Review Article

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
CD79B	Mutation	BCR complex; activation of the NF-κB pathway	Worse
CARD11	Mutation	BCM complex; activation of the NF-κB pathway	No association
MYD88	Mutation	Activation of the NF-κB pathway	Worse
CDKN2A	Loss	Cell-cycle G1 control	Worse
ETV6	Mutation	Required for hematopoiesis and vascular network development	Unknown
TNFAIP3	Mutation	Inhibition of NF-κB activation and TNF-mediated apoptosis	No association
TBL1XR1	Mutation	Transcriptional co-factor: regulates *ETV6* activity	No association
PRDM1	Mutation	Tumor suppressor: terminal differentiation of B-cells	No association
PIM1	Mutation	Serine/threonine protein kinase involved in cell proliferation and survival	Unknown
TOX	Homozygous deletion	B-cell differentiation; T cell development regulation	No association
PD-L1	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-κB, 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-κB) 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), *PRDM*1 (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-κB is the most affected pathway, and NF-κB 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/m^2) combined with other chemotherapeutic agents or WBRT is the most effective treatment for newly diagnosed PCNSL (46,47). At least 3 mg/m^2 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/m^2 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/m^2), 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/m^2) 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 examined 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 PNCSL 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 R^2 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 R^2 regimen (of RTX 375 mg/m^2 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 (R^2) 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/m^2); B, carmustine (mg/m^2); BEAM, carmustine, etoposide, cytarabine, melphalan; bus, busulfan (mg/kg); chemo, chemotherapy; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CR, complete remission; cyclo, cyclophosphamide (mg/m^2); dex, dexamethasone; DEX, dexamethasone (mg/day); eto, etoposide (mg/m^2); FOT, fotemustine (mg/m^2); FTD, fotemustine, teniposide and dexamethasone; HD-MA, high-dose methotrexate plus cytarabine; IB, ibrutinib (mg/day); ifos, ifosfamide (mg/m^2); IT A, intrathecal cytarabine; IT M, intrathecal methotrexate; IT P, intrathecal prednisone; L, lomustine (110 mg/m^2); LEN, lenalidomide (mg/day); M, methotrexate (g/m^2); MA, mitoxantrone, cytarabine; MATRix, methotrexate, cytarabine, thiotepa, and rituximab; NGR-hTNF, tumor necrosis factor-a coupled with NGR (μg/m^2); NR, not reported; OR, overall response; OS, overall survival; P, procarbazine (mg/m^2/day); PCNSL, primary central nervous system lymphoma; PEM, pemetrexed (mg/m^2); PFS, progression-free survival; POM, pomalidomide (mg); PPP, per-protocol population; PR, partial remission; pred, methylprednisolone (mg/m^2); R, rituximab (mg/m^2); R-MPL, rituximab, methotrexate, procarbazine and lomustine; RT, radiation therapy (dose used in Gy); SCT, stem cell transplant; T, temozolomide (mg/m^2); Ten, teniposide (mg/m^2); thio, thiotepa (mg/m^2); TIER, thiotepa in combination with ifosfamide, etoposide, and rituximab; TIR, tirabrutinib (mg/day); TMZ, temozolomide (g/m^2); V, vincristine (mg/m^2); 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
	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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Footnote

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References

1. Ferreri AJ, Marturano E. Primary CNS lymphoma. Best Pract Res Clin Haematol 2012;25:119-30.
2. Ostrom QT, Gittleman H, Fulop J, et al. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008-2012. Neuro Oncol 2015;17 Suppl 4:iv1-iv62.
3. Algazi AP, Kadoch C, Rubenstein JL. Biology and treatment of primary central nervous system lymphoma. Neurotherapeutics 2009;6:587-97.
4. Cazzola M. Introduction to a review series: the 2016 revision of the WHO classification of tumors of hematopoietic and lymphoid tissues. Blood 2016;127:2361-4.
5. Nakamura M, Shimada K, Ishida E, et al. Histopathology, pathogenesis and molecular genetics in primary central nervous system lymphomas. Histol Histopathol 2004;19:211-9.
6. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 2007;114:97-109.
7. Hattab EM, Martin SE, Al-Khatib SM, et al. Most primary central nervous system diffuse large B-cell lymphomas occurring in immunocompetent individuals belong to the nongerminal center subtype: a retrospective analysis of 31 cases. Mod Pathol 2010;23:235-43.
8. Bromberg JE, Breems DA, Kraan J, et al. CSF flow cytometry greatly improves diagnostic accuracy in CNS hematologic malignancies. Neurology 2007;68:1674-9.
9. Ikeguchi R, Shimizu Y, Shimizu S, et al. CSF and clinical data are useful in differentiating CNS inflammatory demyelinating disease from CNS lymphoma. Mult Scler 2018;24:1212-23.
10. Sasagawa Y, Akai T, Tachibana O, et al. Diagnostic value of interleukin-10 in cerebrospinal fluid for diffuse large B-cell lymphoma of the central nervous system. J Neurooncol 2015;121:177-83.
11. Nguyen-Them L, Costopoulos M, Tanguy ML, et al. The CSF IL-10 concentration is an effective diagnostic marker in immunocompetent primary CNS lymphoma and a potential prognostic biomarker in treatment-responsive patients. Eur J Cancer 2016;61:69-76.

12. Prasad V, Kaestner V. Nivolumab and pembrolizumab: Monoclonal antibodies against programmed cell death-1 (PD-1) that are interchangeable. Semin Oncol 2017;44:132-5.
13. Shah NN, Ahn KW, Litovich C, et al. Is autologous transplant in relapsed DLBCL patients achieving only a PET+ PR appropriate in the CAR T-cell era? Blood 2021;137:1416-23. Erratum in: Blood. 2021 May 20;137(20):2854-2855.
14. Onishi S, Kajiwara Y, Takayasu T, et al. Perfusion Computed Tomography Parameters Are Useful for Differentiating Glioblastoma, Lymphoma, and Metastasis. World Neurosurg 2018;119:e890-7.
15. Nabavizadeh SA, Vossough A, Hajmomenian M, et al. Neuroimaging in Central Nervous System Lymphoma. Hematol Oncol Clin North Am 2016;30:799-821.
16. Chen Y, Zhan A. Clinical value of magnetic resonance imaging in identifying multiple cerebral gliomas from primary central nervous system lymphoma. Oncol Lett 2019;18:593-8.
17. Chan CC, Rubenstein JL, Coupland SE, et al. Primary vitreoretinal lymphoma: a report from an International Primary Central Nervous System Lymphoma Collaborative Group symposium. Oncologist 2011;16:1589-99.
18. Morell AA, Shah AH, Cavallo C, et al. Diagnosis of primary central nervous system lymphoma: a systematic review of the utility of CSF screening and the role of early brain biopsy. Neurooncol Pract 2019;6:415-23.
19. Abrey LE, Batchelor TT, Ferreri AJ, et al. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. J Clin Oncol 2005;23:5034-43.
20. Yi C, Shi X, Yu D, et al. The combination of 13N-ammonia and 18F-FDG PET/CT in the identification of metabolic phenotype of primary human brain tumors. Nuklearmedizin 2019;58:272-8.
21. Zhou D, Bao C, Ye X, et al. Clinical and histological features of primary testicular diffuse large B-cell lymphoma: a single center experience in China. Oncotarget 2017;8:112384-9.
22. Önder E, Arıkök AT, Önder S, et al. Corticosteroid pre-treated primary CNS lymphoma: a detailed analysis of stereotactic biopsy findings and consideration of interobserver variability. Int J Clin Exp Pathol 2015;8:7798-808.
23. Baraniskin A, Deckert M, Schulte-Altedorneburg G, et al. Current strategies in the diagnosis of diffuse large B-cell lymphoma of the central nervous system. Br J Haematol 2012;156:421-32.
24. Hegde U, Filie A, Little RF, et al. High incidence of occult leptomeningeal disease detected by flow cytometry in newly diagnosed aggressive B-cell lymphomas at risk for central nervous system involvement: the role of flow cytometry versus cytology. Blood 2005;105:496-502.
25. Quijano S, López A, Manuel Sancho J, et al. Identification of leptomeningeal disease in aggressive B-cell non-Hodgkin's lymphoma: improved sensitivity of flow cytometry. J Clin Oncol 2009;27:1462-9.
26. Baraniskin A, Kuhnhenn J, Schlegel U, et al. Identification of microRNAs in the cerebrospinal fluid as marker for primary diffuse large B-cell lymphoma of the central nervous system. Blood 2011;117:3140-6.
27. Song Y, Zhang W, Zhang L, et al. Cerebrospinal Fluid IL-10 and IL-10/IL-6 as Accurate Diagnostic Biomarkers for Primary Central Nervous System Large B-cell Lymphoma. Sci Rep 2016;6:38671.
28. Rubenstein JL, Wong VS, Kadoch C, et al. CXCL13 plus interleukin 10 is highly specific for the diagnosis of CNS lymphoma. Blood 2013;121:4740-8.
29. Chapuy B, Roemer MG, Stewart C, et al. Targetable genetic features of primary testicular and primary central nervous system lymphomas. Blood 2016;127:869-81.
30. Nakamura T, Tateishi K, Niwa T, et al. Recurrent mutations of CD79B and MYD88 are the hallmark of primary central nervous system lymphomas. Neuropathol Appl Neurobiol 2016;42:279-90.
31. Akhter A, Masir N, Elyamany G, et al. Differential expression of Toll-like receptor (TLR) and B cell receptor (BCR) signaling molecules in primary diffuse large B-cell lymphoma of the central nervous system. J Neurooncol 2015;121:289-96.
32. Vater I, Montesinos-Rongen M, Schlesner M, et al. The mutational pattern of primary lymphoma of the central nervous system determined by whole-exome sequencing. Leukemia 2015;29:677-85.
33. Bruno A, Boisselier B, Labreche K, et al. Mutational analysis of primary central nervous system lymphoma. Oncotarget 2014;5:5065-75.
34. Montesinos-Rongen M, Godlewska E, Brunn A, et al. Activating L265P mutations of the MYD88 gene are common in primary central nervous system lymphoma. Acta Neuropathol 2011;122:791-2.
35. Braggio E, Van Wier S, Ojha J, et al. Genome-Wide

Analysis Uncovers Novel Recurrent Alterations in Primary Central Nervous System Lymphomas. Clin Cancer Res 2015;21:3986-94.
36. Grommes C, DeAngelis LM. Primary CNS Lymphoma. J Clin Oncol 2017;35:2410-8.
37. Ferreri AJM, Calimeri T, Lopedote P, et al. MYD88 L265P mutation and interleukin-10 detection in cerebrospinal fluid are highly specific discriminating markers in patients with primary central nervous system lymphoma: results from a prospective study. Br J Haematol 2021;193:497-505.
38. Bataille B, Delwail V, Menet E, et al. Primary intracerebral malignant lymphoma: report of 248 cases. J Neurosurg 2000;92:261-6.
39. Reni M, Ferreri AJ, Garancini MP, et al. Therapeutic management of primary central nervous system lymphoma in immunocompetent patients: results of a critical review of the literature. Ann Oncol 1997;8:227-34.
40. Bellinzona M, Roser F, Ostertag H, et al. Surgical removal of primary central nervous system lymphomas (PCNSL) presenting as space occupying lesions: a series of 33 cases. Eur J Surg Oncol 2005;31:100-5.
41. Labak CM, Holdhoff M, Bettegowda C, et al. Surgical Resection for Primary Central Nervous System Lymphoma: A Systematic Review. World Neurosurg 2019;126:e1436-48.
42. Yuan XG, Huang YR, Yu T, et al. Primary central nervous system lymphoma in China: a single-center retrospective analysis of 167 cases. Ann Hematol 2020;99:93-104.
43. Qian L, Tomuleasa C, Florian IA, et al. Advances in the treatment of newly diagnosed primary central nervous system lymphomas. Blood Res 2017;52:159-66.
44. Nelson DF, Martz KL, Bonner H, et al. Non-Hodgkin's lymphoma of the brain: can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG): RTOG 8315. Int J Radiat Oncol Biol Phys 1992;23:9-17.
45. Hottinger AF, DeAngelis LM, Yahalom J, et al. Salvage whole brain radiotherapy for recurrent or refractory primary CNS lymphoma. Neurology 2007;69:1178-82.
46. Gavrilovic IT, Hormigo A, Yahalom J, et al. Long-term follow-up of high-dose methotrexate-based therapy with and without whole brain irradiation for newly diagnosed primary CNS lymphoma. J Clin Oncol 2006;24:4570-4.
47. Kobayashi H, Yamaguchi S, Motegi H, et al. Long-Term Evaluation of Combination Treatment of Single Agent HD-MTX Chemotherapy up to Three Cycles and Moderate Dose Whole Brain Irradiation for Primary CNS Lymphoma. J Chemother 2019;31:35-41.
48. Chamberlain MC, Johnston SK. High-dose methotrexate and rituximab with deferred radiotherapy for newly diagnosed primary B-cell CNS lymphoma. Neuro Oncol 2010;12:736-44.
49. Pels H, Schmidt-Wolf IG, Glasmacher A, et al. Primary central nervous system lymphoma: results of a pilot and phase II study of systemic and intraventricular chemotherapy with deferred radiotherapy. J Clin Oncol 2003;21:4489-95.
50. Ferreri AJ, Reni M, Foppoli M, et al. High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial. Lancet 2009;374:1512-20.
51. Ferreri AJ, Cwynarski K, Pulczynski E, et al. Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial. Lancet Haematol 2016;3:e217-27.
52. Houillier C, Taillandier L, Dureau S, et al. Radiotherapy or Autologous Stem-Cell Transplantation for Primary CNS Lymphoma in Patients 60 Years of Age and Younger: Results of the Intergroup ANOCEF-GOELAMS Randomized Phase II PRECIS Study. J Clin Oncol 2019;37:823-33.
53. Thiel E, Korfel A, Martus P, et al. High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial. Lancet Oncol 2010;11:1036-47.
54. Wang A, Cirrone F, De Los Reyes FA, et al. High-dose methotrexate dosing strategy in primary central nervous system lymphoma. Leuk Lymphoma 2022;63:1348-55.
55. Suwinski R. Combination of immunotherapy and radiotherapy in the treatment of brain metastases from non-small cell lung cancer. J Thorac Dis 2021;13:3315-22.
56. Otani R, Yamada R, Kushihara Y, et al. Continuous intrathecal injection therapy of methotrexate is a therapeutic option in primary CNS lymphoma. J Clin Neurosci 2019;69:26-30.
57. Neuwelt E, Abbott NJ, Abrey L, et al. Strategies to advance translational research into brain barriers. Lancet Neurol 2008;7:84-96.
58. Butler RW, Hill JM, Steinherz PG, et al. Neuropsychologic effects of cranial irradiation, intrathecal methotrexate, and systemic methotrexate in childhood cancer. J Clin Oncol

1994;12:2621-9.
59. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002;346:235-42.
60. Batchelor TT, Grossman SA, Mikkelsen T, et al. Rituximab monotherapy for patients with recurrent primary CNS lymphoma. Neurology 2011;76:929-30.
61. Holdhoff M, Ambady P, Abdelaziz A, et al. High-dose methotrexate with or without rituximab in newly diagnosed primary CNS lymphoma. Neurology 2014;83:235-9.
62. Feugier P, Virion JM, Tilly H, et al. Incidence and risk factors for central nervous system occurrence in elderly patients with diffuse large-B-cell lymphoma: influence of rituximab. Ann Oncol 2004;15:129-33.
63. Schmitt AM, Herbrand AK, Fox CP, et al. Rituximab in primary central nervous system lymphoma-A systematic review and meta-analysis. Hematol Oncol 2019;37:548-57.
64. Bromberg JEC, Issa S, Bakunina K, et al. Rituximab in patients with primary CNS lymphoma (HOVON 105/ALLG NHL 24): a randomised, open-label, phase 3 intergroup study. Lancet Oncol 2019;20:216-28.
65. Scordo M, Wang TP, Ahn KW, et al. Outcomes Associated With Thiotepa-Based Conditioning in Patients With Primary Central Nervous System Lymphoma After Autologous Hematopoietic Cell Transplant. JAMA Oncol 2021;7:993-1003.
66. Lee JY, Paik JH, Suh KJ, et al. R-MPV followed by high-dose chemotherapy with thiotepa-based and autologous stem cell transplantation for newly diagnosed primary central nervous system lymphoma: a single-center experience. Blood Res 2021;56:285-92.
67. Schorb E, Fox CP, Fritsch K, et al. High-dose thiotepa-based chemotherapy with autologous stem cell support in elderly patients with primary central nervous system lymphoma: a European retrospective study. Bone Marrow Transplant 2017;52:1113-9.
68. Alnahhas I, Jawish M, Alsawas M, et al. Autologous Stem-Cell Transplantation for Primary Central Nervous System Lymphoma: Systematic Review and Meta-analysis. Clin Lymphoma Myeloma Leuk 2019;19:e129-41.
69. Friedman HS, Kerby T, Calvert H. Temozolomide and treatment of malignant glioma. Clin Cancer Res 2000;6:2585-97.
70. Enting RH, Demopoulos A, DeAngelis LM, et al. Salvage therapy for primary CNS lymphoma with a combination of rituximab and temozolomide. Neurology 2004;63:901-3.
71. Kurzwelly D, Glas M, Roth P, et al. Primary CNS lymphoma in the elderly: temozolomide therapy and MGMT status. J Neurooncol 2010;97:389-92.
72. Makino K, Nakamura H, Hide T, et al. Salvage treatment with temozolomide in refractory or relapsed primary central nervous system lymphoma and assessment of the MGMT status. J Neurooncol 2012;106:155-60.
73. Camilleri-Broët S, Martin A, Moreau A, et al. Primary central nervous system lymphomas in 72 immunocompetent patients: pathologic findings and clinical correlations. Groupe Ouest Est d'étude des Leucénies et Autres Maladies du Sang (GOELAMS). Am J Clin Pathol 1998;110:607-12.
74. Law SC, Hoang T, O'Rourke K, et al. Successful treatment of Epstein-Barr virus-associated primary central nervous system lymphoma due to post-transplantation lymphoproliferative disorder, with ibrutinib and third-party Epstein-Barr virus-specific T cells. Am J Transplant 2021;21:3465-71.
75. Soussain C, Choquet S, Blonski M, et al. Ibrutinib monotherapy for relapse or refractory primary CNS lymphoma and primary vitreoretinal lymphoma: Final analysis of the phase II 'proof-of-concept' iLOC study by the Lymphoma study association (LYSA) and the French oculo-cerebral lymphoma (LOC) network. Eur J Cancer 2019;117:121-30.
76. Grommes C, Tang SS, Wolfe J, et al. Phase 1b trial of an ibrutinib-based combination therapy in recurrent/refractory CNS lymphoma. Blood 2019;133:436-45.
77. Palumbo A, Rajkumar SV, Dimopoulos MA, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia 2008;22:414-23.
78. Vu K, Mannis G, Hwang J, et al. Low-dose lenalidomide maintenance after induction therapy in older patients with primary central nervous system lymphoma. Br J Haematol 2019;186:180-3.
79. Rubenstein JL, Geng H, Fraser EJ, et al. Phase 1 investigation of lenalidomide/rituximab plus outcomes of lenalidomide maintenance in relapsed CNS lymphoma. Blood Adv 2018;2:1595-607.
80. Terziev D, Hutter B, Klink B, et al. Nivolumab maintenance after salvage autologous stem cell transplantation results in long-term remission in multiple relapsed primary CNS lymphoma. Eur J Haematol 2018;101:115-8.
81. Nayak L, Iwamoto FM, LaCasce A, et al. PD-1 blockade with nivolumab in relapsed/refractory primary central nervous system and testicular lymphoma. Blood

2017;129:3071-3.
82. Hoang-Xuan K, Houot R, Soussain C, et al. First Results of the Acsé Pembrolizumab Phase II in the Primary CNS Lymphoma (PCNSL) Cohort. Blood 2020;136:15-6.
83. Frigault MJ, Dietrich J, Martinez-Lage M, et al. Tisagenlecleucel CAR T-cell therapy in secondary CNS lymphoma. Blood 2019;134:860-6.
84. Abramson JS, McGree B, Noyes S, et al. Anti-CD19 CAR T Cells in CNS Diffuse Large-B-Cell Lymphoma. N Engl J Med 2017;377:783-4.
85. Ahmed G, Hamadani M, Shah NN. CAR T-cell therapy for secondary CNS DLBCL. Blood Adv 2021;5:5626-30.
86. Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant 2019;25:625-38.
87. Frigault MJ, Dietrich J, Gallagher K, et al. Safety and efficacy of tisagenlecleucel in primary CNS lymphoma: a phase 1/2 clinical trial. Blood 2022;139:2306-15.
88. DeAngelis LM, Yahalom J, Thaler HT, et al. Combined modality therapy for primary CNS lymphoma. J Clin Oncol 1992;10:635-43.
89. Glass J, Gruber ML, Cher L, et al. Preirradiation methotrexate chemotherapy of primary central nervous system lymphoma: long-term outcome. J Neurosurg 1994;81:188-95.
90. Schultz C, Scott C, Sherman W, et al. Preirradiation chemotherapy with cyclophosphamide, doxorubicin, vincristine, and dexamethasone for primary CNS lymphomas: initial report of radiation therapy oncology group protocol 88-06. J Clin Oncol 1996;14:556-64.
91. O'Neill BP, Wang CH, O'Fallon JR, et al. Primary central nervous system non-Hodgkin's lymphoma (PCNSL): survival advantages with combined initial therapy? A final report of the North Central Cancer Treatment Group (NCCTG) Study 86-72-52. Int J Radiat Oncol Biol Phys 1999;43:559-63.
92. Mead GM, Bleehen NM, Gregor A, et al. A medical research council randomized trial in patients with primary cerebral non-Hodgkin lymphoma: cerebral radiotherapy with and without cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy. Cancer 2000;89:1359-70.
93. O'Brien P, Roos D, Pratt G, et al. Phase II multicenter study of brief single-agent methotrexate followed by irradiation in primary CNS lymphoma. J Clin Oncol 2000;18:519-26.
94. Abrey LE, Yahalom J, DeAngelis LM. Treatment for primary CNS lymphoma: the next step. J Clin Oncol 2000;18:3144-50.
95. Ferreri AJ, Reni M, Dell'Oro S, et al. Combined treatment with high-dose methotrexate, vincristine and procarbazine, without intrathecal chemotherapy, followed by consolidation radiotherapy for primary central nervous system lymphoma in immunocompetent patients. Oncology 2001;60:134-40.
96. DeAngelis LM, Seiferheld W, Schold SC, et al. Combination chemotherapy and radiotherapy for primary central nervous system lymphoma: Radiation Therapy Oncology Group Study 93-10. J Clin Oncol 2002;20:4643-8.
97. Poortmans PM, Kluin-Nelemans HC, Haaxma-Reiche H, et al. High-dose methotrexate-based chemotherapy followed by consolidating radiotherapy in non-AIDS-related primary central nervous system lymphoma: European Organization for Research and Treatment of Cancer Lymphoma Group Phase II Trial 20962. J Clin Oncol 2003;21:4483-8.
98. Abrey LE, Moskowitz CH, Mason WP, et al. Intensive methotrexate and cytarabine followed by high-dose chemotherapy with autologous stem-cell rescue in patients with newly diagnosed primary CNS lymphoma: an intent-to-treat analysis. J Clin Oncol 2003;21:4151-6.
99. Batchelor T, Carson K, O'Neill A, et al. Treatment of primary CNS lymphoma with methotrexate and deferred radiotherapy: a report of NABTT 96-07. J Clin Oncol 2003;21:1044-9.
100. Herrlinger U, Küker W, Uhl M, et al. NOA-03 trial of high-dose methotrexate in primary central nervous system lymphoma: final report. Ann Neurol 2005;57:843-7.
101. Colombat P, Lemevel A, Bertrand P, et al. High-dose chemotherapy with autologous stem cell transplantation as first-line therapy for primary CNS lymphoma in patients younger than 60 years: a multicenter phase II study of the GOELAMS group. Bone Marrow Transplant 2006;38:417-20.
102. Illerhaus G, Marks R, Ihorst G, et al. High-dose chemotherapy with autologous stem-cell transplantation and hyperfractionated radiotherapy as first-line treatment of primary CNS lymphoma. J Clin Oncol 2006;24:3865-70.
103. Morris PG, Correa DD, Yahalom J, et al. Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: final results and long-term outcome. J Clin Oncol

2013;31:3971-9.
104. Rubenstein JL, Hsi ED, Johnson JL, et al. Intensive chemotherapy and immunotherapy in patients with newly diagnosed primary CNS lymphoma: CALGB 50202 (Alliance 50202). J Clin Oncol 2013;31:3061-8.
105. Omuro A, Chinot O, Taillandier L, et al. Methotrexate and temozolomide versus methotrexate, procarbazine, vincristine, and cytarabine for primary CNS lymphoma in an elderly population: an intergroup ANOCEF-GOELAMS randomised phase 2 trial. Lancet Haematol 2015;2:e251-9.
106. Omuro A, Correa DD, DeAngelis LM, et al. R-MPV followed by high-dose chemotherapy with TBC and autologous stem-cell transplant for newly diagnosed primary CNS lymphoma. Blood 2015;125:1403-10.
107. Glass J, Won M, Schultz CJ, et al. Phase I and II Study of Induction Chemotherapy With Methotrexate, Rituximab, and Temozolomide, Followed By Whole-Brain Radiotherapy and Postirradiation Temozolomide for Primary CNS Lymphoma: NRG Oncology RTOG 0227. J Clin Oncol 2016;34:1620-5.
108. Illerhaus G, Kasenda B, Ihorst G, et al. High-dose chemotherapy with autologous haemopoietic stem cell transplantation for newly diagnosed primary CNS lymphoma: a prospective, single-arm, phase 2 trial. Lancet Haematol 2016;3:e388-97.
109. Kasenda B, Ihorst G, Schroers R, et al. High-dose chemotherapy with autologous haematopoietic stem cell support for relapsed or refractory primary CNS lymphoma: a prospective multicentre trial by the German Cooperative PCNSL study group. Leukemia 2017;31:2623-9.
110. Fritsch K, Kasenda B, Schorb E, et al. High-dose methotrexate-based immuno-chemotherapy for elderly primary CNS lymphoma patients (PRIMAIN study). Leukemia 2017;31:846-52.
111. Adhikari N, Biswas A, Gogia A, et al. A prospective phase II trial of response adapted whole brain radiotherapy after high dose methotrexate based chemotherapy in patients with newly diagnosed primary central nervous system lymphoma-analysis of acute toxicity profile and early clinical outcome. J Neurooncol 2018;139:153-66.
112. Wu J, Duan L, Zhang L, et al. Fotemustine, teniposide and dexamethasone versus high-dose methotrexate plus cytarabine in newly diagnosed primary CNS lymphoma: a randomised phase 2 trial. J Neurooncol 2018;140:427-34.
113. Tun HW, Johnston PB, DeAngelis LM, et al. Phase 1 study of pomalidomide and dexamethasone for relapsed/refractory primary CNS or vitreoretinal lymphoma. Blood 2018;132:2240-8.
114. Ghesquieres H, Chevrier M, Laadhari M, et al. Lenalidomide in combination with intravenous rituximab (REVRI) in relapsed/refractory primary CNS lymphoma or primary intraocular lymphoma: a multicenter prospective 'proof of concept' phase II study of the French Oculo-Cerebral lymphoma (LOC) Network and the Lymphoma Study Association (LYSA)†. Ann Oncol 2019;30:621-8.
115. Ferreri AJM, Calimeri T, Conte GM, et al. R-CHOP preceded by blood-brain barrier permeabilization with engineered tumor necrosis factor-α in primary CNS lymphoma. Blood 2019;134:252-62.
116. Dietrich J, Versmee L, Drappatz J, et al. Pemetrexed in Recurrent or Progressive Central Nervous System Lymphoma: A Phase I Multicenter Clinical Trial. Oncologist 2020;25:747-e1273.
117. Ferreri AJM, Calimeri T, Ponzoni M, et al. Improving the antitumor activity of R-CHOP with NGR-hTNF in primary CNS lymphoma: final results of a phase 2 trial. Blood Adv 2020;4:3648-58.
118. Seidel S, Pels H, Schlömer S, et al. Twenty-year follow-up of a pilot/phase II trial on the Bonn protocol for primary CNS lymphoma. Neurology 2020;95:e3138-44.
119. Chiesa S, Hohaus S, Falcinelli L, et al. Chemoradiotherapy with temozolomide after high-dose methotrexate for primary CNS lymphoma: a multicenter phase I study of a response-adapted strategy. Ann Hematol 2020;99:2367-75.
120. Narita Y, Nagane M, Mishima K, et al. Phase I/II study of tirabrutinib, a second-generation Bruton's tyrosine kinase inhibitor, in relapsed/refractory primary central nervous system lymphoma. Neuro Oncol 2021;23:122-33.
121. Fox CP, Ali AS, McIlroy G, et al. A phase 1/2 study of thiotepa-based immunochemotherapy in relapsed/refractory primary CNS lymphoma: the TIER trial. Blood Adv 2021;5:4073-82.
122. Ferreri AJM, Cwynarski K, Pulczynski E, et al. Long-term efficacy, safety and neurotolerability of MATRix regimen followed by autologous transplant in primary CNS lymphoma: 7-year results of the IELSG32 randomized trial. Leukemia 2022;36:1870-8.
123. Abrey LE, Ben-Porat L, Panageas KS, et al. Primary central nervous system lymphoma: the Memorial Sloan-Kettering Cancer Center prognostic model. J Clin Oncol 2006;24:5711-5.
124. Ferreri AJ, Blay JY, Reni M, et al. Prognostic scoring system for primary CNS lymphomas: the International

Extranodal Lymphoma Study Group experience. J Clin Oncol 2003;21:266-72.
125. van der Meulen M, Dirven L, Bakunina K, et al. MMSE is an independent prognostic factor for survival in primary central nervous system lymphoma. J Neurooncol 2021;152:357-62.

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