Primary Mediastinal B Cell Lymphoma: Diagnosis and Treatment Approach

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ABSTRACT

Primary mediastinal B-cell lymphoma (PMBCL) is a distinct B-cell lymphoma, representing only 2–3% of non-Hodgkin lymphoma (NHL). However, diagnosis can be challenging; newer diagnostic tools are required to distinguish PMBCL from overlapping B-cell lymphomas. Dysregulation of various signalling pathways and alteration of the tumour microenvironment are implicated in the pathogenesis of PMBCL. Management is challenging due to the scarcity of prospective studies. The commonly used first line immunochemotherapy regimens are R-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone, and rituximab) and DA-EPOCH R (dose adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, and rituximab). End-of-treatment (EOT) fluorodeoxyglucose positron emission tomography (FDG PET) scans are the recommended imaging modality to assess response. About 10–30% of PMBCL patients may develop relapsed/refractory (RR). The most common approach for RR PMBCL is salvage immunochemotherapy followed by ASCT. Unfortunately, the outcome of RR PMBCL is relatively poor. Therefore, newer therapeutic agents are being developed and evaluated under clinical trials, including CAR-T (chimeric antigen receptor T) cell therapy.

Keywords: Non-Hodgkin lymphoma; primary mediastinal B cell lymphoma, allogeneic stem cell transplantation; Novel agents; Positron emission tomography (PET)-adapted therapy; CAR T cell
like cells can also be seen. PMBCL strongly express B-cell antigens, such as CD20; surface immunoglobulins (Ig) are usually absent.\textsuperscript{10} However, the variable or weak expression of CD30 can mask differentiation from NScHL. Besides, \textit{De novo} DLBCL and MGZL share many of the same antigens as PMBCL making their differentiation challenging by conventional diagnostic tests. The key differentiating points between these entities are illustrated in Table I.\textsuperscript{11,12}

Immunohistochemical biomarkers with high positive predictive value (PPV) for PMBCL include CD23 (98%), p63 (96%), BOB.1 (94%) and CD79a (90%). Some recommend using at least CD79a, BOB.1 and cyclin E (100% PPV in cHL) for accurate differentiation between cHL and PMBCL.\textsuperscript{13} Another immunohistochemical marker MAL, a lipid raft-associated protein found in 70% of cases of PMBCL, is useful to differentiate PMBCL from DLBCL, expressing in only 3% of cases.\textsuperscript{14} Additionally, CD200 has been found to have superior sensitivity (94%) and equivalent specificity (93%) to other markers, including MAL and CD23.\textsuperscript{15} Gene expression profiling can accurately diagnose 80% of PMBCL cases and is expected to play a central role in future diagnostics.\textsuperscript{16} \textit{PDCD1LG2} (PD-L2) RNA \textit{in situ} hybridisation and a 58-gene expression assay (Lymph3Cx) have been investigated to distinguish between PMBCL and DLBCL, which showed a low misclassification rate compared to conventional diagnostics.\textsuperscript{17,18} There is no single diagnostic laboratory biomarker for PMBCL; therefore, combined evaluation of clinical, morphological and immunophenotypic features by expert haematopathologist is necessary in all cases.

**Clinical evaluations, diagnostic tools and prognosis**

PMBCL predominantly affects Caucasian women in their third or fourth decade of lives. However, the incidence is similar in African Americans.\textsuperscript{5} Common presentations include compressive symptoms from the large mediastinal mass, such as cough or breathlessness. About 25–30% of patients have some degree of superior vena cava obstruction at diagnosis.\textsuperscript{6} PMBCL tends to be localised initially, although wide dissemination can occur at relapse. Bone marrow and central nervous system (CNS) involvement are uncommon at presentation, 9% and 5%, respectively.\textsuperscript{6,7} It has been suggested that PMBCL originates from germinal or post-germinal centres thymic B-cells.\textsuperscript{8} The tumour often comprises clear large B-cells with compartmentalised fibrosis.\textsuperscript{9} Rarely, Reed-Sternberg-
predicted a significantly higher 5-year progression-free survival (PFS) (99% vs. 68%, \( p < 0.001 \)) and 5-year OS (100% vs. 83%, \( P<0·001 \)) compared to positive scan in prospective IELSG-26 study. However, a false positive EOT-PET scan can happen due to residual inflammation in the mediastinum. Studies suggest that EOT-PET has a high negative predictive value (NPV) but poor PPV. Newer techniques are being implemented to enhance the predictive ability of FDG-PET. One of them is TLG which combines the assessment of tumour volume and metabolism. Low TLG can predict significantly better 5-year PFS and OS compared to high TLG.

### Table I: Key differences between PMBCL, MGZL, cHL and DLBCL

<table>
<thead>
<tr>
<th></th>
<th>PMBCL</th>
<th>MGZL</th>
<th>cHL</th>
<th>DLBCL</th>
</tr>
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<tbody>
<tr>
<td>Sex predominance</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>35</td>
<td>30</td>
<td>Bi modal</td>
<td>65</td>
</tr>
<tr>
<td>Common presentations</td>
<td>Features of localised mediastinal compression</td>
<td>Features of localised mediastinal compression</td>
<td>Painless neck nodes or incidental mediastinal mass</td>
<td>Rapidly enlarging nodal or extranodal masses</td>
</tr>
<tr>
<td>Morphology</td>
<td>Medium to large cells clear cytoplasm and frequent compartmentalised fibrosis</td>
<td>Heterogeneous with large cells and areas of necrosis</td>
<td>Multinuclear Reed-Sternberg cells in a reactive infiltrate</td>
<td>Medium to large cells with bands of sclerosis</td>
</tr>
<tr>
<td>Immunophenotype</td>
<td>Strong expression of B-cell antigens; Negative for surface Ig; Positive for PAX5, OCT2, BOB1; variable expression of CD30; Majority express CD23, MAL, PDL &lt;1 and PDL &lt; 2</td>
<td>Heterogeneous with variable expression of B-cell antigens; Negative for surface Ig; PAX5, OCT2, BOB1, CD30 usually expressed</td>
<td>Reduced expression of B-cell antigens; Negative for surface Ig; usually negative for OCT2 and BOB1; variable PAX5; CD30 CD15 usually expressed; EBV expressed in 40%</td>
<td>Strong expression of B-cell antigens; Typically positive for Surface Ig; PAX5, OCT2, BOB1 usually positive; CD30 rarely positive; EBV positive in 5%</td>
</tr>
<tr>
<td>5-year OS</td>
<td>79–97%</td>
<td>74%</td>
<td>85%</td>
<td>65%</td>
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PMBCL, primary mediastinal B-cell lymphoma; MGZL, mediastinal grey zone lymphoma; cHL, classical Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus

### Utility of FDG-PET in PMBCL

FDG-PET is the recommended imaging modality for post-treatment response evaluation in aggressive lymphomas, including PMBCL. Among different methods developed for FDG interpretation, the qualitative Deauville score and the quantitative standardised uptake value (SUV) are commonly used in clinical practice, while total lesion glycolysis (TLG) is still primarily used in research. A Deauville score of \(< 3\) (uptake less than or equal to the liver) is considered a negative end of treatment EOT-PET in PMBCL, indicating a complete metabolic response to therapy. A negative EOT-PET scan predicted a significantly higher 5-year progression-free survival (PFS) (99% vs. 68%, \( p < 0.001 \)) and 5-year OS (100% vs. 83%, \( P<0·001 \)) compared to positive scan in prospective IELSG-26 study. However, a false positive EOT-PET scan can happen due to residual inflammation in the mediastinum. Studies suggest that EOT-PET has a high negative predictive value (NPV) but poor PPV. Newer techniques are being implemented to enhance the predictive ability of FDG-PET. One of them is TLG which combines the assessment of tumour volume and metabolism. Low TLG can predict significantly better 5-year PFS and OS compared to high TLG.
Conventionally, CHOP was the usual first-line treatment for PMBCL as it was considered a subtype of DLBCL. Later, the addition of rituximab (R-CHOP) has been shown to improve event-free survival (EFS) compared to CHOP (78% vs. 52%; \( p = 0.012 \)) without OS benefit (88·5% vs. 78·2%; \( p = 0.158 \)) in a DLBCL trial. Alternative regimens include VACOP-B (etoposide, doxorubicin, cyclophosphamide, prednisolone, and bleomycin) and MACOP-B (methotrexate, doxorubicin, cyclophosphamide, prednisolone, and bleomycin). MACOP-B-like regimens have shown to have similar complete response (CR) rates as CHOP-like regimens but better OS; however, the benefit became unclear after the introduction of rituximab to CHOP. Likewise, R-CHOP and V/MACOP-B are considered equivalent. Of note, a UK based R-CHOP-14 vs. 21 trial showed no significant difference in outcomes.

**Current first-line treatment**

An effective first-line treatment is of paramount importance for PMBCL as the cure rate for R/R disease continues to be poor, as mentioned earlier. However, apart from some retrospective studies or subgroup analysis within prospective DLBCL trials, there is no established standard of care for PMBCL to date. Besides, balancing maximum cure against minimum long-term toxicity in young patients with PMBCL remains controversial. Treatment options that are currently available or under evaluation are illustrated in Figure 1.

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Relapsed/refractory disease

Most of the PMBCL patients if not all, usually relapse within 12 months. Relapse is more likely to be widespread and can involve the CNS. The 5-year PFS is around 27% for RR patients.4 For RT-naïve patient with localised relapse, RT alone can be curative.19 The most common approach for RR PMBCL is salvage immunochemotherapy followed by ASCT, like DLBCL.4,36 Unfortunately, one retrospective study reported that only 22% of PMBCL patients achieved enough response to proceed to ASCT despite using second- and third-line salvage therapy.36 Interestingly, patients who proceeded to ASCT had better 2-year post-ASCT OS (67%) and PFS (57%). These improved outcomes after ASCT have been confirmed in another retrospective multicentre study.4 The role of allogeneic stem cell transplant (allo-SCT) in RR PMBCL is debatable, despite its curative potential. However, it may be considered in selected patients, including those who achieved a CR post-CAR-T.37,38 Among novel agents, pembrolizumab, a programmed cell death 1 (PD-1) blocker, has been approved by the US Food and Drug Administration (FDA) for RR PMBCL patients. Interim data from an ongoing phase 2 KEYNOTE trial using pembrolizumab in RR PMBCL patients showed an ORR of was 45% and CR of 13%.39,40 The combination PD-1 blockade and chemotherapy are expected to have greater advantages for RR PMBCL patients.41

Radiotherapy in PMBCL

While PMBCL is a radiosensitive disease, the role of RT is still controversial in the treatment as it increases the risk of secondary cancers and cardiac complications. A retrospective analysis suggested an OS benefit for PMBCL patients receiving RT following multiagent chemotherapy over those who did not.21 Other evidence indicated that the improved outcomes with RT were more marked in those with partial response (PR), classified as Deauville 4-5 on PET, as consolidative RT has the potential to transform a significant number of PR to CR.6,31 While there is evidence for RT in those with residual disease, its benefit in patients in CR is still unknown. Therefore, RT is probably given the high cumulative anthracycline dose with DA-EPOCH-R, currently, there is no randomised trial comparing R-CHOP vs. DA-EPOCH-R to reach a solid conclusion for PMBCL patients. Brentuximab, previously reserved for RR disease, is currently under investigation as part of frontline regimens as it has better safety and efficacy profiles. Studies failed to show any OS benefit for upfront autologous stem cell transplant (ASCT) in PMBCL compared to first-line therapy.30

Novel therapeutic approaches

The ultimate goal for RR PMBCL patients is to take the patients to ASCT, which is only possible if there are sufficient responses to salvage therapy. However, conventional salvage regimens continue to yield unsatisfactory results in PMBCL. Therefore, the focus has been shifted towards novel therapies. Many therapeutic targets have been identified for PMBCL. The JAK-STAT pathway is one of the rational targets because of its role in lymphomagenesis. A small number of trials with the JAK2-specific inhibitors (pacritinib and ruxolitinib) are currently in progress.42,43 STAT3 inhibitors are still in the preclinical stage of development.44
Ibrutinib, a Bruton tyrosine kinase inhibitor targeting NF-κB pathway, has also been tested in a few PMBCL patients with promising results. Antibody-drug conjugates, brentuximab vedotin (BV), was investigated in a phase 2 trial in CD30-positive RR PMBCL patients; ORR was only 13.3%. A trial of BV plus R-CHP (vincristine omitted to reduce the risk of peripheral neuropathy) is also in progress for CD30-positive treatment-naive PMBCL patients. Interim data reported a 1-year PFS of 87%, CI 57-97%.

CAR-T therapies are showing exciting prospect in the treatment of haematological malignancy. However, the major concerns with their use are the possibility of cytokine release syndrome (CRS) and neurotoxicity, termed CAR-T-cell-related-encephalopathy syndrome (CRES). Importantly, CAR-T therapy can cause off-target destruction of healthy B cells, leading to B-cell aplasia. The phase 1-2 single-arm multicentre ZUMA-1 trial investigating Abxicatragene Ciloleucel (axi-cel), an autologous anti-CD19 CAR-T treatment, in RR aggressive NHL patients, has led to approval for RR DLBCL and PMBCL patients by FDA and European Commission. Initial data reported an ORR of 85% and CR of 70% in the combined PMBCL/FL sub-group. About 93% of patients developed CRS and 64% neurotoxicity, although both were largely reversible. Tocilizumab, an anti-IL6R monoclonal antibody, was required for 43% of patients to treat these events with no compromise in CAR-T response. Primary real-world data on axi-cel CAR-T therapy in RR PMBCL, is comparable to the ZUMA-1 trial with ORR of 79% and CR 50% and comparable safety data. There are many trials in progress or planned that include PMBCL, and hopefully, PMBCL patients will benefit from these trials. Lenalidomide, tazemetostat (targeting EZH2 mutations) and bispecific T-cell engager antibodies are currently under investigation in various high-grade B-cell lymphomas, including PMBCL. However, robust data is required to understand the long-term outcomes and delayed toxicities of the above novel therapies.

**Paediatric approach**

Paediatric groups of patients with Burkitt lymphoma (BL), DLBCL, or PMBCL have historically been treated on the same protocols as adults. These regimens consist of alternating cycles of dose-intensive multiagent chemotherapy, including doxorubicin, high-dose methotrexate, and intrathecal chemotherapy for central nervous system prophylaxis. Patients do not typically receive consolidative radiation. Outcomes among patients with PMBCL in paediatrics trials have been inferior compared with the excellent outcomes in BL and DLBCL but are similar to what has been observed in adults. The Berlin-Frankfurt-Munster Group reported pooled outcomes of children and adolescents with PMBCL treated in successive prospective trials from 1986 to 1999. Among 30 patients, the 5-year EFS was 70%. The international FAB/LMB 96 mature B-cell NHL (B-NHL) trial enrolled 42 patients with PMBCL. The 5-year EFS for PMBCL was 66%, which was inferior to DLBCL (5-year EFS 85%, P 0.001). In recognition of inferior results in paediatrics trials, the most recent international paediatric mature B-NHL trial included a separate cohort of patients with PMBCL to evaluate the DA-EPOCH-R regimen. Among the 40 patients included in the primary analysis, the 2-year EFS was 70%. The international FAB/LMB 96 mature B-cell NHL (B-NHL) trial enrolled 42 patients with PMBCL. The 5-year EFS for PMBCL was 66%, which was inferior to DLBCL (5-year EFS 85%, P 0.001). In recognition of inferior results in paediatrics trials, the most recent international paediatric mature B-NHL trial included a separate cohort of patients with PMBCL to evaluate the DA-EPOCH-R regimen. Among the 40 patients included in the primary analysis, the 2-year EFS was 69% (95% confidence interval, 52-82%). This is in contrast to the early encouraging results from the NHL-BFM group that reported a 2-year EFS of 92.8% with the DA-EPOCH-R regimen, although with a small number of patients (5/15). A retrospective study of DA-EPOCH-R found a 3-year EFS of 81% among 38 paediatric patients. As it stands today, the paediatric community has no single standard of care for the front-line treatment of PMBCL. Many centres in the United States use DA-EPOCH-R, whereas many centres in Europe follow the FAB/LMB regimen, with or without rituximab.

**Concluding remarks**

Management of PMBCL is still challenging due to the scarcity of prospective studies. Newer diagnostic tools are required to distinguish PMBCL from related diseases described earlier. Head-to-head comparison of R-CHOP and DA-EPOCH-R is necessary to...
establish front-line immunochemotherapy for PMBCL. Long-term toxicity from RT should be weighed carefully in young patients when selected. A PET directed approach could successfully omit the use of RT. The newly developed ctDNA looks promising in evaluating false-positive EOT-PET. Taking patients to ASCT is the main goal in RR PMBCL; therefore, the role of novel salvage therapies, including CAR-T, needs to be investigated further. Detail understanding of the disease pathogenesis will probably aid the development of new therapeutics in the near future.

References
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