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Primary mediastinal large B-cell lymphoma (PMLBCL): long-term results from a retrospective multicentre Italian experience in 138 patients treated with CHOP or MACOP-B/VACOP-B

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The optimal treatment of primary mediastinal large B-cell lymphoma (PMLBCL) is still undefined. In the absence of randomised studies, we retrospectively analysed: (a) the effectiveness of two chemotherapy regimens (CHOP vs MACOP-B/VACOP-B) in complete remission (CR) achievement and event-free survival (EFS) and (b) the role of mediastinal involved-field radiotherapy (IF-RT) as consolidation. From 1982 to 1999, 138 consecutive patients affected by PMLBCL were treated in 13 Italian institutions with CHOP (43) or MACOP-B/VACOP-B (95). The two groups of patients were similar as regard to age, gender, presence of bulky mediastinal mass, pleural effusion, stage and international prognostic indexes category of risk. Overall, 75.5% of patients in CR received IF-RT as consolidation. Complete remission was 51.1% in the CHOP group and 80% in MACOP-B/VACOP-B ($P < 0.001$). Relapse occurred in 22.7% of CHOP- and in 9.2% of MACOP-B/VACOP-B-treated patients (n.s.). Event-free patients were 39.5% in CHOP and 75.7% in the MACOP-B/VACOP-B group ($P < 0.001$). The addition of IF-RT as consolidation improved the outcome, irrespectively of the type of chemotherapy ($P = 0.04$). At a multivariate analysis, achievement of CR ($P < 0.0001$) and type of CT (MACOP-B/VACOP-B) retained the significance for OS ($P = 0.008$) and EFS ($P = 0.03$). In our experience, MACOP-B/VACOP-B appears to positively influence OS and EFS in patients affected by PMLBCL, as compared to CHOP. Consolidation IF-RT on mediastinum further improves the outcome of CR patients.
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PMLBCL is a subtype of diffuse large B-cell lymphoma (DLCL), recently recognised as a clinical–pathological entity (Harris *et al*, 1994). It accounts for a percentage between 6 and 13% of DLCLs (Falini *et al*, 1995; Cazals-Hatem *et al*, 1996).

PMLBCL histology is characterised by a diffuse proliferation of large B cells with prominent, roundish nuclei, clear cytoplasm and high proliferative index. A thin band of sclerosis often compartmentalises neoplastic elements (Menestrina *et al*, 1986). Lymphoma cells are CD45, CD20, CD19 and CD22 positive, while CD5, CD10, CD21 and HLA-DR are usually absent (Yousem *et al*, 1985; Addis and Isaacson, 1986; Moller *et al*, 1987; Haioun *et al*, 1989; Lamarre *et al*, 1989; Al-Sharabati *et al*, 1991; van Besien *et al*, 2001). Expression of CD30 is often present but weak. Surface and cytoplasmic immunoglobulins are rarely expressed. The thymic origin of the neoplastic B cells has been proven (Scarpa *et al*, 1987; Lamarre *et al*, 1989; Al-Sharabati *et al*, 1991; Rodriguez *et al*, 1994).

The high proliferation rate of neoplastic cells (Todeschini *et al*, 1990; Falini *et al*, 1995) correlates with the rapid growth and with the frequent presence of necrotic areas in the lymphoma mass (Aisenberg, 1999). Sclerosis can explain the frequent persistence of variable degrees of residual mass even after successful treatment (Rohatiner *et al*, 1994).

PMLBCL affects young people with a female prevalence (Todeschini *et al*, 1990; Lazzarino *et al*, 1993; Falini *et al*, 1995). Its rapid growth explains the frequent bulky mediastinal mass infiltrating thoracic structures (pericardium, pleura) and the chest wall. Vessels are frequently involved, leading to Superior Vena Cava Syndrome (SVCS) and to thrombosis (Perrone *et al*, 1986; Lamarre *et al*, 1989; Todeschini *et al*, 1990). Other symptoms at the onset are chest pain, cough and dyspnea (Lamarre *et al*, 1989;

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Todeschini *et al*, 1990; Al-Sharabati *et al*, 1991; Falini *et al*, 1995). Most cases are stage I–II. When the lymphoma spreads beyond the diaphragm, it usually involves the kidney and suprarenal glands (Perrone *et al*, 1986; Haioun *et al*, 1989; Todeschini *et al*, 1990; Kirn *et al*, 1993; Lazzarino *et al*, 1993). Bone marrow involvement is extremely rare (Cazals-Hatem *et al*, 1996; Abou-Ella *et al*, 1999). Diagnosis is mostly obtained by thoracotomy or mediastinoscopy, superficial lymph nodes being rarely involved.

Most published reports on PMLBCL mainly focus on the clinical–pathological features, and few papers only analyse the role of different chemotherapy regimens on the clinical outcome. As a result, the optimal therapy has not been defined yet, as pointed out by a recent review (van Besien *et al*, 2001).

According to literature, CHOP and third-generation regimens, followed or not by involved-field radiotherapy (IF-RT), are the most employed combination therapies (Levitt *et al*, 1982; Jacobson *et al*, 1988; Todeschini *et al*, 1990; Lazzarino *et al*, 1993; Falini *et al*, 1995; Cazals-Hatem *et al*, 1996; Martelli *et al*, 1998; van Besien *et al*, 2001).

A possible superiority of third-generation regimens in DLCLs has not been validated by a large prospective randomised study (Fisher *et al*, 1993). However, this study was not specifically focused on PMLBCLs. By contrast, data from other series suggest that, in this setting, third-generation therapies (usually MACOP-B and VACOP-B) may be more effective than CHOP (Levitt *et al*, 1982; Todeschini *et al*, 1990; Bertini *et al*, 1991; Falini *et al*, 1995; Cazals-Hatem *et al*, 1996; Bieri *et al*, 1999; van Besien *et al*, 2001; Zinzani *et al*, 2001, 2002).

In absence of randomised trials, we retrospectively analysed a large series of PMLBCL consecutive patients treated with CHOP or MACOP-B/VACOP-B observed in 13 different Italian institutions.

The first aim of this analysis was to compare the long-term results of CHOP *vs* MACOP-B/VACOP-B, the two most commonly employed regimens in PMLBCL patients in USA and Europe, respectively (van Besien *et al*, 2001). Patients treated with other regimens and those receiving stem cell transplant (SCT) as consolidation were not analysed. The two therapeutic approaches have been compared, taking into account the recognised international prognostic indexes (IPI) (The International Non-Hodgkin's Lymphoma Prognostic Factors Project, 1993).

The second objective of our analysis was to evaluate the role of consolidation IF-RT on the long-term outcome after CR achievement.

This paper reports our multicentre retrospective experience.

PATIENTS AND METHODS

Patients

Our review includes 138 consecutive patients observed in 13 Italian institutions between 1982 and 1999. Patients received routine staging procedures (complete physical examination, laboratory tests including serum LDH and serum beta-2 microglobulin, chest X-ray, CT scan of the chest, abdomen and pelvis, bone marrow aspirate, and biopsy). Stage was defined according to the Ann Arbor staging system. Bulky disease was defined as a mediastinal mass larger than 1/3 of thoracic diameter or a mediastinal mass larger than 10 cm (major diameter).

Diagnostic criteria

All biopsy specimens were reviewed and confirmed according to the WHO criteria for PMLBCL diagnosis. Immunophenotypical analysis was always performed. Other NHLs involving the mediastinum and not fulfilling these criteria were not considered.

Selection criteria

Only patients treated with CHOP or MACOP-B/VACOP-B were included in this report. Patients who underwent other regimens or patients who received SCT after completing CHOP or MACOP-B/VACOP-B were excluded. Each institution chose treatment (CHOP or MACOP-B/VACOP-B) according to the local policy at the time. Chemotherapy was based on six cycles of CHOP or on a full (12 weeks) cycle of MACOP-B/VACOP-B. In each group of therapy, patients were divided into low/low-intermediate- and high-intermediate/high-risk groups according to IPI.

Involved-field radiotherapy was administered in patients in complete remission (CR)/near-complete remission (NCR). The decision to employ IF-RT or not was made according to the local policy of each centre. The modality of IF-RT administration was the following: (a) when the mass involved only the mediastinum, the whole original disease was irradiated; (b) when the mass spread beyond the mediastinum displacing the lung, IF-RT was administered to involve the mediastinum volume plus 1.5 cm outside its borders. The median dosage of IF-RT was 34 Gy (range 30–45). Only patients who underwent IF-RT after achieving CR or NCR were considered for IF-RT significance on disease outcome.

Response criteria

CR was defined as the disappearance of lymphoma lesions and resolution of symptoms for at least 3 months after the end of CT. Near-complete remission (i.e. unconfirmed CR) was defined as the reduction of mass (lymphoma lesions) >90%, without new growth at physical and imaging examination, without signs and symptoms of disease for at least 3 months. Partial remission (PR) was defined as reduction of at least 50% of the original measurable mass. No remission (NR) was defined as (a) minimal modification (a response less than 50%) or (b) no modification or (c) progression of the mass under CT or (d) new lymphoma growth during CT or within 3 months after the end of CT.

In our review, gallium scan could not be considered in the assessment of CR, since only a minority of patients underwent this procedure. The possible persistence of some degree of fibrosis after CT even in responders makes it difficult to define the real incidence of CR. However, the long-term observation of our study allowed us to clarify this point, since NR or low responsive cases had invariably a rapid fatal outcome. Therefore, the long-term EFS had been judged *a posteriori* as an indicator of CR achievement. OS was calculated from the beginning of chemotherapy to the death or the last follow-up. EFS was defined as survival from the beginning of chemotherapy, in the absence of unfavourable events such as (1) toxic death, (2) NR, PR or progression, (3) relapse and (4) death due to any cause.

Statistical analysis

Statistical analysis was performed using the χ^2 test with Yates correction and with Fisher's exact test for categorical variables. Survival curves were calculated from the beginning of the treatment according to the actuarial method proposed by Kaplan and Meier. Differences between curves were evaluated by log-rank test. Cox regression analysis was performed to determine the independent contribution of the following variables: achievement of CR, type of treatment (CHOP *vs* MACOP-B/VACOP-B) and IPI score (low/low-intermediate *vs* high-intermediate/high). Each variable was compared to the previous one.

Clinical

RESULTS

Among the 138 patients, there were 75 females and 63 males (F/M 1.19). The median age was 39 (range 14–70). Only seven out of 138 patients were over 60. Most patients were in stage I–II (95 out of 138: 68.9%); stage III–IV patients were 43 out of 138 (31.1%).

Bulky mediastinal mass was present in 111 out of 138 (80.4%) and bone marrow involvement in two out of 138 (1.4%) cases. In all, 15 patients in stage IV had organ involvement beyond the diaphragm; in 13 (86.6%) of them, renal and suprarenal glands involvement was present. A total of 43 patients have been treated with CHOP and 95 with MACOP-B/VACOP-B. According to IPI, the different risk groups were: low, 82 out of 138 (59.4%); low-intermediate, 25 out of 138 (18.1%); high-intermediate, 23 out of 138 (16.6%); high, eight out of 138 (5.7%). The two risk categories were balanced in CHOP- and MACOP-B/VACOP-B-treated groups (Table 1).

The median follow-up of all entered patients was 66.5 months (1–199+). The median follow-up of patients alive in CR was 89.5 months (8–199+): 78 months (8–199+) in CHOP- and 91.5 months (10–172+) in MACOP-B/VACOP-B-treated groups.

The overall CR rate was obtained in 98 out of 138 (70%) and event-free patients were 89 out of 138 (64.4%). Complete remission/NCR were 22 out of 43 (51.1%) in the CHOP group and 76 out of 95 (80%) in the MACOP-B/VACOP-B group ($P < 0.0001$). No remission/PD were 18 out of 43 (41.8%) and nine out of 95 (9.4%), respectively ($P < 0.001$). Event-free patients were 17 out of 43 (39.5%) in CHOP- and 72 out of 95 (75.7%) in MACOP-B/VACOP-B-treated groups (Table 2; Figure 1).

Considering IPI, in low/low-intermediate risk, 17 out of 33 (51.1%) CHOP-treated patients achieved CR, as opposed to 62 out of 74 (83.7%) MACOP-B/VACOP-B-treated ones ($P = 0.001$).

Table 1 Clinical characters of patients treated with CHOP or MACOP-B/VACOP-B

	CHOP	MACOP-B/VACOP-B	P
Patients	43	95	
Median age	35 (17–70)	36.5 (14–65)	
Gender (F/M)	27/16 (1.68)	48/47 (1.02)	
B symptoms	9/43 (20.9%)	48/95 (50.5%)	0.002
Bulky mediastinum	32/43 (74.4%)	79/95 (83.1%)	n.s.
Pleural effusion	19/43 (44.1%)	43/95 (45.2%)	n.s.
Pericardial effusion	9/43 (20.9%)	28/95(29.4%)	n.s.
SVCS	25/43 (58.1%)	43/95 (45.2%)	n.s.
Stage I–II	29/43 (67.4%)	66/95 (69.4%)	n.s.
Stage III–IV	14/43 (32.5%)	29/95 (30.5%)	n.s.
IPI			
Low/low-intermediate	25/39 (64.1%)	62/92 (67.3%)	n.s.
High-intermediate/high	14/39 (35.8%)	30/92 (32.6%)	n.s.
Study period			
1982–1990	26 (60.5%)	45 (47.3%)	n.s.
1991–1999	17 (39.5%)	50 (52.6%)	n.s.
Median follow-up (censored patients)	78 mo (8–199+)	91.5 mo (10–172+)	

Table 2 Overall results comparing CHOP to MACOP-B/VACOP-B

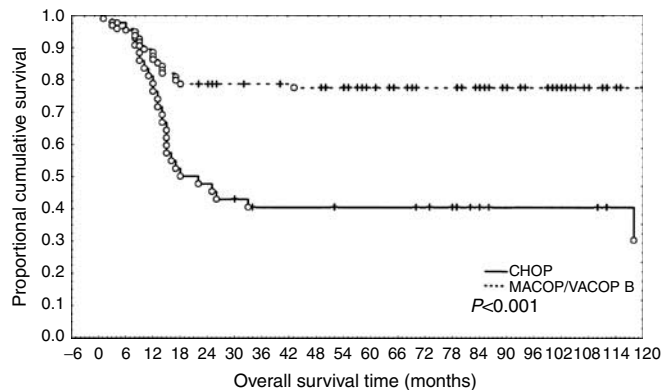|	CHOP	MACOP-B/VACOP-B	P
Patients	43	95	
CR/NCR	22/43 (51.1%)	76/95 (80%)	$P < 0.001$
PR	3/43 (6.9%)	10/95 (10.5%)	n.s.
NR/PD	18/43 (41.8%)	9/95 (9.4%)	$P < 0.001$
REL	5/22 (22.7%)	7/76 (9.2%)	n.s.
EFS	17/43 (39.5%)	72/95 (75.7%)	$P < 0.001$

Figure I Event-free survival in CHOP- *vs* MACOP/VACOP-B-treated patients.

Table 3 Results of CHOP *vs* MACOP-B/VACOP-B in 138 consecutive patients according to IPI

	CHOP	MACOP-B/VACOP-B	P
Low/low-intermediate risk			
Patients	33/43 (76.7%)	74/95 (77.8%)	n.s.
CR/NCR	17/33 (51.5%)	62/74 (83.7%)	$P = 0.001$
PR	1/33	6/74 (8%)	n.s.
NR/PD	15/33 (45.4%)	6/62 (9.6%)	$P = 0.001$
REL	3/17 (17.6%)	5/62 (8%)	n.s.
Event-free patients	14/33 (42.4%)	60/74 (81%)	$P < 0.001$
High-intermediate/high risk			
Patients	10/43 (23.2%)	21/95 (22.1%)	n.s.
CR/NCR	5/10 (50%)	14/21 (66.6%)	n.s.
PR	2/10 (20%)	4/21 (19%)	n.s.
NR/PD	3/10 (30%)	3/21 (14.2 %)	n.s.
REL	2/5 (40%)	1/21 (4.7%)	n.s
Event-free patients	3/10 (30%)	12/21 (57.1%)	n.s.

Event-free patients were 14 out of 33 (42.4%) and 60 out of 74 (81%), respectively ($P = 0.0001$) (Table 3). In the small group (31 out of 138, 22.4%) of high-intermediate/high-risk patients, five out of 10 (50%) CHOP-treated patients achieved CR *vs* 14 out of 21 (66.6%) MACOP-B/VACOP-B-treated ones ($P = 0.068$).

Of the 37 patients in stage IV, only 17 (45.9%) became event-free survivors. Among the 15 patients with organ involvement beyond the diaphragm (four treated with CHOP, 11 with MACOP-B), only five (33.3%) were event-free (all treated with MACOP-B/VACOP-B).

Relapses occurred after a median time of 9 months (range 3–77), mostly (eight out of 12: 66.6%) within 1 year from CR.

Involved-field radiotherapy was considered for patients in CR/NCR

The majority of patients who achieved CR with CT received IF-RT on the mediastinum as consolidation (74 out of 98: 75.5%).

Kaplan–Meier survival curve performed on the population who achieved CR showed a statistically significant difference in event-free survival time in patients receiving IF-RT ($P = 0.04$) (Figure 2).

Considering the achievement of CR, the type of treatment and the IPI levels as covariates, a multivariate Cox regression analysis for survival indicated that the achievement of CR and the type of treatment (MACOP-B/VACOP-B) were statistically significant. Differences between IPI levels did not achieve this condition (Table 4).
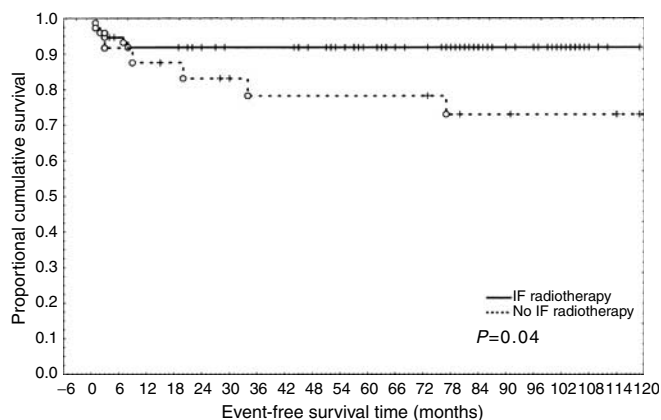
Figure 2 Event-free survival in CR patients treated or not with IF-RT.

Table 4 Multivariate analysis (Cox proportional hazards model) on 138 PMLBCL patients

Covariates	*P* value	Coefficient	95% CI
Type of Chemotherapy (CHOP vs MACOP-B/VACOP-B)	0.027	0.498	0.269–0.923
CR achievement	0.000	11.507	5.378–24.624
IPI level	0.608	1.180	0.626–2.225

DISCUSSION

Our analysis was focused on CHOP *vs* MACOP/VACOP-B, the most commonly regimens used in PMLBCL. The long-term results provided by this retrospective experience indicate that, in this setting, MACOP-B/VACOP-B achieve better results than CHOP, and confirm our previous experience (Todeschini *et al*, 1990). Additional retrospective data are in agreement with our observation (Bertini *et al*, 1991; Lazzarino *et al*, 1993; Falini *et al*, 1995; Cazals-Hatem *et al*, 1996; Lazzarino *et al*, 1997; Martelli *et al*, 1998; Bieri *et al*, 1999; Zinzani *et al*, 2001). Similar results were recently observed in a large retrospective study (Zinzani *et al*, 2002), which included patients treated with chemotherapy other than CHOP or MACOP/VACOP-B. Limiting the observations to CHOP and third-generation therapies, the authors found a projected 10-years progression-free survival (PFS) and OS of 35 and 44% with CHOP, and 67 and 71% with third-generation therapies, respectively.

Although a large randomised study (Fisher *et al*, 1993) showed no difference in outcome for intermediate-high-grade NHLs, in that study, the subgroup of PMLBCL was not separately considered.

In our series, advantages were statistically significant in the MACOP-B/VACOP-B-treated group at low/low-intermediate risk ($P = 0.001$). In the small group of high-intermediate/high-risk patients, an advantage from MACOP-B/VACOP-B as compared to CHOP was observed in terms of CR rate and EFS, but it was not statistically significant ($P = 0.068$).

Based on the results of our experience, we suggest that MACOP-B/VACOP-B can be more effective than CHOP in the treatment of PMLBCL. This assumption is supported by three observations.

First, although this is a retrospective review, the clinical characteristics of the two groups of patients were balanced (age, bulky mediastinum, pleural and pericardial effusion, presence of SVCS, stage I-II *vs* III-IV, type of chemotherapy during the study period) (Table 1).

Second, the IPI risk categories were equally distributed in the two therapeutic groups (Table 1).

Third, the two CT regimens were administered almost uniformly in the study time, thus avoiding the occurrence of possible biases due to different supportive measures.

The achievement of CR was the most significant prognostic factor both for OS and EFS ($P < 0.0001$) (Table 4). A high percentage of patients who reached CR remained event-free, thus suggesting that a therapeutic approach able to increase the CR rate could influence the long-term OS and EFS. In fact, in both chemotherapy groups of our series, patients unresponsive or progressing under CT had invariably a fatal outcome (26 out of 26 died of lymphoma).

Relapse rarely affects PMLBCL patients, although it is the main cause of failure in other large-cell lymphomas. In our series, a very poor outcome was observed in the few relapsed patients (12.2%), since all of them died of lymphoma, independently of first-line therapy and subsequent salvage approaches (Table 2). Involved-field radiotherapy was ineffective in controlling the disease progression too. These findings are in agreement with the majority of reports (Moller *et al*, 1987; Jacobson *et al*, 1988; Cazals-Hatem *et al*, 1996; Zinzani *et al*, 2001), but contrast with the relatively good results described by other authors (Popat *et al*, 1998; Sehn *et al*, 1998) in small groups of refractory/relapsed patients treated with stem cell rescue.

In PMLBCL, the dismal outcome of relapsed/refractory patients seems even worser than in other DLCLs, and it appears as a further characteristic of this lymphoma entity. In fact, in other aggressive NHLs, a variable percentage of patients achieve a second CR and a small but not negligible proportion of them obtain a prolonged survival.

In our experience, patients with advanced stage of disease (i.e. subdiaphragmatic organ involvement) had a lower achievement of CR and a very poor outcome, suggesting that in these patients more intensive approaches, including stem cell transplantation, should be early considered.

Consolidation IF-RT is largely employed in PMLBCL patients, but its role is unclear. In our experience, the administration of IF-RT after CR achievement showed a positive impact on EFS, irrespective of the type of chemotherapy administered ($P = 0.04$) (Figure 2). The favourable role of IF-RT is suggested by a recent large retrospective analysis (Zinzani *et al*, 2002).

The relative high percentage of NR in CHOP-treated patients and the extremely poor outcome of NR/relapsed patients suggest that the maximum effort should be done in the early phase of the disease, given the critical importance of the first-line therapy.

In fact, at the multivariate analysis, CR achievement and type of chemotherapy (MACOP-B, VACOP-B) were independent prognostic factors for EFS, while IPI did not result to be significant (Table 4).

According to these results and in the absence of randomised studies, MACOP-B/VACOP-B followed by IF-RT should be provisionally recommended for PMLBCL patients.

Randomised prospective studies are needed to define the optimal first-line chemotherapy and to assess the role of mediastinal IF-RT in PMLBCL treatment.

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