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Up-to-date approach in diagnosis and treatment of primary mediastinal B-cell lymphoma

Savremeni pristup u dijagnostici i lečenju primarnog medijastinalnog B-ćelijskog limfoma

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Introduction

Primary mediastinal B-cell lymphoma (PMBCL) is a rare type characterized by specific clinical and biological features [1]. It originates from thymic B lymphocytes. It was previously considered a subtype of diffuse large B-cell lymphoma (DLBCL), but the new classification recognizes it as a separate entity [2]. Molecular studies have determined that PMBCL shows increased expression of genes involved in nuclear factor (NF)-kB and Janus kinase (JAK) 2 signaling pathways, as well as amplification of 9p24 with frequent loss of functional human leukocyte antigen class II (HLA-II) complexes [3]. It is believed that these biological differences compared to classic DLBCL form the basis for a more favorable prognosis with fewer late relapses. PMBCL manifests as a mediastinal mass that spreads to surrounding organs and tissues, nearby lymph nodes, lungs, and pleural and pericardial spaces. Distant extranodal localizations, which are initially rare, are more frequently present in disease recurrence [4, 5].

At this time, there are no randomized clinical studies that define the optimal therapy for PMBCL. The foundation of therapy is immunochemotherapy based on rituximab and anthracyclines with the use of interim positron emission tomography (PET) scans, while in cases of disease recurrence, treatment is similar to that of relapsed DLBCL. Treatment in subsequent relapses includes the use of programmed death (PD)-1 inhibitors and chimeric antigen receptor-modified T (CAR-T) cells [6–9].

Pathohistological features

The histological picture of this lymphoma consists of a diffuse proliferation of large lymphoma cells with bands of fibrous tissue, along with cells that can vary in size and shape, sometimes resembling Reed-Sternberg cells [5]. Due to the presence of fibrosis, it can resemble carcinoma or thymoma, making it very important to obtain an adequate sample for pathohistological and immunohistochemical analysis. It can sometimes be very difficult to distinguish it from Hodgkin's lymphoma (HL) with nodular sclerosis and mediastinal gray zone lymphoma [4]. PMBCL and HL, nodular sclerosis type, have similar pathohistological features, as well as similar clinical characteristics (both occur in younger individuals as a large mediastinal mass), and share some biological and molecular characteristics [5]. The cellular composi

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tion of the microenvironment in PMBCL varies and can resemble HL with fewer lymphoma cells and a diverse array of microenvironmental cells, than the one that more closely resembles DLBCL [6].

PMBCL cells express pan B-cell markers (CD20, CD79a, CD19, CD22) and B-cell transcriptional regulators (BOB.1, PU.1, OCT-2, PAX5, BCL6, MUM1/IRF4) [4, 10] with variable expression of BCL6, as well as BCL2, which is associated with a poor prognosis [11]. Expression of CD30 is present to varying degrees in about 80% of patients.

Similar to classic HL (cHL), PMBCL has been found to have amplification of 9p24.1, which results in overexpression of PD ligand 1 (PD-L1) and the formation of an immune "escape" phenotype [12, 13].

Clinical features

PMBCL most commonly occurs in young individuals, presenting as a large mediastinal mass. About 80% of cases are diagnosed at clinical stage I or II of the disease [5]. Local spread of the disease to surrounding structures (lungs, pericardium, pleura) is very often present. Unlike DLBCL, distant extranodal organ involvement is rare. Spread to distant organs is much more common in disease recurrence, but relapse of PMBCL in the central nervous system is rare (occurring in only about 3.0% of patients). The clinical symptoms of the disease are associated with the mediastinal mass. In cases of a large tumor mass, superior *vena cava* syndrome can develop, leading to thrombotic complications, which occur in about 30–40% of patients [14]. In some cases, PMBCL is not localized in the mediastinum, making the correct diagnosis more challenging for these patients [5].

Since PMBCL is a clinicopathological diagnosis, the certainty of the diagnosis can affect the comparison of studies. So far, only a few studies have used molecular diagnostics as the gold standard for diagnosis. For histological diagnosis, excisional biopsy is preferred. However, excisional biopsy is not feasible if the patient has respiratory and cardiac manifestations. In such situations, percutaneous needle biopsy is appropriate.

Molecular features

PMBCL shares significant clinical and histological similarities with HL, particularly with nodular sclerosis, and these similarities have been confirmed by gene profile analysis of the two types of lymphoma [13]. In PMBCL, genes involved in the JAK-STAT pathway and NF-kB activation show increased expression, while genes involved in B-cell receptor signaling pathways have reduced expression [13].

The key molecular characteristics of PMBCL include the amplification of 9p24.1, which leads to increased expression of PD-L1 and PD-L2, and recurrent genetic abnormalities in *B2M, CIITA, CD58, CD274,* and *PDC1LG2*, which contribute to an immunosuppressive tumor microenvironment [3]. A better understanding of the molecular pathways involved in the pathogenesis of PMBCL has opened up opportunities for the development of new targeted approaches in the treatment of this type of lymphoma.

Prognostic factors

The International Prognostic Index (IPI) used for determining the prognosis in DLBCL is not relevant for assessing the prognosis in patients with PMBCL, as these are typically young patients with a limited stage of disease [15–17]. Significant predictive factors in PMBCL include the presence of pleural or pericardial effusion, large tumor mass, extranodal disease localization, and doubled levels of lactate dehydrogenase (LDH) [15–18]. Patients without extranodal localization of the disease and normal LDH levels represent an ultra-low-risk subgroup with an 11% risk of poor therapeutic response and only 1% to 4% five-year mortality from lymphoma [19].

Zhou et al. [15] found that the absence of MUM1 expression and a low lymphocyte-to-monocyte ratio were associated with shorter progression-free survival (PFS) and overall survival (OS). However, another study found that low PD-L1 expression and high MUM1 expression were linked to a shorter time to disease progression [20].

In 2024, Noerenberg et al. [21] analyzed genetic changes in 340 patients with *de novo* PMBCL using whole-genome, whole-exome, and targeted sequencing. They found that several genetic aberrations significantly impacted therapy response and survival in PMBCL patients, which could be used for risk assessment and determining the optimal therapeutic approach [21]. In this study, *CD58* mutations were identified as the most significant adverse prognostic parameter, while patients with *DUSP2* mutations had long-lasting therapeutic responses and extended OS.

The Lymphoma Study Association (LYSA) group showed that a total metabolic tumor volume (TMTV) $\geq$ 360 cm^3 was associated with poor prognosis, regardless of treatment [22]. This group also found that total lesion glycolysis (TLG) $\geq$ 2,500 at the onset of the disease was associated with poorer PFS (p = 0.023). The International Extranodal Lymphoma Study Group (IELSG) 26 study found that combining initial TLG with the Deauville score at the end of treatment provided a better positive predictive value than TLG alone, with patients having TLG > 5.8 and an interim Deauville score of 4–5 experiencing poorer outcomes [23].

New biomarkers in PMBCL

Several studies have analyzed the significance of circulating tumor deoxyribonucleic acid (ctDNA) as a biomarker with potential applications in diagnosis, prognosis, response assessment, and disease remission monitoring. Currently, there is limited data on ctDNA in PMBCL, but studies published so far have revealed a high degree of concordance between the molecular profile of primary tumor biopsies and ctDNA in patients. Analyzing 197 patients with PMBCL, Schroers-Martin et al. [24] found higher ctDNA levels in patients with PMBCL and mediastinal gray zone lymphoma compared to DLBCL, cHL, and trans-

formed low-grade lymphoma. A subsequent multicenter study analyzing samples from 217 patients with DLBCL and PMBCL showed that pre-treatment ctDNA levels have prognostic significance both in *de novo* patients and those with relapsed disease. In the group of patients receiving initial therapy, a reduction in these levels after initial therapy was associated with better outcomes. Patients who achieved a 2-log or greater reduction in ctDNA after the first cycle of therapy had better outcomes after 24 months, with a longer time to adverse events (83% vs. 50%, respectively), and similar results were observed after two cycles of therapy (82% vs. 46%) [25].

First-line treatment

At present, there are no randomized clinical trials that define the optimal therapy for PMBCL. The reason for this is the rarity of this type of lymphoma and the necessity for urgent treatment in most patients, which complicates the inclusion in clinical trials. Treatment data primarily come from non-randomized prospective and retrospective studies [22, 26–37] (Table 1). Studies conducted before using rituximab showed that better treatment outcomes were achieved with more aggressive protocols. Today, several immunochemotherapy protocols are used: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) administered every 14 (R-CHOP14) or 21 (R-CHOP21) days; rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone (R-ACVBP) with consolidation therapy depending on PET findings; dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin (DA-EPOCH) [22, 27–34]. In the rituximab era, one of the most well-known studies conducted by Dunleavy et al. [27] showed that treatment with the DA-EPOCH-rituximab (DA-EPOCH-R) protocol eliminates the need for radiation therapy in patients with chemosensitive PMBCL. Following the publication of this study, the use of DA-EPOCH-R has increased significantly, while the use of radiation therapy has decreased significantly. In this series of patients, a higher percentage of patients achieved complete therapeutic response after DA-EPOCH-R compared to the R-CHOP21 protocol (84% vs. 70%, $p = 0.046$) [27]. The efficacy of these two protocols has been evaluated in several subsequent studies, but the results have been inconsistent [28, 30]. One of the largest recently published retrospective studies by an Italian group of authors involved 891 patients with PMBCL [31]. This study compared the efficacy of R-CHOP21,

Table 1

Studies in patients with PMBCL receiving first-line therapy

Authors	Therapy	Study type	n	PFS (95% CI)	OS (95% CI)
Camus et al. [22]	ACVBP14* R or O	retrospective	313	89.4	92.4
	CHOP14* R or O			89.4	100.0
	CHOP21* R or O			74.7	87.5
Hayden et al. [26]	R-CHOP	retrospective	159	80.0	89.0
Dunleavy et al. [27]	DA-EPOCH-R	prospective	51	93.0 (81–98)	97.0
Shah et al. [28]	R-CHOP	retrospective, multicentric	56	76.0 (64–88)	89.0
	DA-EPOCH-R		76	85.0 (75–94)	91.0
Santarsieri et al. [29]	DA-EPOCH-R	retrospective		3-year 92.8	97.2
Malenda et al. [30]	R-CHOP	retrospective	53	1-year 87.0	100.0
	DA-EPOCH-R			73.9	92.0
Iannitto et al. [31]	R-CHOP21*	retrospective, multicentric	891	71.0	91.0
	R-CHOP14*			89.0	
	R-megaCHOP			93.0	
	R-VACOP-B			83.0	
	R-MACOPB			86.0	
	DAEPOCH-R			77.0	
Rieger et al. [32]	R-CHOP-like	prospective, (subanalysis MInT)	44	78.0 (61.0–88.0)	88.5
Moskowitz et al. [33]	R-CHOP-14*-ICE	prospective	54	78.0	88.0
Gleeson et al. [34]	R-CHOP-14*	prospective	50	80.0	84.0
	R-CHOP21*				
Giulino-Roth et al. [35]	DA-EPOCH-R	retrospective, multicentric	118	87.5	97.1
Halahleh et al. [36]	R-CHOP	retrospective	49	60.0	71.0
Casadei et al. [37]	R-MACOP-B	retrospective	151	69.3	82.6

PMBCL – primary mediastinal B-cell lymphoma; n – number; PFS – progression-free survival; CI – confidence interval; OS – overall survival; R – rituximab; O – obinutuzumab; ACVBP – doxorubicin, cyclophoshamide, vindesine, bleomycin, prednisone; CHOP – cyclophosphamide, doxorubicin, vincristine, prednisone; R-CHOP – rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; DA-EPOCH-R – dose-adjusted etoposide, prednisone, vincristine, cyclophospamide, doxorubicin rituximab; R-megaCHOP – rituximab plus high-dose chemotherapy CHOP; R-VACOP-B – rituximab, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; R-MACOP-B – rituximab, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; R-CHOP-14-ICE – R-CHOP-ifosfamide, carboplatin, etoposide; MInT – Mabthera International Trial Group.

Note: * – immunochemotherapy protocols are used and administered every 14 or 21 days.

R-CHOP14, rituximab plus high-dose chemotherapy cyclophosphamide, doxorubicin, vincristine, prednisone (R-megaCHOP), rituximab, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin (R-VACOP-B), rituximab, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin (R-MACOP-B), and DA-EPOCH-R protocols. The study results indicated that R-CHOP is a suboptimal treatment for patients with PMBCL, whereas survival outcomes with other protocols were comparable to those achieved with the original R-MACOP-B protocol, which resulted in a five-year PFS of 86% [95% confidence interval (CI): 81–90] and a five-year OS of 91% (95% CI: 86–94) [31]. It should be noted that the interpretation of these study results is challenging because the criteria for selecting patients for each regimen are unclear, and most studies do not include a large enough number of patients to detect small differences. Moreover, the DA-EPOCH-R protocol has not been widely adopted in many centers, likely due to its complicated administration and hematologic toxicity compared to R-CHOP14/21. Just a few months ago, the largest meta-analysis of studies involving 4,068 patients was published, focusing on the efficacy of first-line therapy. The results of this study showed that more intensive chemotherapy protocols yield better results compared to the standard R-CHOP protocol, with a reduced need for radiation therapy [38].

Consolidation mediastinal radiotherapy (RT) is often used after the R-CHOP protocol, but it is unclear whether RT affects the risk of disease relapse and OS, especially in those who achieve complete remission after immunochemotherapy. Retrospective studies have shown conflicting results, likely due to different criteria for applying RT. For instance, a Surveillance, Epidemiology, and End Results (SEER) study of 250 patients with stage I or II PMBCL diagnosed between 2001 and 2012 reported a better five-year OS in patients who underwent RT (90% vs. 79 %; $p = 0.029$) [39]. Conversely, another SEER study involving 258 cases in all stages of PMBCL (diagnosed between 2006 and 2011) showed no difference in five-year survival (82.5% vs. 78.6%; $p = 0.470$), although the group not receiving RT had a numerically higher proportion of patients with an advanced stage of the disease (31% vs. 19%) [40].

The Role of PET-CT in PMBCL

PET-computed tomography (CT) – (PET-CT) plays a significant role in assessing the extent of the disease at diagnosis, evaluating the therapeutic response, and determining the need for radiation therapy after immunochemotherapy. CT is insufficient in sensitivity and specificity in PMBCL because patients may have a certain degree of sclerosis in the mediastinum after treatment, resulting in the persistence of residual tumor mass in the mediastinum after therapy in most patients. PET-CT has greater specificity than CT, but there is still the possibility of false-positive findings after therapy due to inflammatory changes post-treatment [41]. Should additional therapy be considered in such cases, a biopsy of the mass positive on PET-CT is necessary.

The results of published studies highlight the importance of assessing the metabolic therapeutic response based on various quantitative PET-CT parameters: tumor volume, including maximum standardized uptake value (SUVmax), TMTV, and TLG, which correlate with the prognosis of PMBCL patients [22, 42, 43]. TLG, which reflects both tumor volume and metabolism determined by PET-CT scan, has proven to be the strongest predictor of outcome, where the five-year PFS was 64% in those with high and 99% in those with low values [22, 41]. Similar results were obtained in a study where patients were treated with the DA-EPOCH-R protocol (two-year PFS was 60% in patients with high TLG and 95% in those with low TLG, $p = 0.006$) [42]. In the IELSG study, multivariate analysis showed that both tumor metabolic heterogeneity and TLG were independently associated with shorter PFS. The combination of these two factors identified a subgroup of 10% of patients with a five-year PFS of only 11% [22, 41]. Thus, quantitative PET-CT parameters are a potential tool for determining optimal therapy for each patient.

The role of mediastinal RT is not fully defined due to the potential for long-term adverse events on one hand and the favorable disease course on the other. A rational approach would be to apply RT based on PET-CT findings, i.e., omitting RT in patients who achieve PET-CT negativity after R-CHOP. The results of the largest prospective study of primary mediastinal B-cell lymphoma, IELSG37, support this approach. The results of this study show that radiation therapy can be omitted in patients who have a complete metabolic response after chemoimmunotherapy [44].

In any case, there is currently no consensus on the optimal therapeutic approach for PMBCL patients in the first-line therapy. However, the cornerstone of therapy consists of rituximab and anthracycline-based immunochemotherapy with interim PET-CT evaluation [5, 38]. Some authors recommend considering DA-EPOCH-R for patients with aggressive presentations and advanced-stage disease that has spread beyond the chest [15, 38].

Given that favorable results are achieved with intensive immunochemotherapy, consolidation therapy with autologous stem cell transplantation is no longer standard in first-line therapy.

Relapsing/refractory PMBCL

Nearly all PMBCL relapses occur within the first two years in approximately 2.5% to 4.5% of patients, except for rare late central nervous system relapses [1, 5]. The treatment of relapsing/refractory (R/R) PMBCL is similar to that of DLBCL, involving salvage therapy followed by high-dose chemotherapy and autologous hematopoietic stem cell transplantation (HSCT). However, few studies have evaluated the outcomes of R/R PMBCL, especially in the rituximab era.

In the Memorial Sloan Kettering Cancer Center study that included 60 patients with R/R PMBCL, a three-year PFS of 57% and OS of 61% were achieved, with a transplant rate of 85% [45]. Other series have also confirmed favorable outcomes after autologous HSCT, with a five-year OS ranging

from 57% to 70% [46, 47]. However, patients with refractory disease had poorer outcomes, making them candidates for the application of new therapeutic modalities.

New therapeutic approaches in PMBCL treatment

Amplification or translocation of the 9p24.1 region, found in over 50% of PMBCL cases, leads to increased expression of PD-L1. This finding has formed the basis for using PD-1 inhibitors in treating PMBCL, especially given the limited treatment options for patients with R/R disease. The first evidence of the efficacy of PD-1 inhibitors in PMBCL came from the phase 1 study KEYNOTE-013, which analyzed the effectiveness of pembrolizumab in patients with R/R lymphoma, including PMBCL [48]. In an updated analysis of this study, a therapeutic response in patients with R/R PMBCL was achieved in 48% (33% complete response – CR) of patients, with similar results observed in the subsequent phase II study, KEYNOTE-170, with a therapeutic response of 45% and CR of 13% after a follow-up of 29.1 months (KEYNOTE-013) [48] and 12.5 months (KEYNOTE-170) [49], respectively. The median PFS was 10.4 and 5.5 months, respectively, and the median duration of response was not reached in either study. Pembrolizumab was used as a bridging therapy to transplantation in nine patients. Grade 3/4 adverse events occurred in 23% of patients, with neutropenia being the most common adverse event. As a result of these findings, the Food and Drug Administration (FDA) approved pembrolizumab for the treatment of adult and pediatric patients with PMBCL who have relapsed after two or more lines of therapy.

Zinzani et al. [12] presented the final results of KEYNOTE-170 after a median patient follow-up of 48.7 months. This study provided the longest follow-up of PMBCL patients treated with pembrolizumab; 24% of patients completed two years of treatment. The overall therapeutic response was recorded in 41.5% (20.8% CR), and the four-year PFS and OS were 33% and 45%, respectively. Grade 3/4 treatment-related adverse events occurred in 22.6% of patients, and 7.5% discontinued treatment due to adverse reactions. Some of the most severe adverse effects were immune-mediated [12]. This study solidified the role of PD-1 inhibitors in the third line of PMBCL therapy but also opened the possibility of using PD-1 inhibitors in earlier lines of treatment. Studies are currently underway that gather data on the use of PD-1 inhibitors in previously untreated PMBCL patients.

To improve the treatment outcomes of patients with R/R PMBCL, there are attempts to combine PD-1 inhibitors with other drugs. For instance, in the CheckMate 436 study, which included a group of patients with R/R PMBCL, nivolumab was administered in combination with brentuximab vedotin (BV) [9]. Although a previous study using BV monotherapy achieved CR in only 13% of patients with R/R PMBCL [50], in this study, CR was achieved in 37% of patients (the overall therapeutic response was 73%), indicating the synergistic effect of PD-1 inhibitors and BV [9]. Half of the responding patients (n = 11) underwent autologous HSCT, and none of the patients relapsed. Grade 3 and 4 treatment-related adverse events were higher (53%) than after PD-1 inhibitor monotherapy. Neutropenia was observed in 30% of patients, and peripheral neuropathy in 27% of patients [9].

CAR-T therapy in PMBCL

CAR-T cell therapy has brought significant changes in the treatment of R/R aggressive B-cell lymphomas, including PMBCL. The ZUMA-1 and TRANSCEND NHL001 studies tested axicabtagene ciloleucel (axi-cell) and tisagenlecleucel (tisa-cel) in patients with R/R B-cell lymphoma (including PMBCL) after failure of at least two lines of therapy [7, 51]. In the ZUMA-1 study, which included 101 patients, the therapeutic response was 83%, with 58% CR; the median OS was 25.8 months, and the five-year OS rate was 42.6% [51]. Similarly, in the TRANSCEND study, a therapeutic response was achieved in 73% (with 53% CR) of all included patients, and in 15 patients with R/R PMBCL, the therapeutic response was 79% [7]. Estimated two-year PFS and OS rates were 40.6% and 50.5%, respectively [7]. The United FDA has approved axi-cell for treating R/R large B-cell lymphoma after the failure of the first lines of therapy, including autologous stem cell transplant. Tisa-cel was approved for the treatment of adults with R/R large B-cell lymphoma after two lines or more of systemic therapy.

Other new therapeutic approaches

Given the presence of CD30 positivity in the majority of PMBCL patients, these patients were included in phase 1/2 studies with $CD30^+$ B-cell lymphomas where a combination of BV and chemotherapy [cyclophosphamide, doxorubicin, prednisone (CHP) + BV] was used. In 22 patients with PMBCL, the two-year PFS was 86%, and the two-year OS was 100%, with no difference observed when consolidative RT was added ($p = 0.950$). However, the molecular profile of PMBCL was confirmed in 11 out of 14 (79%) patients, indicating a diagnostic challenge due to similarities with DLBCL, HL, and mediastinal gray zone lymphoma [52].

The efficacy of the antibody-drug conjugate, loncastuximab (ADCT-402), was also evaluated in patients with R/R B-cell non-HL, including 7 patients with PMBCL. A therapeutic response was achieved in 70 patients (48.3%), including CR in 36 patients (24.8%) [53]. Among 11 patients with a complete therapeutic response, the response was maintained for ≥ 2 years. These results led to FDA approval of the drug.

Bispecific antibodies have been evaluated across various B-cell lymphomas but have not specifically targeted PMBCL. Despite evidence of aberrant JAK/STAT pathway activation in PMBCL, JAK2 inhibitors have not been effective in this patient population [54]. In a pilot study where ruxolitinib was administered to patients with R/R HL and R/R PMBCL, none of the PMBCL patients demonstrated a favorable therapeutic response [54].

Conclusion

There is currently no consensus on the optimal first-line therapeutic approach for patients with PMBCL. Excellent results are achieved with immunochemotherapy based on rituximab and anthracycline, with the use of interim PET scans. DA-EPOCH-R regimen should be considered in those with aggressive presentations and advanced-stage disease spreading beyond the chest. Treatment of R/R PMBCL is similar to that of DLBCL, involving salvage therapy followed by high-dose chemotherapy and autologous HSCT if a favorable response is achieved. Bispecific antibodies have been studied in various B-cell lymphomas but have not specifically included PMBCL. PD-1 inhibitors and CAR-T therapy have found a place in the third-line treatment of PMBCL, with questions arising about their use in earlier lines of treatment.

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