



Recent advances and challenges in primary central nervous system lymphoma: a narrative review

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Background and Objective: Primary central nervous system lymphoma (PCNSL) is a rare and highly invasive non-Hodgkin lymphoma that is challenging to diagnose and treat. It is typically confined to the brain, spinal cord, and eyes. The diagnosis of PCNSL lacks specificity, and the misdiagnosis and missed diagnosis rates of PCNSL are high. Traditional treatments for PCNSL, such as surgery, whole-brain radiation therapy, high-dose methotrexate-based chemotherapy, and rituximab (RTX), have been associated with higher initial remission rates. However, the duration of any remission is short, the recurrence rate is high, and treatment-related neurotoxicity is strong, which are challenges for medical researchers. This review provides an overview of and perspectives on the diagnosis, treatment, and evaluation of patients with PCNSL.

Methods: The PubMed database was searched to retrieve articles published from January 1, 1991, to June 2, 2022 using the following Medical Subject Headings (MeSH) terms: “Primary central nervous system lymphoma” and “clinical trial”. The American Society of Clinical Oncology and the National Comprehensive Cancer Network guidelines were also reviewed to obtain additional information. The search was limited to articles published in English, German, and French. In total, 126 articles were deemed eligible for inclusion in this study.

Key Content and Findings: In terms of the diagnosis of PCNSL, a combination of flow cytometry and cytology has been shown to improve the diagnostic accuracy of PCNSL. Additionally, interleukin 10 and chemokine C-X-C motif ligand 13 are promising biomarkers. In terms of the treatment of PCNSL, programmed death-1 (PD-1) blockage and chimeric antigen receptor T cell (CAR-T) therapy treatments have shown prospective efficacy, but more clinical trials need to be conducted to gather further evidence. We also reviewed and summarized prospective clinical trials on PCNSL.

Conclusions: PCNSL is a rare and highly aggressive lymphoma. The treatment of PCNSL has progressed significantly, and while the survival of patients has improved, relapse and low long-term survival remain huge challenges. Continuous in-depth research is being conducted on new drug therapies and combination therapies for PCNSL. A combination of targeted drugs (e.g., ibrutinib, lenalidomide, and PD-1 monoclonal antibody) and traditional therapy represents the main research direction for future PCNSL treatments. CAR-T has also shown great potential in the treatment of PCNSL. With the development of these new diagnostic and therapeutic methods and further research into the molecular biology of PCNSL, patients with PCNSL should achieve a better prognosis.

Keywords: Primary central nervous system lymphoma (PCNSL); diagnosis; treatment

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Introduction

Primary central nervous system lymphoma (PCNSL) is a rare type of aggressive extranodal non-Hodgkin's lymphoma (NHL). PCNSL is usually confined to the brain, eyes, and in rare cases, the spinal cord or pia mater without other systemic infiltration. The incidence of PCNSL is approximately 0.44 per 100,000 persons, and PCNSL accounts for approximately 2% of all primary central nervous system (CNS) tumors (1). PCNSL patients have a median age of 65 years at the time of diagnosis (1). Since 2000, the incidence of PCNSL has increased in general, especially among patients who are elderly or immunocompromised (2,3).

The most common clinical presentation of patients with PCNSL is non-specific neurocognitive dysfunction. Few patients show focal neurological signs (4). For PCNSL, most of the lesions are single, and only 20% to 40% of the lesions are multiple (4). The most common lesion sites are supratentorial with periventricular subependymal tissues (5). More than 90% of PCNSLs are diffuse large B-cell lymphomas (DLBCLs) (6). Among these, 96% of PCNSLs are classified as the activated B-cell (ABC) subtype (7). At present, the treatment of PCNSL remains a major challenge.

In this review, we focused on advances in the diagnosis and treatment of PCNSL. The combination of flow cytometry (FCM) and cytology has been shown to improve the diagnostic accuracy of PCNSL (8). Further, interleukin 10 (IL-10) and chemokine C-X-C motif ligand 13 (CXCL13) are promising biomarkers (9-11). We evaluated the reported genetic aberrations related to the diagnosis of PCNSL. In terms of treatment, programmed death-1 (PD-1) blockage and chimeric antigen receptor T cell (CAR-T) therapy treatments have shown prospective efficacy (12,13), but more clinical trials need to be conducted to gather further evidence. We reviewed and summarized prospective clinical trials on PCNSL. In addition, we summarized the efficacy evaluation criteria related to follow-up defined by the International PCNSL Collaboration Group (IPCG). We present this article in accordance with the Narrative Review reporting checklist (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-2341/rc>).

Methods

The MeSH terms "Primary central nervous system lymphoma" and "clinical trial" were used to search the PubMed database to retrieve articles published from

January 1, 1991 to June 2, 2022. The American Society of Clinical Oncology and the National Comprehensive Cancer Network (NCCN) guidelines were also searched to obtain additional information. The search was limited to articles published in English, German, and French. The research selection process was divided into the following 3 stages: title review, abstract review, and full-text review. Studies without available abstracts were included in the full-text review phase. Ultimately, 126 articles were deemed eligible and included in this study, including 43 prospective clinical trials on PCNSL. The search strategy is detailed in *Table 1*.

Advances in diagnosis

Routine examinations

The most sensitive imaging method for diagnosing PCNSL is magnetic resonance imaging (MRI), which shows uniform contrast enhancement, clear boundaries, rare non-enhancement lesions, and common vasogenic edema around the lesions (14). PCNSL is also characterized by a low signal on T2-weighting and limited diffusion on diffusion-weighted imaging, which can be explained by the high cellularity and high nucleoplasmic ratio due to tight cell compression. These characteristics help to differentiate PCNSL from multiple gliomas (15,16).

PCNSL affects cerebrospinal fluid (CSF) in 15–20% patients and eyes in 5–20% patients (17). If there is no contraindication, a lumbar puncture should be performed for the CSF analysis. A diagnostic vitrectomy may be performed if a biopsy of the brain lesion is not possible and ocular involvement is suspected at the time of the slit-lamp examination. CSF and vitreous specimens should be evaluated using FCM, cytology, and immunoglobulin heavy chain rearrangement. About 7.1% of newly diagnosed PCNSL patients are cytologically positive for CSF (18). The combination of FCM and cytology improves the diagnostic accuracy of PCNSL (8). However, the stereotactic biopsy of intracranial masses remains the most commonly used and most reliable method for the diagnosis of PCNSL (15).

In addition, a diagnosis of PCNSL must exclude extrinsic neurological diseases. It has been reported that 8% of patients initially thought to have PCNSL show evidence of systemic disease (19). Positron emission tomography (PET)-computed tomography (CT) is more accurate at distinguishing PCNSL from other brain tumors and more sensitive at detecting whole-body diseases than chest, abdomen, and pelvic CT (20). About 3% of patients with

Table 1 The search strategy summary

Items	Specification
Date of the search	June 2, 2022
Databases and other sources searched	PubMed database, American Society of Clinical Oncology, and the National Comprehensive Cancer Network (NCCN) guidelines
Search terms used	Search: (((PCNSL) AND (primary central nervous system lymphoma)) AND (lymphoma)) AND (clinical trial) (“pcnsl”[All Fields] OR “pcnsls”[All Fields]) AND (“primaries”[All Fields] OR “primary”[All Fields]) AND (“central nervous system”[MeSH Terms] OR (“central”[All Fields] AND “nervous”[All Fields] AND “system”[All Fields]) OR “central nervous system”[All Fields]) AND (“lymphoma”[MeSH Terms] OR “lymphoma”[All Fields] OR “lymphomas”[All Fields] OR “lymphoma s”[All Fields])) AND (“lymphoma”[MeSH Terms] OR “lymphoma”[All Fields] OR “lymphomas”[All Fields] OR “lymphoma s”[All Fields]) AND (“clinical trial”[Publication Type] OR “clinical trials as topic”[MeSH Terms] OR “clinical trial”[All Fields])
Timeframe	January 1, 1991 to June 2, 2022
Inclusion and exclusion criteria	The search was limited to articles published in English, German, and French. The research selection process was divided into the following 3 stages: title review, abstract review, and full-text review. Studies without available abstracts were included in the full-text review phase
Selection process	L Ma conducted the article selection independently. Q Gong supervised the article selection

primary testicular lymphoma (PTL) have CNS involvement at the time of diagnosis, and all men diagnosed with PCNSL should be examined by testicular sonography or CT (21).

Biomarkers of PCNSL in liquid biopsy analysis

Regular examinations and tissue biopsies can be used to diagnose some PCNSL early. However, regular physical examinations lack specificity and are prone to missed diagnosis and misdiagnosis. Further, biopsy carries a risk of complications, such as intracranial bleeding and dysfunction. In some cases, a tumor may be in or near important brain structures, and thus a biopsy may not be feasible. In addition, the use of steroids before biopsy to eliminate the mass effect caused by edema may hamper histopathological diagnosis. This may result in a relatively poor diagnostic sensitivity of 48% (22). Thus, a highly specific and less invasive detection method urgently needs to be found.

Recently, liquid biopsies of CSF have been used for cytomorphologic and flow cytometric analyses. However, CSF analyses often fail to detect malignant cells, or the number of cells is too small to analyze (8,23). Gene mutations and new biomarkers have been identified in liquid biopsies to assist in diagnosis and evaluate patient prognosis. Hegde *et al.* (24) conducted a study and reported that the CSF analysis detected lymphoma cells in only 9% (1/11)

of patients. Quijano *et al.* (25) reported that the diagnostic sensitivity of the CSF analysis was only 6% in PCNSL.

Due to the low detection rate of malignant cells, many researchers have focused on the biomarkers in CSF. MicroRNAs are promising biomarkers for the liquid biopsy analysis of PCNSL and can be used to diagnose and monitor of therapy responses (26). Notably, IL-10 and CXCL13 have been reported to be promising biomarkers (9-11). In a retrospective study (27), IL-10 was upregulated in the CSF of 79.4% (27/34) of the PCNSL patients, and the IL-10 level was significantly associated with progression-free survival (PFS). In another retrospective study (28), the level of CXCL13 was more upregulated in the PCNSL patients than the other cerebral tumor patients. Further, the patients with higher CXCL13 expression had poorer overall survival (OS) than those with lower CXCL13 expression.

Genetic aberrations in PCNSL for liquid biopsy analysis

The detection of gene aberrations is also considered a promising method for PCNSL diagnosis. Multiple studies have employed different analysis strategies, such as targeted sequencing, single nucleotide polymorphism arrays, RNA sequencing, immunohistochemistry, and analyses of the loss of heterozygosity in tumor tissues, to try to identify a molecular signature specific for PCNSL (29-33).

Many of the genetic aberrations that have been detected in PCNSL influence a few common pathways, including

Table 2 Genetic aberrations reported in PCNSL, gene-related functions, type of genetic aberration, and prognosis in DLBCL

Gene	Genetic aberration	Function	Prognosis in DLBCL
<i>CD79B</i>	Mutation	BCR complex; activation of the NF- κ B pathway	Worse
<i>CARD11</i>	Mutation	BCM complex; activation of the NF- κ B pathway	No association
<i>MYD88</i>	Mutation	Activation of the NF- κ B pathway	Worse
<i>CDKN2A</i>	Loss	Cell-cycle G1 control	Worse
<i>ETV6</i>	Mutation	Required for hematopoiesis and vascular network development	Unknown
<i>TNFAIP3</i>	Mutation	Inhibition of NF- κ B activation and TNF-mediated apoptosis	No association
<i>TBL1XR1</i>	Mutation	Transcriptional co-factor: regulates <i>ETV6</i> activity	No association
<i>PRDM1</i>	Mutation	Tumor suppressor: terminal differentiation of B-cells	No association
<i>PIM1</i>	Mutation	Serine/threonine protein kinase involved in cell proliferation and survival	Unknown
<i>TOX</i>	Homozygous deletion	B-cell differentiation; T cell development regulation	No association
<i>PD-L1</i>	Copy number gains at chromosome 9p24.1	Immunocorrelation programmed death ligand	Unknown

BCM, *BCL10*, *CARD11* and *MALT1* complex; BCR, B-cell receptor complex; DLBCL, diffuse large B-cell lymphoma; NF- κ B, nuclear factor-kappa B; PCNSL, primary central nervous system lymphoma; PD-L1, programmed death ligand-1; TNF, tumor necrosis factor.

the nuclear factor-kappa B (NF- κ B) pathway, the Toll-like receptor (TLR) pathway, the B-cell receptor (BCR) pathway, and the Janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathway (29). The reported genetic aberrations in PCNSL are presented in *Table 2*, and include *CDKN2A* (29), programmed death ligand-1 (PD-L1) (29), *TBL1XR1* (29), *CD79B* (29-30,34), *CARD11* (35), *ETV6* (29,35), *TNFAIP3* (35), *PRDM1* (35), *PIM1* (29,35), and *TOX* (35).

Due to the small number of patients with PCNSL in the database (The Cancer Genome Atlas), we used GeneCards® (The Human Gene Database) and the highest-performing phenotype (i.e., DLBCL) to evaluate the use of genetic aberrations in the assessment of patient prognosis. In PCNSL, NF- κ B is the most affected pathway, and NF- κ B is mainly affected by frequent recurrent mutations in *CD79B* and *MYD88* (36). A prospective study revealed that IL-10 and *MYD88* have high specificity and sensitivity and were able to identify PCNSL in the CSF of 94% and 98% of 67 patients, respectively (37). In addition, the copy number of PD-L1 increases at chromosome 9p24.1 (29), which suggests that immune evasion might play a role in PCNSL.

Among the genetic aberrations, the biological function of many mutations has yet to be elucidated. Not only do we need to clarify the function of these mutated genes in PCNSL, but we also need to develop more sensitive detection techniques for molecular diagnosis.

Advances in treatment

Traditional treatment

Surgery

Due to the multifocal nature of PCNSL, surgical resection is not the standard treatment for PCNSL. In some retrospective studies, no survival benefit was observed from subtotal or gross total resection (38-40). However, patients with a single lesion, acute symptoms, or cerebral hernia may benefit from tumor removal (41,42). Qian *et al.* (43) recommended surgical cytoreduction before initiating chemotherapy. In Qian's unpublished data, surgical and subsequent chemotherapy showed more promising results than surgery alone. Currently, there is insufficient evidence to recommend an aggressive surgical approach for PCNSL.

Whole-brain radiotherapy (WBRT)

PCNSL is sensitive to radiotherapy. However, WBRT is not routinely recommended for newly diagnosed patients with PCNSL due to its insufficient disease control, lack of lasting efficacy, and risk of neurotoxicity. Nelson *et al.* (44) conducted a prospective trial that included 41 patients with PCNSL treated with WBRT (36–40 Gy) as the primary therapy and reported that nearly 50% of the patients achieved complete response (CR) or near CR after undergoing WBRT. However, 61% of the patients relapsed during the period of consolidation radiotherapy. In total, 48% of the patients

survived for 1 year, and 28% of the patients survived for 2 years; however, the median survival of the patients was only 11.6 months. In addition, the combination of WBRT with systemic chemotherapy was found to increase the risk of neurotoxicity. However, WBRT remains an option for patients with contraindications to chemotherapy. It can also be used as a rescue treatment for relapsed and refractory patients (45).

Chemotherapy

MTX-based chemotherapy

High-dose methotrexate (HD-MTX) (3–8 mg/m²) combined with other chemotherapeutic agents or WBRT is the most effective treatment for newly diagnosed PCNSL (46,47). At least 3 mg/m² of MTX needs to be administered within 24 hours to achieve an adequate therapeutic concentration in brain parenchyma and CSF (47). Chamberlain (48) conducted a prospective phase-II study of HD-MTX and rituximab (RTX) with WBRT in 40 patients with newly diagnosed PCNSL and reported that the entire cohort had a median survival time of 29 months. Pels *et al.* (49) conducted a phase-II study of 65 consecutive patients with PCNSL to evaluate HD-MTX without radiotherapy and reported that 37 (61%) patients achieved CR, 6 (10%) achieved partial response (PR), and 12 (19%) progressed under therapy.

Ferreri *et al.* (50) conducted a randomized phase-2 clinical trial at 24 centers in 6 countries with 79 patients. Of these patients, 40 were treated with HD-MTX alone, and 39 were treated with high-dose cytarabine plus HD-MTX. The results suggested that the addition of high-dose cytarabine to HD-MTX improved the outcomes with acceptable toxicity compared to HD-MTX alone. The International Extranodal Lymphoma Study Group-32 (IELSG32) conducted an international randomized phase-II trial (51) of 227 eligible patients and reported that those treated with RTX and thiotepa had a complete remission rate of 49% [95% confidence interval (CI): 38–60%], those treated with MTX-cytarabine alone had a complete remission rate of 23% (95% CI: 14–31%) of those treated with methotrexate-cytarabine alone [hazard ratio (HR): 0.46, 95% CI: 0.28–0.74] and those treated with MTX-cytarabine plus RTX had a complete remission rate of 30% (95% CI: 21–42%) of those treated with methotrexate-cytarabine plus RTX (HR: 0.61, 95% CI: 0.40–0.94). The IELSG32 trial provides high-level evidence supporting the use of the MATRix (methotrexate, cytarabine, thiotepa, and RTX) combination as the new standard

chemoimmunotherapy for patients aged up to 70 years with newly diagnosed PCNSL.

Notably, research has shown that MATRix and autologous stem cell transplantation (ASCT) did not result in higher non-relapse mortality than HD-MTX therapy or second tumor incidence (52). Thiel *et al.* (53) conducted a phase-III, randomized, non-inferiority clinical trial at 75 centers with 551 patients, of whom 318 received HD-MTX with WBRT (45 Gy), and 233 received HD-MTX alone. The median PFS of the patients who received HD-MTX with WBRT was 18.3 months (95% CI: 11.6–25.0) and that of those who did not receive WBRT was 11.9 months (7.3–16.5; P=0.14). The results demonstrated that the PFS benefit provided by HD-MTX with WBRT must be weighed against the increased risk of neurotoxicity in long-term survivors. Thus, HD-MTX combined with other chemotherapeutic agents or WBRT may bring benefits in the short term. However, these benefits must be considered alongside the side effects of the combination therapy in the long term.

Wang *et al.* (54) conducted a retrospective study that showed that HD-MTX dosed at 3–5 g/m² had a similar efficacy but a lower toxicity than higher doses in patients with PCNSL. Thus, reducing the initial HD-MTX dose may help ensure the tolerability of side effects and completion of induction therapy, especially in patients with comorbidities or those of an older age who typically have poorer outcomes.

Intrathecal chemotherapy

It is widely assumed that large molecules, including many monoclonal antibodies and PD-1/PD-L1 inhibitors, cannot penetrate the blood-brain barrier (BBB) (55). The intrathecal injection of MTX was shown to significantly improve the survival of patients with conventional PCNSL (56). In addition, the presence or absence of CSF lymphoma spread was found to have no significant effect on the efficacy of the intrathecal injection of MTX (46).

Recently, some researchers have developed drugs that cross the BBB to improve the treatment of brain malignancies. Neuwelt *et al.* (57) conducted a review and reported that many studies suggest that HD-MTX (at least 1 g/m²), although the permeability of the BBB is only 5% of plasma level, combined WBRT can prolong PFS and OS. Butler *et al.* (58) found that intrathecal chemotherapy combined with radiotherapy effectively eliminated brain tumors; however, the side effects of this combination therapy may also affect patients' cognitive function. Thus, more efficient and gentle ways to treat PCNSL need to be found.

RTX

RTX is a chimeric monoclonal antibody targeting the CD20 (cluster of differentiation 20) antigen. The combination of RTX with a CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy regimen has been shown to have excellent efficacy in the treatment of DLBCL (59). To study its efficacy, different dosages of RTX (ranging from 375 to 800 mg/m²) were administered to patients with PCNSL. The results showed that the permeability of RTX was low in CSF, and ranged from 0.1% to 4.4% of the serum concentration (60). Holdhoff *et al.* (61) conducted a study to examine whether RTX combined with chemotherapy regimens had a higher rate of CR than chemotherapy without RTX. However, there was a controversy, they found that RTX did not influence the outcome of elderly PCNSL patients possibly due to low RTX diffusion in CSF, the effectiveness of using RTX to treat PCNSL remains unclear (62).

Schmitt *et al.* (63) conducted a meta-analysis of PCNSL treatments and assessed the benefits and harms of RTX in the treatment of 343 immunocompetent patients with PCNSL from 2 randomized controlled trials. There was no statistically significant improvement in the OS of the patients (HR =0.76; 95% CI: 0.52–1.12; low certainty: the CI includes no effect parts, resulting in inaccurate results). Similarly, an intergroup, multicenter, open-label, randomized phase-III study conducted at 23 centers (HOVON 105/ALLG NHL 24) showed that the addition of RTX to MTX, carmustine, teniposide, and prednisone chemotherapy in primary CNS lymphoma produced no clear benefit (64). However, the result of the IELSG32 trial showed that patients treated with RTX plus HD-MTX had a better complete remission rate than patients treated with HD-MTX alone. Thus, the role of RTX in PCNSL treatment is still unclear. Further research needs to be conducted to clarify the effect of RTX on the prognosis of patients with PCNSL.

Thiotepa-based ASCT

Thiotepa-based ASCT is an accepted and effective consolidation strategy for the treatment of PCNSL. Scordo *et al.* (65) conducted an observational cohort study of 603 patients who underwent ASCT. These patients received 1 of the 3 following conditioning regimens: (I) thiotepa/busulfan/cyclophosphamide (TBC; n=263); (II) thiotepa/carmustine (TT-BCNU; n=275); and (III) carmustine/etoposide/cytarabine/melphalan (BEAM; n=65). Notably, the PFS rates were higher in the TBC cohort (75%) and TT-BCNU cohort (76%) than the BEAM cohort (58%;

P=0.03). Lee *et al.* (66) conducted a retrospective study of 22 newly diagnosed PCNSL patients who received high-dose chemotherapy with thiotepa-based conditioning regimen and ASCT. The patients had a median follow-up time of 19.6 months (range, 7.5–56.5 months), and 2-year PFS and OS rates is 84% and 88%, respectively. A European retrospective study was conducted of 52 patients who all underwent thiotepa-based HDT-ASCT at 11 centers (67). The study reported a median follow-up time of 22 months after HDT-ASCT, and a median PFS and OS of 51.1 and 122.3 months, respectively. The 2-year PFS and OS rates were 62.0% and 70.8%, respectively. Alnahhas *et al.* (68) conducted a systematic review and meta-analysis of ASCT for PCNSL and their subgroup analysis showed that the use of carmustine and thiotepa as a conditioning regimen had the lowest risk of transplant-related mortality than those of using thiotepa, busulfan, and cyclophosphamide. Conversely, the thiotepa, busulfan, and cyclophosphamide regimen had numerically superior OS and PFS rates. In summary, thiotepa-based ASCT therapy has shown encouraging results in the treatment of PCNSL.

Temozolomide

Temozolomide is an oral alkylating agent that was approved by the Food and Drug Administration for use in the first-line treatment of glioblastoma (69). Enting *et al.* (70) used a combination of RTX and temozolomide as salvage therapy to treat progressive PCNSL and reported that 15 patients with a median age of 69 years had a 53% objective response rate (ORR) with acceptable toxicity. Thus, this combination provides a reasonable therapeutic alternative for older patients with progressive PCNSL.

A retrospective series explored the use of temozolomide monotherapy in elderly patients with PCNSL and severe comorbidities (71). In 17 patients (aged 62–90 years), the CR rate was 47%, the median PFS was 5 months, and the median OS was 21 months. Of the 17 patients, 5 (29.4%) had prolonged responses for at least 12 months and survived for >24 months. Thus, temozolomide monotherapy appears to be effective in treating a subgroup of elderly patients with PCNSL.

Makino *et al.* (72) conducted a cohort study of salvage treatment with temozolomide in 17 patients with refractory or relapsed PCNSL and found that temozolomide resulted in CR in 29% of the patients and was well-tolerated without any major toxicity. Thus, temozolomide may be a good candidate agent for induction, consolidation, and maintenance therapy for patients with PCNSL and for salvage treatment.

New therapeutic strategies

Ibrutinib

Traditional treatments for PCNSL have good effectiveness; however, the duration is short, and the side effects are strong. More than 90% of PCNSL patients have the ABC subtype of DLBCL and are highly dependent on BCR transduction signals (73). Ibrutinib is a small-molecule drug with a good distribution in CNS. It binds permanently to Bruton tyrosine kinase and inhibits BCR signal transduction, and thus represents a promising treatment for PCNSL (74).

A prospective, multicenter, phase-II study examined the use of ibrutinib monotherapy (560 mg/day) in the treatment of relapsed/refractory PCNSL (75) in 52 patients. After 2 months of treatment, the disease control rate was 70% in 44 evaluable patients, of whom 10 (19%) achieved CR and 17 (33%) achieved PR. The median follow-up time was 25.7 months, and the median PFS and OS times were 4.8 and 19.2 months, respectively. Of the patients, 13 were treated with ibrutinib for >1 year, and 2 patients developed pulmonary aspergillosis. This trial confirmed the clinical efficacy of ibrutinib in PCNSL.

Another phase-I study of ibrutinib combined with HD-MTX and RTX examined 15 patients with CNSL (of whom 9 had primary CNSL and 6 had secondary CNSL), including 9 patients with R/R (relapsed/refractory) (76). The patients were treated with HD-MTX combined with ibrutinib (560 mg/840 mg) with or without combination RTX. Notably, all the patients with R/R were treated with the 3-drug combination. This study also examined the concentration of ibrutinib in CSF. CR was achieved in 56% of the patients who received the treatment with RTX. Conversely, CR was only achieved in 33% of the patients who received the treatment without RTX. No dose-limiting toxicity, treatment-related deaths, or aspergillosis were observed. The ibrutinib treatment results were comparable to those of HD-MTX alone in patients with R/R; however, the patients who received the combination regimen had a longer recurrence time (>2 years) and PFS time than those receiving RTX alone. Thus, ibrutinib combined with HD-MTX and RTX showed good anti-tumor activity. However, due to the non-randomized nature and small sample size of the study, the effects of the combination of ibrutinib need to be evaluated further in the future.

Lenalidomide (LEN)

LEN is an oral immunomodulator and thalidomide

derivative with anti-tumor proliferative properties. A phase-II clinical trial evaluated the efficacy of low-dose LEN (5–10 mg/day in a 21-day cycle) in maintenance therapy in patients aged over 70 years who received MTX/RTX induction to treat PCNSL. The median follow-up time was 31.64 months, and the median PFS was not achieved (77). In a phase-II study, the use of LEN combined with RTX (the R² regimen) was evaluated in the treatment of PCNSL and primary vitreoretinal lymphoma (PVRL) (78). A total of 50 patients received a 28-day cycle of the R² regimen (of RTX 375 mg/m² for the first cycle, RTX combined with LEN 20 mg/day for day 1 to day 21, and LEN 25 mg/day for subsequent cycles). At the end of the induction therapy, the ORR of the 45 evaluable patients (of whom, 34 had PCNSL and 11 had PVRL) was 36% (CR: 29% and PR: 7%). The median follow-up time was 19.2 months, and the median PFS and OS times were 7.8 and 17.7 months, respectively. The LEN + RTX (R²) regimen had a significant effect in the treatment of patients with R/R PCNSL, who had an ORR of 35.6% and a median PFS time and overall OS time of 7.8 and 17.7 months, respectively, without unexpected toxicity. The recommended dose of LEN during chemotherapy is 20 mg/day for day 1 to day 21 and 25 mg/day for the subsequent cycles, and the recommended induction treatment should be followed by a maintenance phase comprising 28-day cycles of LEN alone (10 mg/day, day 1–day 21) (79).

PD-1 blockage

Nivolumab is a humanized monoclonal antibody PD-1 that activates T cell function (12). The PD-1 ligands PD-L1 and PD-L2 are overexpressed in PCNSL, resulting in reduced T cell proliferation and survival. One case study reported that 1 patient with PCNSL, who was sensitive to MTX chemotherapy, achieved CR after receiving HD-MTX chemotherapy and ASCT. Thus, the subsequent administration of nivolumab was found to maintain and prolong remission (80).

Another study examined the use of nivolumab in the treatment of R/R PCNSL and PTL in 5 patients, of whom, 4 had PCNSL and 1 had intracranial PTL (81). All 5 patients received intravenous (IV) treatment with nivolumab 3 mg/kg once every 2 weeks. The adverse reactions included pruritus, fatigue, and renal insufficiency. The radiographic response was observed in all the patients after treatment. The median follow-up time was 17 months, and all the patients survived. One PCNSL patient developed systemic recurrence at 14 months, but no intracranial involvement

was detected.

A multicenter, single-arm, open-label, phase-II trial for R/R PCNSL with analogous anti-PD-1 pembrolizumab treatment demonstrated an obvious therapeutic effect (82). In that study, 50 patients with a median age of 72 years received 200 mg of pembrolizumab on the first day of treatment for 21 days. Of the 50 patients, 13 had an ORR (8 had CR and 5 had PR), 5 had stable disease (SD), and 29 had progressive disease (PD). After 6 months, the patients had a PFS rate of 29.8% and an OS rate of 60.4%. The median time of remission was 10 months (95% CI: 2.7–12.5 months). No related poisoning deaths were reported. Thus, the PD-1 blockade has promising efficacy in the treatment of patients with R/R PCNSL.

CAR-T

CAR-T has revolutionized the treatment of B-lymphatic tumors, and several CAR-T cells have been approved for the treatment of R/R DLBCL due to their high remission rates (13). Recently, Frigault *et al.* (83) conducted a phase-I, 1/2 clinical trial of tisagenlecleucel with 8 secondary CNS lymphoma patients who were treated with commercial tisagenlecleucel. No patient experienced neurotoxicity > grade 1. The biomarker analysis suggested the presence of CAR-T cell expansion, and the early response assessments demonstrated the activity of IV-infused CAR-T cells within the CNS space.

Studies have also been conducted on the use of CAR-T in secondary central nervous system lymphoma (SCNSL) patients. A 68-year-old female patient with brain involvement of DLBCL showed a poor response to multiple chemotherapy treatments, including allogeneic hematopoietic stem cell transplantation. She then participated in a trial with Transcend-NHL-001. This patient was pre-treated with fludarabine combined with cyclophosphamide and then received the CAR-T cell product JCAR017 targeting CD19. The PET-CT and brain MRI results showed that CR was achieved after 1 month of follow-up. In the second month of follow-up, a biopsy confirmed subcutaneous recurrence. The CAR-T cells proliferated spontaneously after the biopsy, and CR was confirmed again in the 3rd month of follow-up. The patient's remission lasted for 12 months, and the patient did not experience neurotoxicity, graft-versus-host disease, or cytokine release syndrome (CRS). The patient eventually died of recurrence of the tumor more than 1 year after receiving CAR-T treatment, but the disease never recurred in the brain (84).

A retrospective review was conducted on the use of CAR-T in 8 SCNSL patients with DLBCL (of whom, 4 had the germinal center type, 1 had the non-germinal center type, 2 had high-grade B-cell lymphoma, and 1 had primary mediastinal B-cell lymphoma). The patients had a median age of 48.5 years (85). Under the American Society for Transplantation and Cell Therapy's 2019 consensus on grading CRS and immunoeffector cell-related neurotoxicity (86), 7 of the patients developed grade 1 CRS after treatment, and 1 patient did not. Neurotoxicity was observed in 1 patient but not in the other patients. In addition, CRS and neurotoxicity did not require treatment in all patients. After 28 days of reinfusion, 2 patients had CR, 2 had PR, 2 had SD, and 2 had PD. In addition, 1 patient with CR relapsed 90 days after reinfusion, local radiotherapy was added to the treatment, and CR was achieved 180 days later. One patient maintained CR after 90 days, 1 patient with PR remained in remission after 90 days, and 1 patient with PR maintained 180 days and then was evaluated as CR.

Given the encouraging results of CA-T in patients with SCNSL, further research on the use of CAR-T in the treatment of PCNSL should be undertaken in the future. Frigault (87) conducted a prospective study on the use of CA-T treatment in PCNSL and found that 7 of the 12 patients (58.3%) demonstrated a response, including CR in 6 of the 12 patients (50%). In addition, no treatment-related deaths occurred. These trials suggest that CA-T is effective and safe in the treatment of PCNSL.

We reviewed and summarized prospective clinical trials on PCNSL (*Table 3*). *Table 3* contains details of the references, treatment strategies, number of patients, the year of publication, median age (years), rates of OR, PR, and CR, median PFS (months), and median OS (months).

Efficacy evaluation and follow-up

Two prognostic integral models have been established to evaluate PCNSL (123,124). The Memorial Sloan-Kettering Cancer Center prognostic model was divided into 3 groups according to age and Karnofsky Performance Status (KPS) score. The IELSG selected the following 5 variables as independent predictors of a poor prognosis: an Eastern Cooperative Oncology Group (ECOG) score >1, an age >60 years, the serum lactate dehydrogenase level, the CSF protein concentration, and tumor involvement in the deep brain region. The OS rates were 80%, 48%, and 15%, respectively, in patients with 0–1, 2–3, or 4–5 points of adverse factors (125).

Table 3 Prospective clinical trials on PCNSL

Reference	Year	Treatment strategies	Number of patients	Median age (years)	Median PFS (months)	Median OS (months)	OR, PR + CR [%]
DeAngelis (88)	1992	M [1] + RT [40 + 14 boost] + AraC [3]	31	58	41	42.5	27/31 [87]
Nelson (44)	1992	RT [40 + 20 boost]	41	NR	NR	12.2	21/26 [81]
Glass (89)	1994	M [3.5] + RT [30–40]	25	56	32	33	23/25 [92]
Schultz (90)	1996	CHOP + RT [41.4 + 18 boost]	52	NR	9.2	16.1	10/52 [19]
O’Neill (91)	1999	CHOP + RT [50.4] + AraC	55	60	6.7	9.7	32/53 [60]
Mead (92)	2000	RT [40 + 14 boost] ± CHOP	53	57	10 vs. 22	NR	NR
O’Brien (93)	2000	M [1] + RT [45 + 5.4 boost]	46	58	NR	33	44/46 [96]
Abrey (94)	2000	M [3.5] + P [100] + V [1.4] + AraC [3] + IT M + IT A + RT [45]	52	65	NR	60	49/52 [94]
Ferreri (95)	2001	M [3] + P [100] + V [1.4] + AraC [3] + RT [45]	13	54	18	≥25	12/13 [92]
DeAngelis (96)	2002	M [2.5] + V [1.4] + P [100] + AraC [3] + IT M + RT [45]	102	56.5	24	37	47/50 [94]
Poortmans (97)	2003	M [3] + Ten [100] + B [100] + pred [60] + IT M + IT A + RT [40]	52	51	NR	46	42/52 [81]
Abrey (98)	2003	M [3.5] + AraC [3]; BEAM	28 (14 transplanted)	53	5.6	Not reached	Induction: 16/24 [57], SCT: 11/14 [79]
Batchelor (99)	2003	M [8]	25	60	12.8	22.8	17/23 [74]
Pels (49)	2003	M [5] + AraC [3] + V [2] + ifos [800] + dex [10] + cyclo [200] + IT M + IT A + IT P	65	62	21	50	43/61 [71]
Herlinger (100)	2005	M [8]	37	60	10	25	13/37 [35]
Colombat (101)	2006	M [3] + B [100] + eto [100] + pred [60]; BEAM + RT [30]	25 (17 transplanted)	52	40	Not reached	Induction: 21/25 [84], SCT 16/16 [100]
Illerhaus (102)	2006	M [8] + AraC [3] + thio [40 mg/m ²]; B [400] + thio [5 mg/kg] + RT [45]	30 (23 transplanted)	54	NR	Not reached	Induction: 21/30 [70], SCT 21/21 [100]
Ferreri (50)	2009	M [3.5] + AraC [2] + RT [45]	79	59; 58	3; 18	NR	27/39 [69]; 16/40 [40]
Thiel (53)	2010	M [3; + ifos] + RT [45]	526 (all); 318 (PPP)	61	18.3; 11.9	32.4; 37.1	283/526 [54]
Morris (103)	2013	R [500] + M [3.5] + V [1.4] + P [100] + RT [23.4]	52	60	92.4	Not reached	41/52 [79]
Rubinstein (104)	2013	R [375] + M [8] + T [150] + AraC [2] + eto [40]	44	61	48	Not reached	34/47 [72]
Omuro (105)	2015	M [3.5] + V [1.4] + P [100] + AraC [3]; M [3.5] + T [150]	95	72; 73	9.5; 6.1	31; 14	37/45 [82]; 34/42 [74]
Omuro (106)	2015	R [500] + M [3.5] + V [1.4] + P [100]; thio [250] + cyclo [60] + bus [3.2]	32 (26 transplanted)	57	Not reached	Not reached	Induction: 31/32 [97]; SCT 24/26 [92]

Table 3 (continued)

Table 3 (continued)

Reference	Year	Treatment strategies	Number of patients	Median age (years)	Median PFS (months)	Median OS (months)	OR, PR + CR [%]
Ferreri (51)	2016	M [3.5] + AraC [2] + R [375] + thio [30]	227	58; 57; 57	6; 20; not reached	12; 30; not reached	40/75 [53]; 51/69 [74]; 65/75 [87]
Glass (107)	2016	R [375] + M [3.5] + T [100] + RT [36]	66	57	63	90	30/35 [86]
Illerhaus (108)	2016	R [375] + M [8] + AraC [3] + thio [40]; R [375] + B [400] + thio [5 mg/kg]	79 (73 transplanted)	56	74	Not reached	Induction: 73/79 [92]; SCT: 72/79 [91]
Kasenda (109)	2017	R [375] + AraC [3] + thio [40]; R [375] + B [400] + thio [5 mg/kg]	39 (32 transplanted)	57	12.4	Not reached	Induction: 22/39 [56]; SCT: 22/32 [69]
Fritsch (110)	2017	R [375] + M [3] + P [60] + L [110]	107 (all); 69 (R-MPL)	73	10.3 (all); 9.6 (R-MPL)	20.7 (all); 15.4 (R-MPL)	53/107 [50]; 32/69 [46% R-MPL]
Adhikari (111)	2018	AraC [3] + RT [45]	22	51.5	11.25	19	18/22 [82]
Rubenstein (79)	2018	LEN [10] + R [375]; LEN [15] + R [375]; LEN [20] + R [375]	14	66	NR	NR	9/14 [64]
Wu (112)	2018	FTD: FOT [100] + Ten [60] + dex [40]; HD-MA: M [3.5] + AraC [1]	49 (FTD: 24, HD-MA: 25)	FTD: 56; HD-MA: 57	17.4; 16.7	48.8; 44.9	FTD: 21/24 [88]; HD-MA: 21/25 [84]
Tun (113)	2018	POM [5] + DEX [40]	25	60	9	4.7	12/25 [48]
Ghesquieres (114)	2019	LEN [20] + R [375]	34	69	7.8	17.7	12/34 [35]
Houillier (52)	2019	R [375] + M [3] + AraC [3] + RT [40]; R [375] + M [3] + AraC [3] + ASCT	140 (70 transplanted)	47; 53	NR	NR	44/70 [63]; 61/70 [87]
Ferreri (115)	2019	R [375] + CHOP + NGR-hTNF [0.8]	12	61	NR	NR	9/12 [75]
Soussain (75)	2019	IB [560]	52	70	4.8	19.2	27/52 [52]
Dietrich (116)	2020	PEM [900]	17	63.7	4.2	44.5	12/17 [71]
Ferreri (117)	2020	R [375] + CHOP + NGR-hTNF [0.8]	28	58	NR	NR	21/28 [75]
Seidel (118)	2020	IT M [3] + AraC [3]	65	62	NR	53	42/65 [65]
Chiesa (119)	2020	TMZ [3.5] + RT [30]	9	67	Not reached	79	6/9 [67]
Narita (120)	2021	TIR [480]	44	60	2.9	Not reached	28/44 [64]
Fox (121)	2021	TIER	27	64	3	5	14/27 [52]
Ferreri (122)	2022	MA; MATRix; WBRT or ASCT	219	62	NR	21% vs. 37% vs. 56%	NR

A, cytarabine; AraC, cytarabine (g/m²); B, carmustine (mg/m²); BEAM, carmustine, etoposide, cytarabine, melphalan; bus, busulfan (mg/kg); chemo, chemotherapy; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CR, complete remission; cyclo, cyclophosphamide (mg/m²); dex, dexamethasone; DEX, dexamethasone (mg/day); eto, etoposide (mg/m²); FOT, fotemustine (mg/m²); FTD, fotemustine, teniposide and dexamethasone; HD-MA, high-dose methotrexate plus cytarabine; IB, ibrutinib (mg/day); ifos, ifosfamide (mg/m²); IT A, intrathecal cytarabine; IT M, intrathecal methotrexate; IT P, intrathecal prednisone; L, lomustine (110 mg/m²); LEN, lenalidomide (mg/day); M, methotrexate (g/m²); MA, mitoxantrone, cytarabine; MATRix, methotrexate, cytarabine, thiotepa, and rituximab; NGR-hTNF, tumor necrosis factor- α coupled with NGR (μ g/m²); NR, not reported; OR, overall response; OS, overall survival; P, procarbazine (mg/m²/day); PCNSL, primary central nervous system lymphoma; PEM, pemetrexed (mg/m²); PFS, progression-free survival; POM, pomalidomide (mg); PPP, per-protocol population; PR, partial remission; pred, methylprednisolone (mg/m²); R, rituximab (mg/m²); R-MPL, rituximab, methotrexate, procarbazine and lomustine; RT, radiation therapy (dose used in Gy); SCT, stem cell transplant; T, temozolomide (mg/m²); Ten, teniposide (mg/m²); thio, thiotepa (mg/m²); TIER, thiotepa in combination with ifosfamide, etoposide, and rituximab; TIR, tirabrutinib (mg/day); TMZ, temozolomide (g/m²); V, vincristine (mg/m²); WBRT, whole-brain radiotherapy; ASCT, autologous stem cell transplantation.

Table 4 Response assessment of PCNSL

Curative effect	Imageological examination	Corticoid dose	Ophthalmic examination	CSF cytology
CR	No enhanced lesions	No	Normal	Negative
Unconfirmed CR	No enhanced lesions	Any	Normal	Negative
CR	Minimal anomaly	Any	Slight abnormal retinal pigment epithelium	Negative
PR	Enhanced lesions were reduced by 50%	Unrelated	Normal or Slight abnormal retinal pigment epithelium	Negative
	No enhanced lesions	Unrelated	Reduced vitreous or retinal infiltration	Suspicious positive
SD	Enhanced lesions were reduced by 25%	Unrelated	Recurrent or new lesions	Relapse or Positive
PD	All cases except those mentioned above			

CR, complete response; CSF, cerebrospinal fluid; PCNSL, primary central nervous system lymphoma; PR, partial remission; SD, stable disease; PD, progressive disease.

The IPCG has established criteria for efficacy assessments, including all the sites involved (brain, CSF, and eyes) and glucocorticoid doses. Enhanced MRI is the standard test for assessing lesions in brain or spinal cord tumors. CSF and ophthalmic evaluations are required when the pia mater and eyes are involved or when related clinical manifestations are present (19).

An NHL phase-III study revealed that the Mini-Mental State Examination score was an independent prognostic factor for survival in 153 newly diagnosed PCNSL patients (85). The efficacy evaluation criteria defined by the IPCG are shown in *Table 4*. Most relapses occurred within 5 years of the end of treatment. However, due to the presence of late recurrence, follow-up for 10 years after the end of treatment is recommended (once every 3 months during years 1 and 2, once every 6 months during years 3 to 5, and once a year during years 5 to 10). In addition, if the patient has clinical symptoms, the performance of an ophthalmic examination and a CSF analysis should be considered.

Discussion

Currently, the prognosis of patients with PCNSL remains poor. The median survival time of PCNSL patients without treatment is only 2 months, the median survival time from first disease progression to death from any cause is 7.2 months, and the OS time is less than 2 years (1-3). Many factors affect prognosis, including treatment sensitivity, age, salvage therapeutic schemes, relapse time, and relapse location. In general, rescue treatment and recurrence time are still important factors affecting the prognosis and

quality of life of patients (2,3).

In recent years, the medical community has made significant progress in understanding the pathogenesis and improving the treatment of PCNSL. Indeed, patients with recurrent PCNSL have more and more treatment options, and NCCN guidelines now include some drugs for the treatment of R/R PCNSL. However, there are still many challenges in the diagnosis, treatment, and follow-up of recurrent PCNSL, especially given the low diagnostic rate of traditional imaging follow-up examinations and the lack of personalized treatment options; however, some new technologies may provide us with additional help.

MRI-based machine learning has achieved good results in differentiating between PCNSL and other CNS tumors. Compared to manual reading, machine learning based on PCNSL recurrence imaging may be helpful in the early and accurate diagnosis of PCNSL. IL-10 and CXCL13 are also promising biomarkers in the CSF of patients. IL-10 and CXCL13 levels are significantly associated with patients' PFS and OS, respectively. However, the best treatment method for PCNSL has yet to be determined.

Chemotherapy based on HD-MTX is still considered the standard induction treatment for patients newly diagnosed with PCNSL. For patients with R/R PCNSL, individualized treatment based on research progress at the cellular and molecular level can also be carried out to improve patient prognosis. In addition, the current new treatment strategies still lack evidence from large-scale prospective trials. Thus, more prospective studies, especially those examining reasonable combinations of new treatment strategies, need to be conducted in the future.

Conclusions

PCNSL is a rare and highly aggressive lymphoma. The treatment of PCNSL has progressed significantly and while the survival of patients has improved, relapse and poor long-term survival remain huge challenges. The early and accurate diagnosis of PCNSL is crucial to the prognosis of patients. If PCNSL is suspected based on clinical symptoms, MRI and CSF are irreplaceable examination methods. Continuous in-depth research is being conducted on new drug therapies and combination therapies for PCNSL. A combination of targeted drugs (e.g., ibrutinib, LEN, and PD-1 monoclonal antibody) and traditional therapy represents the main research direction for future PCNSL treatments. CAR-T has also shown great potential in the treatment of PCNSL. With the development of these new diagnostic and therapeutic methods and further research into the molecular biology of PCNSL, patients with PCNSL should achieve a better prognosis.

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