Primary Mediastinal B-Cell Lymphoma in Children and Young Adults

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ABSTRACT

Primary mediastinal B-cell lymphoma (PMBCL) is a rare but aggressive mature B-cell lymphoma that arises from thymic B cells and most commonly affects adolescents and young adults. PMBCL is now recognized by the WHO as a distinct entity from diffuse large B-cell lymphoma (DLBCL), not otherwise specified, with a unique clinical presentation and distinct morphologic features and molecular alterations. Similar to classic Hodgkin lymphoma, PMBCL tumors are characterized by alterations in the nuclear factor-κB and JAK/STAT pathways. These tumors also exhibit an immune evasion phenotype marked by upregulation of PD-L1 and loss of B2M. Historic data indicates that outcomes for pediatric patients with PMBCL are inferior compared with pediatric patients with DLBCL treated on the same protocols, and there is no current standard approach to initial treatment. Common regimens used for children with PMBCL include multiagent chemotherapy regimens designed for Burkitt lymphoma, such as Lymphomes Malins B (LMB)-based or Berlin-Frankfurt-Münster (BFM)-based chemotherapy ± rituximab. Based on initial data in adults showing excellent outcomes with the use of DA-EPOCH-R regimens, these regimens have also been adopted in pediatrics, although with mixed results. Novel agents are currently being studied in PMBCL with the goal of improving outcomes and reducing reliance on radiation and/or high-dose chemotherapy. Immune checkpoint blockade with PD-1 inhibition is of particular interest given the upregulation of PD-L1 in PMBCL and the known efficacy of these agents in the relapsed setting. Future efforts in PMBCL will also seek to determine the role of FDG-PET in evaluating response to therapy and the role of biomarkers in risk stratification.


Primary mediastinal B-cell lymphoma (PMBCL) is a rare but aggressive mature B-cell lymphoma arising from thymic B cells. Although previously thought to be a subtype of diffuse large B-cell lymphoma (DLBCL), it exhibits clinicopathologic characteristics that have led to its recognition as a distinct entity by the WHO. PMBCL represents approximately 2% to 4% of non-Hodgkin lymphoma, with a predominance among females. PMBCL exhibits a number of clinical and biologic characteristics that are similar to classic Hodgkin lymphoma (cHL), including a peak incidence in adolescents and young adults, presentation as a mediastinal mass, alterations in nuclear factor-κB (NF-κB) and JAK/STAT signaling, and upregulation of PD-L1. This review discusses the biology, diagnosis, and treatment of PMBCL in children and young adults and summarizes future directions to advance outcomes in this distinct lymphoma subtype.

Biology of PMBCL

The morphologic and immunophenotypic appearance of PMBCL in children is similar to that observed in adult patients. The neoplastic cells in PMBCL are large with round to oval hyperchromatic or vesicular nuclei and scant to abundant pale cytoplasm. The infiltrate is diffuse, but often the cells are compartmentalized by fine to dense fibrous tissue (Figure 1A). Commonly, a subset of the lymphoma cells are pleomorphic and may resemble Reed-Sternberg cells. The neoplastic cells express pan-B-cell markers (CD20, CD79a, CD19) as well as transcriptional regulators of the B-cell program (BOB.1, PU.1, OCT-2, PAX5, BCL6, MUM1/IRF4). CD30 and CD23 are expressed in 77% and 67%, respectively, of childhood cases of PMBCL. However, the CD30 expression by the neoplastic PMBCL cells, in contrast to that seen on Reed-Sternberg cells in cHL, is heterogenous and relatively dim (Figure 1B). PMBCL is associated with a variety of genetic abnormalities, including gains/amplifications at chromosome 9p24.1, including the JAK2/PDCD1LG2/PDCD1LG1 locus, which is seen in most cases and can be identified by karyotyping (Figure 2).

Genomics of PMBCL

PMBCL is distinct from other subtypes of DLBCL in terms of clinical and immunophenotypic characteristics.
Genomic and molecular studies have further confirmed its standing as a distinct entity, but have also shown several commonalities with cHL, suggesting a relationship between these 2 entities.

Early efforts to characterize PMBCL through gene expression profiling identified common gains or amplifications involving 2p16 (REL/BCL11A, 41%) and 9p24 (JAK2/PD-L2, 59%). Similar to what has been observed for cHL,
more extensive genomic analyses identified recurrent driver mutations leading to constitutive activation of oncogenic signaling via NF-κB (TNFAIP3, NFKBIE, NFKB2, IKKKB) and JAK/STAT (STAT6, PTPN1, IL4R, JAK1, CISH).\textsuperscript{4,5–8} Also similar to cHL, multiple studies have identified recurrent amplifications involving 9p24.1 resulting in overexpression of PD-L1, and thereby promoting an immune evasion phenotype in PMBCL.\textsuperscript{9,10} This phenotype was further highlighted by studies identifying genomic alterations in B2M, CIITA, CD58, CD274, PDCD1LG2, which have direct roles in major histocompatibility complex (MHC) expression/stability, NK interaction, and T-cell-mediated immune responses.\textsuperscript{3} Chapuy et al\textsuperscript{6} identified several genomic alterations more common to PMBCL relative to cHL, impacting epigenetic modifiers (ZNF217, EZH2), transcription factors (PAX5, IRF2BP2), and TP53. Overall, these findings have driven efforts to overcome the immune evasion capabilities of these tumors through inhibition of the PD-1/PD-L1 pathways in addition to other immunotherapeutics aimed at enhancing T-cell-mediated killing.

\textbf{Initial Presentation and Diagnostic Workup}

Patients typically present with symptoms related to bulky, localized mediastinal masses, which also frequently directly involve the chest wall, lung, pleura, or pericardium. Many patients also have associated pleural or pericardial effusions. Involvement of the bone marrow or central nervous system (CNS) at initial presentation are uncommon.\textsuperscript{11,12} Elevated levels of lactate dehydrogenase and overt B symptoms are observed in a subset of patients.\textsuperscript{11–12} For histologic diagnosis, an excisional biopsy is preferred but is often not feasible because patients can present with respiratory and cardiac compromise. In this setting, an image-guided percutaneous needle biopsy is also appropriate. Staging workup should include a baseline FDG-PET/CT (Figure 3). Bilateral bone marrow biopsy and lumbar puncture should also be considered. Workup and staging should be expedited to allow for rapid initiation of therapy, because patients can present with a significant burden of disease. Staging for PMBCL varies between pediatric and adult practices and must be considered when interpreting data across age groups. Use of the St. Jude NHL staging classification\textsuperscript{13} is common practice among many pediatric groups, whereas the Lugano staging classification system\textsuperscript{14} is commonly used in adults.\textsuperscript{14} More recently, an international multidisciplinary panel developed a revised international pediatric NHL staging system (IPNHLSS) and response criteria to address staging and response of distinct pediatric histologic entities with considerations for contemporary molecular diagnostics and advanced imaging.\textsuperscript{15,16}

\textbf{Figure 3.} FDG-PET/CT of a pediatric patient with primary mediastinal large B-cell lymphoma. Fused (A) coronal and (B) axial views. Images obtained with patient consent.
Clinical Management of Adult Patients With PMBCL

There is no single standard of care for adults with PMBCL. Most approaches include rituximab combined with an anthracycline-containing regimen ± radiation therapy (RT) (Table 1). The most common chemotherapy regimens used in the United States are R-CHOP (rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone) and dose-adjusted (DA) EPOCH-R (etoposide/prednisone/vincristine/cyclophosphamide/doxorubicin/rituximab). R-CHOP has historically been given in combination with RT; however, recent approaches have sought to reduce exposure to RT given the risk for long-term toxicity. Outcomes in prospective trials evaluating R-CHOP ± RT have demonstrated progression-free survival (PFS) ranging from 78% to 84%. A single-center phase II trial of DA-EPOCH-R without RT conducted in adults with PMBCL demonstrated excellent outcomes (3-year PFS, 93%). A retrospective multicenter analysis of DA-EPOCH-R demonstrated a 3-year event-free survival (EFS) of 87%. Caution should be taken in comparing outcomes across trials, however, and there have been no randomized phase III trials in PMBCL comparing R-CHOP and DA-EPOCH-R.

Clinical Management in Pediatric Patients

Data specific to pediatric patients with PMBCL treated on prospective trials is limited because patients with PMBCL have historically been treated on the same trials as those with Burkitt lymphoma and DLCBL, which are more common diagnoses in children. A summary of the outcome data for pediatric patients with PMBCL treated on various regimens is provided in Table 2. Seidemann et al evaluated a subset of 30 pediatric patients with PMBCL treated on consecutive trials of the NHL-Berlin-Frankfurt-Münster (NHL-BFM) Study Group from 1886 to 1999 and reported a probability of EFS of 0.7. A similar analysis was performed on patients enrolled on FAB/LMB96. Among 42 patients with mediastinal large B-cell lymphoma treated on that prospective trial, the 5-year EFS was 66% (95% CI, 51–76%)

Table 1. Summary of Up-Front Therapies in Adult Patients With PMBCL

<table>
<thead>
<tr>
<th>Reference</th>
<th>Regimen</th>
<th>Type of Study</th>
<th>n</th>
<th>Median Age</th>
<th>EFS (95% CI)</th>
<th>OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rieger et al17</td>
<td>R-CHOP-like</td>
<td>Prospective, multicenter (subanalysis of MInT trial)</td>
<td>44</td>
<td>36 y</td>
<td>78% (61–88%)</td>
<td>88.5% (71–96%)</td>
</tr>
<tr>
<td>Moskowitz et al19</td>
<td>R-CHOP-14-ICE</td>
<td>Prospective, single center</td>
<td>54</td>
<td>34 y</td>
<td>78%</td>
<td>88%</td>
</tr>
<tr>
<td>Gleeson et al18</td>
<td>R-CHOP-14 (n=22) R-CHOP-21 (n=28)</td>
<td>Prospective, multicenter</td>
<td>50</td>
<td>38.5 y</td>
<td>80%</td>
<td>84%</td>
</tr>
<tr>
<td>Dunleavy et al21</td>
<td>DA-EPCOH-R</td>
<td>Prospective, single center</td>
<td>51</td>
<td>30 y</td>
<td>93% (81–98%)</td>
<td>97% (81–99%)</td>
</tr>
<tr>
<td>Giulino-Roth et al12</td>
<td>DA-EPCOH-R</td>
<td>Retrospective, multicenter</td>
<td>118</td>
<td>34 y</td>
<td>87.4%</td>
<td>97.1%</td>
</tr>
<tr>
<td>Shah et al21</td>
<td>R-CHOP</td>
<td>DA-EPOCH-R</td>
<td>56</td>
<td>35 y</td>
<td>76% (64–88%)</td>
<td>89% (80–99%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>76</td>
<td></td>
<td>85% (75–94%)</td>
<td>91% (82–99%)</td>
</tr>
</tbody>
</table>

Abbreviations: EFS, event-free survival; OS, overall survival; PMBCL, primary mediastinal large B-cell lymphoma.

Table 2. Summary of Studies in Pediatric Patients With PMBCL

<table>
<thead>
<tr>
<th>Reference</th>
<th>Regimen</th>
<th>Type of Study</th>
<th>n</th>
<th>Median Age</th>
<th>EFS (95% CI)</th>
<th>OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dourthe et al25</td>
<td>LMB2001</td>
<td>Prospective, multicenter</td>
<td>42</td>
<td>15 y</td>
<td>88% (75–94.8%)</td>
<td>95.2% (84–98.7%)</td>
</tr>
<tr>
<td>Knörr et al24</td>
<td>DA-EPCOH-R NHL-BFM-04 N95</td>
<td>Prospective, multicenter, retrospective comparison</td>
<td>116</td>
<td>16.2 y</td>
<td>DA-EPOCH-R: 84% (72–91%)</td>
<td>DA-EPOCH-R: 90% (79–95%)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BFM-04: 59% (39–74%)</td>
<td>BFM-04: 72% (51–85%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N95: 39% (19–60%)</td>
<td>N95: 70% (45–85%)</td>
</tr>
<tr>
<td>Burke et al11</td>
<td>DA-EPCOH-R</td>
<td>Prospective, multicenter</td>
<td>46</td>
<td>15.4 y</td>
<td>69.6% (55.2–80.9%)</td>
<td>84.8% (71–92.4%)</td>
</tr>
<tr>
<td>Giulino-Roth et al12</td>
<td>DA-EPCOH-R</td>
<td>Retrospective, multicenter</td>
<td>38</td>
<td>16 y</td>
<td>81.0%</td>
<td>90.7%</td>
</tr>
<tr>
<td>Gerrard et al23</td>
<td>FAB/LMB96</td>
<td>Prospective, multicenter</td>
<td>42</td>
<td>15.7 y</td>
<td>66.0% (49–78%)</td>
<td>73% (56–84%)</td>
</tr>
<tr>
<td>Seidemann et al22</td>
<td>NHL-BFM 86/90/95</td>
<td>Pooled analysis</td>
<td>30</td>
<td>14.3 y</td>
<td>70%</td>
<td></td>
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</table>

Abbreviations: EFS, event-free survival; OS, overall survival; PMBCL, primary mediastinal large B-cell lymphoma.
rates in adults with PMBCL treated with rituximab + chemotherapy ± RT present conflicting results on the impact of RT on OS.26-27 Early results from the UNFOLDER trial from the German Lymphoma Alliance (GLA) indicated that adults with PMBCL randomly assigned to treatment with R-CHOP without RT had an increased risk of a partial response.28 The role for RT in the setting of more dose-intensive regimens in combination with rituximab, such as DA-EPOCH-R, is less clear.19-21

Pediatric data on the use of RT in initial management of PMBCL is limited. The prospective pediatric studies outlined earlier, including the prospective DA-EPOCH-R trial,11 and the LMB25 and BFM24 approaches, do not include RT. In the retrospective analysis on the use of DA-EPOCH-R, RT was only administered in a small subset of pediatric patients (4/36 patients) highlighting the limited use of RT among pediatric patients treated outside of clinical trials.12

An ongoing prospective, randomized phase III trial being conducted by the International Extranodal Lymphoma Study Group (IELSG) is evaluating the role of RT following rituximab-containing chemotherapy regimens in adult patients with PMBCL (ClinicalTrials.gov identifier: NCT01599569).

Overall, when determining a chemotherapy and radiation plan for patients with PMBCL, the balance of efficacy and long-term toxicity should be considered. Higher-intensity chemotherapy regimens may allow for the omission of RT, which is associated with late effects including cardiac toxicity and secondary malignancy. Cardiac toxicity is also a risk with any anthracycline-containing chemotherapy regimen and the total cumulative anthracycline dose should be considered as well.

Role for FDG-PET Imaging in PMBCL
The utilization of metabolic response as determined by interval or end-of-treatment (EoT) PET/CT scans is now widely used in the management of lymphomas.14 However, the role of PET imaging in prognostication and determining the need for consolidative RT in PMBCL is not defined. Numerous studies in adults have indicated a negative EoT PET, defined as a Deauville response score of 1 to 3, is associated with a strong likelihood of prolonged EFS.12,29,30 Hayden et al31 retrospectively identified 113 adults treated with R-CHOP ± RT across the pre-PET and post-PET era. In patients with a negative EoT PET, the 5-year time to progression was 91%. Martelli et al32 prospectively enrolled 125 patients for central review of EoT PET imaging following chemoimmunotherapy, and negative PET imaging predicted a 5-year PFS/OS of 98%/100%.

In contrast, the utility of a positive PET scan remains unclear. Data from the pediatric phase II trial for DA-EPOCH-R

RT in PMBCL
PMBCL is a radiation-sensitive malignancy; however, the role of RT, particularly in the up-front setting, is not clearly defined. Retrospective analyses comparing OS

49%-78%), which was inferior compared with the 5-year EFS in patients with DLBCL on the same trial (85%; 95% CI, 71%-92%; P ≤ .001).23

Following the promising results of the NCI phase II trial of DA-EPOCH-R in adults with PMBCL, this regimen has been evaluated in pediatric patients.21 A single-arm, prospective, international phase II trial of DA-EPOCH-R was conducted, enrolling children aged ≤18 years with PMBCL. In total, 46 patients with a median age of 15.6 years were enrolled, with a 4-year EFS of 69.6% (95% CI, 55.2%-80.9%) and overall survival (OS) of 84.8% (95% CI, 71.8%-92.4%).11 These outcomes were not different when compared with historic outcomes in pediatric patients treated on traditional NHL chemotherapy regimens. In a multi-institutional retrospective analysis evaluating the use of DA-EPOCH-R, 38 pediatric patients (median age, 16 years) were reported with a 3-year EFS of 81.0%. A comparison with the EFS among adult patients (n = 118) did not demonstrate a statistical difference (3-year EFS, 87.4%; P = .338).12

More recently, the NHL-BFM Study Group reported outcomes of pediatric patients with PMBCL treated on the 3 trials: NHL-BFM 95, which used B-NHL-type combination chemotherapy (n = 52); B-NHL-BFM-04, which included intensified B-NHL therapy (n = 29) and later DA-EPOCH-R (n = 16); and the NHL-BFM Registry 2012 on which patients were treated with DA-EPOCH-R (n = 52). Treatment with DA-EPOCH-R resulted in superior outcomes (5-year EFS, 84%; 95% CI, 72%-91%) compared with intensified B-NHL therapy on B-NHL-BFM-04 (5-year EFS, 59%; 95% CI, 39%-74%; P = .016) and B-NHL therapy on the NHL-BFM 95 trial (5-year EFS, 39%; 95% CI, 19%-60%; P = .001).24

Dourthe et al25 reported on the recent French experience on the LMB2001 trial, which treated patients with 4 to 8 cycles of Lymphomes Malins B (LMB)–based chemotherapy without RT. A total of 42 patients were enrolled with a median age of 15 years (range, 8–18 years), with 21 receiving rituximab. The 5-year EFS and OS for the entire cohort was 88.1% (95% CI, 75.0%-94.8%) and 95.2% (95% CI, 84.0%-98.7%), respectively, with a trend toward a superior outcome in patients receiving rituximab (5-year EFS, 81.0% [95% CI, 60.0%-92.3%] vs 95.2% [95% CI, 77.3%-99.2%]; hazard ratio, 0.24; 95% CI, 0.03–2.2).

Ultimately, like adults with PMBCL, a standard approach to up-front therapy is yet to be identified and various approaches are reasonable.

PMBCL in Children

49%-78%), which was inferior compared with the 5-year EFS in patients with DLBCL on the same trial (85%; 95% CI, 71%-92%; P ≤ .001).23
demonstrated that the positive predictive value of an EoT PET/CT was 63.6% (95% CI, 30.8%–89.1%). Similarly, in adults treated on the phase II trial of DA-EPOCH-R, Melani et al. identified 25 patients with a positive EoT PET/CT, with only 5 (20%) experiencing a subsequent treatment failure. Serial PET imaging off-therapy indicated that further improvement in FDG activity occurred over time in patients with a positive EoT PET who did not experience a later progression, supporting a possible monitoring strategy for these patients. Regardless, based on these data, a repeat biopsy should be strongly considered before starting additional therapy for patients suspected of having refractory disease based on EoT PET alone.

**Emerging Biomarkers in PMBCL: Circulating Tumor DNA**

Given the limited predictive value of FDG-PET in PMBCL, additional biomarkers predictive of response could help to better identify patients at risk for relapse. Circulating tumor DNA (ctDNA) is widely being evaluated as a potential biomarker across the field of oncology, with potential applications in diagnosis, prognosis, response assessment, and remission monitoring. Currently data on ctNDA in PMBCL are limited, but studies thus far have found a high degree of concordance between primary biopsies of patients and mutational profile observed in matched ctDNA. The most common mutations identified in PMBCL tumors and ctDNA in one study were **B2M** (61%), **SOCS1** (61%), **GNA13** (44%), **STAT6** (44%), **NFKBIA** (39%), **ITPKB** (33%), and **NFKBIE** (33%).

**Novel Agents in PMBCL**

The recent emergence of novel agents has altered the approach to R/R PMBCL and offers the opportunity to advance outcomes in up-front therapy as well. Recurrent translocation and amplification events involving 9p24.1 result in increased expression of PD-L1 and PD-L2, making checkpoint inhibitors an attractive therapeutic option. As such, adults with PMBCL were included on the phase IB KEYNOTE-013 and phase II KEYNOTE-170 studies, which evaluated pembrolizumab as a single agent in R/R PMBCL. Patients with PMBCL had an objective response rate (ORR) of 48% (complete response [CR] rate, 33%) and 45% (CR rate, 13%) on the phase Ib and II trials, respectively. Based on these results, pembrolizumab is now FDA-approved in children and adults with PMBCL that has relapsed after 2 prior therapies.

Brentuximab vedotin (BV), an antibody–drug conjugate targeting CD30, is also a rational therapeutic approach in PMBCL, because most cases express CD30. A phase II trial evaluated BV monotherapy in patients with R/R PMBCL (n = 15) and demonstrated tolerability but minimal efficacy, with a 13% ORR. BV has also been studied in combination with nivolumab. It has been shown that BV may enhance the antitumor effect of checkpoint inhibitors.
inhibition through depletion of regulatory T cells that have upregulated CD30. In a phase II trial of combination BV/ nivolumab in 36 patients with R/R PMBCL, the ORR was 70% (95% CI, 51.1%–85%) and CR rate was 43%. CD19, which is a commonly expressed antigen in PMBCL, also represents a promising therapeutic target for emerging immunotherapies. Multiple studies have been conducted using autologous anti-CD19 CAR T cells for the treatment of R/R mature B-cell lymphomas in adults, including PMBCL. The multicenter phase II trial for axicabtagene ciloleucel enrolled 111 patients with mature B-cell lymphoma, including 24 with PMBCL, resulting in an ORR of 84% and CR rate of 54%. Notably, at a median follow-up of 15.4 months, 42% of patients had an ongoing response. Similar results were achieved in the TRANSCEND NHL 001 trial evaluating a separate CD19-directed CAR T-cell therapy, lisocabtagene maraleucel, in patients with R/R mature B-cell lymphomas, with 15 of 256 having PMBCL, demonstrating an ORR of 73% (95% CI, 66.8%–78.0%) and CR rate of 53% (95% CI, 46.8%–59.4%) across the entire cohort. Currently there are limited data in pediatric patients with PMBCL. A pediatric/adolescent young adult phase II, single-arm, global trial evaluating tisagenlecleucel in patients with CD19+ R/R mature B-cell lymphoma has recently completed accrual, but results are still pending.

Bispecific T-cell engagers (BITEs) are emerging as promising agents for the treatment of B-cell NHL, with a number of agents in development. These agents bring T cells into direct contact with tumor cells through dual binding of CD3 on T cells and either CD19 or CD20 on B-cell tumors. Recent trials investigating these agents in R/R aggressive and indolent B-NHL have resulted in promising CR rates, ranging from 19% to 45%. However, a limited subset of patients with R/R PMBCL have been included in these studies, and dedicated trials will likely be needed to understand the potential role for these agents in PMBCL.

Novel agents also have the potential to improve outcomes for patients with previously untreated PMBCL. Given the success of immune checkpoint inhibition in the relapsed setting, there is currently an ongoing randomized phase III trial evaluating chemotherapy alone versus chemotherapy + nivolumab for children and adults with previously untreated PMBCL (ClinicalTrials.gov identifier: NCT04759586). This trial is being conducted across the National Clinical Trials Network (NCTN) with representatives from all cooperative groups, including pediatric and adult patients.

Summary and Future Directions
PMBCL is now recognized as a distinct NHL subtype with molecular and clinical features that overlap with cHL. With a peak incidence in adolescents and young adults, and no data to suggest significant differences in the biology of the disease in children and adults, this disease provides the opportunity for pediatric and adult groups to work together to advance outcomes. The development of novel therapies that target key vulnerabilities in PMBCL, including immune checkpoint blockade and CD19-directed CAR T-cell therapy, provides the potential to improve outcomes and reduce the reliance on toxic therapies in this vulnerable population. Still some key unanswered questions remain in PMBCL, including: What is the role for PET/CT in dictating therapy? Can genomic or radiographic biomarkers be used identify high- and low-risk populations? Can novel therapies replace radiation or high-dose chemotherapy in upfront therapy? Given the rare nature of this disease, collaboration will be essential to help answer these questions and improve outcomes for both children and adults with PMBCL.

References


