



Primary central nervous system lymphoma: clinicopathological and genomic insights for therapeutic development

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Abstract

Primary central nervous system lymphoma (PCNSL) is a highly aggressive, extra-nodal non-Hodgkin lymphoma that is confined to the central nervous system (CNS) and the eyes. Most PCNSLs arise in immunocompetent older patients and less frequently in immunocompromised patients with Epstein-Barr virus infection. Although a patient's initial response to chemotherapy and radiation therapy is favorable, the clinical outcome of PCNSL remains poor compared to that of systemic lymphoma. Radiation-induced neurotoxicity is also a critical problem for patients with PCNSL. Therefore, a novel therapeutic strategy is required to overcome these challenges. Recent studies have largely uncovered the genomic landscape and associated histopathological features of PCNSL. Based on this background, novel therapeutic agents, such as Bruton's tyrosine kinase inhibitors and immune checkpoint inhibitors, have been introduced for patients with PCNSL. Here, we provide an overview of the updated histopathological and genomic characterization of PCNSL and summarize the current therapeutic strategies. We also review current preclinical PCNSL models for translational research.

Keywords Primary central nervous system lymphoma · Histopathology · Genetics · Preclinical model · Molecular targeted therapy

Introduction

Primary central nervous system lymphoma (PCNSL) is a highly aggressive, extra-nodal subtype of non-Hodgkin lymphoma, which is confined to the central nervous system (CNS) and the eyes. PCNSL occurs in immunocompetent patients and less frequently in immunocompromised patients. Epstein-Barr virus (EBV)-positive PCNSL is common in immunocompromised individuals. Although the initial response to chemotherapy and radiotherapy is favorable, the clinical outcome of PCNSL is still worse than that of systemic lymphoma. Therefore, a better understanding of tumor biology and the establishment of novel therapeutic strategies are needed for this progressive disease. Here, we provide an overview of the histopathological and genomic characterization, along with preclinical models of PCNSL. We also summarize the current therapeutic approaches,

including molecular targeted therapy and immunotherapy for PCNSL.

Epidemiology

PCNSL accounts for 4–6% of all extra-nodal lymphomas and approximately 4% of intracranial neoplasms [1]. The incidence of newly diagnosed PCNSL in the United States and Japan is approximately 1500 and 200 cases per year, respectively, with a high proportion of patients being male [1, 27]. Although PCNSL mainly occurs in immunocompetent patients, it is also occasionally found in immunocompromised patients. In immunocompetent PCNSL, patients aged > 60 years are highly affected, with a peak incidence in those aged 70–79 years [42]. Although its incidence is very rare, PCNSL has been observed in children with increased risk among immunodeficient patients [3]. EBV-associated PCNSL commonly occurs in immunocompromised patients with human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS), organ transplantation, or treatment with immunosuppressive agents [23, 27]. The median age of HIV-positive PCNSL patients is lower than that of HIV-negative PCNSL patients (37 years

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and 63 years, respectively). Despite advances in treatment, the prognosis of PCNSL remains poor, particularly in HIV-positive PCNSL patients.

Histopathological characteristics

Most PCNSLs (~95%) are classified as distinct subtypes of diffuse large B-cell lymphoma (DLBCL). Although the incidence is rare, T cells, Burkitt, lymphoblastic, and low-grade lymphomas are occasionally found [4]. Typical histopathological characteristics include diffuse infiltrative and highly proliferating lymphoma cells with angiocentric growth patterns [27]. PCNSL cells invade the neural parenchyma or subarachnoid spaces, which resembles encephalitis. EBV-positive PCNSL tends to contain larger areas of necrosis [64]. Immunohistochemical analysis typically demonstrates a high Ki-67 labeling index [41]. The pan B-cell markers CD19, CD20, and CD79a are universally positive, whereas CD3, a pan T-cell marker, is negative in DLBCL. In EBV-positive PCNSL, in situ hybridization shows positive EBV-encoded small RNA (EBER) [64]. Latent membrane protein 1 (LMP1), a major transforming protein of EBV that activates the nuclear factor kappa B (NF- κ B) pathway, is highly expressed in EBV-positive PCNSL [66]. Multiple myeloma oncogene 1 (MUM-1)/interferon regulatory factor 4 (IRF4) plays a role in B-cell differentiation in the terminal stages and is used as a marker for late germinal center or early post-germinal center B (GCB) cell. Importantly, MUM-1/IRF4 immunohistochemistry is reportedly highly positive (> 80%) in PCNSL. In addition, 35–65% of PCNSL represents positive immunostaining of B-cell lymphoma 6 (Bcl-6), which plays a role in regulating the differentiation of normal GCB cells and is used as a marker for GCB, whereas CD10, which is expressed in pre-B cells and GCB, immunostaining is present in only 2–20% of PCNSL. Based on the Hans algorithm using CD10, Bcl-6, and MUM1 immunostaining [33], most PCNSLs are classified as a non-GCB subtype (72–96%) [9, 39, 41], which is more frequent in PCNSL than in systemic DLBCL [9, 21, 29, 39]. Plasma cell markers CD38 and CD138 are absent in PCNSL [39, 41]. Collectively, the majority of PCNSL (CD10⁻Bcl-6⁺MUM1/IRF4⁺ or CD10⁻Bcl-6⁻MUM1/IRF4⁺ immunophenotype) originate from the late germinal center to early post-germinal center B cells. In systemic DLBCL, the prognosis of the non-GCB subtype is unfavorable compared to that of the GCB subtype [33]. On the other hand, the prognostic significance of immunophenotyping and cell of origin markers remain unclear in PCNSL, although a prospective study demonstrated that Bcl-6 expression was associated with shorter progression-free survival (PFS) [37]. In addition to the cell of origin markers, B-cell lymphoma 2 (Bcl-2) expression, which regulates mitochondrial apoptosis, is frequently expressed. Intranuclear p65 staining and

phospho-p65 expression were also highly positive in patients with PCNSL [66]. Recent histopathological studies also demonstrated that programmed cell death ligand 1 (PD-L1) and PD-L2 expression was low in tumor cells, but high in tumor-infiltrating immune cells [22, 63].

Genetic characterization

Recent comprehensive genomic studies have provided the mutational landscapes of PCNSL [10, 21, 29, 46, 49]. Importantly, either single nucleotide variant (SNV) or co-SNVs of *MYD88*^{L265P} (toll-like receptor [TLR] signaling) and *CD79B* (B-cell receptor (BCR) signaling), which are involved upstream of the NF- κ B signaling pathway, have been largely identified in PCNSL. The genomic classification system has proposed several genetic subtypes of DLBCL. Among them, the MCD subtype [60] and C5 subtype [11], which frequently harbor mutations in *MYD88*^{L265P} and *CD79B*, showed poor prognosis. This underlies the fact that common mutations (*MYD88*^{L265P} and *CD79B*) may induce unfavorable prognosis in PCNSL. In addition, other NF- κ B pathway-related gene alterations, such as mutations within the coiled-coil domain of *CARD11* and inactivating lesions in *TNFAIP3*, were also observed in a subset of PCNSL [21, 29, 46, 49]. These genomic alterations promote constitutive activation of the NF- κ B signaling pathway and promote tumorigenesis. In addition, the chronic activation of the BCR signaling has been shown to upregulate constitutive PI3K/AKT signaling, and conversely, constitutive activity of PI3K and downstream PDK1 promoted the activation of NF- κ B signaling in activated B-cell (ABC)-like systemic DLBCL [13, 34]. Furthermore, the somatic hypermutation (SHM) process that targets rearranged immunoglobulin genes also aberrantly targets proto-oncogenes. This aberrant SHM, for instance, mutations in *PIM1* and *BTG2*, have been widely identified in immunocompetent PCNSL patients [21, 49].

In addition to SNVs, gene expression profiling identified two major subtypes of DLBCL, which are associated with the cell of origin: GCB-like and ABC-like subtype. Accordingly, the prognosis of ABC-like systemic DLBCL is poor [2]. In PCNSL, the ABC-like subtype is high in immunocompetent tumors and this subtype commonly harbors *MYD88*^{L265P} and *CD79B* mutations [23]. In addition, we as well as another group also identified *MYD88*^{L265P} and *CD79B* mutations in PCNSL with GCB immunophenotype [21, 66]. Taken together, *MYD88*^{L265P} and *CD79B* mutations are genetic hallmarks of immunocompetent PCNSL.

Copy number alterations (CNAs) are genomic features of immunocompetent PCNSL patients. For instance, the loss of chromosome 6p21.33 (*HLA-B*, *HLA-C*), 6q21-23 (*TNFAIP3*, *PTPRK*, and *PRDM1*), 9p21.3 (*CDKN2A*), along with the gain of chromosome 12q (*STAT6*, *MDM2*, *CDK4*) and 9p24.1 (*JAK2*, *PD-L1*, *PD-L2*) have been frequently

observed [10, 49]. Phylogenetic analysis demonstrated the loss of *CDKN2A* as well as *MYD88*^{L265P} mutation as early clonal events [49]. Intriguingly, genomic characteristics (SNVs and CNAs) in PCNSL are broadly shared with those of primary testicular lymphoma [10]. On the other hand, in EBV-positive PCNSL, the mutational burden was lower than that in immunocompetent PCNSL, mutations in *MYD88*^{L265P}, *CD79B*, and *PIMI1* were absent, and the ABC subtype was low. Moreover, few CNAs, including the loss of HLA class I/II and antigen-presenting or processing genes, were observed in EBV-positive PCNSL [23]. These findings indicate a distinct genomic landscape of EBV-positive PCNSL from that of immunocompetent PCNSL.

Cytokines for tumor development

Several clinical studies have demonstrated that cerebrospinal fluid interleukin-10 (IL-10) is a useful diagnostic and prognostic biomarker in PCNSL [57, 58]. The Janus kinase 2 (JAK2)/STAT3 signaling pathway is downstream of IL-10 and is highly activated in PCNSL [43]. This signaling pathway has been shown to complement the TLR signaling pathway, which synergizes NF- κ B pathway deregulation [51, 65] and promotes cell proliferation and survival in ABC-like DLBCL [15]. These data suggest that JAK/STAT signaling plays a pivotal role in PCNSL. Intriguingly, O'Connor et al., found that lymphoma cells entered the normal CNS, but quickly exited along an endothelial C-X-C motif chemokine ligand 12 (CXCL12) gradient. In contrast, gliosis in the brain and astrocyte-derived CCL19, which counteracted CXCL12, enhanced CCR7 expressed lymphoma cell retention in the CNS and promoted the development of CNSL [52]. These findings suggest that the CCL19-CCR7 axis may promote PCNSL formation.

Experimental models

To date, only a few PCNSL cell lines (e.g., HKBML and JCRB1206 TK) are available for preclinical investigations. Notably, HKBML was derived from EBV-positive patients with PCNSL, and JCRB1206 TK was derived from a young immunocompetent patient (aged 22-years), implying that these cell lines may be derived from atypical PCNSL cases. Therefore, preclinical PCNSL models that mimic patient tumor characteristics are required to uncover its tumor biology and explore potential therapeutic targets. Recently, others and we have established orthotopic xenograft models derived from immunocompetent and immunocompromised (EBV-positive) PCNSL patients [56, 66]. These xenograft models broadly recapitulated the phenotype, genotype, and response to chemotherapy in patient tumors (Fig. 1). We confirmed that these features were largely retained in serial passages in vivo. We also found that xenograft models could be formed not only

from primary cultured cells but also from frozen cells, indicating the potential of these materials for broad use in future preclinical investigations. Pouzoulet et al., demonstrated that plasma IL-10 levels paralleled with tumor engraftment and therapeutic response [56], suggesting a critical role of IL-10 in PCNSL development. Using patient tumors and xenograft models, we identified that *MYD88*^{L265P} and *CD79B*^{Y196} mutations were early genetic events in PCNSL. Importantly, we found that these mutations (immunocompetent PCNSL) or *LMP1* (EBV-positive PCNSL) accelerated the NF- κ B canonical pathway and glycolysis by activating hexokinase 2, which indicated high fluorodeoxyglucose uptake on PET imaging, and promoted xenograft formation [66]. Using these xenograft models, we are now exploring potent therapeutic targets to block the canonical NF- κ B pathway in PCNSL. Our results indicate that these genomic alterations are driver mutations in PCNSL. We also found that the overexpression of peptidyl-prolyl isomerase Pin1, which stabilizes RelA/p65, is crucial for xenograft formation [66] (Fig. 2). Unfortunately, we could not propagate long-term cultured cells from freshly dissociated xenografts, except for EBV-positive PCNSL, although orthotopic xenograft formation was relatively feasible. Further biological and molecular development may allow stable culture in vitro, which would contribute to the field of PCNSL research.

Current therapeutic approach for patients with PCNSL

Methotrexate (MTX)

In addition to competitive inhibition of dihydrofolate reductase and subsequent blocking of DNA synthesis, MTX also suppresses the JAK/STAT and NF- κ B canonical pathways [66, 67]. High-dose methotrexate (HD-MTX) allows penetration of the blood–brain barrier (BBB) when high doses of drug (> 1.5 g/m²) are rapidly administered [6]. The introduction of HD-MTX combined with whole brain radiation therapy (WBRT) resulted in an overall response rate (ORR) of 71%–94% and improved prognosis with a median overall survival (OS) of 30–60 months [14, 19]. In addition, a randomized phase 2 trial using HD-MTX plus cytarabine provided improved outcomes (ORR, 69%) with acceptable toxicity compared to HD-MTX monotherapy (ORR, 40%) [19]. These results suggest that HD-MTX-based combination chemotherapy may be more effective for PCNSL.

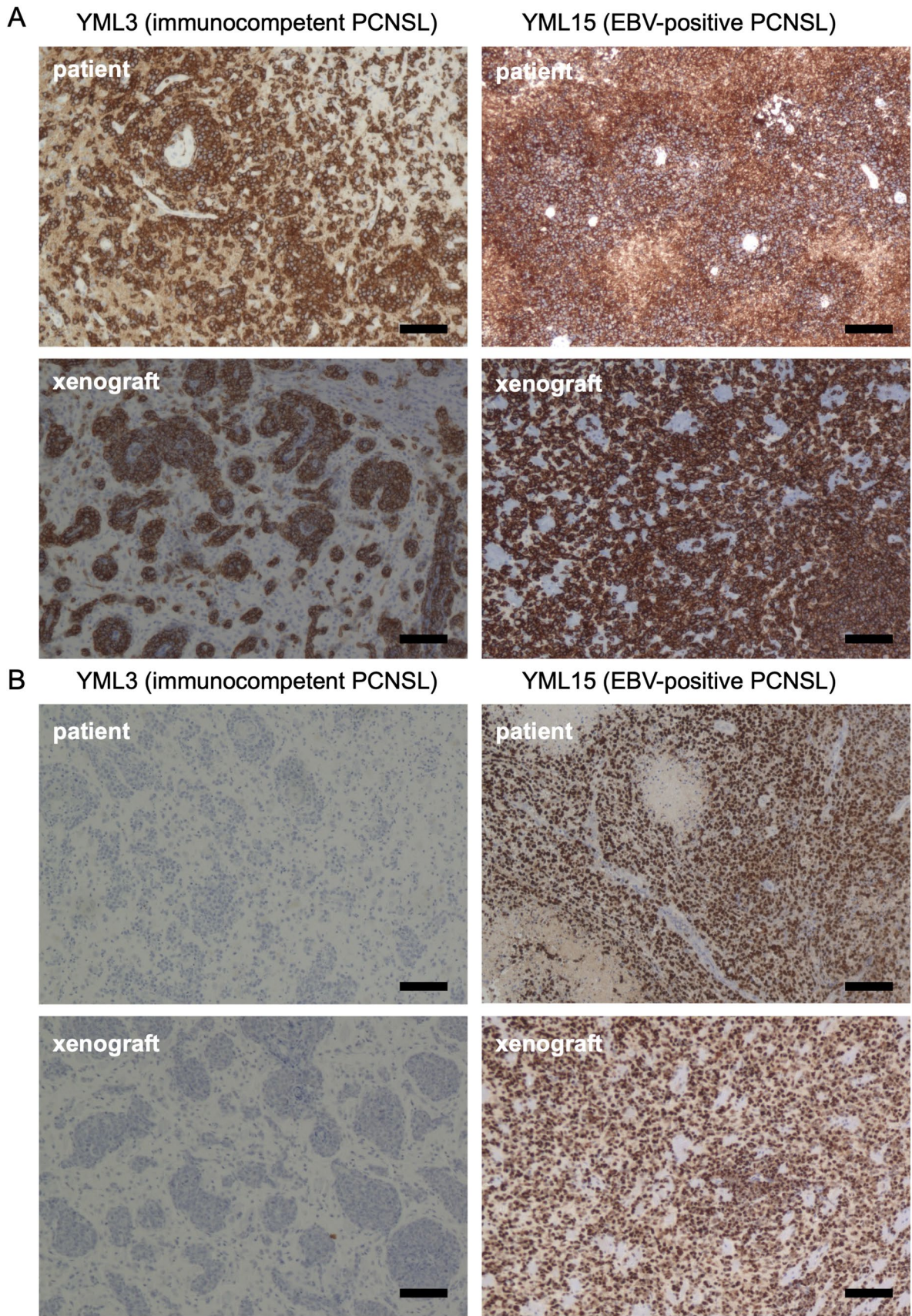


Fig. 1 Immunohistochemistry of immunocompetent primary central nervous system lymphoma (PCNSL) (YML3, left) and Epstein–Barr virus (EBV)-positive PCNSL (YML15, right). **A** CD20 immunostaining and **B** EBV-encoded RNA (EBER) in-situ hybridization of patient tumor (upper) and corresponding xenograft (lower). Bars, 100 μ m

Rituximab; rituximab, methotrexate, procarbazine, vincristine (R-MPV); and high-dose chemotherapy with autologous stem cell transplantation (HDC-ASCT)

Rituximab is a chimeric monoclonal antibody that targets CD20 cell surface proteins. In older patients with systemic DLBCL, a combination therapy with cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab increased the complete response rate and survival [12]. In PCNSL, there is no evidence that rituximab increases the severity of toxicity or treatment-related mortality [59]. However, a recent randomized phase 3 study did not find any benefits of additional rituximab for HD-MTX-based chemotherapy (HD-MTX, carmustine, intravenous teniposide, and prednisone; MBVP) in PCNSL [7]. On the other hand, a subgroup analysis revealed its benefits in younger patients with better median event-free survival in rituximab (R)-contained regimen (MBVP, 19.7 months versus R-MBVP, 59.9 months). Collectively, the evidence of rituximab as an additive agent remains inconclusive in PCNSL. Of note, Morris et al., demonstrated the efficacy and reduced neurotoxicity of combination therapy with rituximab, methotrexate, procarbazine, and vincristine (R-MPV) followed by consolidation reduced-dose (rd) WBRT (23.4 Gy) and cytarabine. They reported that five–seven cycles of R-MPV with consolidation rdWBRT and cytarabine were associated with a high ORR (ORR, 78%), long-term PFS (median PFS, 7.7 years), and minimal neurotoxicity [44].

High-dose chemotherapy with autologous stem cell transplantation (HDC-ASCT) has been performed in PCNSL to obtain disease control with tolerable neurotoxicity. Omuro et al., reported favorable results using R-MPV, followed by HDC-ASCT with thiotepa-based regimens and no radiotherapy [53]. The IELSG32 trial randomly assigned HIV-negative PCNSL patients (aged 18–70 years) to receive either (1) HD-MTX and cytarabine; (2) HD-MTX and cytarabine plus rituximab; or (3) HD-MTX, cytarabine, and rituximab plus thiotepa (MATRix regimen). The complete response rate and 2-year PFS were (1) 23% and 36%, (2) 30% and 46%, and (3) 49% and 61%, respectively. Importantly, the MATRix regimen was associated with significantly improved response and survival rates without high rates of severe complications [18].

Radiation therapy

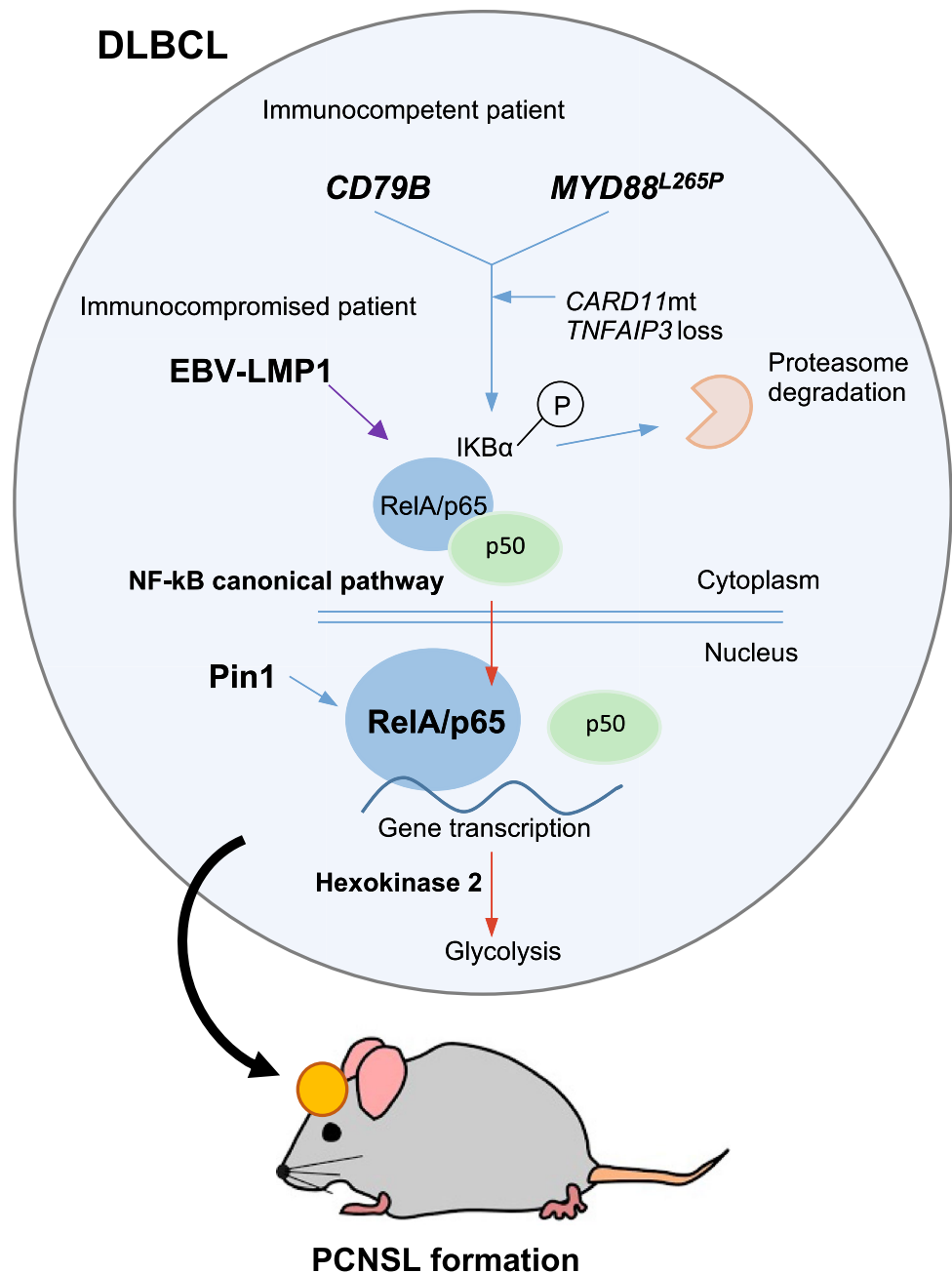
Single WBRT has been used to treat newly diagnosed PCNSL in the past. Although the ORR had reached 90%, the OS was limited to 12–18 months [50, 61]. Patients treated with chemotherapy and WBRT significantly contributed to prolonged survival, but also induced severe neurotoxicity. The neuronal changes are mainly attributed to the synergistic toxicity of HD-MTX and WBRT. Neurotoxicity was found in up to 40% of all patients with PCNSL treated with chemotherapy and 45 Gy of WBRT, and 75% of those over 60 years of age [24]. In contrast, reduction of WBRT from 45 Gy to 30.6 Gy resulted in an increased risk of relapse and short OS in younger patients [5]. In the IELSG32 trial, secondary randomization with WBRT and HDC-ASCT as consolidation therapy was performed in patients with response or stable disease. Accordingly, there was no significant difference in the 2-year PFS. Although hematological toxicity was more common in the HDC-ASCT group, both consolidation therapies were well tolerated. Importantly, significant impairments in attention and executive functions were observed in the WBRT group, whereas the quality of life and most of the cognitive functions were improved in the HDC-ASCT group [17]. Collectively, these studies suggest that therapeutic strategy by intensive chemotherapy with rdWBRT or deferred WBRT should be considered in patients with PCNSL.

Molecular targeted therapy and immunotherapy

Bruton's tyrosine kinase (BTK) inhibitor

The molecular pathogenesis and genomic landscapes of PCNSL have led to the development of novel therapies targeting the BCR and TLR pathways, and subsequently, the NF- κ B pathway. Ibrutinib is the first BTK inhibitor, which irreversibly and covalently binds to a cysteine residue (C481) at the BTK active site and attenuates its downstream signaling. In PCNSL, Grommes et al., investigated ibrutinib monotherapy for refractory or recurrent PCNSL. Overall, 10 of 13 (77%) patients showed clinical response with a median PFS and OS of 4.6 months and 15 months, respectively [29]. Soussain et al., also investigated ibrutinib monotherapy for r/r PCNSL, resulting in a response rate of about 60%; the median PFS and OS were 4.8 months and 19.2 months, respectively [62]. Although these results indicated a higher response rate compared to DLBCL outside the CNS (25% response rate) [68], a relatively short PFS suggests the presence of an early resistance mechanism. To overcome this issue, Lionakis et al., explored ibrutinib monotherapy followed by

Fig. 2 Schematic illustration of distinct nuclear factor kappa beta (NF- κ B) canonical pathway activation to induce tumor progression in immunocompetent and Epstein–Barr virus-positive primary central nervous system lymphoma patients



temozolomide, etoposide, liposomal doxorubicin, dexamethasone, ibrutinib, and rituximab with intraventricular cytarabine combination (DA-TEDDi-R). Among 18 patients, including 13 r/r and 5 treatment-naïve PCNSL, 94% showed tumor reduction with ibrutinib alone. The DA-TEDDi-R regimen resulted in PFS for 15.3 months [40]. Another study demonstrated that the combination of ibrutinib with HD-MTX and rituximab induced a high response rate (ORR 80%) with acceptable toxicity in r/r PCNSL patients [31]. In addition to ibrutinib, a second-generation BTK inhibitor tirabrutinib was investigated in

r/r PCNSL with an ORR of 64% and PFS of 2.9 months [47].

Although *CD79B* and *MYD88* mutations contributed to BTK inhibitor's sensitivity [68], *CD79B* mutation conversely attenuated BTK dependence by activating PI3K/AKT/mTOR signaling axis, which is independent of BTK/NF- κ B signaling [29]. In addition, it has been demonstrated that coiled-coil domain mutations in *CARD11* contribute to NF- κ B activation, which is independent of BTK activation [38]. Thus, *CARD11* mutation is considered a crucial gene alteration for resistance to BTK inhibitors. However, clinical

studies of PCNSL indicated that the efficacy of BTK inhibitors varied independent of the genomic status, including *MYD88*, *CD79B*, and *CARD11* mutations [29, 47], suggesting that the mechanism of BTK inhibitor resistance may be more complicated than the hypothesized mechanism. In addition, *BTK^{C481S}* was identified as an acquired mutation in ibrutinib resistance in chronic lymphocytic leukemia [69]. This may also induce a short PFS in PCNSL. Further study is necessary to determine the predictive biomarker for sensitivity to BTK inhibitors in PCNSL.

Inhibitors for the PI3K/AKT/mTOR pathway

Constitutive activation of the BCR pathway activates the PI3K/AKT/mTOR pathway in ABC-like DLBCL [55]. PI3K inhibition, particularly of the delta isoform, has shown promising clinical results in some B-cell malignancies [8]. Therefore, this signaling pathway is expected to be another molecular therapeutic target for PCNSL. Temsirolimus, an mTOR inhibitor, was evaluated in 37 patients with r/r PCNSL. The overall response rate was 54%, but the median PFS was only 2.1 months [36]. Buparlisib, a pan-PI3K inhibitor, resulted in a lower response rate (25%) [30]. In a preclinical study, the PI3K/AKT/mTOR signaling pathway contributed to resistance to BTK inhibitors, whereas a combination with ibrutinib and a PI3K inhibitor (copanlisib) had synergistic effects in vitro [29]. Currently, ibrutinib with copanlisib for r/r PCNSL is under investigation (NCT03581942).

Immunomodulatory imide drugs (IMiDs)

IMiDs have been shown to inhibit NF- κ B and PI3K signaling pathways [16, 70]. Lenalidomide, a second-generation IMiD combined with rituximab, was investigated in r/r PCNSL patients. This combination resulted in an ORR of 35.6% and a median PFS of 7.8 months [25]. Pomalidomide, a higher CNS-penetrating third-generation IMiD, combined with dexamethasone resulted in an ORR of 48% and a median PFS of 5.3 months [28]. These IMiDs showed clinical activity for PCNSL, but their efficacy was limited. In contrast, a preclinical study demonstrated that lenalidomide synergized with ibrutinib to block IRF4 and kill ABC-DLBCL cells [70]. Clinical trials of ibrutinib and rituximab plus lenalidomide (NCT03703167), and rituximab and nivolumab plus lenalidomide (NCT03558750) are currently in progress.

Immune checkpoint inhibitor

Since genomic investigations revealed a high frequency of chromosome 9p24.1 CNAs, high tumor mutational burden, and increased PD-L1 expression in patients with PCNSL

[10, 22, 54, 63], treatment with PD-L1 inhibitor is also expected to be a possible therapeutic agent. Notably, a study with although a small sample size, but one comprising four patients with r/r PCNSL and a patient with CNS relapse of primary testicular lymphoma, showed clinical and radiographic responses to nivolumab [48]. Three patients remained progression-free at 13–17 months. Additionally, pembrolizumab was shown to prolong remissions in three of five patients with PCNSL and secondary CNS lymphoma (SCNSL) [26].

CAR T-cell therapy

Chimeric antigen receptor (CAR) T therapy is expected to be a novel treatment for B cell malignancies, by incorporating a domain for CD19 recognition and T-cell activation to remove CD19-expressing malignant cells [35]. Intracranial injection of anti-CD19 CAR T-cells invaded the tumor and induced tumor regression in DLBCL xenograft models [45]. In addition, CAR T-cells can penetrate the BBB [32], suggesting a possible future therapeutic strategy for CAR T-cell therapy in PCNSL. However, because of strict eligibility criteria, patients with PCNSL were excluded from clinical trials. Of note, the retrospective study demonstrated that four of eight patients with SCNSL who were treated with tisa-genlecleucel CAR T-cells demonstrated a clinical response, and none of the patients experienced grade 1 neurotoxicity [20]. A clinical trial of immunotherapy using CAR T-cells to target CD19 is currently recruiting eligible PCNSL patients (NCT04443829).

Conclusions

The updated histopathological and genomic insights and multidisciplinary therapeutic approaches have shed light on the clinical course of patients with PCNSL. However, despite intensive therapy, the prognosis of PCNSL remains unsatisfied. To overcome this issue, large-scale, multi-omics studies and translational research using highly reproducible PCNSL models are required, which may lead to the development of novel therapeutic strategies.

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