Review Article

Updates in the Management of Primary Mediastinal B Cell Lymphoma

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Abstract

Primary mediastinal B cell lymphoma (PMBCL) is considered a distinct pathology according to the WHO classification of lymphoid malignancies. Patients have a better prognosis after the addition of Rituximab to anthracycline-based chemotherapy. The role of consolidative radiotherapy is controversial after the approval of dose-adjusted R-EPOCH and the selection of patients to undergo radiotherapy is based on end-of-therapy PET CT. In the relapsed/refractory setting, new approved drugs and other under investigation have improved patient outcomes. This review summarizes the different treatment modalities in (PMBCL) in the frontline and the relapsed/refractory settings.

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Introduction

Primary mediastinal B cell lymphoma (PMBCL) is a rare and aggressive disease that tends to occur in young females as a large mediastinal mass with local invasion.[1] Tumor cells originate from thymic B cells with overlapping features between diffuse large B cell lymphoma (DLBCL) and classical Hodgkin lymphoma (cHL).[2] The 4th and 5th WHO classification of lymphoid malignancies describe PMBCL as an independent pathology.[3,4]

Morphologically, PMBCL cells are medium sized with pale cytoplasm and moderate sized nuclei but can resemble to Reed-Sternberg cells. Immunophenotypically, tumor cells express B-cell markers (CD19, CD20, CD22, and CD79a), CD23 and CD45 but negative for surface immunoglobulin (Igs). CD30 expression is weak and heterogenous, different from that seen in Reed-Sternberg cells in cHL.[5,6] Several markers are specific for PMBCL and can differentiate it from DLBCL such as CD200, MAL, TRAF-1 and nuclear c-REL.[7-9] P63 expression and the absence of GATA3 can distinguish PMBCL from cHL.[10] Neoplastic cells also express transcriptional regulators of B-cell program (BOB.1, PU.1, OCT-2, PAX5, BCL6, MUM1/IRF4).[6] Programmed death ligands 1 and 2 (PDL1 and PDL2) can be detected by immunohistochemistry with a more frequent expression of PDL2 in PMBCL.[11]

PMBCL shares also common genetic features with cHL including gains or amplification involving 9p24.1 locus leading to Janus Kinase 2 (JAK2) amplification, dysregulation in JAK/STAT pathway and overexpression of PDL1 and PDL2.[12,13] The activation of nuclear factor κB (NF-κB) signaling pathway and the decrease in major histocompatibility complex expression, also contribute to immune escape of malignant cells. Other genetic alterations that are more specific for PMBCL have been identified including epigenetic modifiers (ZNF217 and EZH2), transcription factors (PAX5 and IRF2BP2) and TP53.[14] Based on these findings, potential targeted therapies have been studied in PMBCL especially PD1/PDL1 pathway inhibition and other immunotherapies.

Even though, we still have many answered questions including the optimal frontline treatment and the role of consolidative radiation therapy. Due to the rarity of this disease and to other limitations that restrict patients' recruitment, we lack randomized controlled trials that could help us to achieve these unmet needs and improve patient outcomes especially in the relapsed/refractory cases where prognosis remains poor despite novel therapeutic agents.

In this review, we summarize the different treatment options studied in PMBCL in the frontline and relapsed/refractory settings.

Treatment Options in the Frontline Setting

Chemoimmunotherapy

Before Rituximab era, the fist-line treatment of PMBCL was based on anthracycline-based chemotherapy regimen (CHOP, MACOP-B/VACOP-B) with or without radiotherapy, with a low rate of complete response and high risk of disease relapse.[15,16] The addition of Rituximab to chemotherapy improved outcome of these patients.

In the Mabthera international trial group study, 87 patients with PMBCL were included. The addition of Rituximab to CHOP vs. CHOP alone increased the rate of complete remission (from 54% to 80%, $P = .015$) with improvement in 3-year-event-free-survival (EFS) (78% vs. 52%, $P = .012$) and overall survival (OS) (89% vs. 78%, $P = .158$)[17] (Table 1). Another trial by Vassilakopoulos et al.

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Table 1 Studies Evaluating Frontline Treatment in PMBCL.

Trial	Type	Treatment	N	Results
Mabthera International Trial[17]	Prospective	RCHOP vs. CHOP	87	CRR: 80%, 3-year EFS 78%, OS 89% CRR 54% 3-year EFS 52%, OS 78%
Vassilakopoulos et al[18]	Retrospective	RCHOP vs. CHOP	121	5-year EFS: 80%, OS: 89% 5-year EFS 47%, OS 69%
Lisenko et al.[19]	Retrospective	RCHOP vs. CHOP	80	10-year PFS: 95%, OS: 92% 10-year PFS 67%, OS 72%
LYSA[22]	Retrospective	R-ACVBP	313	CMRR 86.3%, 3-year PFS 89.4%
		R-CHOP-14 vs. R-CHOP-21		CMRR 86.8%, 3-year PFS 89.4% CMRR 76.6%, 3-year PFS 74.7%
Dunleavy et al.[26]	Prospective	Da-R-EPOCH	51	5-year PFS 93%, 5-year OS 98%
Giulino-Roth et al.[27]	Retrospective	Da-R-EPOCH	156	3-year EFS 85.9%, 3-year OS 95.4%
Shah et al.[28]	Retrospective	RCHOP vs. Da-R-EPOCH	132	CRR 70%, 2-year OS 89% CRR 84%, 2-year OS 91%
Zhou et al.[29]	Retrospective	Da-R-EPOCH vs. RCHOP	166	Better OS ($P = .048$) and PFS ($P = .0067$)
		R-HCAVD vs. RCHOP		Better OS (0.095) and PFS ($P = .0088$)
Malenda et al.[30]	Retrospective	RCHOP vs. Da-R-EPOCH	53	ORR 92%, CRR 60% ORR 92.6%, CRR 70.4% No difference in PFS and OS
Elhagracy et al.[31]	Retrospective	RCHOP vs. Da-R-EPOCH	41	CRR 92.6% CRR 85.7% No difference in PFS and OS
Morgenstern et al.[32]	Retrospective	RCHOP/RICE	56	PFS 2.1 years, OS 2.5 years
		Da-R-EPOCH		PFS 2.4 years, OS 2.7 years

Abbreviations: CRR = complete remission rate; CMRR: complete metabolic response rate; EFS = event-free survival; OS = overall survival; PFS = progression-free survival.

have shown less early treatment failure with RCHOP, better 5-year freedom from progression rate (81% vs. 48%, $P < .0001$), better 5-year EFS (80% vs. 47%, $P < .0001$) and better OS and lymphoma-specific survival rates (89% vs. 69%, $P = .003$ and 91% vs. 69%, $P = .001$ respectively)[18] (Table 1). Similar results were reported by Lisenko et al. with 10-year progression free survival (PFS) of 95% with Rituximab vs. 67% with CHOP alone ($P = .001$) and 10 -year OS 92% vs. 72% ($P = .023$). The benefit in PFS was seen in all patients independently of their international prognostic index (IPI) risk[19] (Table 1). A subgroup analysis of the phase III UK National Cancer Research Institute comparing RCHOP-14 (given every 2 weeks) to RCHOP-21 (given every 3 weeks) suggested the possibility of better outcome with RCHOP-14.[20] However, a recently published retrospective study did not show a superiority of RCHOP-14 over RCHOP-21 in PMBCL.[21] Large, randomized trials are needed validate these results. A multicenter retrospective study in Lymphoma Study Association (LYSA) centers included 313 patients with PMBCL treated with R-ACVBP or RCHOP-14 or RCHOP-21. The complete metabolic response rate was 86.3%, 86.8%, and 76.6% ($P = .23$) respectively. The 3-year PFS probabilities were 89.4% (95% confidence interval [CI], 84.8-94.2), 89.4% (95% CI, 82.7-96.6), and 74.7% (95% CI, 64-87.1) ($P = .018$)[22] (Table 1).

Most patients with PMBCL treated with chemoimmunotherapy have received consolidation with mediastinal radiotherapy. Given the increased risk of breast cancer in young females and cardiovascular toxicity associated with mediastinal radiotherapy, efforts were focused on developing new treatment strategies to avoid radiotherapy without affecting treatment outcome especially for young patients.[23,24] In addition, RCHOP was associated with a high rate of primary refractory disease especially in high-risk patients.[25] Thus, more intensive chemoimmunotherapy have emerged with dose adjusted R-EPOCH (Da-R-EPOCH) being the most used.

Dunleavy et al. demonstrated favorable outcome of Da-R-EPOCH with a 5-year EFS rate of 93% and OS rate of 97% with decreased need for radiotherapy[26] (Table 1). A multicenter retrospective analysis of 156 patients (children and adults) with PMBCL treated with Da-R-EPOCH in the first line setting showed a 3-year EFS of 85.9% (95% CI, 80.3-91.5) and OS of 95.4% (95% CI 91.8-99.0), with 75% of patients achieving complete response on PET scan (Deauville score 1-3) after chemoimmunotherapy[27] (Table 1). Other retrospective studies have compared patient's outcome between R-CHOP and Da-R-EPOCH. Shah et al. reported a decreased need for radiation therapy with Da-R-EPOCH compared to R-CHOP (13% vs. 59%, $P < .001$) with a higher complete response rate (84% vs. 70%, $P = .046$) and a better 2-year OS rate (91% vs. 89%)[28] (Table 1). Zhou et al. also showed

a better OS ($P = .048$) and PFS ($P = .0067$) in patients treated with Da-R-EPOCH then R-CHOP[29] (Table 1). However, other retrospective analysis did not show the superiority of Da-R-EPOCH over RCHOP[30,31] (Table 1). Sequential R-CHOP/R-ICE is another therapeutic option that was associated with similar outcome and less toxicity profile compared to Da-R-EPOCH[32] (Table 1).

Based on these results, most centers are using R-CHOP or Da-R-EPOCH as a first-line treatment in PMBCL with a trend to favor Da-R-EPOCH to avoid consolidative radiotherapy. Prospective trials are mandatory to determine the optimal treatment in this setting.

Mediastinal Radiotherapy

Even though PMBCL is very sensitive to radiotherapy, the role of this modality in the frontline setting remains a debatable topic. Retrospective analysis about the impact of mediastinal radiotherapy on PFS and OS after chemoimmunotherapy showed conflicting results.[33-37] Historically, consolidative radiotherapy was performed systematically in all patients. In the last few years, a PET guided approach has been evaluated in order to select patients that will benefit from radiotherapy after systemic treatment and to avoid unnecessary radiation.

End-of-treatment (EOT)-PET is correlated with disease outcome and survival and can help to define the best candidate for consolidative radiotherapy. This was demonstrated by several retrospective analysis and some prospective trials. The International Extranodal Lymphoma Study Group IELSG-26 defined PET positivity based on liver uptake, as an effective tool to determine patients at high risk of failure after chemoimmunotherapy.[38] A retrospective study by Pinnix et al. including 97 patients with stage I/II PMBCL, showed that patients who had a Deauville 5-point scale (D5PS) score of 4 and 5 after Rituximab and chemotherapy, are at the highest risk of progression/relapse and need further consolidative treatment.[39] Vassilakopoulos et al. also demonstrated higher failure rates in patients with D5PS score of 4 or 5 and SUVmax>5 after frontline treatment. However, most of those patients can be salvaged by radiotherapy and some of them can remain PET positive during follow-up but remain in long term remission. This study also suggested the possibility of the omission of consolidative radiotherapy based on the negativity of EOT-PET.[40] Similar results were reported by Filippi et al. with a D5PS score of 5 being associated with worse outcome (OS at 2 years, 33.3% vs. 100%). All patients with a D5PS score of 3 and 4 on EOT-PET experienced a complete response after radiotherapy compared to 25% in patients with D5PS score of 5.[41] Another retrospective analysis included patients treated with RCHOP with radiotherapy before 2005 and those treated with RCHOP with or without radiotherapy depending on their EOT-PET (considered positive if D5PSS 4-5). Using the PET-guided approach, we had a reduction of 64% in the need for consolidative radiotherapy without affecting treatment outcome.[42] Similarly, the results of a single-center retrospective analysis of 74 patients with PMBCL treated with MACO-B and Rituximab, favored a PET-guided radiotherapy approach. No differences were seen in disease free survival between patients with positive EOT-PET treated with radiotherapy and negative EOT-PET in whom radiotherapy was omitted.[43]

The IELSG37 trial is a large randomized controlled trial including 530 patients with PMBCL treated with 6 cycles of chemoimmunotherapy followed by a PET/CT scan. Patients who achieved complete metabolic response after chemoimmunotherapy (Deauville score of 1-3) were randomized to mediastinal radiotherapy 30Gy or observation. At 30 months, the PFS was 98.5% (95% CI, 94.3-99.6) in the radiotherapy arm and 96.2% (95% CI, 91.1-98.4) in the observation arm ($P = .278$). The estimated relative effect of radiotherapy vs. observation in terms of hazard ratio (HR) was 0.47 without adjustments and 0.79 after stratification for the variables used for randomization. At 30 months the absolute risk reduction from radiotherapy was 2.3% unadjusted, and 0.8% with stratified HR. The 5-year OS was 99% in both arms.[44]

Melani et al. enrolled 93 patients with PMBCL treated with Da-R-EPOCH without radiotherapy and EOT-PET was performed in 80 patients. Fifty-five patients had a negative PET (D5PSS 1-3) with 1 treatment failure (8-year EFS and OS of 96.0% and 97.7%) and 25 patients had a positive PET (D5PSS 4 and 5) with 5 treatment failures (8-year EFS and OS of 71.1% and 84.3%). Linear regression analysis of serial PET showed a decrease in SUV max in positive EOT-PET non progressors. Using serial PET scans in patients with positive EOT-PET can identify true progressors and avoid unnecessary radiotherapy.[42] These results raised the question about the prognostic significance of EOT-PET and its value to detect disease progression/relapse. Freitas et al. also concluded a low positive predictive value (PPV) for EOT-PET (47%, 95% CI, 0.24-0.71) compared to a negative predictive value (NPV) of 100% (95% CI, 0.88-1.00).[45]

Furthermore, studies have shown that the use of interim PET scan during treatment with chemotherapy with or without Rituximab is associated with low PPV and many patients with positive PET had a negative histological restaging showing inflammation and necrosis and no lymphoma.[46-49]

Central Nervous System (CNS) Prophylaxis

CNS involvement in not well studied and it seems to occur in approximately 2% of cases of PMBCL in the Rituximab era. A retrospective study of 100 patients showed an incidence of CNS relapse of 4.4% in patients treated with CHOP +/− radiotherapy compared to 2% in patients treated with RCHOP +/− radiotherapy.[47] Hayden et al. reported in their retrospective study of patients treated with RCHOP a 2.5% of CNS relapse involving brain parenchyma or leptomeninges.[50] Risk factors associated with CNS involvement are not well defined. CNS-IPI prognostic scoring system including IPI factors in addition to adrenal/kidney involvement, is validated for DLBCL but not for PMBCL.[51] However, a recently published trial evaluating CNS relapse in 564 PMBCL patients showed that CNS relapse appears to be strongly associated with kidney and/or adrenal involvement. The 2-year cumulative incidence of relapse was 1.47% with no difference between patients treated with RCHOP or Da-R-EPOCH.[52]

Given the limited data about CNS involvement, CNS prophylaxis is not systematically recommended and is performed in some centers for patients considered at high risk of relapse.

Table 2 Studies Evaluating Treatment Options in Relapsed/Refractory PMBCL.

Drug	Study	Type	N	Results
Axi-cell CAR T-cell	**ZUMA-1**[58,59]	Prospective	111	ORR 83%, CRR 58% OS 25.8 mo 5-year disease specific survival 51%
Lisocabtagene maraleucel	**TRANSCEND-NHL-001**[60]	Prospective	256	ORR 73%, CRR 53% 12- mo PFS 44.1% 12- mo OS 57.9%
	TRANFORM[61]	Prospective	184	CRR 74% vs. 43% 18-mo OS rate 73% vs. 54%
Pembrolizumab	**KEYNOTE-013**[62]	Prospective	21	ORR 48%, CRR 33%
	KEYNOTE-170[63,64]	Prospective	53	ORR 41.5% mPFS 4.3 mo. mOS 22.3 mo 48-mo PFS rate 33% 48-mo OS rate 45.3%
BV	**Zinzani et al.**[65]	Prospective	15	ORR 13.3%
	Jacobsen et al.[66]	Prospective	6	ORR 17%
Nivolumab + BV	**CheckMate 436**[67]	Prospective	30	ORR 73%, CMRR 43%

Abbreviations: CRR = complete response rate; CMRR = complete metabolic response rate; CRR = complete response rate; mPFS = median PFS; mOS = median OS; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

Treatment Options in the Relapsed/Refractory Setting

Despite advances in the frontline treatment of PMBCL, 10% to 30% of patients still experience relapse or progression, and most relapses occur early after frontline treatment. Salvage treatment followed by consolidation with high dose chemotherapy and autologous stem cell transplantation (autoHSCT), remain the cornerstone of the treatment of those patients. Studies have shown that chemo sensitive patients benefit the most from autoHSCT compared to patients with primary refractory disease and those who are chemo refractory at the time of autoHSCT. Allogenic stem cell transplantation (alloHSCT) should be also considered an option in relapsed/refractory patients with durable remissions in treatment responders. However, response to salvage treatment remains poor with an ORR of 25% and a 2-year OS of 15% according to Kuruvilla et al. Patients who are refractory to salvage chemotherapy could not undergo stem cell transplantation which highlights the importance of chimeric antigen receptor T-cell therapy (CAR T-cell) as a best therapeutic option.[53-57] CAR T-cell and other novel agents for relapsed/refractory patients are discussed in this section.

Chimeric Antigen Receptor T-Cell Therapy (CAR T-cell)

CAR T-cell has changed the management of refractory B cell lymphomas. Three CD19-targeted CAR T products are approved for DLBCL. However, patients with relapsed/refractory PMBCL were included in 3 of the CAR T-cell trials: ZUMA-1 (axicabtagene ciloleucel) and TRANSCEND-NHL-001 and TRANSFORM trials (lisocabtagene maraleucel). Patients enrolled in these trials underwent peripheral blood mononuclear cell apheresis for CAR T-cell production. After the manufacture of CAR T product, patients received conditioning chemotherapy regimen before receiving CAR T-cell infusion.

The ZUMA-1 trial is a phase II single-arm multicenter trial of axicabtagene ciloleucel (axi-cel) CAR T-cell that enrolled 111 patients with large B-cell lymphoma including 24 patients with PMBCL. At a median follow up of 63.1 months, the ORR was 83% with a CRR of 58% in the entire population. Median OS was 25.8 months, and the 5-year OS rate was 42.6%. Disease-specific survival at 5 years was 51%. Regarding safety profile, cytokine release syndrome (CRS) occurs in 93% with grade ≥3 events occurring in 11%. Neurologic complications occurred in 64% of patients with grade ≥3 events in 30%[58,59] (Table 2).

TRANSCEND-NHL-001 trials evaluated the efficacy of another CD19 targeted CAR T-cell, lisocabtagene maraleucel (Liso-cel). Among 256 patients enrolled, 15 patients had PMBCL. ORR was 73% with a CRR of 53%. Twelve-months PFS was 44.1% and OS was 57.9 %. Most common adverse events described were CRS and other neurologic events of low grade in most cases[60] (Table 2).

Liso-cel was also studied in the TRANFORM trial that randomized 184 patients with relapsed/refractory large B cell lymphoma (17 PMBCL patients) between liso-cel and standard of care (SOC). At a 17.5 months median follow-up, the median event free survival (EFS) was not reached for liso-cel vs. 2.4 months for SOC. CRR was 74% for liso-cel vs. 43% for SOC ($P < .0001$) and median PFS was not reached for liso-cel vs. 6.2 months for SOC (HR = 0.400; $P < .0001$). Eighteen-month OS rates were 73% for liso-cel and 54% for SOC (HR = 0.415). No high-grade adverse events were described[61] (Table 2).

Based on these results, axi-cel and liso-cel were approved in the relapsed/refractory large B-cell lymphomas including PMBCL.

Immune Checkpoint Inhibitors

As mentioned before, PMBCL is characterized by genetic alterations at 9p24.1 locus leading to overexpression of PDL1 and probably high sensitivity to PD1 blockade.

KEYNOTE-013 is a phase IB, open-label multicohort study of Pembrolizumab in patients with hematologic malignancies. The primary endpoints were safety and ORR. Twenty-one patients with relapsed/refractory PMBCL were included. All patients received prior Rituximab with a 3 median prior lines treatment, 15 patients received prior radiation and 8 patients underwent prior transplantation. At a median follow up of 29.1 months, the ORR was 48% (95% CI, 26%-70%) with a CRR of 33%. The median duration of response was not reached. Median PFS was 10.4 months (95% CI, 3.4 months to not reached) and median OS was 31.4 months (95% CI, 4.9 months to not reached). Seventy-one percent of patients experienced adverse events including 24% of grade 3 and 4[62] (Table 2).

KEYNOTE-170 is a phase II multicenter multicohort study evaluating the efficacy and safety of Pembrolizumab in patients with relapsed/refractory PMBCL or Richter transformation. Patients received Pembrolizumab 200 mg every 3 weeks on day 1, for a maximum of 35 cycles or up to 2 years until progression or intolerance. Primary endpoint was ORR. Fifty-three patients with relapsed/refractory PMBCL were enrolled. Seventeen patients received prior radiation and 14 patients underwent prior transplantation. At a median follow-up of 48.7 months, 13 completed 2 years of treatment and 40 patients discontinued. The ORR was 41.5% (95% CI, 30.0-53.7), with 20.8% complete response rate and 20.8% partial response rate. Median depth of response (DOR) was not reached and 80.6% of patients had a response ≥48 months. Median PFS was 4.3 months (95% CI, 2.8-13.8) and the 48-month PFS rate was 33.0%. Median OS was 22.3 months (95% CI, 7.3-NR) and the 48-month OS rate was 45.3%[63,64] (Table 2). Based on these interesting results, Pembrolizumab was approved by the FDA in the treatment of relapsed/refractory PMBCL after 2 or more prior treatments.

Brentuximab Vedotin

PMBCL cells had an heterogenous expression of CD30.[5,6] BV is an anti-CD30 antibody drug conjugate that has been studied in different lymphoma subtypes. A single-arm phase II multicenter clinical trial conducted by the Italian Lymphoma Foundation included patients with relapsed/refractory CD30 + PMBCL. Patients received BV at a dose of 1.8 mg/kg at day 1 of each 21-day cycle. Patients who had stable disease or better had to accomplish a minimum of 8 cycles and not more than 16 cycles. The primary endpoint was objective response rate (ORR). Among 15 patients enrolled, 12 patients had refractory disease to the last treatment, 8 patients had stage IV disease, 8 patients received autoHSCT, 9 patients received radiation therapy and all patients received Rituximab. The ORR was 13.3% (2 patients achieved PR) and the duration of response was less than 3 to 4 months also including a consolidation with alloHSCT[65] (Table 2). Another phase II study evaluating BV in patients with several NHL subtypes CD30+ showed a complete response in 1/6 patients with PMBCL[66] (Table 2).

The phase II CheckMate 436 trial studied the combination of Nivolumab and BV in patients with relapsed/refractory PMBCL treated with either autoHSCT or 2 or more prior chemotherapy regimens. Patients received Nivolumab 240 mg and BV 1.8 mg/kg every 3 weeks until disease progression or toxicity. The primary endpoint was ORR. Thirty patients were included. At a median follow up of 11.1 months, the ORR was 73% (65% CI, 54% to 88%) with 43% complete metabolic response. Median duration of response, median progression-free survival, and median overall survival have not been reached. Five responders proceeded to autoHSCT and 6 responders had alloHSCT. Most adverse events were low grade[67] (Table 2).

Bispecific Antibodies

Bispecific antibodies (BsAbs) are being evaluated as a new immunotherapeutic approach in patients with relapsed/refractory NHL. BsAbs have 2 targets: CD3 on T-cells and CD20 or CD20 on malignant B-cells. BsAbs targeting CD20 and CD3 include odronextamab, mosunetuzumab, glofitamab, and epcoritamab. These agents have shown promising results in relpased/refractory NHL. However, few patients with PMBCL were enrolled in BsAbs trials and more trials are needed to determine the benefit of these drugs in PMBCL.[68-70]

Ruxolitinib

Even though the JAK/STAT pathway is upregulated in PMBCL, the inhibition of JAK2 was not demonstrated an effective strategy in the treatment of relapsed/refractory PMBCL. In the study conducted by Kim et al., all responders to Ruxolitinib had HL and all PMBCL patients progressed after the first or second cycle.[71]

Future Perspectives

Role of Circulating Tumor DNA (ctDNA)

ctDNA is a promising biomarker that is under evaluation in the oncology field due to its potential role to predict prognosis, response, and resistance to treatment. As discussed before, PET CT has a limited ability to guide treatment decision in PMBCL that underlines the necessity of new biomarkers to improve patient's outcome. ctDNA is being evaluated in PMBCL patients with limited available data till now. Different mutations were identified by ctDNA with high concordance with tissue biopsy: *B2M* (61%), *SOCS1* (61%), *GNA13* (44%), *STAT6* (44%), *NFKBIA* (39%), *ITPKB* (33%), and *NFKBIE* (33%).[72,73] A multicenter analysis including patients diagnosed with different lymphoma subtypes, demonstrated higher levels of circulating free DNA (cfDNA) in patients with PMBCL and mediastinal grey zone lymphoma, and the lowest levels were seen in follicular lymphoma.[74] Kurtz et al. showed a prognostic role of ctDNA in patients with large B-cell lymphoma. Two-hundred seventeen patients were enrolled in this multicenter trial including 24 patients with PMBCL and 193 patients with DLBCL. ctDNA was detected in 98% of cases. Pretreatment ctDNA levels were prognostic in the front-line and salvage settings. Early molecular response (EMR) was a defined as a 2-log decrease in ctDNA levels after 1 cycle of treatment and major molecular response (MMR) as a 2.5-log decrease after 2 cycles. Patients who achieved EMR or MMR had a better EFS at 24-months in the front-line setting (EMR: EFS, 83% vs. 50%; $P = .0015$; MMR: EFS, 82% vs. 46%; $P < .001$) and after salvage treatment (EFS, 100% vs. 13%; $P = .011$).[75]

Further trials are mandatory to validate the prognostic value of ctDNA and its ability to detect minimal residual disease in order to incorporate this technique in routine practice.

Ongoing Studies

Despite advances in the management of PMBCL, patients still have a high risk of disease relapse or progression. To improve patient's outcome, many clinical trials are evaluating new therapies or drug combinations in frontline and relapsed/refractory settings.

The large cooperative group study ANHL1931 is a phase III trial evaluating the combination of Nivolumab with chemoimmunotherapy for 6 cycles vs. immunochemotherapy alone in newly diagnosed PMBCL patients. The primary endpoint is PFS (NCT04759586).

In patients with relapsed/refractory PMBCL, a phase II study will assess the combination of Pembrolizumab and CAR T-cell with the primary endpoint being the CRR at 6 months (NCT05934448). Other drugs are being evaluated in this setting including LP002, an anti-PDL1 (NCT04600947) and the combination of Zanubrutinib (a bruton tyrosine kinase inhibitor) and Tislelizumab (an anti-PD1) (NCT04705129).

Conclusion

PMBCL is a distinct entity that shares clinical, molecular, and pathologic features with DLBCL and cHL. Frontline treatment is based on chemoimmunotherapy regimens with or without radiotherapy. In order to decrease the use of consolidative radiotherapy especially in young patients without affecting outcomes, more intensified therapeutic regimens have emerged like Da-R-EPOCH. Furthermore, using EOT-PET is essential to select candidates for consolidative radiotherapy. To overcome the low PPV of PET CT, the use of serial PET in positive EOT-PET patients can detect true progressors after frontline treatment. ctDNA is a promising biomarker under investigation that could be more useful than PET CT in the different treatment settings.

The treatment of relapsed/refractory disease have evolved with the approval of new drugs like ICIs and CAR-T cell. However, the best sequence for these therapies must be defined to provide the best outcome.

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