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Primary Central Nervous System Lymphoma: Molecular Pathogenesis and Advances in Treatment[1]

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Abstract

Primary central nervous system lymphoma (PCNSL) is a group of extranodal non-Hodgkin lymphoma that exhibits specific biological characteristics and clinical behavior, with an aggressive disease course and unsatisfactory patient outcomes. It is of great importance to identify aberrant genetic loci and important molecular pathways that might suggest potential targets for new therapeutics and provide prognostic information. In this review, we listed various genetic and epigenetic alterations that are involved in PCNSL pathogenesis. In the aspect of treatment, we summarized the related literatures and evaluated the efficacy of surgery, induction chemotherapy, radiotherapy, intrathecal chemotherapy, and autologous stem cell transplantation in PCNSL. We also proposed the possible new agents for recurrent and relapse PCNSL based on the result of recent clinical researches.

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Introduction

Primary central nervous system lymphoma (PCNSL) represents a rare form of extranodal, malignant non-Hodgkin lymphoma. It is an aggressive type of cancer confined to the craniospinal axis without evidence of systemic involvement (brain>eyes>leptomeninges>spinal cord), with more than 90% of cases histologically classified as diffuse large B-cell lymphoma (DLBCL) [1].

While, clearly, high-dose methotrexate (HD-MTX) alone with additional agents is the mainstay of first-line therapy, it is often inadequate to achieve a complete response and requires treatment consolidation. The most challenging conundrum is which consolidation therapy has the optimal therapeutic index for balancing lasting cure with minimal early mortality and long-term neurotoxicity risk. The typical options for consolidation seem to be dose-reduced whole-brain radiotherapy (dr-WBRT) and high-dose chemotherapy with autologous stem cell transplantation (HDC-ASCT). Consolidation with dr-WBRT is simple to deliver and now has an adequate long-term record of efficacy and safety. The latter may be suitable for younger patients with adequate performance status. However, treatment outcomes are still unsatisfactory for patients with relapsed/refractory PCNSL, and further clinical trial data are needed to guide the therapeutic management for this group of patients.

Epidemiology

PCNSL accounts for 4%-6% of all extranodal lymphomas, up to 1% of all lymphomas, and about 2% of all central nervous system tumors [2]. Although the incidence of PCNSL increased by three-fold from 1973 to 1984, recent data from the Surveillance, Epidemiology, and End Results (SEER) database demonstrates that an incidence plateau has been reached [3]. The median age at diagnosis is 65 years old. PCNSL has been observed to occur with increased frequencies in individuals with acquired immunodeficiencies [acquired immune deficiency syndrome (AIDS) or posttransplant conditions] and/or congenital immunodeficiencies (X-linked lymphoproliferative syndrome, Wiskott-Aldrich syndrome, or ataxia telangectasia) [4]. PCNSL is one of the most common AIDS-related malignancies in individuals with low CD4 cell counts (<50 cells/mL) and Epstein-Barr virus (EBV) infection [5,6]. However, since the discovery and

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implementation of combined antiretroviral therapy (the highly active antiretroviral therapy, HAART), a decreasing incidence of PCNSL has been reported among AIDS patients [7]. By contrast, epidemiological data have shown a progressively increasing PCNSL incidence among elderly individuals [8].

Molecular Pathogenesis

Pathology and Histogenetic Origin

PCNSL represents a histologically and immunohistochemically homogeneous type of lymphoma. Typical histological features include a vasocentric growth pattern and high lymphocyte proliferation, explaining its diffuse infiltration in the central nervous system (CNS). DLBCLs account for most PCNSLs (>90%), and the remainder comprise of Burkitt's lymphomas, low-grade lymphomas, or T-cell lymphomas (peripheral T-cell lymphomas and anaplastic large T-cell lymphomas) [1,5]. EBV early RNA transcripts are often detectable by *in situ* hybridization in immunocompromised patients.

The B cell differentiation process may provide clues to the understanding of the histogenetic origins of PCNSL. The first step is the assembly of the V, D, and J gene segments of the heavy and light chains of immunoglobulin (Ig) genes in the bone marrow [9,10]. Upon successful gene segment assembly, naive B cells leave the bone marrow and start their next maturation step, where they encounter antigens in the germinal centers (GCs) of secondary lymphoid organs, such as the spleen and lymph nodes, to improve the binding affinity of their B cell receptors (BCRs). The process of somatic hypermutation (SHM) in the first 1.5-2.0 kb of the V region genes of BCR heavy and light chains is activated in the GCs [11]. The processes of SHM and affinity maturation require the presence of the specific antigens, antigen-presenting cells and T cells, and BCL6 [12]. The SHM process may either increase or decrease the affinity of BCR and results in the selection of B cell clones for further rounds of SHM and, finally, to either go through apoptosis or exit the GCs [13]. After SHM, B cells can undergo Ig class switch recombination, which replaces the μ constant region of the BCR with other constant regions located downstream to generate diverse antibodies. Differentiation into memory or plasma cells completes B cell's differentiation [14] (Figure 1).

PCNSL cells morphologically resemble centroblasts, and the introduction of SHMs into rearranged Ig segments proves that they have participated in a GC reaction [15]. Expression of B cell markers, including CD19, CD20, and CD79a, is detectable in almost all PCNSLs. CD10 is present in 10%-20% of PCNSLs, and plasma cell markers (CD38, CD138) are generally absent. BCL6 and BCL2 are expressed in 60%-80% and 56%-93% of PCNSLs, respectively [16]. BCL6 is the main regulator of the GC reaction and represses the exit of B cells from GCs [17,18]. The strong IRF4/MUM1 expression is observed in about 90% of PCNSLs, which indicates that the tumor cells are transitioning to leave the GC. The IRF4/MUM1 expression is usually associated with memory B cells rather than GC-B cells. This $CD10^{-}BCL6^{+}IRF4/MUM1^{+}$ phenotype indicates that further B cell maturation is impaired, which corresponds to the late germinal center B cell phenotype [6] and correlates with a poor prognosis [14] (Figure 1).

It is still unclear whether PCNSL truly originates within the CNS or whether it is part of a systemic lymphoma that escapes from the

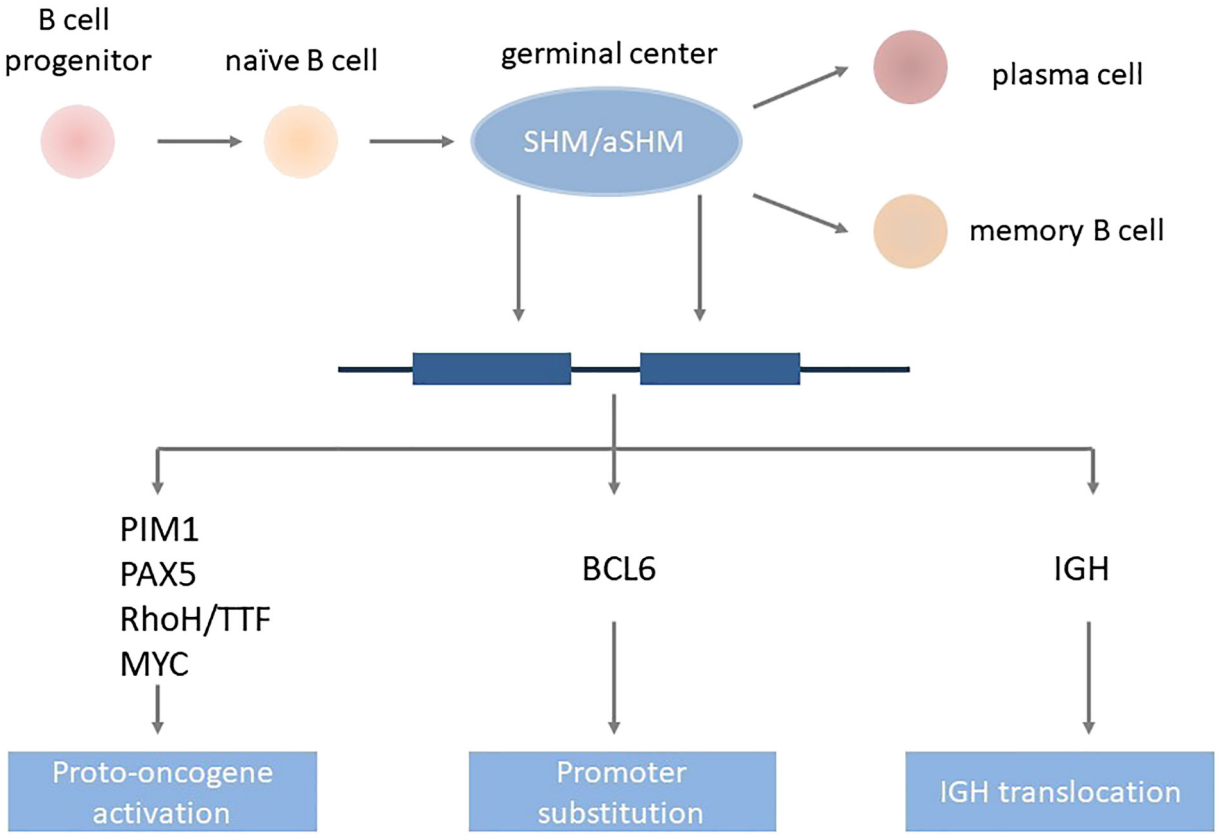

Figure 1. Histogenetic origin of PCNSL. The $CD10^{-}BCL6^{+}IRF4/MUM1^{+}$ phenotype of PCNSL cells indicates that they have participated in GC reactions and that further B cell maturation is impaired, which corresponds to the late GC B cell phenotype.Abbreviations: aSHM, aberrant somatic hypermutation; SHM, somatic hypermutation, IGH, immunoglobulin heavy locus.

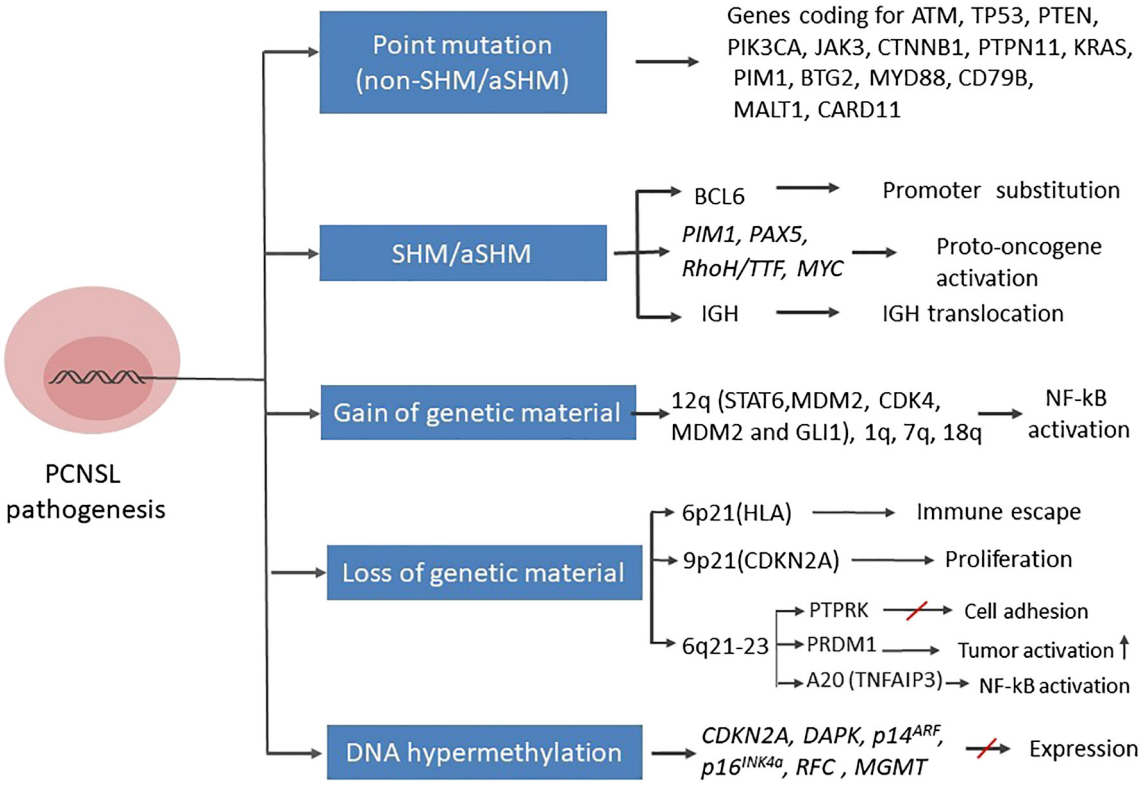

Figure 2. Molecular pathogenesis of PCNSL. Different mechanisms of genetic alteration are involved in the pathogenesis of PCNSL. These mechanisms target a variety of genes, which become dysregulated, ultimately leading to uncontrolled B cell proliferation and differentiation or impairment of B cell apoptosis. Genetic changes may also interfere with the sensitivity of tumor cells to immune responses in the CNS.Abbreviations: aSHM, aberrant somatic hypermutation; SHM, somatic hypermutation, IGH, immunoglobulin heavy locus.

immune system and grows in the "sanctuary" of the CNS. B cells recruited to the brain in the case of an immune reaction may stay for extended periods and eventually transform while residing inside the CNS. On the other hand, B cells might also have transformed to a malignant state outside the CNS, i.e., during a GC reaction in a secondary lymphoid organ. It is assumed that each of these two mechanisms is probable. However, homing of a malignant B cell exclusively to the brain is hard to explain and difficult to confirm experimentally. To date, no cell adhesion molecule or a chemokine predicting B cell homing selectively to the brain has been identified in the development of PCNSL [14].

Genomic alterations

As all steps of B cell differentiation, especially SHM, require DNA double-strand breaks, the failure of DNA double-strand breaks may lead to the formation of malignant cells. PCNSL cells often carry translocations affecting *Ig* and *Ig*-related genes, especially *Bcl6* [18]. A substitution in the promoter of the *Bcl6* gene results in constitutive BCL6 activity, which can have tumorigenic effects. The Cancer and Leukemia Group B (CALGB) 50202 trial demonstrated that BCL6 overexpression is associated with poorer survival and refractory PCNSL condition [19]. While some other studies have confirmed this finding [20,21], several small retrospective analyses have provided conflicting results [22–24]. Variation in treatment regimens, sample sizes, and analytical procedures may explain this discrepancy. Aberrant SHM (aSHM) can target proto-oncogenes including *Myc*, *Pim1*, *Pax5,* and *Rhoh*/*Ttf*; these genes are often involved in the modulation of B cell activity, proliferation, and apoptosis (Figure 1). Other recurrent targets of aSHM include genes coding for TBL1XR1, TRDM1, BTG2, and PRDM1 [25,26].

Next-generation sequencing (NGS) analyses have shown that over 80% of nonconservative mutations are introduced at loci encoding eight proteins (ATM, TP53, PTEN, PIK3CA, JAK3, CTNNB1, PTPN11, and KRAS) [27]. Mutations in genes encoding PTEN and SMO may correlate with poorer survival and earlier relapse, and mutations in genes encoding TP53 and ATM could be involved in the molecular pathophysiology of PCNSL. Nonsynonymous somatic mutations in *im1*, *Btg2*, and *MYD88* have also been detected at high frequency by whole-exome sequencing in PCNSL samples, which are in agreement with previous studies [28] (Figure 2).

Insertions and deletions of genetic material are also very common in PCNSL. The most frequent genomic alteration in PCNSL involves the deletion of a region of chromosome 6p21 harboring the HLA locus [29]; this lesion occurs in immune-privileged sites and potentially represents a DLBCL immune escape mechanism. Chromosome 6q deletions occur frequently in PCNSL, in particular, deletions at the 6q21-23 [30] region containing: i) PTPRK, a protein tyrosine phosphatase involving in cell adhesion signaling; ii) PRDM1, a suppressor of tumor activity and regulator of B cell differentiation; and iii) A20 (TNFAIP3), which downregulates nuclear factor-kB (NF-kB) signaling. Recurrent chromosomal losses have also been detected at the 9p21 region [30], which encodes loci involved in cell cycle regulation including CDKN2A. Chromosome 12 insertions are very common, especially in the 12q region harboring genes encoding STAT6, MDM2, CDK4, and GLI1.

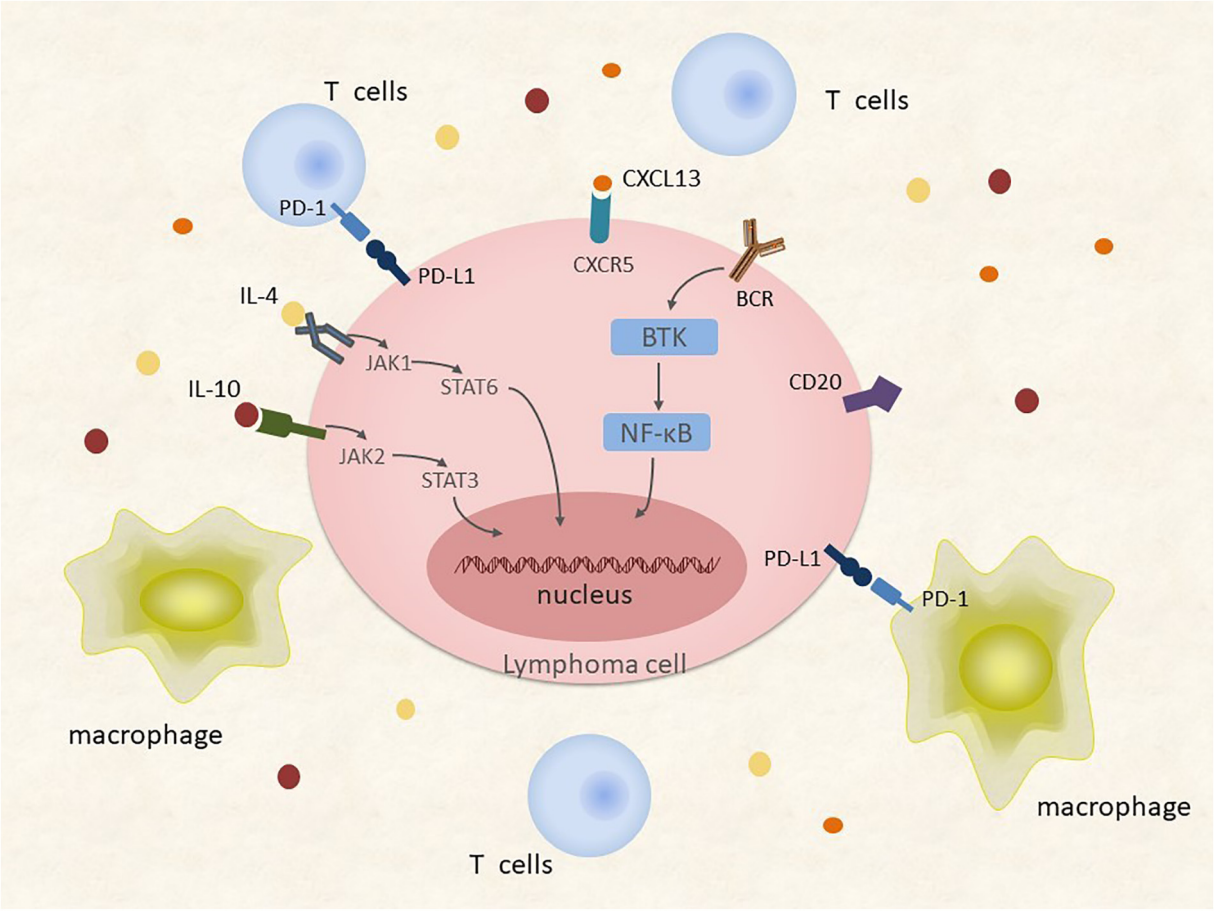

Figure 3. Tumor microenvironment and aberrant activation pathways of PCNSL. Amplification of 9p24 and resulting gene expression increase the dosage of PD-L1/2 and contribute to the immune escape of PCNSL cells. High concentrations of cytokines such as IL-4, IL-10, and CXCL13 correlate with adverse prognosis in PCNSL patients, suggesting that related pathways are aberrantly activated and result in tumorigenesis.Abbreviations: NF-kB, nuclear factor-kB; BCR, B cell receptor; PD-L1, programmed death-ligand 1; PD-1, programmed cell death-protein 1; IL-4, interleukin-4; IL-10, interleukin-10; JAK, Janus kinase; STAT, signal transducer and activator of transcription.

Recurrent insertions also occur on the long arms of chromosomes 1, 7, and 18 [31] (Figure 2). Copy number alterations and translocations at chromosome 9p24, involving the genes coding for programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2), appear to be frequent in PCNSL. This finding suggests that immune escape may be important in the PCNSL pathophysiology [32] (Figure 3).

Molecular investigations have uncovered evidence suggesting that the Janus kinase (JAK)/STAT signaling pathway mediates the PCNSL biology. Transcript and protein levels of interleukin (IL)-4 and IL-10, which are mediators of the JAK/STAT intracellular signaling pathway and B cell proliferation, are upregulated in the microenvironment of tumor vessels, which are correlated with tumor response and progression [33–35] (Figure 3). Importantly, the upregulation of IL-4 and IL-10 and downstream JAK/STAT signaling correlate with aberrant activation of MYD88, which is involved in the Toll-like receptor (TLR) signaling pathway [36]. Elevated concentrations of intratumoral JAK1 transcripts have also been identified in PCNSL [23,33,37] (Figure 4). The BCR and TLR signaling pathways, along with their target NF-kB, are influenced by common mutations introduced by aSHM, especially in genes encoding MYD88 and CD79B. NF-kB signaling may be the core pathway involved in the regulation of PCNSL [25,32,38–40]. An L265P substitution in MYD88 occurs in 38%-50% of PCNSL patients, and CD79B is mutated in approximately 20% of patients [23,29,41]. *MYD88* encodes a signaling adaptor protein that induces activation of NF-κB and the JAK/STAT3 pathway after stimulation of Toll-like receptors, interferon-β production, and IL-1/IL-18 receptors. The *CD79B* gene encodes a BCR subunit that is essential for BCR signaling, resulting in NF-κB activation. The BCR pathway transmits its signals to the CBM signalosome complex composed of BCL10, CARD11, and MALT1. Less frequent mutations and overexpression of MALT1 [42] and CARD11 [43] have also been demonstrated in PCNSL (Figure 4).

Epigenetic Alterations in PCNSL

Epigenetic silencing by DNA methylation also contributes to PCNSL pathogenesis. DNA hypermethylation was observed in several loci including *CDKN2A, DAPK, p14^{ARF}, p16^{INK4a}, RFC*, and *MGMT* [44,45]. Using array-based DNA methylation profiling, 194 differentially methylated genes have been identified comparing PCNSL to control patients; a significantly enriched CpG content was detected in these differentially methylated genes. However, no differences between the methylation patterns of PCNSL and systemic DLBCL patients was identified [46]. The presence of methylated MGMT promoter sequences was demonstrated to correlate with a better overall survival (OS) among patients who received high-dose

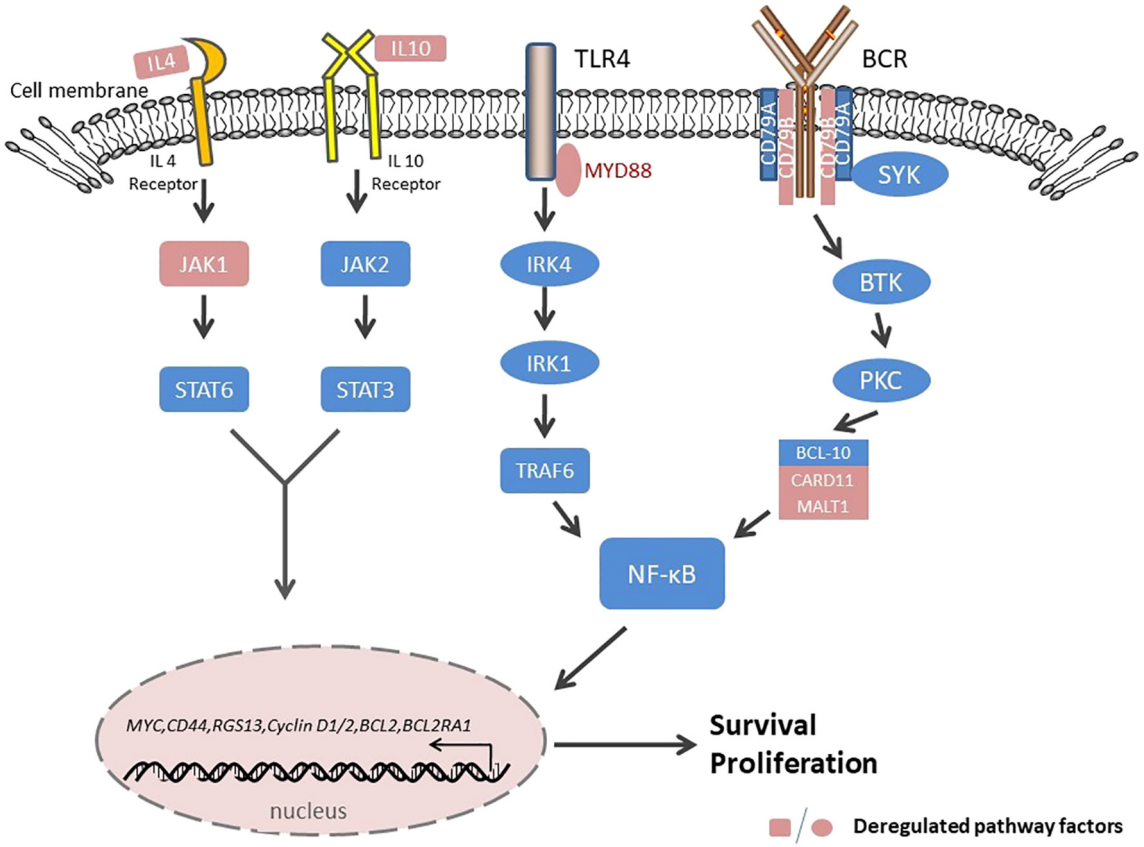

Figure 4. Components of oncogenic survival signaling in PCNSL. Activation of TLR4/MYD88 and the BCR complex may contribute to prosurvival signaling via NF-κB. Enhanced production of IL-4/10 also contributes to survival signals along with the JAK/STAT pathway. Abbreviations: BCR, B cell receptor; IL-4, interleukin-4; IL-10, interleukin-10; TLR, Toll-like receptor; NF-kB, nuclear factor-kB; JAK, Janus kinase; STAT, signal transducer and activator of transcription.

chemotherapy. Also, elderly PCNSL and patients with recurrent PCNSL bearing a methylated MGMT promoter have been shown to have a superior response to temozolomide [47–49] (Figure 2).

As in other malignancies, microRNA may also play an important role in the PCNSL pathogenesis. MiR-17-5p, which targets the proapoptotic gene *E2F1*, was shown to be significantly upregulated in nine PCNSL patients as compared to nodal DLBCL patients [50]. Upregulation of miRNAs associated with overexpression by inflammatory cytokines (miR-155), inhibition of terminal B cell differentiation (miR-30b/c, miR-9), or the MYC pathway (miR-92, miR-17-5p, miR-20a) has also been demonstrated [51]. Notably, the results by Robertus et al. were contradictory, in which they reported that miR-155 showed the lowest expression level compared with other miRNAs involved in PCNSL [50]. Analysis of cerebrospinal fluid (CSF) from PCNSL patients showed that miR-19, miR-21, and miR-92 were expressed at significantly higher levels compared to controls with inflammatory CNS disorders, suggesting the usefulness of these miRNAs as clinical biomarkers [52]. In a study of PCNSL miRNA associated with short- and long-term survival, 12 annotated miRNAs were detected to be significantly dysregulated between the short- and long-term survival groups. Among these miRNAs, miR-151a-5p and miR-151b showed the most significant differences in expression [53] (Figure 5).

Tumor microenvironment

The mechanisms of intracerebral tropism and dissemination of lymphoma cells are important in PCNSL pathogenesis. These mechanisms might be related to the expression of chemokines CXCL12 (SDF-1) and CXCL-13 (Figure 3). The impact of IL-10 and CXCL-13 concentration in the diagnosis of CNS lymphoma has been demonstrated [35,54]. High CXCL-13 and IL-10 levels in CSF also correlate with adverse prognosis in PCNSL patients [55,56].

Under normal physiological conditions, the brain is immunologically quiescent, while some PCNSL specimens show evidence of inflammatory responses, with activated macrophage and reactive T cell infiltration (Figure 3). In the perivascular space of CNS, T cells residing in the perivascular space may interact with perivascular antigen-presenting macrophages. The subsequent invasion of the CNS parenchyma requires the stimulation of antigen. If the antigen is absent, T cells may remain confined to the perivascular space [57]. Activated perivascular CD8 T cell infiltration may correlate with favorable outcomes, suggesting the potential efficacy of immunotherapy in enhancing T cell–mediated immunosurveillance [58]. Inflammatory activation may precede or accompany PCNSL. These "sentinel" inflammatory lesions may represent the first immune responses generated against PCNSL. Therefore, demyelination or neuroinflammation should be considered as radiographic features for some PCNSL cases [59].

Clinical Features

Patients of PCNSL develop neurologic symptoms over weeks including focal neurologic deficits (70%), neuropsychiatric symptoms (~43%), symptoms of increased intracranial pressure (~33%), and seizures (~14%). Clinical presentation is determined by the

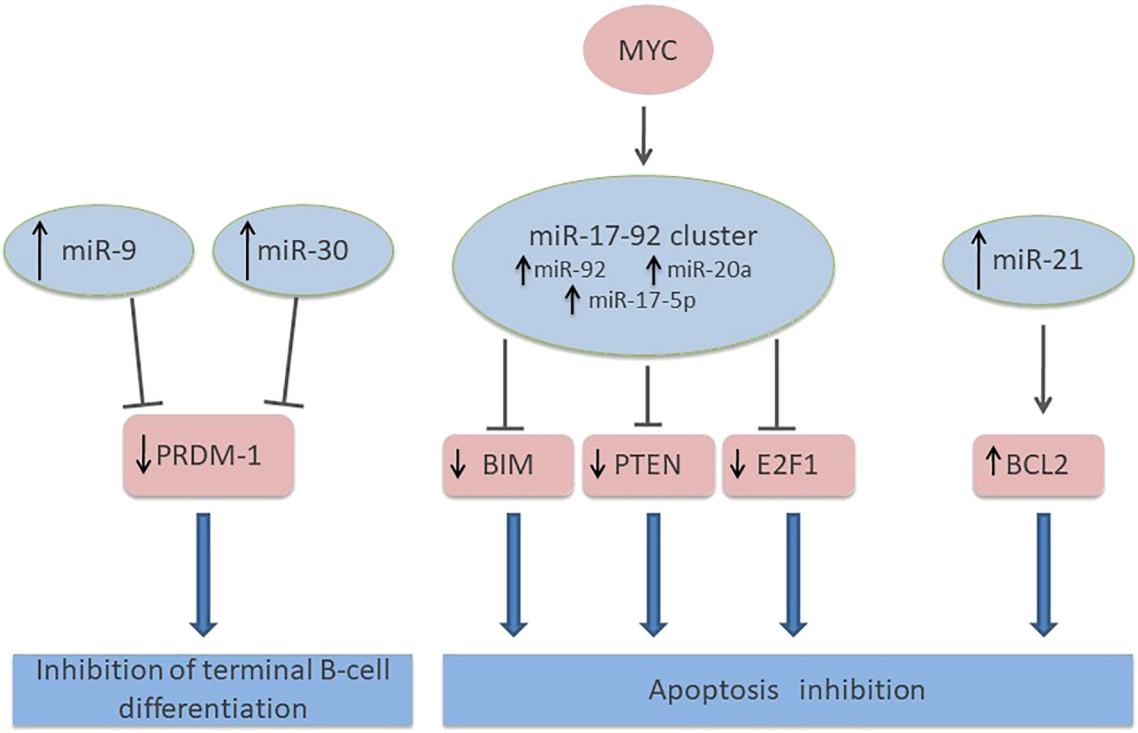

Figure 5. Relevant miRNA regulation and signaling pathways in PCNS. The major miRNAs involved in PCNSL pathogenesis: the miR-9, miR-30, miR-17-92 clusters, and miR-21. The arrows indicate the expression level of each miRNA in PCNSL. Solid lines indicate suppression of the target gene. Blue arrows lead from the gene to the final effect of the miRNA intervention.

neuroanatomical location of the lymphoma [60]. Leptomeningeal involvement occurs in 11%-20% of PCNSL cases, usually without any clinical manifestations. Intraocular involvement occurs in 15%-25% of PCNSL patients, often with insidious onset and delayed diagnosis. Ocular symptoms are represented by floaters, blurred vision, eye pain, and photophobia due to the involvement of the retina and/or vitreous [61]. Systemic B symptoms are uncommon in PCNSL.

Diagnostic Procedure and Prognostic Factors

Imaging

Radiologic evaluation is crucial to define the location and extension of the disease. Cranial magnetic resonance imaging (MRI) using fluid-attenuated inversion recovery (FLAIR) and T1-weighted sequences before and after contrast injection are the preferred methods [62]. Advanced imaging techniques, including diffusion-weighted imaging (DWI), perfusion and permeability imaging, magnetic resonance spectroscopy (MRS), susceptibility-weighted imaging (SWI), are helpful for differential diagnosis and to increase the diagnostic accuracy [63]. Positron emission tomography–computed tomography (PET/CT) is also a useful tool but in the assessment of accompanying systemic disease [64].

Histopathology

The gold standard diagnosis is stereotactic brain biopsy or a subtotal resection if deemed to be safe. Steroid pretreatment should be avoided before biopsy [62] since it may alter the sensitivity of histopathological diagnosis. For patients with corticosteroids pre-treatment, in case of inconclusive biopsy or disease remission, a second biopsy is recommended when serial MRIs indicate evident tumor progression. Flow cytologic analysis of CSF lymphoma cells in patients with leptomeningeal involvement and vitrectomy in patients with intraocular involvement might be helpful to establish the diagnosis. Bivariate elevated CXCL13 plus IL-10 is demonstrated to be highly specific for the diagnosis of CNS lymphoma [35].

Extent-of-Disease Evaluation

Staging evaluation aims to rule out systemic lymphoma and eye involvement. A comprehensive physical, neurological, and cognitive evaluation should be conducted in all newly diagnosed PCNSL patients. Laboratory evaluation includes renal and hepatic function in patients who will receive HD-MTX, HIV, hepatitis B and C, and lactate dehydrogenase (LDH) testing. Computed tomography (CT) scan of the chest, abdomen, and pelvis, as well as testicular ultrasound in elderly males, is also essential. Whole-body fluorodeoxyglucose PET may be an optimal choice. Lumber puncture for CSF cytology and bone marrow biopsy should be performed for systemic staging. Ophthalmologic evaluation with a fundoscopy and a slit lamp examination in all patients (even without ocular symptoms) is also recommended [62,65].

Prognostic Factors

Several clinical factors may influence the survival of PCNSL patients. Age and performance status have been consistently acknowledged as the baseline prognostic variables [66]. Two scoring systems have been established to stratify PCNSL patients into several risk groups to predict prognosis [67,68] (Table 1.). A complete response on neuroimaging after two courses of chemotherapy has also been found to be predictive for improved OS and progression-free survival (PFS) [69].

Table 1. Prognostic Models for PCNSL

IELSG Prognostic Score for PCNSL [67]		
Variable	Favorable Feature (Value 0)	Unfavorable Feature (Value 1)
Age (years)	<60	>60
ECOG PS	0-1	>1
LDH serum level	Normal	Elevated
CSF protein level	Normal	Elevated
Involvement of deep regions of the CNS	No	Yes

MSKCC Prognostic Model for PCNSL [68]			
Variable	**Good Risk**	**Intermediate Risk**	**High Risk**
Age	<50	≥50	≥50
ECOG PS		≥70	<70

PCNSL, primary central nervous system lymphoma; ECOG, Eastern Cooperative Oncology Group; PS, performance status; LDH, lactate dehydrogenase; CSF, cerebrospinal fluid; MSKCC, Memorial Sloan-Kettering Cancer Center.

Treatment Advances

Surgery

Surgery is considered to have no role in PCNSL treatment, and its use is limited to stereotactic biopsy for histopathologic diagnosis. PCNSL has a multifocal and infiltrating nature and tends to extend beyond visible margins, contributing to the poor efficacy of surgical interventions [70]. The high radiosensitivity and chemosensitivity of PCNSL, as well as the high risk of surgical complications in PCNSL patients, have resulted in the limited application of surgical resection. However, this clinical consensus is based on small retrospective analyses, which have shown that surgical treatment alone has no survival advantage compared with supportive care [71] and postoperative radiotherapy or chemotherapy [72,73]. The phase 3 trial of the German Primary CNS lymphoma study group-1 (G-PCNSL-SG-1) [74] which enrolled a high proportion of postoperative PCNSL patients has demonstrated that the OS and PFS were significantly improved in patients with subtotal or gross total resection compared with patients who received biopsies, which were independent of performance status and age. Since patients who had a biopsy more often had multiple deeply seated CNS lesions than resected patients, this difference may contribute to the unfavorable outcome in biopsied patients. When adjusted based on the number of lesions (site of the lesions was not analyzed in the study), the survival benefit remained significant for PFS but not for OS. Anyway, surgical resection may be crucial in patients suffering from large occupying lesions and symptoms of brain herniation [75]. In conclusion, there is insufficient clinical evidence to advise surgical resection in PCNSL patients.

Systemic Chemotherapy

High-dose methotrexate–based regimen is the first-line induction therapy for newly diagnosed PCNSL. The most effective dose of HD-MTX has not been established. A dose range of 1-8 g/m^2 is sufficient

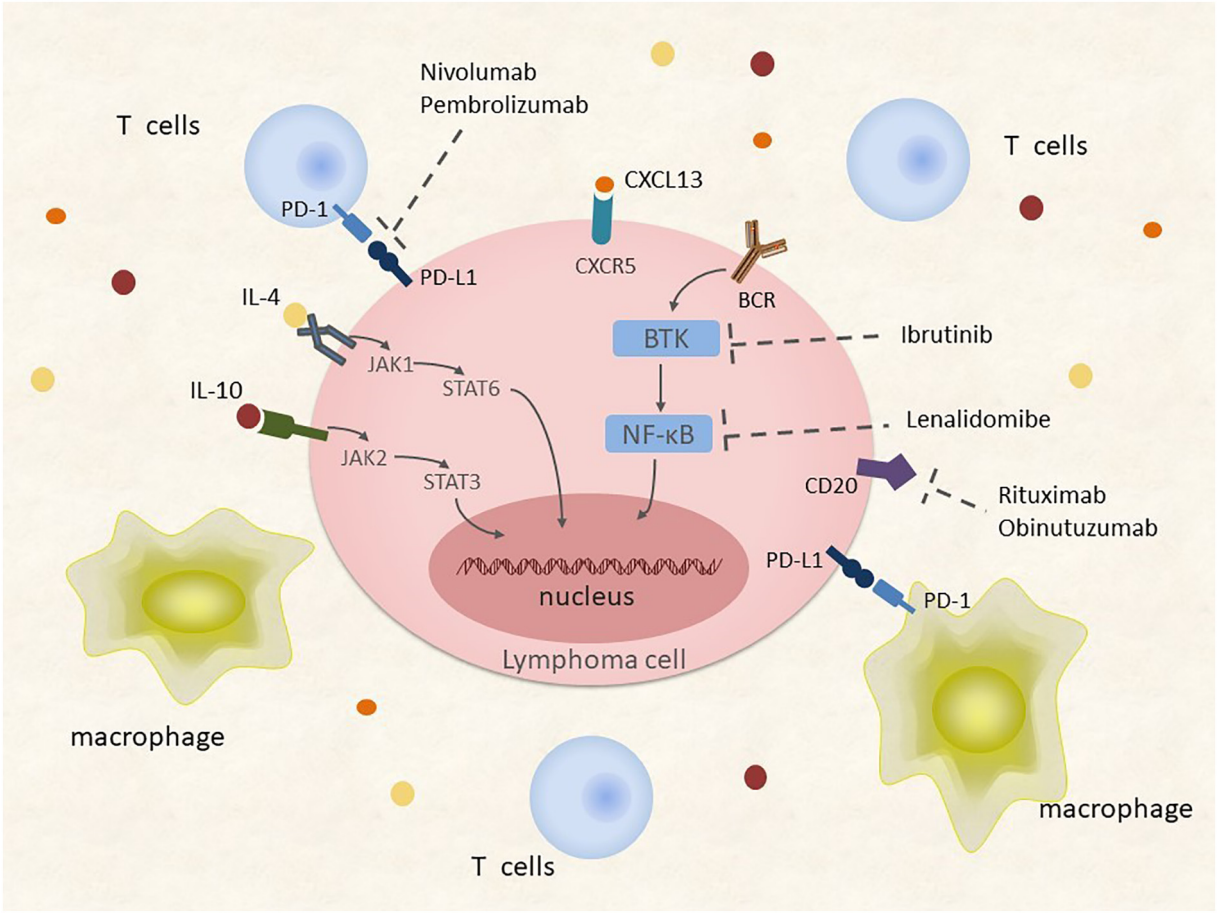

Figure 6. Therapeutic agents and targets in PCNSL. Novel therapeutic agents affect tumor pathways directly but also influence the tumor microenvironment, DNA transcription, translation of antiapoptotic factors, and immune modulation of tumor cells.Abbreviations: NF-kB, nuclear factor-kB; BCR, B cell receptor.

Table 2. Studies of Combination Chemotherapy in PCNSL

Study	*N*	Median Age (Range)	Therapy	CR (%)	PFS	OS	Neurotoxicity
Ferreri et al. (IELSG20) [91]	40	58(27-72)	Methotrexate	18	3 years 21%	3 years 32%	-
	39	59 (25-74)	Methotrexate-cytarabine	46	3 years 38%	3 years 46%	3%
Rubenstein et al. (CALGB 50202) [19]	44	61 (12-76)	R-MT (induction)-EA (consolidation)	66 (after R-MT)	2 years 57%	-	none
Glass et al. (RTOG 0227) [93]	53	57 (24-73)	R-MT (induction)-WBRT (consolidation)	51 (after R-MT)	2 years 63.6% (R-MT + WBRT)	2 years 80.8% (R-MT + WBRT)	5/45
Morris et al. [79]	52	60 (30-79)	R-MPV (induction)-rdWBRT (consolidation)	60 (after R-MPV)	2 years 77% (R-MPV + rdWBRT)	Median 6.6 years	none
Omuro et al. [94]	32	57 (23-67)	R-MPV (induction)-ASCT (consolidation)	44 (after R-MPV)	2 years 81% (R-MPV + ASCT)	2 years 81% (R-MPV + ASCT)	-
Ferreri et al.(IELSG32) [88]	75	58 (50-64)	Methotrexate-cytarabine	23	2 years 36%	2 years 42%	-
	69	57 (53-63)	Methotrexate-cytarabine-rituximab	30	2 years 46%	2 years 56%	-
	75	57 (53-62)	MATRix	49	2 years 61%	2 years 69%	-

PCNSL, primary central nervous system lymphoma; CR, complete response; EA, etoposide and cytarabine; R-MT, methotrexate, temozolomide, and rituximab; R-MPV, rituximab, methotrexate, procarbazine, and vincristine; MATRix, methotrexate, cytarabine, rituximab and thiotepa; rd, reduced-dose; WBRT, whole-brain radiation therapy; ASCT, autologous stem cell transplantation; OS, overall survival; PFS, progression-free survival; -, not mentioned.

to cross the blood-brain barrier (BBB), and evidence of a dose-response association is unclear [76,77]. Doses of HD-MTX ≥ 3.5 g/m^2 administered by rapid intravenous infusion (within 2-3 hours) are thought to have cytotoxic levels in the CSF [78]. A minimum of four to six injections at an interval of 14-21 days is delivered in most induction protocols, especially in the absence of subsequent consolidation treatment. Patients achieving only partial response (PR) after four or five courses of HD-MTX are recommended to receive additional courses of chemotherapy [79]. Infusion of HD-MTX requires pretreatment and posttreatment hyperhydration, urine alkalinization, leucovorin rescue, and serum methotrexate level monitoring. Significant variations in MTX metabolism exist among PCNSL patients. However, the individualized dosing schedule for HD-MTX based on pharmacokinetic analysis instead of body surface area is not well established in the current clinical practice, only in a few clinical trials [80].

Rituximab has been shown to effectively improve clinical outcomes in systemic lymphoma, which is suggestive of its potential efficacy in PCNSL (Figure 6). Single-arm trials have reported encouraging survival outcomes achieved with rituximab at doses of 375-500 mg/m^2 as induction or salvage chemotherapy [79,81–87]. Results from the recent International Extranodal Lymphoma Study Group (IELSG) 32 trial [88] have shown that patients treated with HD-MTX in combination with cytarabine and rituximab had a complete remission (CR) rate of 30% compared with 23% for those not receiving rituximab. The efficacy of single-agent rituximab has also been reported in refractory and relapsed PCNSL patients [89]. However, encouraging outcomes were not observed in a recent randomized phase III trial (HOVON 105 PCNSL/ALLG NHL24 trial) [90], and despite such, the routine use of rituximab has been incorporated in initial treatment regimens for PCNSL in most centers. Several ongoing clinical trials are evaluating the effectiveness of other CD20 antibodies such as obinutuzumab in PCNSL (NCT02498951) (Table 5).

Currently, the combination of HD-MTX with other chemotherapeutic agents has been shown to improve therapeutic responses as compared to the use of HD-MTX alone (Table 2). Chemotherapeutic agents used in combination with HD-MTX should be active drugs known to cross the blood-brain barrier, such as high-dose **cytarabine, ifosfamide, vincristine**, **procarbazine, temozolomide and thiotepa.** Combination regimens currently used are **R-MT, R-MPV, and MATRix**.

The IELSG20 trial evaluated the role of HD-MTX combined with **cytarabine** [91]. This study demonstrated a better CR rate and improvements in PFS but not OS in PCNSL patients receiving combination chemotherapy. Although the study consisted of a relatively small population (79 patients in two groups), it was the first randomized trial of combination chemotherapy in PCNSL. The IELSG32 trial [88] recruited a larger control group (75 patients) who received the HD-MTX and cytarabine combination regimen. However, this control group showed lower response rates than patients in the IELSG20 trial. This finding may be related to the differences in patient populations. In fact, unfavorable prognostic features were more common among patients enrolled in the IELSG32 trial. The addition of ifosfamide to HD-MTX was evaluated in the G-PCNSL-SG-1 phase 3 trial, which demonstrated an improvement of response rate, but not PFS and OS [92].

The **CALGB 50202** multicenter study used induction therapy with rituximab, HD-MTX, and **temozolomide (R-MT**) followed by high-dose consolidation with etoposide plus cytarabine (**EA**) without WBRT. A CR to R-MT of 66% and PFS at 2 years of 57% were observed [19]. Similarly, the **Radiation Therapy Oncology Group (RTOG) 0227** trial employed the **R-MT** regimen **followed by WBRT consolidation**. Only 66% of patients were assessable for radiographic response. The CR rate was 51% and PR rate was 34%, with a median PFS of 90 months [93].

Several single-arm phase 2 trials have evaluated the combination of methotrexate, alkylating agents, and rituximab [79,94]. The efficacy of rituximab, methotrexate, procarbazine, and vincristine (**R-MPV**) followed by dose-reduced WBRT was investigated in 52 newly diagnosed PCNSL patients, for which a CR rate of 47% and a PR rate of 49% were observed [79]. The R-MPV regimen followed by consolidative ASCT was assessed in 33 patients in another phase 2 trial, in which 42% of the patients achieved CR and 48% achieved PR after the R-MPV induction chemotherapy [94]. The efficacy of MT and MPV combination was compared in an elderly population in a multicenter phase 2 trial, and the result favored the MVP regimen [95]. Future randomized trials are expected to evaluate the therapeutic difference between R-MT and R-MPV regimens.

The IELSG32 phase 2 trial assessed the combination of methotrexate, cytarabine, thiotepa, and rituximab (**MATRix**) in 78 PCNSL patients. At a median follow-up of 30 months, patients treated with the MATRix regimen had significantly higher CR rate (49%) as compared to a CR of 23% and 30% in those treated with

methotrexate-cytarabine alone and methotrexate-cytarabine plus rituximab, respectively. This new combination has also shown significant improvement in the PFS and OS of these patients. This MATRix regimen was proved to be a new standard chemoimmunotherapy for patients aged up to 70 years with newly diagnosed PCNSL [88].

The BBB disruption by intra-arterial infusion of hypertonic mannitol followed by intra-arterial methotrexate has been identified to increase the drug concentrations in the CNS [96–98]. This procedure demonstrated a good safety profile and neurocognitive tolerance in newly diagnosed PCNSL. Active drugs for lymphoma with a poor BBB infiltration should be evaluated with this procedure in PCNSL. Notably, patients should be carefully selected for this approach since safety depends on the extent of intracranial mass effect and contraindications, to general anesthesia should be ruled out. We suggest that only teams highly trained in BBB disruption could provide this procedure as it requires cannulation of the intracranial vessels.

Intrathecal Chemotherapy

The clinical role of intrathecal chemotherapy in PCNSL is still under debate. Several single-arm studies using identical HD-MTX in combination with cytarabine regimens have reported an additional benefit of intrathecal therapy (1-year PFS of 40% and median OS of 14.3 months) and a higher risk of early relapse without intrathecal therapy [99,100]. The addition of rituximab to HD-MTX regimens with intraventricular administration also showed encouraging treatment efficacy [82]. However, encouraging outcomes have not been replicated in other studies [101,102]. The efficacy and neurotoxicity of such treatments remain unclear. In conclusion, there is a lack of strong evidence supporting the routine use of intrathecal chemotherapy in PCNSL.

Radiotherapy

Radiotherapy alone as a first-line treatment for PCNSL was investigated in a phase 2 trial by the RTOG 8315 [103]; it was found that patients receiving radiotherapy had a poor survival and tumor relapse occurred in areas receiving the highest doses of radiation.

The G-PCNSL-SG-1 phase 3 trial [92] further assessed the role of radiotherapy combined with chemotherapy. In this trial, 318 patients were randomly allocated to receive HD-MTX–based chemotherapy with or without WBRT. No significant benefit in median OS or PFS was observed in patients receiving WBRT. Moreover, neuropsychological evaluation showed inferior cognitive function and quality of life after combination therapy [104]. Therefore, it may be supposed that WBRT has no role in patients achieving CR after induction chemotherapy. However, contradictory results were demonstrated in other studies [105,106]. Retrospective analyses [105] have shown improved PFS but no OS benefit in patients receiving WBRT in addition to chemotherapy. A systematic review [106] has also suggested that consolidation WBRT confers significantly prolonged survival in younger patient (<60 years).

Given the neurotoxicity of WBRT, dr-WBRT combined with immune chemotherapy has been taken under consideration. Morris et al. reported encouraging disease control in 31 patients given dr-WBRT (23.4 Gy) as consolidation therapy following a regimen of R-MPV (rituximab, methotrexate, procarbazine, and vincristine); these patients achieved CRs, with a 2-year PFS rate of 77%, a 3-year OS of 87%, and PFS of 7.7 years [79]. Comprehensive neuropsychiatric tests have also demonstrated improvement in verbal memory and baseline executive function with no evidence of a significant cognitive decline in 12 patients. However, this promising result represents a small and single-institution experience, and PCNSL relapse and late neurotoxicity effects can occur many years after treatment. Thus, longer follow-up is necessary to clarify long-term oncologic outcomes. There has also been interest in assessing whether immune-chemotherapy alone would be able to provide similar benefits; a randomized study comparing R-MPV-rd-WBRT to R-MPV alone has been started, and the results are highly anticipated (RTOG1114, NCT01399372) (Table 5).

In summary, the value of consolidation WBRT, as well as the optimal dose of radiotherapy, remains controversial, especially for patients achieving CR after induction chemotherapy.

HDC-ASCT

The efficacy of HDC-ASCT as a first-line treatment for PCNSL has been reported in several studies. In a phase 2 trial [107], 30 patients <65 years of age were treated with HDC-ASCT following WBRT, achieving a 5-year OS of 69%. Further, another trial conducted by the same group which used a similar regimen in 13 patients <70 years of age [108] demonstrated a 3-year OS of 77%. Long-term follow-up data were reported for a subset of the patients involved in these two trials [109]. Thirty-four of the 43 patients proceeded to ASCT, and the resulting 5-year OS and event-free survival (EFS) for this cohort were observed to be 82% and 79%, respectively. After a 10-year follow-up of the patients who had completed the HDC-ASCT regimen, those with or without WBRT demonstrated excellent health and cognitive function in seven of the eight living patients [110]. In a single-center phase 2 study [94], PCNSL patients who achieved CR or PR after R-MPV chemotherapy were prescribed consolidation HDC-ASCT without radiotherapy in 32 patients, and excellent disease control rates (overall response rate of 97% and 2-year PFS of 79%) were obtained. Outcomes from the largest reported cohort (105 patients) treated with HDC-ASCT were also encouraging, with 2-year and 5-year OS rates of 82% and 79%, respectively [111], and a median PFS and OS of 85 and 121 months, respectively (Table 3).

HDC-ASCT is a common therapeutic strategy in relapsed systemic DLBCL after chemotherapy. The efficacy of HDC-ASCT has also been assessed in relapsed/refractory PCNSL [112]. The median OS was 58.6 months among patients who completed HDC-ASCT compared with 18.3 months in the overall PCNSL population.

In summary, HDC-ASCT is a promising consolidation strategy in PCNSL, especially in younger (<60-65 years) and sufficiently fit patients. Different conditioning regimens across different studies have demonstrated varying results. Among these regimens, thiotepa-based chemotherapy has conferred superior outcomes, possibly because of the thiotepa's small and lipophilic nature which allows it to efficiently penetrate the BBB. However, this intervention should be reserved for centers with a high level of experience with the application of HDC-ASCT. Ongoing multicenter randomized trials in the United States (Alliance 5110u1, NCT01511562) and Europe (ANOCEF/GOELAMS, NCT00863460) are assessing the roles of WBRT or chemotherapy versus HDC-ASCT for consolidation.

The significance of consolidation therapy in patients who achieved CR with HD-MTX–based induction chemotherapy is currently controversial in PCNSL. Generally, nearly half of these patients will relapse [113], and from this perspective, subsequent consolidation is

Table 3. Selected Studies of Autologous Stem Cell Transplantation in PCNSL

Authors/ Study	*N*	Median Age (Range)	Therapy Line	Therapy (Induction)	Reaction to Induction	Conditioning Regimen	WBRT	OS	Neurotoxicity
Abrey et al. [139]	28	53 (25-71)	First	HD-MTX-ARAC	OR 50% CR 8/28	BEAM	No	2 years 25%	None
Illerhaus et al.(2006) [107]	30	54 (27-64)	First	HD-MTX-ARAC/TT	OR 24/30 CR 10/30	BCNU/TT	Yes	5 years 69%	None
Illerhaus et al.(2008) [108]	13	54 (38-67)	First	HD-MTX-ARAC/TT	OR 8/13 CR 4/13	BCNU/TT	Yes	3 years 77%	None
Kasenda et al. [109]	43		First	HD-MTX-ARAC/TT		BCNU/TT	Yes †	5 years 82%	None
Soussain et al. [112]	43	52 (23-65)	Salvage	CYVE	OR 20/43 CR 15/43	TT/BU/ ARAC	No	2 years 45%	None
Kiefer et al. [110]	23	54 (18-69)	First	HD-MTX	-	BU/ TT	Yes †	10 years 35%	10/23
Schorb et al. [111]	105	54 (23-70)	First	HD-MTX based protocols	OR 84/105 CR 43/105	BCNU/TT or BEAM	Yes †	5 years 79%	None
Omuro et al. [94]	32	57 (23-67)	First	R-MPV	OR 31/32 CR 21/32	TT/BU/ ARAC	No	2 years 81%	None

PCNSL, primary central nervous system lymphoma; ARAC, cytarabine; BCNU, carmustine; BEAM, carmustine, etoposide, cytarabine, and melphalan; BU, busulfan; CYVE, cytarabine and etoposide; HD, high dose; MTX, methotrexate; OS, overall survival; R-MPV, rituximab, methotrexate, procarbazine, and vincristine; TT, thiotepa; WBRT, whole brain radiation therapy; -, not mentioned.

This study was based on two studies above [Illerhaus et al. (2006) and Illerhaus et al. (2008)].

† Only for patients not achieving a complete remission.

crucial. However, there are neither conclusive data showing whether there is an overall benefit from additional consolidation nor clear data demonstrating how much additional therapy is needed for those patients who already achieved CR. Thus, in clinical practice, the benefit and risk of each of the consolidation regimens (conventional chemotherapy, radiotherapy, HDC-ASCT, or their combinations) should be balanced as per individual cases. Prognostic models should be developed through multicenter collaborations and to help in deciding the optimal therapeutic schedule.

The significantly high 5-year OS reported with the HDC-ASCT consolidation suggests that PCNSL patients could potentially be cured. However, these data were obtained from either clinical trials comprising of small cohort of patients or retrospective studies. Moreover, the improvement of survival depends on both the optimal induction and consolidation treatment. The combination of the new standard induction regimen (MATRix) with consolidation HDC-ASCT has not been investigated. In an ongoing randomized phase 3 trial conducted by the IELSG group (NCT02531841) (Table 5), newly diagnosed PCNSL patients are prescribed the MATRix regimen for induction, and those achieving partial or complete response are randomly assigned to receive high-dose chemotherapy with BCNU (or busulfan) and thiotepa followed by autologous stem cell transplantation (HDC-ASCT), or conventional chemotherapy for consolidation. These combination approaches could be promising and may improve the long-term survival of PCNSL patients.

Salvage Treatment

Although the response rates to multimodality treatments are high, nearly half of the responders will relapse, and about one-third of the patients with PCNSL are primary refractory [62,114]. The median time to relapse is 10-18 months, and relapse occurs within 2 years after initial diagnosis in most CR patients [114]. Moreover, relapse may also be observed in some patients even after more than 5 years following treatment [115,116]. The prognosis of primary refractory or relapsed PCNSL remains poor, with a median survival of 2 months without additional treatment [117].

Salvage treatment is dependent on age, performance status, site of relapse within the CNS, previous treatments, and duration of response (Table 4). Currently, no consensus on treatment for relapsed and refractory PCNSL has been established. Retreatment with HD-MTX–

Table 4. Recent Studies of Salvage Treatment in PCNSL

Study	*N*	Median Age (Range)	Therapy	OR	PFS	OS
Kim et al. [130]	8	56.5 (36-72)	Procarbazine/ Lomustine/Vincristine	50% (CR: 37.5%)	Median 7 months	Median 8 months
Korfel et al. [131]	37	70 (22-83)	Temsirolimus	54% (CR: 13.5%)	Median 2.1 months 1 year 5.4%	Median 3.7 months 2 year 16.2%
Grommes et al. [135]	25	68 (21-85)	Ibrutinib	68% (CR: 10/25)	Median 4.6 months	-
Tun et al.	21	-	Pomalidomide	43% (CR: 4/21)	-	-
Nayak et al. [136]	5	64 (54-85)	Nivolumab (PD-1 blockade)	5/5 (CR: 4/5)	1 year 3/5	-

CR, complete response; OR, overall response; OS, overall survival; PFS, progression-free survival; -, not mentioned.

Table 5. Selected Ongoing Phase 2 and 3 Randomized Clinical Trials in PCNSL

Trial	Phase	*N* Patients	Eligibility	Control arm	Intervention Arm	Primary Endpoint
Radiation Therapy Oncology Group (RTOG 1114) (NCT01399372)	Phase 2	91	>18 years, KPS ≥50	Sequential R-MPV and HD-AraC	Sequential R- MPV, lower-dose WBRT(23.4 Gy) and HD-AraC	PFS
ANOCEF/GOELAMS (PRECIS) (NCT00863460)	Phase 2	140	18 to 60 years	Sequential R-MBVP and R-HD-AraC→WBRT(40 Gy)	Sequential R-MBVP and R-HD-AraC→HDC-ASCT with thiotepa, busulfan, cyclophosphamide	2 year PFS
Alliance for Clinical Trials in Oncology (NCT01511562)	Phase 2	113	18 to 75 years, KPS: ≥30 (≥50 for patients aged 60-70).	Induction therapy for five cycles as defined in the protocol→consolidation chemotherapy.	Patients undergo induction therapy for five cycles as defined in the protocol→ stem cell transplant	2 year PFS and up to 10 years
International Extranodal Lymphoma Study Group (IELSG43) (NCT02531841)	Phase 3	250	18-65 years irrespective of ECOG or 66-70 years (with ECOG PS< 2)	MATRix induction for 4 cycles→ R-DeVIC consolidation for 2 cycles	MATRix induction for 4 cycles→BCNU-thiotepa-conditioned ASCT as consolidation	PFS
OHSU Knight Cancer Institute (NCT02498951)	Phase 2	120	≥ 18 years, $CD20^+$ PCNSL, CR after first line treatment	Observation	Obinutuzumab	CR duration

PCNSL, primary central nervous system lymphoma; CR, complete response; EFS, event-free survival; KPS, Karnofsky performance status; ECOG, Eastern Cooperative Oncology Group; PS, performance status; Gy, gray; HD-AraC, high-dose cytarabine; HD-MTX, high-dose methotrexate; BCNU, carmustine; HDC-ASCT, high-dose chemotherapy with autologous stem cell transplantation; OS, overall survival; PFS, progression-free survival; R-MBVP, rituximab, HD-MTX, carmustine, etoposide, HD-AraC; R-MPV, rituximab, HD-MTX, procarbazine, vincristine, WBRT, whole brain radiotherapy; -, not mentioned; MATRix, methotrexate, cytarabine, thiotepa, and rituximab, R-DeVIC, rituximab, dexamethasone, etoposide, ifosfamide and carboplatin.

based regimens is probably the most commonly used approach by many clinicians if the time interval from initial diagnosis is considerably long. Rechallenge with HD-MTX led to a significant OR rate of 85%-91% in a retrospective analysis, with median OS of 41-62 months [118,119]. HDC-ASCT is another typical therapeutic option. Data from the largest cohort of relapsed PCNSL patients (n = 79) reported an excellent result in patients treated with thiotepa-based HDC-ASCT, with a 5-year EFS and OS rates of 37.8% and 51.4%, respectively [120]. The efficacy of WBRT as a salvage treatment seems to be equivalent to that of many salvage chemotherapy regimens, with overall radiographic response rates of 74%-79% and OS of 10-16 months [121].

Salvage chemotherapy regimens containing rituximab and temozolomide, either in combination or as a single agent, have resulted in response rates of 14%-53% and 1-year OS of 31%-55% in both prospective and retrospective studies [89,122–124]. The efficacy of topotecan has been evaluated in two studies of relapsed PCNSL patients, with OR rates of 33%-40% and OS of 8.4 and 35 months [125,126]. Single-agent pemetrexed has also shown therapeutic activity in recurrent and relapsed PCNSL, with an OR rate of 55.0%-71.4% and median PFS of 5.8 months observed in prospective and retrospective studies [127–129]. In a retrospective study assessing the effects of a combination regimen of procarbazine, vincristine, and CCNU (lomustine), an OR rate of 86% was reported [130]. The utility of single-agent temsirolimus as salvage treatment has been reported in a recent phase 2 study (NCT00942747), with an OR rate of 54% and median PFS of 2.1 months in 37 patients. However, responses were usually short-lived [131]. The role of an ifosfamide-etoposide combination as a second-line salvage treatment has also been studied, together with rituximab (R-IE) or cytarabine (VIA). In patients receiving the R-IE regimen, an OR rate of 41% was reported, and 8 of 22 patients did not experience relapse during the median 24-month follow-up [132]. In patients receiving the VIA regimen, a CR rate of 37% and a 12-month OS of 41% were observed [133].

The Bruton's tyrosine kinase (BTK) inhibitor ibrutinib has shown efficacy in PCNSL with mutations altering the BCR subunit CD79B and MYD88. In one trial, 86% of patients achieved CR with dose-adjusted

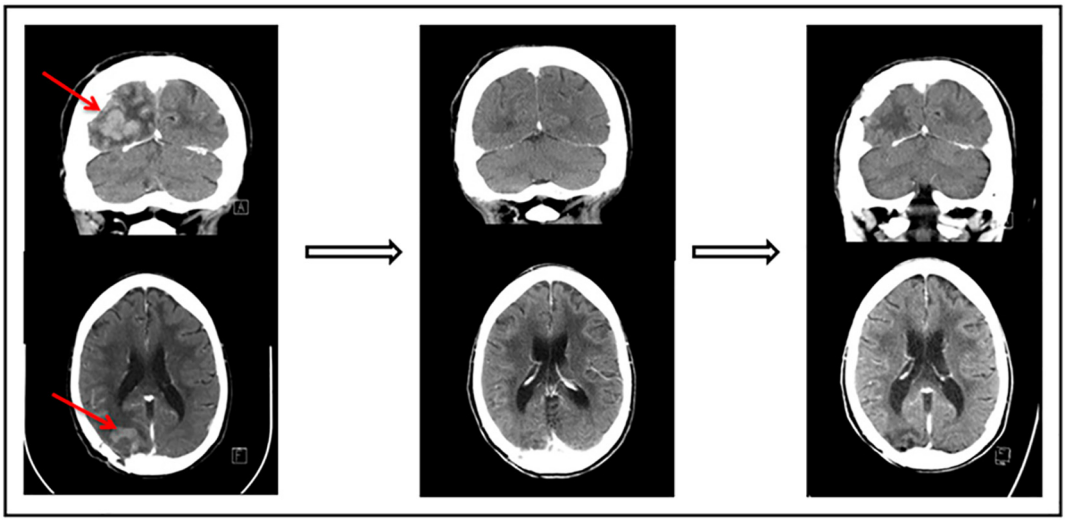

Figure 7. Nivolumab pre- and posttreatment head CTs with contrast in a patient with primary refractory PCNSL. (Left) The contrast-enhancing lesion before treatment with nivolumab. (Middle) Complete response following 2 months of therapy with nivolumab. (Right) Continued complete response 13 months following initiation of therapy. This figure is reprinted from Nayak et al.

temozolomide, etoposide, doxil, dexamethasone, ibrutinib, and rituximab (DA-TEDDi-R) [134]. The efficacy of single-agent ibrutinib in refractory and recurrent PCNSL is also being studied. Recent results from a trial investigating single-agent ibrutinib showed an OR rate of 68% and median PFS of 4.6 months in 25 patients [135] (Figure 6).

The efficacy of immunotherapy for salvage therapy of PCNSL is also being considered. Pomalidomide has shown some therapeutic activity with an OR rate of 43% in 21 patients. Several ongoing clinical trials are evaluating the effectiveness of lenalidomide as salvage treatment (NCT01956695 and NCT01542918). The result from one of these trials (NCT01542918) has demonstrated that lenalidomide is effective in relapsed CNS DLBCL and that maintenance lenalidomide significantly prolongs time to progression after salvage therapy and delays WBRT (Figure 6). The activity of PD-1 blockade has been demonstrated in other lymphomas with 9p24.1 alteration. Nayak et al. recently reported a retrospective study of salvage therapy with nivolumab. Clinical and radiographic responses to PD-1 blockade were observed in all five patients studied, and three patients remained progression-free after >13-17 months [136] (Figure 7). Several ongoing clinical trials are evaluating the efficacy of other PD-1 antibodies such as pembrolizumab (NCT02498951 and NCT02779101).

Histone deacetylase inhibitors (HDAC inhibitors) have recently been investigated as possible cancer therapies and have shown promising outcomes in several types of tumors. Durable clinical remission using romidepsin has been achieved in a refractory peripheral T-cell lymphoma case with CNS involvement [137]. Patients with cerebral metastasis of non–small-cell lung cancer were given chidamide combined with paclitaxel and carboplatin, and complete disappearance of the metastatic tumor after chemotherapy was observed [138]. This evidence suggests the potential efficacy of HDAC inhibitors in CNS tumors.

As there are still a few remaining long-term survivors and the toxicity of multiple courses of systemic therapy and WBRT is high, there is still ample interest in evaluating the efficacy of other agents targeting the various molecules involved in PCNSL pathogenesis.

Conclusion

Improvements in our understanding of PCNSL genomics, optimal drug dosing, sequence and timing of therapies, and patient care strategies over recent years will continue to influence the management of PCNSL. Biological studies will refine our knowledge of PCNSL pathogenesis and provide potential biomarkers for diagnosis, prognosis, or treatment with novel agents. Prospective randomized clinical trials will offer further evidence for clinicians to establish optimal doses or combinations of induction chemotherapy and consolidation strategies. Results of ongoing and future trials incorporating immunological agents currently under investigation in systemic lymphomas will continue to change the disease landscape and treatment options for patients with PCNSL.

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