cells and is considered a peripheral B-cell neoplasm. There have been no ran-

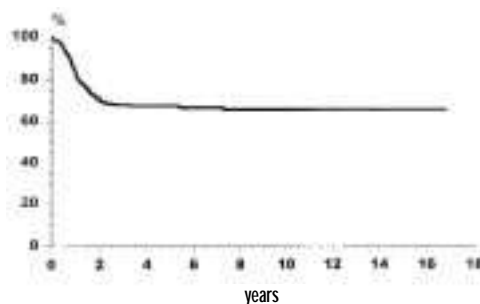


Figure 1. OS curve of all 426 patients with PMLBCL with sclerosis.

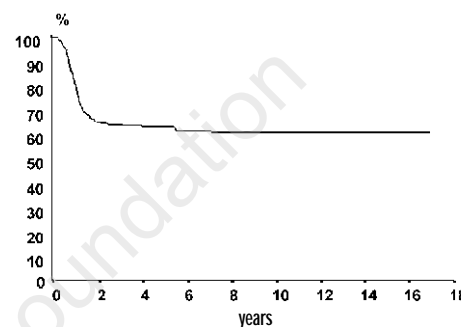


Figure 2. PFS curve of all patients who obtained a CR after combined modality therapy (induction chemotherapy plus radiation therapy).

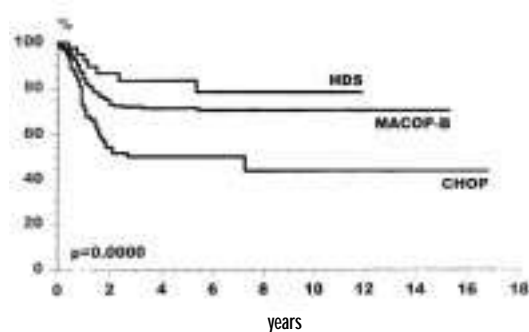


Figure 3. OS curves of the three main chemotherapy subgroups.

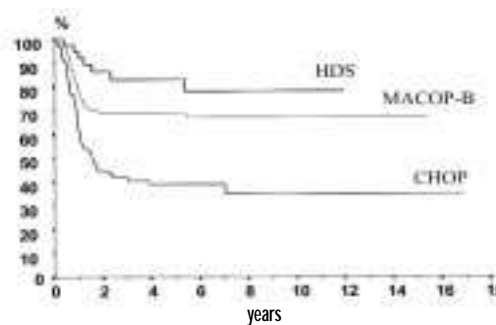


Figure 4. PFS curves of the three main chemotherapy subgroups.

domized treatment trials focusing on patients with PMLBCL with sclerosis. However, the reports that do exist⁴⁰ permit some tentative conclusions to be drawn. Use of first-generation chemotherapy (CHOP or CHOP-like regimens) led to the early impression that the prognosis of patients with PMLBCL with sclerosis was worse than that of patients with the more common diffuse large-cell lymphoma.^{5,11}

However, with the application of more aggressive combination chemotherapy programs (third-generation regimens), it appears that the CR, relapse-free survival (RFS) and OS rates of patients with PMLBCL with sclerosis are at least as good and probably better than those for diffuse large cell lymphoma.¹²⁻²⁰ While radiation therapy alone is known to be ineffective, it has frequently been administered to responding patients; it is difficult to evaluate whether and how much this has improved the eventual outcome. The excellent results obtained in the GELA studies¹⁴ without radiation therapy have questioned its necessity. In centers that have used both first-generation chemotherapy regimens such as CHOP, and the more aggressive third-generation ones such as MACOP-B, the results have clearly favored the latter. Todeschini *et al.*¹⁵ used CHOP without achieving a single CR; in contrast, with MACOP-B or F-MACHOP (5-fluorouracil, methotrexate, cytosine arabinoside, cyclophosphamide, doxorubicin, vincristine, and prednisone)⁴¹ regimens, 87% of patients achieved a CR. Lazzarino *et al.*¹³ reported a CR rate after CHOP of 36%, while that after MACOP-B or VACOP-B was 73%. In a multicenter study of 106 patients, the 3 year-RFS was 38% with CHOP, while it was 58% with MACOP-B or VACOP-B.¹⁸ In two previous studies^{25,26} we used the MACOP-B regimen in 50 patients (a two-center prospective trial) and in 89 patients (an Italian multicenter prospective trial) and obtained CR rates of 86% and 88%, respectively, while the 5-year RFS rates were 93% and 91%, respectively.

In this retrospective multinational study comparing first-generation, third-generation and high-dose induction chemotherapy strategies, the more recent strategies provided slightly better initial response rates. In particular, the CR rates were 53% after HDS or ABMT, 51% after MACOP-B or other third-generation protocols and 49% after CHOP or CHOP-like regimens; overall response rates were 88%, 87% and 81%, respectively. Among the patients who achieved PR, 124 (84%) were submitted to radiation therapy, and 100 (81%) of them obtained a CR status. After this, the eventual CR rates became 75% for the high-dose chemotherapy subgroup, 79% for the third-generation one and only 61% for the first-

Table 5. Multivariate analysis of poor prognostic factors that influence OS.

	<i>p</i> -value	Exp(B)	95% CI
Increasing age	0.0002	1.02	1.01-1.03
Male sex	0.02	1.49	1.05-2.12
Poor performance status	0.001	0.51	0.34-0.77
Advanced stage	0.004	0.57	0.39-0.83
Induction chemotherapy	0.0002	0.49	0.34-0.71

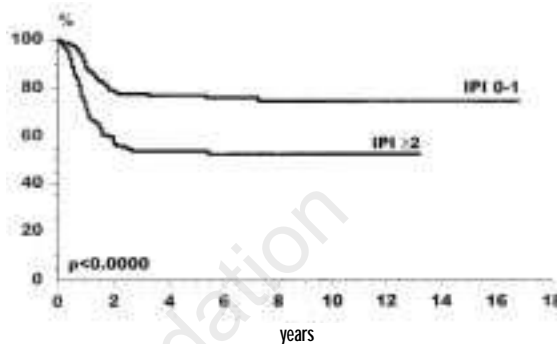


Figure 5. OS curves according to IPI score.

generation subgroup. After a median follow-up of over 3 years, relapses have occurred in 23% of the patients treated with first-generation regimens, as against only 12% of those treated with the third-generation ones and 0% among the high-dose chemotherapy subgroup ($p=0.004$ among the 3 different chemotherapeutic subsets and $p=0.02$ between CHOP and MACOP-B). Survival analysis clearly indicates the superiority of the third-generation approaches over the first-generation ones. In particular, after median follow-ups of over 4 years, the projected 10-year OS and PFS of the third-generation chemotherapy group are 71% and 67%, respectively, as against only 44% and 35% in the first-generation group ($p=0.0001$ and $p=0.0003$, respectively). The survival data of the high-dose chemotherapy subgroup also appear encouraging: after median follow-ups of over 2.5 years, the projected 10-year OS and PFS are 77% and 78%, respectively. At multivariate analysis five prognostic factors for poor OS were identified: increasing age, male sex, poor performance status, advanced stage and the different chemotherapy induction.

To our knowledge, the present study describes the largest series of patients with PMLBCL with sclerosis yet reported. The survival data, in particular, strongly reinforce the concept that third-generation chemotherapy regimens (MACOP-B or MACOP-B like) are better than first-generation (CHOP or CHOP-like) ones in terms of both OS and PFS. Third-

generation regimens should now constitute the induction strategy of choice in most cases. The encouraging results of the high-dose chemotherapy subgroup of patients are very interesting. However, in view of the low number of patients treated, further studies are needed to assess the validity of using HDS or ABMT in particularly high-risk subsets. The present study also provides convincing evidence that radiation therapy may be regarded as a powerful tool for increasing the CR rate or reinforcing existing CRs after induction chemotherapy. Concerning restaging, over 40% of patients have residual radiographic abnormalities in the mediastinum even after CR, so chest radiographs and computed tomography scans do not provide a valid basis for therapeutic decision making. ^{67}Ga SPECT and PET could be the best tools for selecting those patients who really require the addition of radiation therapy after chemotherapeutic induction.^{25,42,43}

In conclusion, this retrospective multinational study on 426 patients with PMLBCL with sclerosis, with a median follow-up of over 3 years, confirms the superiority of the third-generation chemotherapy strategies over first-generation ones in terms of survival. While third-generation protocols should now be the induction treatment of choice in the majority of cases, high-dose approaches (including ABMT) may be considered in particularly high-risk patients. Prospective randomized studies are needed to confirm the validity of this promising therapeutic option. Our study also highlights the role of radiation therapy (preferably after ^{67}Ga SPECT and/or PET restaging) for converting cases of PR to CR, and probably also of reinforcing existing CRs. Our data suggest that, with appropriate application of such combined-modality therapy strategies, the long-term OS of patients with PMLBCL with sclerosis may be as high as 70-75%.

Contributions and Acknowledgments

PLZ designed the study and was primarily responsible for the publication. MM, MB, AMG, LD, MF, GP, JM, EZ, MC, SC, AW, AJMF, FZ, FL, ADR, MAL, BF, MB, AC, AZ, PG, PPF, EP, MKA, LA, MB, NDR: responsible for the care of patients and data collection. FB: responsible for the statistical analysis. SAP: responsible for the histologic revision. All authors contributed to revising the manuscript. The last author (FC) had a major role as senior author in interpreting the data with PLZ. We are grateful to Robin M.T. Cooke for helping work up the manuscript. PLZ: responsible for Tables 1, 2, 3, and 4. FB: responsible for Table 5 and Figures 1-5.

Disclosures

Conflict of interest: none.

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PEER REVIEW OUTCOMES

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Gilles Salles, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Prof. Salles and the Editors. Manuscript received June 14, 2002; accepted October 22, 2002.

What is already known on this topic

Primary mediastinal lymphoma is a recognized entity among aggressive B-cell lymphomas. Whether or not the treatment and the prognosis of this lymphoma subtype is different from other diffuse large B-cell lymphomas is a matter of debate.

What this study adds

This retrospective study constitutes the largest series of mediastinal large cell lymphomas ever published and indicates that about two-third of the patients are being cured.

Potential implications for clinical practice

This retrospective analysis suggests that high-dose therapy and radiotherapy may be of benefit for these patients. These data should be interpreted keeping in mind other randomized trials on these topics and the therapeutic approaches should be tested in prospective comparative studies.

Gilles Salles, Associate Editor (Lyon, France)