Chapter 6
Current and Emerging Treatment Strategies for Primary Mediastinal B-Cell Lymphoma

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Introduction

Primary mediastinal B-cell lymphoma (PMBCL) is an aggressive subtype of non-Hodgkin lymphoma (NHL) arising from thymic B-lymphocytes. PMBCL shares clinical and biologic features with classic nodular sclerosing Hodgkin lymphoma (HL). First reported in a 1980 case series, PMBCL was first recognized as a distinct clinicopathologic entity in the 2001 World Health Organization lymphoma classification [1]. Herein is an overview of the epidemiology, pathogenesis, standard management, and emerging treatment strategies for PMBCL.

Epidemiology

PMBCL is rare, representing 2.4% of all NHLs [2]. Based on a surveillance, epidemiology, and end results (SEER) analysis, the age-adjusted incidence is 0.4 per million-person years, which has been steadily increasing over the past decade for unclear reasons [3]. The majority of PMBCL patients are young women in their third to fourth decade of life [3]. Despite females being more commonly affected than males, hormonal factors do not appear to play a role in the risk or pathogenesis

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of PMBCL [4]. Aside from gender, the only other known risk factor is inheritance of a germline mutation in the MLL gene (5533C>A) [5].

Clinical Presentation

Most patients will present with constitutional symptoms and a symptomatic bulky anterior mediastinal mass, resulting in chest discomfort, cough, and dyspnea [6]. Superior vena cava syndrome and pleural and pericardial effusions are not uncommon, and in advanced cases, patients can have a pericardial tamponade [7]. Patients with bulky disease (≥10 cm in diameter) can present with tumor lysis syndrome. Bone marrow and subdiaphragmatic involvement are unusual but can sometimes occur at initial presentation [8]. Relapsed PMBCL is often extranodal and may involve organs such as the liver, gastrointestinal tract, kidneys, ovaries, and central nervous system.

Pathology and Gene Expression

PMBCL is comprised of medium to large B-lymphocytes morphologically resembling centroblasts, centrocytes, and less commonly immunoblasts. Morphologically, PMBCL is similar to HL in that there is a background of sclerosis and occasional Reed-Sternberg cells [8]. However, unlike HL, which has a characteristic immunophenotype of being strongly CD15 and CD30 positive with weak to negative expression of B-cell markers, PMBCL is characterized by negative CD15, patchy or weak CD30, and strong expression of common B-cell antigens including CD20 and CD79a. PMBCL is also distinct from mediastinal gray zone lymphoma, which has morphological and immunohistochemical features in between PMBCL and HL. Factors that drive thymic B-cell formation toward one entity over the others are not completely understood [9]. Gene expression studies have revealed an overlap in more than one third of overexpressed genes between PMBCL and HL, including PD-L2 [10]. In addition to overlapping gene expression, PMBCL and HL share dysregulated JAK-STAT and NF-kB signaling pathways and an “immune privilege” phenotype evidenced by downregulation of MHC class I/II and upregulation of PD-L1 through 9p.24 amplifications, which result in reduced immunogenicity and “immune privilege” [11–15].

Diagnosis

The differential for an anterior mediastinal mass is broad and includes PMBCL, other types of NHL, HL, thymoma, thymic carcinoma, thymic cysts, germ cell

tumors to include teratoma, and ectopic thyroid tissue. Therefore, to confirm the diagnosis of PMBCL, a tissue biopsy is required. An excisional or core needle biopsy may not be possible because of the location or may not be diagnostic due to fibrosis and/or necrosis. Therefore, a surgical biopsy obtained through mediastinoscopy or thoracoscopy may be necessary in certain situations.

Staging

The Lugano classification includes recommendations for staging and response assessments of all NHLs [16]. Compared to Ann Arbor which is descriptive and can only be used for staging, Lugano incorporates fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT scan into the initial evaluation and response criteria. As PMBCL rarely involves the bone marrow, a biopsy is not needed to complete staging. Irrespective of whether the disease burden is limited or extensive, all patients are treated with advanced stage treatment strategies.

Work-Up

As with all aggressive NHLs, the work-up requires a complete history and physical, laboratory studies including complete blood count (CBC) with differential, complete metabolic panel (CMP), lactate dehydrogenase (LDH), tumor lysis labs, HIV testing, and viral hepatitis serologies, as well as a FDG-PET/CT scan. Central nervous system (CNS) involvement is also rare, and brain imaging should only be considered if neurologic deficits are present. All patients will need an echocardiogram prior to receiving an anthracycline-containing regimen.

Prognosis

The prognosis of PMBCL is excellent, with a 5-year relative survival of 86% based on the SEER-18 database [17]. Unlike other NHLs, the international prognostic index is not prognostic for PMBCL in the rituximab era [18]. However, age above 38 years, the presence of pleural or pericardial effusions, the presence of constitutional symptoms, and a poor performance status are prognostic and associated with inferior outcomes in certain studies [7]. A negative end-of-treatment PET scan is also prognostic and identifies patients at very low risk of relapse. Patients with relapsed or refractory PMBCL do poorly and have outcomes inferior to that of relapsed or refractory DLBCL. Thus, optimization of frontline treatment is paramount.

Frontline Management

PMBCL patients tend to tolerate therapy well due to their young age, and as with many other aggressive lymphomas, PMBCL is highly curable. Because relapsed/refractory PMBCL portends a dismal prognosis, it is imperative to offer an optimal frontline treatment strategy that balances the benefits of treatment intensity with the risks of late and long-term treatment toxicities. Published studies on the frontline management of PMBCL are limited to single arm studies, retrospective studies, or subgroup analyses of larger studies for NHL and are listed in Table 6.1. Although PMBCL was first described nearly 40 years ago, due to its rarity, there are yet to be any prospective randomized controlled trials to guide management [19]. Despite the paucity of studies, R-CHOP chemotherapy (rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone) with consolidative mediastinal radiotherapy has historically been a standard approach.

Before rituximab gained approval with CHOP, multiple studies assessed the impact of treatment intensity on outcomes for PMBCL and found that dose-intensity correlated with better treatment outcomes. For example, high-intensity regimens such as MACOP or VACOP-B (methotrexate with leucovorin rescue or etoposide with doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin) and ProMACE-CytaBOM (cyclophosphamide, doxorubicin, etoposide, bleomycin, vincristine, methotrexate, and prednisone) produce better response rates and long-term survival than CHOP for PMBCL [20–22]. Similarly, when compared to CHOP, high-dose chemotherapy followed by autologous stem cell rescue (HDC/ASCR) has produced superior rates of complete responses (CR), 75% vs. 61%; 10-year progression free survival (PFS), 78% vs. 35%; and 10-year overall survival (OS), 77% vs. 44% [22].

The approval of rituximab for NHL closed the efficacy gap between CHOP and higher-intensity regimens. In a subset analysis of patients with PMBCL in the phase III MabThera International Trial (MInT), the incorporation of rituximab to CHOP chemotherapy improved the rates of CR from 54% to 90% ($p = 0.015$), the 3-year event-free survival (EFS) from 52% to 78% ($p = 0.012$), and the 3-year OS from 78% to 89% ($p = 0.158$) while substantially decreasing the rate of progressive disease (PD) from 24% to 2.5% ($p < 0.001$) [23]. In another retrospective study including 80 unselected patients with PMBCL, the addition of rituximab to CHOP-based regimens raised the 10-year PFS from 67% to 95% and the 10-year OS from 72% to 92% [17]. The addition of rituximab to higher-intensity regimens, however, did not improve outcomes. In an Italian retrospective study that included PMBCL patients treated with R-MACOP-B, the CR rate was 80%, and projected 5-year OS rate was 80%, which was not dissimilar to historical controls using MACOP-B in the pre-rituximab era [24]. Likewise, when compared with R-CHOP, R-VACOP-B did not produce better 5-year PFS or OS rates [25]. As a result of these studies, it was generally accepted that incorporation of rituximab into frontline treatment for PMBCL obviates the need for chemotherapy regimens of higher intensity than CHOP.

Table 6.1 Studies for de novo PMBCL

Reference	Study type	# of patients	Regimen	% receiving RT	CR (%)	RFS (%)	OS (%)
Lazzarino et al. [20]	Case series	30	CHOP ± RT	All with CR	36	72[a] (3 years)	36[a] (3 years)
			V/MACOP-B ± RT		73		
Todeschini et al. [21]	Retrospective	138	CHOP ± IFRT	76% with CR	51	39 (5 years)	NR
			V/MACOP-B ± IFRT		80	76 (5 years)	NR
Mazzarotto et al. [25]	Retrospective	53	ProMACE-MOPP, V/MACOP-B + IFRT	100%	38	93 (5-year)	86 (5-years)
Zinzani et al. [22]	Retrospective	426	CHOP/CHOP-B ± IFRT	All with CR and 84% with PR	61	33 (10 years)	44 (10 years)
			V/MACOP-B/ProMACE CytaBOM ± IFRT		79	67 (10 years)	71 (10 years)
			HDC/ASCR		75	78 (10 years)	77 (10 years)
Savage et al. [7]	Retrospective	153	MACOP-B	39% total	N/A	N/R	87[b] (5 years)
			CHOP		N/A	N/R	71[b] (5 years)
			R-CHOP		N/A	N/R	82 (5 years)
Rieger et al. [23]	Subgroup analysis of prospective phase III study	87	CHOP	67.40%	54	52 (3 years)	78 (3 years)
			R-CHOP	72.80%	80	78 (3 years)	89 (3 years)
Zinzani et al. [24]	Retrospective	45	R + V/MACOP-B + radiotherapy	100%	80	88 (5 years)	80 (5 years)
	Retrospective	95	R-VACOP-B	None	N/A	83[c] (5 years)	97 (5 years)
			R-CHOP21		N/A	69[c] (5 years)	

(continued)

Table 6.1 (continued)

Reference	Study type	# of patients	Regimen	% receiving RT	CR (%)	RFS (%)	OS (%)
			VACOP-B		N/A	62 (5 years)	88 (5 years)
			CHOP21		N/A	20 (5 years)	
Soumerai et al. [28]	Retrospective	63	R-CHOP ± radiotherapy	77%	79	68 (5 years)	79 (5 years)
Vassilakopoulos et al. [27]	Retrospective	76	R-CHOP ± radiotherapy	76%	N/A	81 (5 years)	89 (5 years)
Ahn et al. [29]	Retrospective	21	R-CHOP ± radiotherapy	57%	N/A	79 (3 years)	83 (3 years)
	Subgroup analysis of prospective phase III study	50	R-CHOP14 or 21 ± radiotherapy	58%	43	80 (5 years)	84[d] (5 years)
Dunleavy et al. [34]	Prospective phase II study	51	DA-EPOCH-R	4%	N/A	93 (5 years)	97 (5 years)
Giulino-Roth et al. [44]	Retrospective	156	DA-EPOCH-R	15%	N/A	86 (5 years)	95 (5 years)
Shah et al. [45]	Retrospective	132	DA-EPOCH-R	59%	84	NR	89 (2 years)
			R-CHOP	13%	70	NR	91 (2 years)

NR not reported

[a]Includes total cohort

[b]The difference in survival was only significant between MACOP-B and CHOP

[c]The PFS difference between R-MACOP-B and R-CHOP was nonsignificant

[d]There was a trend toward improved OS with R-CHOP14 > R-CHOP21

Although consolidative involved field radiotherapy played a pivotal role in the management of PMBCL in the pre-rituximab era, currently there are yet to be any studies demonstrating a survival benefit [26, 27]. Additionally, 20–25% of patients will experience a relapse or primary refractory disease after treatment with R-CHOP and consolidative mediastinal radiotherapy [28, 29]. The late and long-term toxicities of irradiation are not inconsequential, including bone marrow toxicity, accelerated coronary artery disease, a heightened risk of breast cancer, thyroid cancer, and therapy-related myeloid neoplasms, some of which can occur up to 40 years after initial treatment [30–32]. Because radiotherapy has long-term risks and does not appear to impact survival, other studies have assessed omission of radiotherapy or the use of imaging to guide end of treatment radiation.

Treatment Response Assessment

The presence of a residual anterior mediastinal mass after treatment is very common and is often due to fibrosis, sclerosis, or necrosis of the initial tumor bulk. However, it can be difficult to discriminate residual disease versus fibrosis with a CT scan alone. Several studies have assessed the role of end-of-treatment PET imaging in PMBCL using the 5-point Deauville scoring system, revealing that this measure is associated with a high negative predictive value for treatment failures. The landmark prospective phase II IELSG 26 study demonstrated that using the liver uptake as a cut-off (Deauville 1–3 vs. 4–5) effectively stratified patients into low and high risk for treatment failure after receiving a rituximab and anthracycline-based treatment regimen, with a 5-year progression-free survival (PFS) of 99% vs. 68% and OS of 100% vs. 83%, respectively [33]. When used after DA-EPOCH-R, end-of-treatment PET imaging is associated with a very good negative predictive value of 100%, further supporting that a negative end-of-treatment PET scan can identify patients at low risk of relapse [34].

Most patients in the IELSG 26 study received mediastinal radiotherapy; therefore it is not clear if treatment can be "de-escalated" with radiotherapy omission based on the results of a negative end-of-treatment PET scan. In a retrospective Canadian study by Savage et al., patients with a positive end-of-treatment PET after R-CHOP received consolidative radiotherapy, whereas those with a negative PET did not. Using risk-adapted radiotherapy consolidation, there was no difference in the 5-year time to progression (78% vs. 83%, $p = 0.735$) or overall survival (88.5% vs. 95%, $p = 0.271$), supporting the notion that radiotherapy omission in low-risk patients can be safe and feasible [35]. This proof of principle is being tested prospectively in the ongoing phase III IELSG-37 study, which omits consolidative radiotherapy among patients who achieve a complete metabolic response on their end-of-treatment PET scan after a rituximab and anthracycline-based regimen (NCT01599559).

False-positive end-of-treatment PET scans can occur about 40% of the time and are often due to inflammation [27]. To mitigate false positives due to rebound thymic uptake, imaging should be obtained 6–8 weeks after receipt of chemotherapy or

myeloid growth factor support and 12 weeks after receipt of radiotherapy [36]. Although consensus guidelines recommend a biopsy consideration in the case of a positive end-of-treatment PET scan, this exposes the patient to a potentially unnecessary procedure. There are some data to support the use of serial PET imaging to decipher true refractory disease from false-positive disease, as the former will demonstrate persistent FDG avidity and the latter will improve with time [37, 38].

Management of Relapsed or Refractory PMBCL

There is no accepted standard treatment approach for relapsed/refractory PMBCL. Among those with relapsed or refractory disease, the prognosis is dismal and is inferior to that of relapsed/refractory DLBCL, with an inferior response to salvage chemotherapy (25% vs. 48%, $p = 0.01$) and inferior 2-year overall survival (15% vs. 34%, $p = 0.018$) [39]. High-dose chemotherapy followed by autologous stem cell rescue (HDC/ASCR) might be a good option for patients with late relapses (≥12 months) that demonstrate chemosensitivity but is unlikely to be beneficial for primary refractory or chemorefractory early relapsed disease [40, 41]. Patients who have primary refractory or early relapsed disease have a particularly bleak prognosis with a median survival of approximately 6 months, and better treatments in this population are needed [42]. Allogeneic transplant can be utilized, but limited retrospective data suggest the benefit is minimal and transplant-related mortality high [43]. Published studies on management of relapsed or refractory PMBCL are listed in Table 6.2.

Novel Approaches for Untreated PMBCL

In an attempt to omit mediastinal radiotherapy, the National Cancer Institute (NCI) led a prospective phase II study assessing the efficacy of infusional dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab (DA-EPOCH-R) with myeloid growth factor support for untreated PMBCL [33]. Fifty-one patients with median age of 30 and 59% females were enrolled. Many participants in the study had high-risk features – 65% had bulky disease, 53% had extranodal disease, 47% had pleural effusions, and 29% had stage IV disease. All had malignant cells that expressed CD20. After a median follow-up of 63 months, the EFS and OS were 93% and 97%, respectively. Eighteen patients had a positive end-of-treatment PET (defined by the study as Deauville 3–5), of which only three had confirmed residual disease and two of these received mediastinal irradiation. Hospitalization for febrile neutropenia occurred in 13% of the cycles, and there were no episodes of cardiotoxicity. Although not directly compared with R-CHOP and consolidative radiotherapy, the results of this study show that higher-intensity chemoimmunotherapy can have high response rates and also support omission of radiotherapy in frontline treatment. A retrospective study assessed the efficacy of frontline DA-EPOCH-R for PMBCL and included 156

Table 6.2 Studies for R/R PMBCL

Reference	Study type	# of patients	Regimen	CR (%)	RFS (%)	OS (%)
Neelapu et al. [48]	Phase II study	24	Autologous anti-CD19 CAR-T cells	71	NR	NR
Zinzani et al. [50]	Phase Ib study	18	Pembrolizumab	12	NR	NR
Zinzani et al. [50]	Phase II study	15	Brentuximab vedotin	0	NR	NR
Jacobsen et al. [52]	Phase II study	6	Brentuximab vedotin	17	NR	NR
Aoki et al. [40]	Retrospective	44	HDC/ASCR	64	61 (4 years)	70 (4 years)
Avivi et al. [41]	Retrospective	44	HDC/ASCR – chemosensitive disease	NR	64 (3 years)	85 (3 years)
		24	HDC/ASCR – chemorefractory disease	NR	39 (3 years)	41 (3 years)
Khouri et al. [43]	Retrospective	17	Allogeneic transplant	3-year PFS and OS 41% and 46%	41 (3 years)	46 (3 years)

NR not reported, *CAR-T cells* chimeric antigen receptor T cells, *HDC/ASCR* high dose chemotherapy followed by autologous stem cell rescue

adults and children, of whom 14.9% received radiotherapy. The 3-year EFS and OS were 85.9% and 95.4%, respectively, and 75% achieved a negative end-of-treatment PET scan which correlated with an improved EFS [44]. Although DA-EPOCH-R has never been prospectively compared to standard R-CHOP with consolidative radiotherapy, a multicenter retrospective analysis involving 132 patients compared these two frontline treatment approaches and reported that recipients of DA-EPOCH-R were less likely to receive radiotherapy (13% vs. 59%) and had higher CR rates (84% vs. 70%, $p = 0.046$). The 2-year OS rates were similar at 89% for R-CHOP recipients and 91% for DA-EPOCH-R recipients [45]. DA-EPOCH-R is associated with relatively low rates of female infertility in patients under the age of 40, which is important given the patient demographics of this disease [46].

Novel Approaches in the Relapsed and Refractory Setting

Immunotherapy

Given the "immune privilege" phenotype of PMBCL and similarity to classic HL, the role of immunotherapy for the management of PMBCL is currently being

explored. Bone marrow transplant is the oldest form of immunotherapy, and new therapies such as chimeric antigen receptor T-cells (CAR-T cells) and checkpoint inhibitors appear promising. Immunotherapy approaches mentioned below are novel, and as such it is unclear how to best combine or sequence these agents with traditional treatment approaches.

CAR-T Cells

CAR-T cells have made dramatic differences for patients with relapsed or refractory acute lymphoblastic leukemia and DLBCL and have recently been granted full food and drug administration (FDA) approval for PMBCL. CAR-T cells are autologously derived cytotoxic T-lymphocytes that are engineered ex vivo to incorporate tumor antigen recognition moieties and T-cell signaling domains [47]. Because PMBCL is characterized by immune exhaustion and expresses the immunogenic CD19 antigen, CAR-T cells have been studied for use in PMBCL. The phase II ZUMA-1 study assessed the efficacy of the autologously derived anti-CD19 CAR-T cells, axicabtagene ciloleucel, and included patients with refractory DLBCL (cohort 1) and PMBCL or transformed follicular lymphoma (cohort 2) [48]. After leukapheresis with CAR-T manufacturing, patients received a fixed low-dose conditioning regimen consisting of fludarabine and cyclophosphamide followed by two million CAR-T cells per kg of body weight. Of the 111 patients included in the study, 8 had PMBCL. The median time from leukapheresis to infusion of CAR-T cells was 17 days. In cohort 2, the overall response rate (ORR) was 83% which included 71% CRs. Responses were not adversely affected by the use of tocilizumab or corticosteroids. At 18 months of follow-up, about half of the patients were still alive. The most common drug-related adverse events were cytopenias, cytokine release syndrome, and neurotoxicity, the latter two of which have issued FDA black box warnings. As a result of the ZUMA-1 study, the FDA granted full approval of axicabtagene ciloleucel for use in relapsed or refractory large B-cell lymphoma, including PMBCL that has been previously treated with at least two lines of systemic therapy.

Checkpoint Inhibitors

The immune privilege phenotype of PMBCL lends an opportunity to be exploited with immune checkpoint inhibitors. Up to 100% of cases of PMBCL are associated with enhanced PD-L1 expression, due to 9p24.1 gains in about half of cases and rearrangements at the PDL1/2 locus in about 20% of cases [49]. The phase Ib keynote-013 study assessed the efficacy of the anti-PD1 antibody pembrolizumab for relapsed/refractory PMBCL [50]. Eighteen patients were enrolled and treated. The median age was 30 and over 70% were female. The patients were heavily

pre-treated – with a median of three prior treatments, one third had received prior HDC/ASCR, and nearly two thirds had undergone prior radiotherapy. Sixty-one percent of patients experienced grade 1/2 toxicities, including hypothyroidism, diarrhea, nausea, and fatigue. There were only two grade 3/4 toxicities which included neutropenia and veno-occlusive disease post-allogeneic transplant. The ORR was 41%, which included two patients who achieved a CR. After a median follow-up duration of 11.3 months, the median duration of response had not been reached. A subsequent phase II study confirmed a similar treatment efficacy of pembrolizumab for patients with relapsed/refractory PMBCL resulting in FDA drug approval (NCT02576990).

Anti-CD30 Directed Therapy

Most cases of PMBCL overexpress CD30, and hence there is scientific rationale that CD30-directed therapies may be efficacious. Despite the success of the anti-CD30 antibody-drug complex brentuximab vedotin (BV) for use in classic HL, systemic and primary cutaneous anaplastic large cell lymphoma, and mycosis fungoides, this agent does not have a role as monotherapy for the treatment of PMBCL based on the results of two phase II studies. The first is an Italian study which assessed the safety and efficacy of standard-dosed BV for relapsed/refractory CD30+ PMBCL [51]. Fifteen patients were enrolled. The median age was 29 and the majority were female. The median prior number of treatments was 3, and over half had received HDC/ASCR and radiotherapy. The ORR was 13.3% and consisted of all partial responses that lasted less than 3 months. Forty percent experienced drug-related adverse events, which were comprised of mostly grade 1/2 peripheral neuropathy, atrial fibrillation, transaminitis and anemia. The second study was a phase II trial assessing the efficacy of BV for DLBCL with variable CD30 expression and included six patients with PMBCL [52]. There was only one response to BV which was a CR, producing an ORR of 17%. The discrepancy in the treatment efficacy of BV between PMBCL and other CD30-expressing lymphomas likely has to do with the characteristics of CD30 expression. Although most cases of PMBCL are associated with CD30 overexpression, up to one third do not express CD30 [53]. Among those that do express CD30, the expression is typically at low levels and can be very heterogeneous [54].

Clinical Trials

The ongoing clinical trials for untreated and relapsed/refractory PMBCL are listed in Table 6.3.

Table 6.3 Ongoing clinical studies

Therapy	Study type	Setting	Clinical trial #
Mediastinal radiotherapy	Phase III study	Untreated PMBCL achieving CMR after chemoimmunotherapy	NCT01599559
DA-EPOCH-R	Phase II study	Children and adolescents with untreated PMBCL	NCT01516567
Pembrolizumab	Phase II study	R/R PMBCL	NCT02576990
Autologous anti-CD19 CAR-T cells + durvalumab	Phase I study	R/R NHL including PMBCL	NCT02706405
Autologous anti-CD19 CAR-T cells	Phase I study	R/R DLBCL, PMBCL, grade 3B FL, MCL	NCT2631044
Nivolumab + varlilumab	Phase II study	R/R NHL including PMBCL	NCT03038672
Ibrutinib + pembrolizumab	Phase 1 study	R/R NHL including PMBCL	NCT02950220
Vorinostat + pembrolizumab	Phase I study	R/R NHL including PMBCL	NCT03150329
Gemcitabine/vinorelbine/ doxorubicin + PD-1 antibody ± low-dose decitabine	Phase I/ II study	R/R PMBCL	NCT03346642
Bendamustine + rituximab + ibrutinib	Phase II study	R/R NHL including PMBCL	NCT02747732
Obinutuzumab + ICE	Phase II study	R/R CD20+ B-cell NHL	NCT02393157
Lenalidomide + R-ICE	Phase I/ II study	R/R DLBCL including PMBCL	NCT02628405
Idelalisib + R-ICE	Phase I study	R/R DLBCL and PMBCL	NCT03349346
Tazemetostat	Phase I/ II study	R/R B-cell NHL including PMBCL	NCT01897571

R/R relapsed/refractory, *CMR* complete metabolic response, *NHL* non-Hodgkin lymphoma, *DLBCL* diffuse large B-cell lymphoma, *FL* follicular lymphoma, *MCL* mantle cell lymphoma

Consolidative Radiotherapy

To determine whether consolidative mediastinal radiotherapy can be omitted, the ongoing IELSG-37 phase III study (NCT01599559) which opened in 2012 is enrolling patients with a negative end-of-treatment PET/CT scan after receipt of a rituximab-based chemotherapy regimen, including CHOP-14 or CHOP-21, DA-EPOCH, Mega-CHOP, VACOP-B, or MACOP-B. Enrollees are assigned to either observation or 3-D conformal radiotherapy with a total dose of 30 Gy. The primary and secondary endpoints of this study are PFS and OS, respectively. Notably this is the first and only phase III study on PMBCL to date.

Small Molecule Inhibitors

Given their success in indolent and aggressive NHLs, multiple ongoing early phase trials are assessing the efficacy of small molecule inhibitors for treatment of DLBCL including PMBCL. Ongoing studies include various combinations of targeted agents with salvage chemotherapy regimens including the oral Bruton tyrosine kinase inhibitor ibrutinib in combination with bendamustine and rituximab (NCT02747732), the immunomodulatory agent lenalidomide and the PI3K inhibitor idelalisib partnered with salvage R-ICE (NCT02628405, NCT03349346), and lastly the EZH2 histone methyltransferase inhibitor tazemetostat as monotherapy (NCT01897571).

Immunotherapy

A multitude of clinical trials are assessing the feasibility and efficacy of combination therapy utilizing checkpoint inhibitors. An ongoing phase II study evaluates the anti-PD1 antibody nivolumab alongside the co-stimulatory CD27 agonist varlilumab (NCT03038672). Ongoing phase I studies are evaluating potential synergy between pembrolizumab and ibrutinib (NCT02950220) as well as the histone deacetylase inhibitor vorinostat (NCT03150329). The type II glycoengineered anti-CD20 antibody obinutuzumab is partnered with salvage ifosfamide, carboplatin, and etoposide (ICE) chemotherapy in another early phase study for patients with relapsed aggressive lymphoma including PMBCL (NCT02393157). Another phase I/II study in China is assessing gemcitabine, vinorelbine, doxorubicin, and checkpoint inhibition with or without low-dose decitabine priming (NCT03346642).

As checkpoint inhibitors can enhance the longevity of CAR-T cells by dampening their exhaustion in vitro, it is possible that combining these remedies may produce synergistic immune toxicity in vivo [55]. A phase I study at the Fred Hutchinson Cancer Research Center (NCT02706405) will assess the safety and pharmacokinetic profile of autologous anti-CD19 CAR-T cells in combination with the anti-PDL1 antibody durvalumab. In this study, patients with relapsed/refractory NHL including subsets of PMBCL will receive JCAR014 on day 0, followed by durvalumab on day 28, which will continue every 4 weeks for up to 10 doses in the absence of disease progression or unacceptable toxicity. Other clinical trials are exploring CAR-T cells for NHL patients including PMBCL, to include the phase I TRANSCEND-NHL-001 trial which utilizes JCAR017 for relapsed/refractory DLBCL, PMBCL, grade 3B follicular lymphoma, and mantle cell lymphoma (NCT 02631044).

In summary, given the strong immune privilege phenotype of PMBCL, the role of immunotherapy in the relapsed and refractory is becoming increasingly recognized. Combinations and sequences of checkpoint inhibitors and CAR-Ts in addi-

tion to small molecule inhibitors and monoclonal antibodies are being assessed in ongoing early phase studies.

Preclinical Studies

Given that enhanced JAK2 signaling plays a role in the pathogenesis of PMBCL, it is possible that JAK2 inhibitors might be efficacious for management. A selective JAK2 inhibitor, fedratinib, was studied in vitro and in vivo for PMBCL and HL [56]. When utilized in cell lines and murine xenograft models, JAK2 inhibition resulted in decreased cell proliferation, increased apoptosis, and increased survival with simultaneous decreased expression of PD-L1. There was an inverse correlation between the effective drug concentration and 9p24.1/JAK2 copy number.

Recommended Treatment Approach

Frontline Management

The two generally accepted frontline treatment approaches consist of 6–8 cycles of DA-EPOCH-R without radiotherapy and R-CHOP with consolidative radiotherapy. The frontline treatment approach should be individualized and incorporate the patient's age, cardiac reserve, candidacy for intensive chemotherapy and radiotherapy, the presence of disease outside of a radiation field, pleural/pericardial effusions, bulky disease, and the patient's desire for fertility. DA-EPOCH-R should be strongly recommended based on the low efficacy of R-CHOP and toxicity of radiotherapy.

Once a management approach has been selected, patients should be monitored for treatment toxicities and response assessment. An interim CT scan after at least two cycles of treatment should be performed to ensure the disease is not progressing on treatment. An end-of-treatment FDG PET/CT should be obtained at least 6–8 weeks following chemotherapy and at least 12 weeks following radiotherapy. If a complete metabolic response is achieved, the patient should enter surveillance, which generally consists of a history, physical exam, and labwork (with or without CT imaging) every 6 months for the first 2 years after treatment completion.

If a residual FDG-avid mass is present on the end-of-treatment PET scan, in the absence of clinical suspicion for refractory disease, it would be reasonable to perform repeat PET imaging at 6–8 weeks to evaluate for resolution. FDG-avid lesions that are falsely positive will improve with time, whereas residual disease will remain PET positive and increase in uptake. If refractory disease is suspected or if repeat PET imaging does not normalize, then a tissue biopsy is needed to confirm presence of lymphoma.

Management of Relapsed or Refractory PMBCL

Since relapsed or refractory PMBCL portends a dismal prognosis, a clinical trial should be strongly considered for all patients. If the patient is not a clinical trial candidate or if a clinical trial is not available, then management strategies employing salvage chemotherapy, radiotherapy, HDC/ASCR, CAR-T cells, checkpoint inhibitors, and allogeneic transplant can be utilized. If not given in the frontline setting, salvage radiotherapy can be curative if the disease is confined to the mediastinum. As relapsed or refractory disease can involve extranodal sites to include the gastrointestinal tract and CNS, careful assessments of any gastrointestinal or neurologic symptoms should ensue.

The treatment approach must take into account the patient's age, burden of disease, likelihood of having chemosensitive disease, fitness for intensive therapy, likelihood of being able to perform proper cell collections HDC/ASCR or CAR-T cells, and general goals of care. The standard approach to relapsed PMBCL in a transplant-eligible patient is salvage chemotherapy to autologous SCT [57]. For transplant-ineligible patients with chemotherapy-sensitive disease, a course of salvage chemotherapy should be pursued. In chemotherapy-resistant patients, a PD-1 inhibitor is reasonable.

Eligible patients who have received at least two prior lines of therapy can consider axicabtagene ciloleucel based on the aforementioned ZUMA-1 trial which revealed excellent response rates surpassing 70% in this population. However, the duration of response is not known, and it would be important to also human leukocyte antigen (HLA) type the patient and refer the patient to an allotransplant center.

Conclusions

PMBCL is a rare and underrepresented subtype of NHL with a predilection for young females in their third or fourth decade of life. Despite nearly 40 years of awareness of this distinct clinicopathologic entity, there are yet to be any randomized phase III trials to guide management, highlighting the importance of clinical trial enrollment. Despite a lack of high-level evidence, the standard de facto treatment has historically consisted of R-CHOP followed by consolidative mediastinal radiotherapy. However, due to late and long-term toxicities of irradiation, higher-intensity treatments with high remission rates omitting radiation such as DA-EPOCH-R should be highly considered. Additionally, end-of-treatment PET scan can stratify patients after chemotherapy and aid in risk-adapted, individualized treatment approaches. Given the immune privilege phenotype of PMBCL, the role of immunotherapy for relapsed or refractory disease has been promising in early studies.

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