Favorable outcome of primary mediastinal large B-cell lymphoma in a single institution: the British Columbia experience


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Received 14 April 2005; revised 31 August 2005; accepted 2 September 2005

Background: Primary mediastinal large B-cell lymphoma (PMBCL) is a distinct clinico-pathological subtype of diffuse large B-cell lymphoma (DLBCL). The optimal treatment is unknown, with some studies suggesting a superior outcome with dose-intensive chemotherapy regimens, and the role of radiotherapy remains ill-defined.

Patients and methods: The British Columbia Cancer Agency lymphoma database was searched and records reviewed to identify those patients presenting with a prominent mediastinal mass and considered to be PMBCL based on the current REAL/WHO classifications. Patients were treated based on era-specific BCCA guidelines (1980–1992 MACOPB/VACOPB; 1992–2001 CHOP-type; 2001–present CHOP-R). Beginning in January 1998 involved-field radiotherapy was recommended to be routinely administered following chemotherapy. Prior to this, use of radiotherapy was individualized in advanced disease.

Results: In total, 153 patients with newly diagnosed PMBCL were identified between 28 July 1980 and 30 June 2003. The median age was 37 years (range 13–82) and the majority had stage I/II (74%), bulky mediastinal disease (75%). Overall (OS) and progression-free (PFS) survival at 5 years for the entire cohort were 75% and 69%, respectively. In direct comparison with a cohort of patients with DLBCL, OS (P = 1.0001) and PFS (P = 0.0016) favored PMBCL. The age-adjusted International Prognostic Index (aaIPI) was not predictive of survival (P = 0.18). Five-year OS in patients <65 years old treated with MACOPB/VACOPB, CHOP-R and CHOP-type was 87%, 81% and 71% respectively (P = 0.048). In pair-wise survival comparisons, only MACOPB/VACOPB and CHOP-type treated patients were significantly different (P = 0.016). In Cox multiple regression analysis, poor performance status remained the only predictor of survival, with treatment received demonstrating a trend to worse outcome for patients treated with CHOP-type regimens (P = 0.09). In an intention-to-treat analysis comparing the era before radiotherapy was routinely administered with after, there was no significant difference in 5-year PFS (74% versus 62%; P = 0.09) or OS (78% versus 69%; P = 0.14).

Conclusions: In this single institution, population-based retrospective study, we found that PMBCL patients have excellent survival rates and a distinct plateau is observed in PFS, in striking comparison to DLBCL. The aaIPI was not predictive of survival in this population, suggesting that other prognostic models may be better suited for risk stratification. Dose-intensified chemotherapy with MACOPB or VACOPB demonstrated a trend to superior outcome over CHOP-type chemotherapy. However, further randomized studies are needed and the impact of rituximab on these comparisons must be considered. Finally, the routine addition of radiotherapy does not improve survival.

Key words: Chemotherapy, outcome, primary mediastinal large B-cell lymphoma

introduction

In the Real European–American Lymphoma Classification (REAL) and WHO classification systems, specific diffuse large B-cell lymphoma (DLBCL) variants and subtypes can be distinguished based on unique morphology, disease site presentation and clinical behavior. Primary mediastinal large B-cell lymphoma (PMBCL) is one such entity with distinct clinical, pathological and genetic features [1, 2]. It is believed to arise from thymic medullary B-cells, suggesting a unique histogenesis [3]. Patients are typically young females, presenting in their third to fourth decade with bulky mediastinal masses, often with intrathoracic extension. Tumors display a diffuse growth pattern with variable degrees of sclerosis. Distinct chromosomal aberrations have been observed including consistent gains in chromosomes 9p and 2p corresponding to the JAK2 and cREL loci, respectively [4, 5].
Despite these clear clinical and pathological features there is imprecision in the diagnosis of PMBCL. This diagnostic uncertainty can influence reports on biological characteristics and survival analyses, complicating comparisons between studies. Thus, there have been varied reports regarding survival in PMBCL, in part due to the difficulty in separating PMBCL from DLBCL with secondary mediastinal or hilar involvement. This problem is highlighted in earlier studies where a more aggressive course was observed [6–10] with cure rates similar to DLBCL despite the younger age of presentation. In contrast, more recent analyses have suggested survival patterns equivalent or in some cases superior to DLBCL [11–14]. Recent microarray studies revealed a unique molecular signature of PMBCL distinguishing it from DLBCL, with striking overlap with the nodular sclerosis subtype of classical Hodgkin’s lymphoma (NS cHL) [15, 16] and provide insight into potential useful diagnostic markers [15]. Survival comparisons of PMBCL defined by the gene expression signature support the notion that PMBCL may have a different natural history from DLBCL [16].

The optimal management of PMBCL is unknown. Patients are usually treated with multiagent chemotherapy combined with thoracic radiation. Several retrospective analyses support the use of dose-intensified therapy using MACOPB [17] or VACOPB [18], with suggestive evidence of superiority to CHOP-type regimens using historical comparisons [13, 14]. However, no direct randomized comparisons with CHOP have been undertaken in PMBCL. Further, analyses were made in the ‘pre-rituximab’ era of CHOP chemotherapy [13, 14] and it is unknown whether the addition of rituximab (CHOP-R) will improve observed survival rates over CHOP alone. The added benefit of consolidative radiotherapy to the mediastinum is also ill-defined, with no studies demonstrating a clear overall survival advantage. Given the potential for cardiac damage and secondary malignancies [19], radiation should only be included if a clear benefit has been demonstrated.

The goal of this analysis was to evaluate the outcome and long-term natural history of PMBCL patients diagnosed, staged and treated in a uniform manner under British Columbia Cancer Agency (BCCA) era-specific guidelines. We further sought to determine whether the type of chemotherapy regimen influenced survival. Finally, the role of consolidative radiotherapy was evaluated.

**materials and methods**

This is a population-based retrospective analysis with the primary aim to identify all patients with PMBCL diagnosed and treated according to era-specific BCCA treatment policy guidelines. The computerized lymphoma clinical database, containing all patients treated since July 1980, was searched and medical records were reviewed to identify those patients presenting with a prominent mediastinal mass and considered to be PMBCL based on the current REAL/WHO classifications. Patients with minimal mediastinal involvement as part of more extensive lymphoma elsewhere were excluded. To ensure adequate follow-up for outcome analysis, only those patients diagnosed before 1 July 2003 were included. In total, 153 patients were identified. Patients were treated based on era-specific BCCA guidelines (1980–1992 MACOPB/VACOPB; 1992–2001 CHOP-type; 2001–present CHOP-R). Beginning in January 1998 involved-field radiotherapy (IFRT) was recommended to be routinely administered following chemotherapy. Prior to this, use of radiotherapy was planned for limited stage and individualized in advanced disease.

**diagnosis, staging and response assessment**

All patients had a biopsy proven histological diagnosis of large B-cell lymphoma, usually with sclerosis, reviewed by the Lymphoma Tumour Group pathologist at the Vancouver site of the BCCA. Patients were staged using a conservative interpretation of the Ann Arbor definitions [20] based on physical examination, routine laboratory tests, chest radiograph, computed tomography scan of the thorax, abdomen and pelvis and bone marrow aspirate and biopsy. Stage was not assessed as ‘IV’ unless non-contiguous extensive spread of lymphoma to extranodal sites was documented. Contiguous spread within the thorax was considered stage II even in the presence of radiologic chest wall, lung, pleural or pericardial involvement. Bulky disease was defined as a mass of 10 cm or more in greatest dimension. Response to treatment was assessed one to three months after completion of the planned treatment. Gallium scans were performed post-treatment at the discretion of the treating physician. Complete response (CR) was defined as complete disappearance of all symptoms and any physical or radiological evidence of the disease. Small residual masses in the mediastinum were considered acceptable for the assignment of complete response. Partial response (PR) as defined as a >50% reduction of the tumor mass as assessed by the sum of the products of the largest perpendicular diameters of any measurable lesions. No response (NR) was defined as a <50% response in tumor mass size. Progressive disease was defined as either growth during therapy or regrowth following remission. The age-adjusted International Prognostic Index (aaIPI) was determined for the cohort based on performance status (0, 1 versus ≥2), lactate dehydrogenase (LDH) (normal or elevated) and stage (I/II versus III/IV) (0 factors, low risk; 1 factor, low-intermediate risk; 2 factors, high-intermediate risk; 3 factors, high risk). The Eastern Cooperative Oncology Group scale was used to assess performance status. The LDH was unavailable in six patients and these cases were excluded for calculation of the aaIPI and in univariate and multivariate analyses. Information about additional prognostic factors not included in the aaIPI were also determined [pleural/pericardial involvement, B symptoms, bulky disease, LDH >2× upper limit of normal (ULN)].

**primary treatment**

Patients with limited stage disease (defined by: stage I/II and maximal tumor diameter <10 cm and the absence of B symptoms) were intended to receive brief anthracycline-based chemotherapy followed by IFRT. Patients with advanced stage disease (all others) received an extended course of chemotherapy. Patients were generally treated based on era-specific BCCA chemotherapy treatment guidelines (1980–1992 MACOPB/VACOPB for patients <65 years [17]; 1992–2001 CHOP-type; 2001–present CHOP-R [21, 22]). MACOPB/VACOPB regimens were introduced in the 1980s as weekly, dose intensive regimens completed over a 2-week duration [17]. Owing to increased toxicity, patients >65 years old were typically excluded from receiving these regimens. CHOP-type chemotherapy included standard CHOP [23] in addition to BCCA-specific regimens, ACOP12 [24] and dose-intensified ECV [25]. These regimens have been described previously and have been demonstrated at our institution to be equivalent to CHOP [25]. After 1 March 2001 all patients with advanced stage disease were recommended to receive CHOP-R, based on the initial report of superiority over CHOP chemotherapy [26].

Prior to January 1998, the decision to use radiotherapy in advanced disease was individualized, often guided by gallium imaging. After this time period, the lymphoma tumor group endorsed the use of routine consolidative IFRT following chemotherapy in all patients. Radiation treatment consisted of 3500 cGy in 20 fractions over 4 weeks prescribed to...
the midplane of the mediastinum using megavoltage parallel opposed fields to the involved regions with an adequate safety margin.

**treatment for relapse or progressive disease**

Patients whose lymphoma either progressed on initial therapy or recurred following primary treatment were treated with a variety of salvage regimens. If chemosensitivity to salvage regimens was demonstrated, patients <65 years were eligible to undergo high dose chemotherapy and stem cell transplantation (HDC/SCT).

**statistical methods**

Overall survival (OS) was calculated from the date of diagnosis to the date of last follow-up or death from any cause. Progression-free survival (PFS) was calculated from the date of diagnosis to the date of documented disease progression or death from toxicity; patients alive without progressive disease were censored on the date of their last follow-up visit and patients dying of causes unrelated to lymphoma or therapy were censored at the time of death. Survival curves were plotted using the method of Kaplan and Meier and compared using the log-rank test [27]. Log-rank tests were used to determine the prognostic significance of the following factors: aaIPI, age > 40, PS (0, 1 versus ≥2), stage (I/II versus III/IV), LDH, LDH >2× ULN, chemotherapy regimen, addition of radiation in advanced disease, bulky mediastinal mass, B symptoms, and presence of pleural or pericardial involvement. Multiple regression analysis using a Cox proportional hazards model and forward selection method was used in patients receiving either CHOP or MACOPB/VACOPB to determine the impact of prognostic variables and treatment type on OS. The χ²-test was used for the comparison of covariate frequencies across treatment groups. Differences were considered significant if the two-tailed P value was ≤0.05. All analyses were performed using SPSS version 11.0.1 and 13.0.0.

**results**

**patient characteristics**

A total of 153 patients were identified with PMBCL, diagnosed between July 1980 and 1 July 2003, with a median follow-up of ~9 years. Nine patients were lost to follow-up; however, they had all been observed for an extended duration of time (3.8–18.7 years) and remained free of disease at their last clinic visit. The clinical characteristics of the entire cohort is shown in Table 1. There were 67 females and 86 males, median age 37 years (range 13–82). Only one patient was <18 years of age. The majority of patients had stage I/II (74%), bulky mediastinal disease (75%) with direct intrathoracic extension (76%). By the aaIPI, most had intermediate risk disease (Table 1). Four patients had a family history of Hodgkin’s lymphoma (one syngeneic twin, two siblings, one grandmother), which is of interest given the clinico-pathologic overlap between these diseases and recent microarray studies suggesting a shared pathogenesis [15, 16].

The actual treatments received were CHOP (n = 67 including CHOP, ACOP12 and ECV), MACOPB/VACOPB (n = 47), CHOP-R (n = 19), elderly anthracycline-based regimens (n = 6) and frail/refused (n = 2). There was no difference in OS between conventional CHOP, ACOP12 and intensified ECV (results not shown) and thus these regimens were all considered ‘CHOP-type’ chemotherapy. There further was no difference in OS between MACOPB- and VACOPB-treated patients (results not shown). One patient received a single cycle of CVPP/ABV at the treating physicians discretion and owing to lack of response, IFRT was subsequently administered. Eleven patients received brief CHOP-type (CHOP-type × 3 cycles, n = 8; ‘abbreviated’ VACOPB 6 weeks, n = 3) chemotherapy followed by IFRT.

**survival analyses**

The OS and PFS for the whole PMBCL cohort at 5 years were 75% and 69% (Figure 1A and B), respectively. For patients <40 years of age, the 5-year OS and PFS were slightly superior, at 81% and 73%, respectively. The overall response rate was 90% (77% CR; 12% PR). In total, 52 patients have died, 38 from lymphoma, 14 from other causes [cardiac (n = 6), pneumonia (n = 1), suicide (n = 1), Alzheimer’s disease (n = 1), secondary malignancy (n = 3), renal failure (n = 1), cirrhosis (n = 1)].

**survival comparison: PMBCL versus DLBCL**

Given the excellent outcome and striking plateau seen for PFS in our PMBCL cohort, we sought to compare the survival of PMBCL to a series of DLBCL patients diagnosed and treated over the same time period (1 July 1980 to 1 July 2003). For this analysis, DLBCL patients with primary CNS/ocular lymphoma or who were HIV positive were excluded. There were 1273 patients identified: 43% females and 57% males, median age 64 years, 70% advanced stage, 30% limited stage. There was a significant difference in 10-year PFS (69% versus 47%; P = 0.0001) and 10-year OS (66% versus 43%; P = 10⁻⁴), favoring PMBCL (Figure 2A and B). These same significant differences were also observed even if the comparison was restricted to patients <65 years old (results not shown).

Furthermore, unlike PMBCL, a continuous risk of relapse

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**Table 1.** Presenting clinical features of all primary mediastinal large B-cell lymphoma patients

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Total patients [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>153</td>
</tr>
<tr>
<td>Sex (female: male)</td>
<td>67:86</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>37</td>
</tr>
<tr>
<td>Bulky (≥10 cm)</td>
<td>114 (75)</td>
</tr>
<tr>
<td>B symptoms</td>
<td>72 (47)</td>
</tr>
<tr>
<td>PS &gt;1</td>
<td>61 (40)</td>
</tr>
<tr>
<td>Elevated LDH³</td>
<td>113 (77)</td>
</tr>
<tr>
<td>LDH &gt;2× ULN⁴</td>
<td>46 (30)</td>
</tr>
<tr>
<td>Stage I/II</td>
<td>113 (74)</td>
</tr>
<tr>
<td>aaIPI</td>
<td></td>
</tr>
<tr>
<td>0 factors</td>
<td>18</td>
</tr>
<tr>
<td>1 factors</td>
<td>73</td>
</tr>
<tr>
<td>2 factors</td>
<td>41</td>
</tr>
<tr>
<td>3 factors</td>
<td>18</td>
</tr>
<tr>
<td>Pleural or pericardial effusion</td>
<td>77 (50)</td>
</tr>
<tr>
<td>Radiotherapy included in primary therapy⁵</td>
<td>50 (39)</td>
</tr>
<tr>
<td>Median follow-up (years)</td>
<td>9</td>
</tr>
</tbody>
</table>

¹LDH not available in seven patients.
²aaIPI not available in three patients.
³Excluding: primary progressors, radiation as part of ‘limited stage disease n = 11’, frail or patient refusal.
⁴LDH, lactate dehydrogenase; ULN, upper limit of normal; aaIPI, age-adjusted International Prognostic Index.
⁵Excluding: primary progressors, radiation as part of ‘limited stage disease n = 11’, frail or patient refusal.
was observed in the DLBCL group with 20 years of follow-up, further highlighting the distinct difference in natural history between these two diseases (Figures 1B and 2B).

### analysis of prognostic factors and chemotherapy regimen received in PMBCL

The IPI has been extensively validated in DLBCL but its usefulness in PMBCL has varied across studies. Given the younger age of presentation of PMBCL patients, we evaluated the aaIPI in our cohort and it was not predictive of survival (5-year OS IPI 0 83%, IPI 1 76%, IPI 2 68%, IPI 3 62%; \( P = 0.18 \)). Evaluation of individual IPI risk factors in addition to other risk factors demonstrated that a LDH > 2 × ULN, poor performance status (>1) and age >40 years correlated with reduced survival rates (Table 2) in univariate analysis.

Eleven patients were considered to have ‘limited’ stage disease and received brief chemotherapy followed by IFRT and had a 5-year PFS and OS of 82%. Of interest, in retrospect, four of these patients fit our current criteria for advanced stage disease (two with B symptoms, two with mediastinal mass ≥10 cm); however, none of these individuals relapsed despite fewer chemotherapy cycles. To evaluate the impact of the type of chemotherapy regimen on OS in patients with advanced stage disease as defined above, three treatment groups were considered: CHOP-type; MACOPB/VACOPB; and CHOP-R (Figure 3). This analysis was limited to patients <65 years of age due to the age restriction necessary for the administration of VACOPB/MACOPB. One patient, aged 69 years, was in excellent health and was able to receive a full-course of VACOPB and therefore was also included in the survival analysis comparing chemotherapy regimens. The 5-year OS in patients treated with MACOPB/VACOPB \( (n = 47) \), CHOP-type \( (n = 63) \) and CHOP-R \( (n = 18) \) were 87%, 71% and 82% \( (P = 0.048) \), respectively (Figure 3). However, pair-wise comparisons of survival using the Kaplan–Meier method showed that only MACOPB/VACOPB and CHOP-type patients were significantly different \( (P = 0.016) \) (results not shown). In contrast, there was no difference in 5-year OS between CHOP and CHOP-R, and similarly between CHOP-R and MACOPB/VACOPB (results not shown). Comparison of baseline characteristics of patients who received CHOP and MACOPB/VACOPB demonstrated

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**Figure 1.** (A) Overall survival of primary mediastinal large B-cell lymphoma (PMBCL). (B) Progression-free survival of PMBCL.

**Figure 2.** (A) Overall survival primary mediastinal large B-cell lymphoma (PMBCL) (black) versus diffuse large B-cell lymphoma (DLBCL) (gray) \( (P = 10^{-4}) \). (B) Progression-free survival PMBCL (black) versus DLBCL (1273 gray) \( (P = 0.0001) \).
that there was a greater proportion of patients with poor performance status and LDH elevated 2× ULN in the CHOP group (Table 3). Patients who received CHOP-type regimens were more likely to have received primary radiotherapy ($P = 0.003$), in part due to the era in which they were treated. In Cox multiple regression analysis limited to patients who received CHOP or MACOPB/VACOPB, poor performance status (>1) remained the only predictor of reduced survival, although treatment received demonstrated a marginally significant trend for worse outcome (Table 4) (hazard ratio for CHOP-type 2.9; $P = 0.09$).

**consolidative radiation therapy**

Starting in January 1998, the lymphoma tumor group recommended consolidative IFRT following a full-course of CHOP-type chemotherapy (after March 2001, CHOP-R) in all patients with advanced stage PMBCL. In an intention-to-treat analysis, comparing the era before January 1998 ($n = 103$) with after (radiotherapy era, $n = 50$), there was no difference in 5-year OS (78% versus 69%; $P = 0.14$) or PFS (73% versus 62%; $P = 0.10$) (Figure 4). In a separate analysis evaluating patients who actually received radiotherapy (excluding: patients treated with brief chemotherapy and IFRT for ‘limited’ stage disease; primary progressors; patients treated on elderly protocols; patients who refused or were too frail for potentially curative treatment), there was no impact on PFS ($P = 0.65$) or OS ($P = 0.77$) regardless of whether radiation was received ($n = 50$) or not ($n = 75$). Evaluation of patients with mediastinal bulky disease similarly failed to reveal any impact of radiotherapy on PFS or OS (results not shown). Of interest, in the treatment era prior to standard radiotherapy, 54 patients

**Table 2.** Univariate analysis of prognostic factors effect on overall survival in primary mediastinal large B-cell lymphoma patients treated with CHOP or MACOPB/VACOPB

<table>
<thead>
<tr>
<th>Covariate</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>aaIPI</td>
<td>0.14</td>
</tr>
<tr>
<td>Treatment type (CHOP versus MACOP/VACOP)</td>
<td>0.02</td>
</tr>
<tr>
<td>age &lt;65 years</td>
<td></td>
</tr>
<tr>
<td>Bulky disease</td>
<td>0.20</td>
</tr>
<tr>
<td>B symptoms</td>
<td>0.26</td>
</tr>
<tr>
<td>Pleural or pericardial effusion</td>
<td>0.66</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>0.45</td>
</tr>
<tr>
<td>LDH &gt;2× ULN</td>
<td>0.025</td>
</tr>
<tr>
<td>Stage III/IV</td>
<td>0.21</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.22</td>
</tr>
<tr>
<td>Age &gt;40 years</td>
<td>0.003</td>
</tr>
<tr>
<td>Extranodal sites &gt;1</td>
<td>0.93</td>
</tr>
<tr>
<td>Performance status &gt;1</td>
<td>0.006</td>
</tr>
</tbody>
</table>

aaIPI, age-adjusted International Prognostic Index; LDH, lactate dehydrogenase; ULN, upper limit of normal.

**Figure 3.** Overall survival by treatment regimen: MACOPB/VACOPB (black); CHOP-R (gray); CHOP (dashed) ($P = 0.047$).

**Table 3.** Clinical features of CHOP and MACOPB/VACOPB patients <65 years

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>CHOP, &lt;65 years [n (%)]</th>
<th>MACOPB/VACOPB, &lt;65 years [n (%)]</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>63</td>
<td>47</td>
<td>NA</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>41:22</td>
<td>24:23</td>
<td>0.14</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>37</td>
<td>33</td>
<td>NA</td>
</tr>
<tr>
<td>Bulky (≥10 cm)</td>
<td>51 (81)</td>
<td>38 (81)</td>
<td>0.99</td>
</tr>
<tr>
<td>B symptoms</td>
<td>35 (56)</td>
<td>14 (30)</td>
<td>0.007</td>
</tr>
<tr>
<td>Performance status &gt;1</td>
<td>29 (46)</td>
<td>10 (21)</td>
<td>0.007</td>
</tr>
<tr>
<td>Elevated LDH*</td>
<td>53 (87)</td>
<td>34 (76)</td>
<td>0.13</td>
</tr>
<tr>
<td>Elevated LDH &gt;2× ULN</td>
<td>27 (43)</td>
<td>9 (19)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

*LDH not available in two MACOPB/VACOPB and two CHOP patients. Excluding: primary progressors, radiation as part of ‘limited stage disease’ $n = 11$, frail or patient refusal.

NA, not applicable; LDH, lactate dehydrogenase; ULN, upper limit of normal; aaIPI, age-adjusted International Prognostic Index.

**Table 4.** Cox proportional hazard ratios of covariates in multivariate analysis

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Hazard ratio</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOP versus MACOPB/VACOPB</td>
<td>2.85</td>
<td>0.09</td>
</tr>
<tr>
<td>Performance status &gt;1</td>
<td>2.66</td>
<td>0.01</td>
</tr>
<tr>
<td>LDH &gt;2× ULN</td>
<td>2.44</td>
<td>0.12</td>
</tr>
<tr>
<td>Age &gt;40 years</td>
<td>1.23</td>
<td>0.37</td>
</tr>
</tbody>
</table>

LDH, lactate dehydrogenase; ULN, upper limit of normal.
due to chemoresistance (intensified therapy. Thirteen did not proceed to HDC and SCT remission, 25 of whom were young and fit enough to receive chemoresistant diseases all succumbed to lymphoma. post-transplant and died of lymphoma. The seven patients with SCT (one allotransplant, one autotransplant). Both relapsed had an adequate performance status to proceed with HDC and only two demonstrated tumor chemosensitivity and years following the original diagnosis. Of the remaining nine subsequently died of mitral valve-associated cardiac failure 20 years following the original diagnosis. All but one of these patients died of lymphoma and the remaining individual died of renal failure.

failure of primary therapy

Fourteen patients progressed during primary therapy and 31 relapsed after achieving an initial remission. Interestingly, 97% of relapses occurred within the first 2.5 years from diagnosis, most within the first year (77%).

Of the patients with initial refractory disease, four were frail and received palliative regimens only (three >65 years of age, one <65 years). One additional patient received radiotherapy only at progression and entered a complete remission but subsequently relapsed. Both patients with an equivocal gallium scan remain in a sustained remission even though they did not receive radiation. There was no difference in OS between gallium-positive and gallium-negative patients (results not shown).

Figure 4. Progression-free survival by radiotherapy era: pre-radiotherapy (black); post-radiotherapy (gray) (P = 0.10).

had a gallium scan after chemotherapy to guide decisions regarding the use of radiotherapy: 43 were gallium negative; nine gallium positive; two equivocal. Only one patient with a gallium-negative scan subsequently received IFRT at the treating physician’s discretion and has remained in a durable remission. Of the remaining 42 gallium-negative patients, nine subsequently relapsed. All of the patients with a gallium-positive scan received IFRT and only one subsequently relapsed. Both patients with an equivocal gallium scan remain in a sustained remission even though they did not receive radiation. There was no difference in OS between gallium-positive and gallium-negative patients (results not shown).

Discussion

Primary mediastinal large B-cell lymphoma was first classified as a distinct entity in the REAL classification based on unique clinico-pathological features that overlap to some degree with the NS cHL. Evidence of an overlapping pathogenic relationship between PMBCL and NS cHL at a molecular level has been supported by recent gene expression profiling [15, 16] and, using this refined molecular signature, a more favorable prognosis than that for DLBCL was observed [16]. Consistent with recent literature, we also observed excellent survival rates in our PMBCL cohort that were superior to DLBCL. Furthermore, unlike DLBCL, relapses beyond 2 years of primary, potentially curative therapy were rare (Figures 1B and 2B), with most occurring within the first year of treatment completion. This may in part be due to a lack of discordant relapse, a phenomenon that occurs in a small but significant proportion of patients with nodal DLBCL [28].

The optimal management of PMBCL has been widely debated. Comparison of CHOP with second- and third-generation regimens failed to show superiority of the intensified regimens in DLBCL; however, PMBCL was not specifically assessed in this landmark study [29]. Recent studies have suggested that more aggressive regimens may be associated with better outcomes [13, 14]; however, no prospective randomized studies comparing these regimens have been performed to answer this question definitively. Furthermore, diagnostic imprecision can cloud comparison of studies evaluating outcome. New molecular markers such as TRAF1, STAT6 or MAL [15, 30, 31] that can reliably and reproducibly differentiate PMBCL from DLBCL with mediastinal involvement are needed to ensure that the same populations are being studied. In the present study, the MACOPB/VACOPB regimens was associated with superior survival rates; however, despite the fact that our treatment regimens were based on era-specific guidelines, there were more patients in the CHOP group with a poor performance status and elevated LDH and in multivariate analysis, only a trend to improved outcome was associated with the more intensified regimens. Given the limitations of such historical comparisons, randomized controlled studies are necessary to compare these therapies.

A minority of patients presented with limited stage disease and these individuals were successfully treated with brief
CHOP-type chemotherapy followed by IFRT. This is potentially a treatment option for this rarely encountered situation, particularly if there is a contraindication to an extended course of chemotherapy.

Recent interest has turned to the use of rituximab in combination with CHOP for the treatment of DLBCL. Consistently superior outcomes in DLBCL have been demonstrated using the combination of CHOP-R compared with CHOP [21, 22, 32]; however, specific evaluation of CHOP-R in PMBCL has not been extensively studied. At the BCCA, a policy was introduced in March 2001 recommending that rituximab should be added to each cycle of CHOP chemotherapy in patients with advanced stage DLBCL, including PMBCL [22]. Comparison of CHOP-R with CHOP in PMBCL in our study failed to reveal any survival advantage of the former regimen; however, those treated with CHOP-R represent a small group with relatively short median follow-up. It is possible that over time with larger treatment groups to compare, the same survival benefit of CHOP-R in DLBCL may be seen in PMBCL with cure rates similar to that observed with the more dose-intensive regimens.

Patients with progressive disease during primary treatment have very poor prognosis and, in our experience, there were no long-term survivors. Disease in the majority of these patients did not demonstrate chemosensitivity when treated with a salvage regimen and both patients who underwent SCT relapsed and died of lymphoma, in contrast to some prior reports [33]. Patients fared slightly better in the relapsed setting, with over half of the eligible patients able to proceed with HDC and SCT with a modest long-term survival rate, suggesting that salvage therapy can be successful in well selected patients with relapsed PMBCL. With recent evidence supporting activation of NF-kB in the majority of patients with PMBCL [15, 34], targeted therapy with bortezomib warrants further study in patients who have failed primary therapy.

A major clinical challenge in the management of PMBCL is the evaluation of residual masses post-chemotherapy with poor correlation between the size of a residual mass on computed tomography and risk of relapse [35, 36]. In many instances the residual density represents fibrotic tissue rather than active lymphoma, similar to the problem encountered in bulky mediastinal NS cHL [35]. Many patients are given radiotherapy as consolidative treatment in PMBCL for this reason; however, it is unclear whether this impacts relapse or cure rates. Some studies have suggested an improvement in event-free survival when radiotherapy is given to in patients achieving a CR [13]; however, other studies have failed to demonstrate a survival benefit [37]. The retrospective nature of such analyses, including imprecise definitions of response rates, is problematic and randomized studies addressing this question are lacking in this population. Furthermore, similar to the treatment approach in NS cHL, there is an inherent concern of long-term toxicities of mediastinal radiotherapy, including increased risk of cardiovascular disease and secondary malignancies, particularly given the young population at risk [19]. In January 1998, our BCCA lymphoma tumor group endorsed the addition of radiotherapy at the end of an extended course of chemotherapy in all patients with advanced stage PMBCL. An intention-to-treat analysis failed to reveal any survival advantage or reduced local relapse rate with the addition of radiotherapy. In fact, there is an unexplained trend to improved PFS in the era before routine radiotherapy. Other studies have seen similar favorable survival rates without the routine usage of radiotherapy [11]. Improved identification of patients who may benefit from the addition of radiotherapy would be desirable.

$^{67}$Ga scintigraphy has been used to detect persistent viable tumor in patients with a residual mass after therapy [38]. In our center, gallium scanning was often utilized in the era before routine radiotherapy to guide usage of radiotherapy after chemotherapy. It was withheld in 42 of the 43 patients with a negative gallium scan and of these, nine (21%) relapsed. All nine patients with a positive gallium scan after chemotherapy received radiotherapy and only one (11%) has relapsed. Although it is possible that radiotherapy is converting patients to true CRs, false positives cannot be ruled out. Furthermore, our results highlight the difficulty in detecting minimal residual disease; thus, it is unclear whether gallium scans assist in selecting patients who may benefit from consolidative radiotherapy. Preliminary studies suggest that $^{18}$F-fluorodeoxyglucose (FDG) PET may be superior to $^{67}$Ga for the detection of residual disease [39]. Studies evaluating FDG PET for this purpose are needed to determine which patients, if any, would benefit from radiotherapy and identify those cases where it can be safely withheld without compromising cure rates, with the goal of reducing secondary long-term complications.

In summary, this population-based retrospective study demonstrates that patients with PMBCL have a favorable outcome, with those who survive beyond 2 years very unlikely to relapse, further highlighting it as distinct entity from DLBCL. While there was a trend to improved survival with the dose-intensive regimens MACOPB/VACOPB, superiority can only be addressed in a well-designed randomized clinical trials. Furthermore, the full impact of rituximab in survival comparisons is not yet fully appreciated, and long-term follow-up of a larger number of patients treated with chemotherapy in combination with rituximab is needed to determine the impact on outcome of rituximab in this population. Finally, our analysis does not support the routine usage of radiotherapy in PMBCL. Studies incorporating FDG PET into decision-making are needed and may provide the potential to avoid long-term toxicities in this young patient population most of whom are cured by chemotherapy alone.

**references**


