

Lymphoma Series: Variants of Large-Cell Lymphoma

Primary Mediastinal Large B-Cell Lymphoma

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. List the key clinical features of PMBCL.
2. Discuss the literature on chemotherapy in PMBCL and the role of radiotherapy in PMBCL.
3. Describe the pathologic features of PMBCL.

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ABSTRACT

Primary mediastinal large B-cell lymphoma represents a distinct entity with unique clinicopathologic features and a molecular gene-expression signature reminiscent of nodular sclerosis subtype of classical Hodgkin's lymphoma. Recent studies, including those using a refined molecular signature, suggest that the outcome is more favorable than that of diffuse large B-cell lymphoma. Using historical comparisons, dose-dense and dose-

intensive regimens may be more effective than cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy; however, the impact of adding rituximab to these regimens and effect on outcome comparisons is unknown. Clinical trials exploring these questions in addition to the benefit of consolidative radiotherapy are necessary to definitively answer these questions. *The Oncologist* 2006;11:488-495

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoid tumor, representing 30%–40% of all non-Hodgkin's lymphomas (NHLs). This group of diseases is defined pathologically by large neoplastic cells with B-cell derivation and clinically by aggressive presentation. Variants and subtypes have been recognized in the Real European-American Lymphoma (REAL) and World Health Organization (WHO) classifications based on unique morphologic and clinical presentations. Primary mediastinal large B-cell lymphoma (PMBCL) is one such entity with distinct clinical, pathologic, and genetic features [1, 2] and is believed to arise from thymic medullary B cells, suggesting a unique histo-

genesis [3]. It accounts for approximately 2% of patients with NHL, with a propensity to affect young adults. 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 results regarding survival in PMBCL that may in part be a result of the difficulty in separating PMBCL from DLBCL with secondary mediastinal involvement. This problem is highlighted in earlier studies in which a more aggressive course was observed [4–8] with cure rates similar to those of DLBCL despite the younger age of presentation. In contrast, more recent analyses have suggested

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survival patterns equivalent or in some cases superior to those of DLBCL [9–13]. 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 (NScHL) [14, 15]. Survival comparisons of PMBCL defined by the gene-expression signature support the notion that PMBCL may have a different natural history from that of DLBCL [15].

CLINICAL PRESENTATION

PMBCL typically affects young women, presenting in their third to fourth decade of life with rapidly growing mediastinal masses, often with respiratory symptoms and evidence of intrathoracic extension on imaging [2] (Fig. 1A, B). Up to 50% can have signs and symptoms of superior vena cava syndrome at presentation, with facial edema, neck vein distention, and occasionally, upper extremity swelling and/or deep vein thrombosis. Bulky masses >10 cm are common, often with local infiltration into the lung, chest wall, pleura, and pericardium. Despite local invasiveness, distant spread, including bone marrow infiltration, is infrequent at initial presentation. At relapse, however, unusual extranodal sites, such as the liver, kidneys, and central nervous system, are not uncommon [2].

PATHOLOGY

Tumors display a diffuse growth pattern of large cells with a pale or "clear" cytoplasm and variable degrees of sclerosis (Fig. 2). PMBCL is derived from B cells, as indicated by the presence of immunoglobulin rearrangements and expression of B-cell antigens (CD19, CD20, CD22); however, unlike other B-cell lymphomas, they often lack surface Ig [2] despite expression of the Ig co-receptor CD79a. CD30 can be expressed but is usually weak and inhomogeneous in contrast to the uniform and strong expression seen in cHL or anaplastic large cell lymphoma.

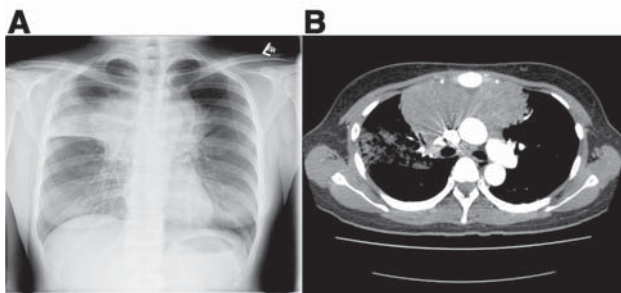


Figure 1. Imaging of primary mediastinal large B-cell lymphoma (PMBCL). (A): Chest x-ray of patient with PMBCL demonstrating an anterior mediastinal mass. (B): Computed tomography scan of patient with PMBCL demonstrating bulky anterior mediastinal mass with extension into the chest wall and patchy airspace disease.

The location of PMBCL and occasional presence of Hassall's corpuscles, thymic lobules, and epithelial-lined cysts all support a thymic origin. Despite being primarily a site of T-cell maturation, the thymus does contain a small number of B cells characterized by a unique phenotype showing the presence of CD19, CD20, CD22, and IgM and the absence of CD21 [3]. Hypermutated immunoglobulin heavy chain variable region (*IgVH*) and *bcl-6* genes of a similar pattern have been observed in both PMBCL tumor cells and thymic B cells, supporting derivation from the thymus and suggesting exposure to the germinal center at some point in histogenesis [16].

GENETIC FEATURES

PMBCLs also harbor distinctive chromosomal aberrations, including consistent gains in chromosome 9p and 2p corresponding with Janus kinase (*JAK*)-2 and c-Rel, respectively [17, 18]. Gains in 9p are relatively specific for PMBCL, observed in up to 75% of cases and occurring only sporadically in other NHLs. Gains in segments of chromosome X are found in approximately one third of cases; however, the significance is unknown. Conversely, *bcl-2* and *bcl-6* rearrangements, found in a subset of DLBCL, are notably absent in PMBCL. More recently, a more sensitive technique than standard comparative genomic hybridization (CGH), which uses a tiling resolution array CGH, has also demonstrated a significant number of chromosomal losses, including 1p13.2 and 17p12 [19].

Recently, biallelic mutations in the MedB1 mediastinal cell line were discovered that result in sustained activity of phospho-JAK-2 through delayed protein turnover. Muta-

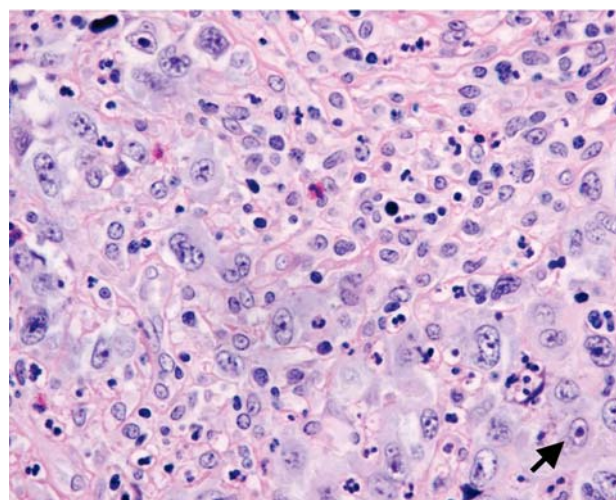


Figure 2. Histologic analysis of primary mediastinal large B-cell lymphoma. Hematoxylin and eosin staining demonstrates an infiltration of large malignant cells compartmentalized by fine delicate bands of fibrosis. Occasional mononuclear Reed-Sternberg variants are also present (arrow).

tions in the suppressor of cytokine signaling 1 (*SOCS-1*) gene have also been observed at a high frequency in PMBCL tumors, correlating with gains at the 9p24 JAK-2 locus [20]. Similarly, Karpas 1106, another PMBCL cell line, harbors a homozygous deletion at 16p13.13 and absent expression of *SOCS-1*, providing further evidence that *SOCS-1* qualifies as a novel suppressor in PMBCL [21].

CLINICOPATHOLOGIC OVERLAP OF PMBCL WITH NScHL

It has long been recognized that there is distinct clinical and pathologic overlap between PMBCL and NScHL (Table 1). Both PMBCL and NScHL commonly present in young patients as localized, mediastinal tumors. Pathologically, fibrosis is prominent, and PMBCL tumors often lack surface Ig, a feature that also typifies the Hodgkin Reed-Sternberg (HRS) cell. MAL (lipid raft component) has been identified as being differentially expressed in PMBCL and found in some cases of NScHL [15, 22, 23]. PMBCL malignant cells and HRS cells also exhibit common genetic abnormalities, including gains of chromosome 2p and 9p [18, 24], the latter being unique to these two diseases. In addition to these striking clinical, immunologic, and molecular similarities, there are rare reported cases of composite or sequential NScHL and PMBCL in addition to “mediastinal gray zone lymphomas” with features between NScHL and PMBCL [25].

Despite these similarities, there are still important differences between PMBCL and NScHL. Unlike HRS cells, PMBCL tumor cells retain several B-cell differentiation markers (e.g., CD20, CD79a) and, histologically, they appear more similar to other DLBCLs and usually lack HRS cells. The brisk inflammatory background seen in cHL is usually absent in PMBCL.

GENE-EXPRESSION PROFILING

These clinical observations and molecular studies suggest that PMBCL may be pathogenetically related to NScHL. This hypothesis of an overlapping relationship is further supported by two recent gene-expression profiling studies

that demonstrated that the molecular signature of PMBCL had a striking resemblance to the expression profile of HRS cell lines [14, 15] (Fig. 3A, B). A prominent cytokine pathway with overexpression of interleukin-13 receptor alpha 1 (IL-13R α 1) and the downstream effectors JAK-2 and signal transducer and activator of transcription (STAT)-1 [26] were present (Fig. 3A, B) in addition to the chemokines thymus and activation-regulated chemokine (TARC) and regulated upon activation, normal T-cell expressed and presumably secreted (RANTES), both of which have been identified in HRS cells [27]. Further, a prominent tumor necrosis factor (TNF) signature was identified in both cHL and PMBCL including the adaptor protein TNF-receptor-associated factor (TRAF)-1 [14, 15]. Nuclear factor kappa B (NF κ B) has previously been determined to be important in the pathogenesis of cHL and contributes to the viability of HRS cells. Nuclear c-Rel subcellular localization in PMBCL was demonstrated, consistent with activation of NF κ B, and a subsequent study demonstrated the increased expression of downstream targets of NF κ B that promote cell survival, supporting that this pathway is also critical in the pathogenesis of PMBCL [14, 28]. TRAF-1 and nuclear c-Rel expression together may aid in differentiating PMBCL from the morphologically similar DLBCL [29]. These and other future markers that can reliably and reproducibly differentiate PMBCL will also facilitate future study comparisons.

PROGNOSTIC FEATURES

There have been varied reports regarding survival in PMBCL, which may in part be a result of diagnostic imprecision and the difficulty in separating PMBCL from DLBCL with secondary mediastinal involvement. This problem was highlighted in earlier studies in which a more aggressive course was observed [4–8], with cure rates similar to or in some cases worse than those of DLBCL despite the younger age at presentation. In contrast, more recent analyses have demonstrated outcome patterns equivalent or superior to those of DLBCL [10–13] (Fig. 4A, B). Further, survival comparisons using molecular signatures to define

Table 1. Comparison of clinical and pathological features of primary mediastinal large B-cell lymphoma (PMBCL) and nodular sclerosis classic Hodgkin’s lymphoma (NScHL)

Feature	PMBCL	NScHL
Age distribution	Third to fourth decade	Peak at 15–35 years
Gender	Female predominance	Slight female predominance
Site of disease	Anterior mediastinum	Anterior mediastinum most common
Pathology	Sclerosis	Sclerosis
Immunophenotype	CD30 variable and weak; surface Ig absent in ~70%	CD30 usually strong; surface Ig absent in all
Genetics	2p (<i>REL</i>) and 9p (<i>JAK-2</i>) amplification	2p (<i>REL</i>) and 9p (<i>JAK-2</i>) amplification

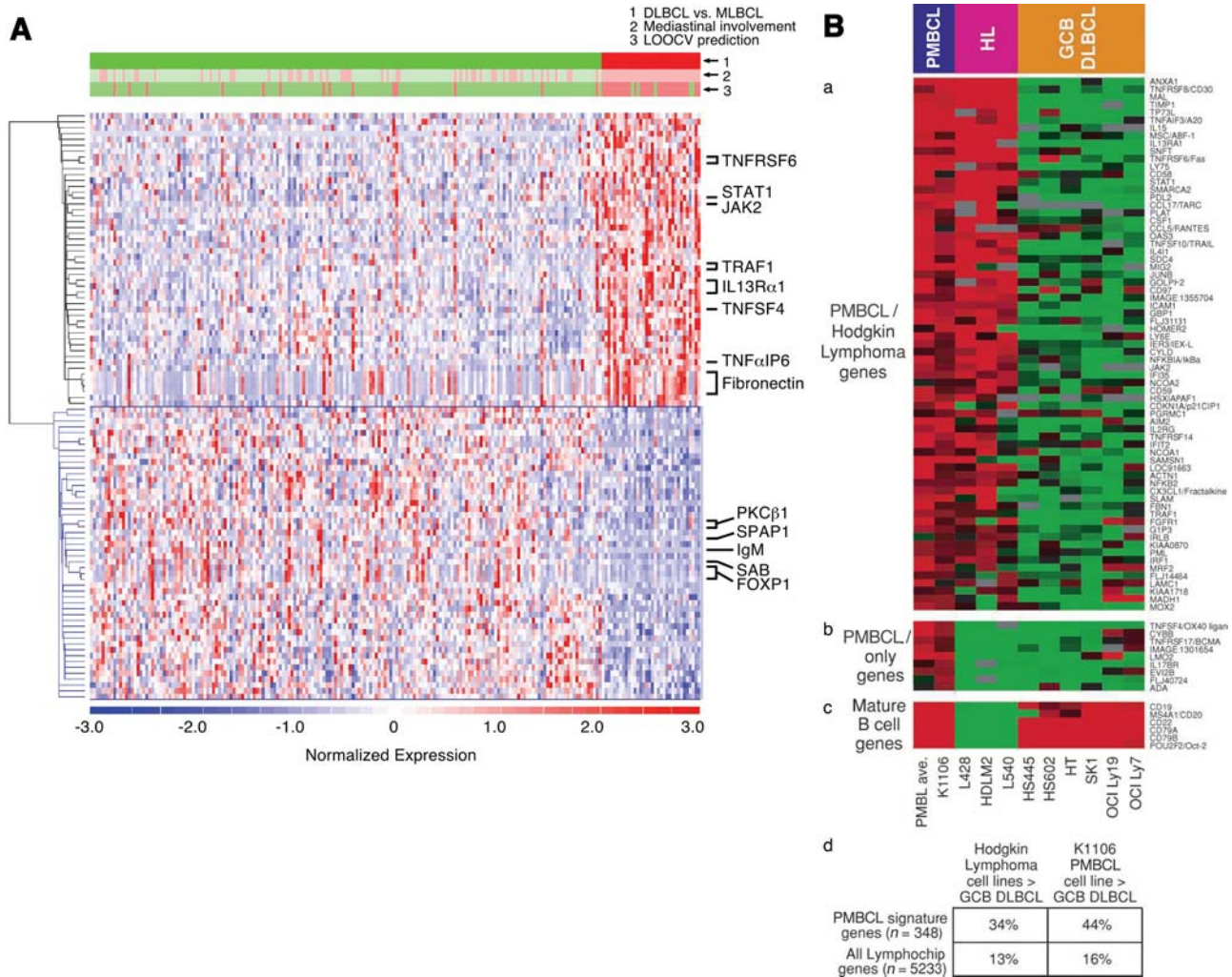


Figure 3. Gene-expression profiling of PMBCL. **(A):** Comparative gene-expression profiles of diffuse large B-cell lymphoma (DLBCL) and mediastinal large B-cell lymphoma (MLBCL). At the top, the actual clinical/pathologic diagnosis of DLBCL versus MLBCL (green vs. red), presence or absence of mediastinal disease (pink vs. light green), and molecular prediction of DLBCL versus MLBCL (green vs. red) are compared. Genes are clustered using hierarchical clustering. Expression profiles of 176 DLBCLs are on the left; profiles of 34 MLBCLs are on the right. Red indicates a high relative expression; blue indicates low expression. Each column represents one sample; each row represents one gene. From Savage KJ, Monti S, Kutok JL et al. The molecular signature of mediastinal large B-cell lymphoma differs from that of other diffuse large B-cell lymphomas and shares features with classical Hodgkin’s lymphoma. *Blood* 2003;102:3871–3879, with permission from the American Society of Hematology. **(B):** Relationship of primary mediastinal B cell lymphoma (PMBCL) to Hodgkin’s lymphoma (HL). Relative gene expression is shown in PMBCLs (average of all biopsy samples), the PMBCL cell line K1106, three HL cell lines, and six germinal center B cell (GCB) DLBCL cell lines, according to the color scale shown at the top. **(a):** PMBCL signature genes that are also expressed at high levels in HL cell lines compared with GCB DLBCL cell lines. **(b):** PMBCL signature genes not expressed in HL cell lines. **(c):** Mature B cell markers expressed in PMBCL and GCB DLBCL but not in HL. **(d):** Enrichment within the set of PMBCL signature genes of genes highly expressed in HL cell lines or in the K1106 PMBL cell line relative to GCB DLBCL cell lines. From Rosenwald A, Wright G, Leroy K et al. Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to Hodgkin lymphoma. *J Exp Med* 2003;198:851–862, with permission from The Rockefeller University Press.

PMBCL and DLBCL support the notion that PMBCL may have a different natural history from that of DLBCL [15]. This is further highlighted by the rarity of relapses beyond 2 years from diagnosis in PMBCL [13] in comparison with DLBCL (Fig. 4B).

The international prognostic index (IPI) was originally developed for use in DLBCL, and its use in PMBCL was not specifically addressed. Studies have been discrepant as to the clinical utility of the IPI in PMBCL [11–13, 30]. This may in part reflect differences between studies

in assigning patients as stage IV or stage 2E if multiple but contiguous extranodal sites are involved. Even if the age-adjusted IPI is used, which eliminates the number of extranodal sites as a risk factor, most patients have an elevated lactate dehydrogenase (LDH) level, thus reducing the usefulness of its discriminatory power [30]. Other factors that have been used in some studies to prognosticate include pleural or pericardial involvement, poor performance status, and LDH elevation $>2\times$ the upper limit of normal [13, 31].

PRIMARY TREATMENT OF PMBCL

The optimal chemotherapy and role of consolidative radiotherapy in the management of PMBCL is unknown. There is emerging evidence that dose-intensified therapy using

methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B) [32] or etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (VACOP-B) [33] may be superior to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-type regimens using historical comparisons [11–13]. The landmark Southwest Oncology Group study comparing CHOP with second- and third-generation regimens in the treatment of DLBCL was carried out prior to the recognition of PMBCL as a distinct entity; thus, there is no direct randomized comparisons of these regimens with CHOP [34]. More recently, an intensive chemotherapy regimen, NHL-15 (using dose-dense sequential induction with doxorubicin followed by cyclophosphamide with G-CSF support), demonstrated superiority to CHOP-like regimens that included some of the familiar second- and third-generation regimens. However, the number of patients receiving specific regimens was too small for individual comparisons. Further, there is an inherent selection bias of patients chosen to be treated with more intensive regimens.

Some researchers support using autologous stem cell transplant in the primary treatment of PMBCL, with a report of 15 patients achieving a disease-free survival rate of 93% after a median follow-up of 35 months with transplant [35]. However, all but two patients were in a PR or CR prior to transplant with induction therapy consisting of VACOP-B, and because of the high frequency of residual masses in this disease, many of the patients in PR according to imaging may be in pathological CR.

Further complicating the evaluation of the effectiveness of dose-dense and dose-intensive regimens is that these studies were undertaken in the “pre-rituximab” era. The addition of rituximab to CHOP chemotherapy has been shown in several studies to produce superior cure rates in DLBCL over CHOP alone [36–38]. The value of adding rituximab to CHOP (CHOPR) in PMBCL is unknown; however, it is likely that the same magnitude of benefit will be observed. Dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and hydroxydaunorubicin (DA-EPOCH) was recently evaluated in 36 patients with PMBCL, 22 of whom received DA-EPOCH in combination with rituximab (DA-EPOCH-R). This regimen administers the natural product chemotherapy agents by continuous infusion (etoposide, doxorubicin, vincristine) in addition to bolus cyclophosphamide and oral prednisone with dose adjustments based on the neutrophil nadir [39]. With a median follow-up of 8.6 years, patients treated with DA-EPOCH had 2-year event-free survival and overall survival rates of 94% and 100%, respectively [40]. However, the utility of more intensive chemotherapy regimens in the treatment of PMBCL can only be evaluated in a well-designed

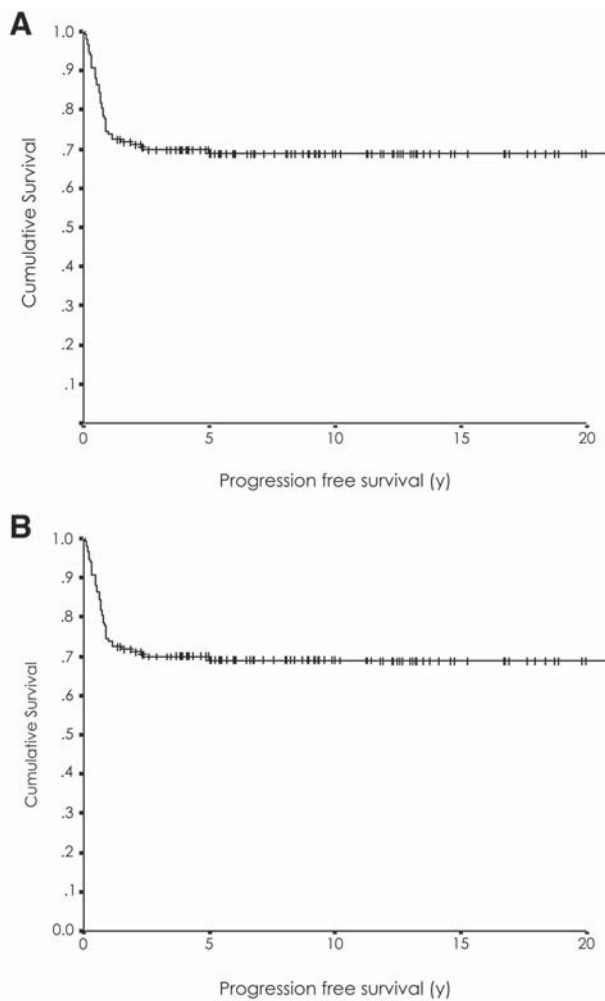


Figure 4. Overall (A) and progression-free (B) survival of 153 patients with primary mediastinal large B-cell lymphoma. From Savage KJ, Al-Rajhi N, Voss N et al. Favorable outcome of primary mediastinal large B-cell lymphoma in a single institution: the British Columbia experience. *Ann Oncol* 2006;17:123–130, with permission.

clinical trial that includes the addition of rituximab to each regimen. Until such studies are available, it is reasonable to consider CHOPR chemotherapy as the standard treatment in PMBCL.

CONSOLIDATIVE RADIOTHERAPY IN THE TREATMENT OF PMBCL

A major challenge in the management of PMBCL is the evaluation of residual masses postchemotherapy. There is poor correlation between the size of a residual mass on computerized tomography and the risk for relapse [41, 42]. In many instances, the residual density represents fibrotic tissue rather than active lymphoma, similar to the problem encountered in bulky mediastinal NScHL [41]. Many patients are given mediastinal radiotherapy as consolidative treatment for this reason; however, it is unclear whether this impacts relapse or cure rates. There is an inherent concern of long-term toxicities of mediastinal radiotherapy, including an increased risk for cardiovascular disease and secondary malignancies, particularly given the young population at risk [43], akin to treatment considerations NScHL. Further, several studies have demonstrated that chemotherapy alone is effective in many cases [9, 13, 30, 40], suggesting that radiotherapy is not necessary in all patients. A longer event-free survival time was reported in one study when radiotherapy was given to patients achieving a CR [11]. However, a recent analysis evaluating the impact of a treatment policy change recommending routine consolidative radiotherapy following primary chemotherapy, failed to demonstrate a benefit [13]. The retrospective nature of such analyses, including definitions of response rates, is problematic, and randomized studies addressing this question are lacking. Better identification of patients who may benefit from the addition of radiotherapy is needed.

Gallium-67 (^{67}Ga) scintigraphy has been used to detect persistent viable tumor in patients with a residual mass

after therapy [44]. ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG-PET) is superior to ^{67}Ga for the detection of residual disease [45]. Future studies are needed to evaluate the utility of ^{18}F -FDG-PET to select patients with PMBCL who may benefit from radiotherapy and to identify those cases in which it can be safely withheld without compromising cure rates, with the goal of reducing secondary long-term complications.

SALVAGE THERAPY

Treatment failures in PMBCL tend to occur within the first 6–12 months after treatment completion, with recurrences rare beyond 2 years [12, 13]. Like DLBCL, chemosensitivity to the salvage regimen is predictive of a more favorable outcome with autologous stem cell transplant (ASCT) [46]. Limited data suggest that PMBCL patients may be less likely to respond to salvage chemotherapy and proceed to ASCT than DLBCL patients; however, in those patients who can be transplanted, outcomes appear to be similar [47].

SUMMARY

PMBCL represents a distinct entity with unique clinicopathologic features and a molecular gene-expression signature reminiscent of NScHL. Recent studies, including those using a refined molecular signature, suggest that the outcome is more favorable than that of DLBCL. Using historical comparisons, dose-dense and dose-intensive regimens may be more effective than CHOP chemotherapy; however, the impact of adding rituximab to these regimens and effect on outcome comparisons is unknown. Clinical trials exploring these questions in addition to the benefit of consolidative radiotherapy are necessary to definitively answer these questions.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The author indicates no potential conflicts of interest.

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