Primary Central Nervous System Lymphomas

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KEYWORDS

• Primary central nervous system lymphoma • High-dose methotrexate
• Whole-brain radiation therapy • Thiotepa • Autologous stem cell transplant

KEY POINTS

- Most of the primary central nervous system lymphomas (PCNSL) are diffuse large B-cell lymphomas.
- Genomic analysis has demonstrated Toll-like receptor (TLR) signaling as a result of *MYD88* mutation and frequent concurrent B-cell receptor (BCR) pathway activation as mechanisms of pathogenesis of PCNSL.
- Age and performance status are independently associated with the prognosis of PCNSL.
- High-dose methotrexate in combination with chemotherapy is associated with improved outcomes.
- Consolidation with high-dose chemotherapy and autologous transplant, chemotherapy alone, or whole-brain radiation reduces recurrence risk.

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is an aggressive variant of extranodal non-Hodgkin lymphoma (NHL) arising within the brain, leptomeninges, eyes, or spinal cord, in the absence of systemic disease.[1] Unlike other primary brain tumors like glioblastoma, PCNSL has a favorable response to treatment. However, the prognosis is inferior to that of other subtypes of NHL, including other extranodal NHL. The 5- and 10-year relative survival rates for PCNSL are 35.2% and 27.5%, respectively.[2] The diagnosis and management of PCNSL differ from that of other primary brain cancers and systemic NHL.

EPIDEMIOLOGY

PCNSL is rare brain cancer and accounts for 6% of malignant primary central nervous system (CNS) tumors. Approximately 1500 new cases of PCNSL are diagnosed each

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year in the United States. The number of cases is expected to increase further with the aging of the US population.[2] The median age at diagnosis is 66, and PCNSL is slightly more common among men. Congenital or acquired immunodeficiency is the only established risk factor for PCNSL. The incidence of PCNSL as a result of human immunodeficiency virus (HIV) infections has decreased significantly since the 2000s due to effective treatments and decreased incidence of AIDS. Since 2000, there has been an increase in the incidence of PCNSL, especially in the elderly.

PATHOLOGY

Approximately 90% of PCNSL are diffuse large B-cell lymphomas (DLBCLs), with the remainder consisting of T-cell lymphomas, low-grade lymphomas, or Burkitt's lymphomas.[3] Primary CNS DLBCL is highly proliferative tumor cells clustered in the perivascular space, with reactive lymphocytes, macrophages, and activated microglial cells intermixed with the tumor cells. Malignant cells express pan–B-cell markers, including CD19, CD20, CD22, and CD79a. The molecular mechanisms underlying transformation and localization to the CNS are poorly understood.[4,5] Systemic DLBCL can be classified into 3 molecular subclasses by gene expression profiling including germinal center B-cell-like lymphoma (GCB), and activated B-cell–like (ABC) lymphoma and type 3 large B-cell lymphoma. In general, the ABC subtype is associated with an inferior prognosis than the GCB subtype. The ABC gene expression profile subtype accounts for the majority (>95% in 1 series) of primary CNS DLBCL cases.[6]

Genomic analysis of PCNSL has demonstrated a high prevalence of *MYD88* and *CD79B* mutations, less frequently *CARD11* and *TNFAIP3 mutations,* and other genetic alterations consistent with activation of the B-cell receptor (BCR), toll-like receptor (TLR), and nuclear factor-κB pathways in greater than 90% of cases. Other genes with mutations in PCNSL include *PIM1, BTG2, PRDMI, TOX,* and *IRF4.* Inactivation of *CDKN2A* has also been noted. These observations have provided insight into potential targets for clinical trials in PCNSL.[4,7]

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The presenting symptoms and signs of PCNSL are variable and depend on the location of the nervous system involved. Patients can present with focal neurologic deficits, neuropsychiatric signs, symptoms of raised intracranial pressure, or ocular symptoms.[8] Seizures occur in less than 14% of patients and are less common than with other types of brain tumors, likely because PCNSL involves predominantly subcortical and deep white matter. Concurrent leptomeningeal and ocular involvement occurs in approximately 15% to 20% and 5% to 20% of PCNSL patients, respectively. Presenting symptoms of ocular involvement include blurred vision and floaters. Unlike patients with systemic NHL, PCNSL patients rarely manifest B symptoms like fever, night sweats, or weight loss.

A gadolinium-enhanced brain magnetic resonance imaging (MRI) is the most sensitive radiographic study for the detection of PCNSL. Most PCNSL patients (66%) present with a single brain mass which is homogeneously enhancing on postcontrast T1 images.

The diagnosis of PCNSL is preferably made by brain biopsy. In case a brain biopsy cannot be performed, the diagnosis can be made by the analysis of cerebrospinal fluid (CSF) or vitreous aspirate in patients with ocular involvement. However, given the possible delay in diagnosis and treatment with the latter 2 methods, prompt brain biopsy is advised in cases that are surgically accessible.[9] Corticosteroids should be

avoided if possible before a biopsy, given the risk of disrupting cellular morphology, resulting in a nondiagnostic pathologic specimen.

In case of diagnostic difficulties such as nondiagnostic brain biopsy, cytology, or flow cytometry from CSF and vitreous fluid, *MYD88*^{L265P} PCR can be helpful in making the diagnosis.[10–12]

A thorough diagnostic evaluation is needed to establish the extent of the lymphoma and to confirm localization to the CNS. Physical examination should consist of a comprehensive neurologic examination as well as the examination of the body for lymph nodes and testicular masses in men. A lumbar puncture should be performed if not contraindicated, and CSF should be assessed by flow cytometry, cytology, and immunoglobulin heavy-chain gene rearrangement. Systemic disease must be excluded to establish a diagnosis of *primary* CNS lymphoma, and computed tomography/positron emission tomography scans of the chest, abdomen, and pelvis are advised to exclude occult systemic disease. Bone marrow biopsy can be considered if high suspicion. Involvement of the optic nerve, retina, or vitreous humor should be evaluated with a comprehensive eye evaluation including a slit-lamp examination. Blood tests should include a complete blood count, a basic metabolic panel, liver function tests, serum lactate dehydrogenase, and HIV serology.[13] As PCNSL is a multicompartmental disease involving the brain, spinal cord, CSF, and eyes, the IPCG recommends an extent-of-disease evaluation that enables clinicians to follow the response to therapy in each compartment as well as with attention to corticosteroid dosing.[13]

Two prognostic scoring systems have been developed specifically for PCNSL; the International Extranodal Lymphoma Study Group (IELSG) scoring system and the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score.[14,15] The IELSG identified age greater than 60 years, Eastern Cooperative Oncology Group performance status greater than 1, elevated serum lactate dehydrogenase level, elevated CSF protein concentration, and involvement of deep regions of the brain as independent predictors of poor prognosis. Patients are divided into 3 groups; low-risk (with 0–1 factors), intermediate-risk (2–3 factors), and high-risk (4–5 factors). In the MSKCC prognostic model, PCNSL patients are divided into 3 groups based on age and Karnofsky Performance Status (KPS) score only: (1) <50 years of age regardless of the KPS, (2) ≥50 years with a KPS score of ≥70, and (3) ≥50 years with a KPS score <70. Based on these 3 divisions, significant differences in overall and progression-free survival were observed with both scoring systems.

UPFRONT TREATMENT

Treatment of newly diagnosed PCNSL consists of an induction phase and a consolidation phase. Induction therapy consists of chemotherapy with the objective of achieving a complete response/remission. The goal of consolidation is to prevent disease recurrence. Defining response to treatment in PCNSL requires the assessment of all documented sites of involvement (brain, CSF, eye) on the baseline assessment. The IPCG has established response criteria that have been adopted into most prospective clinical trials of PCNSL (**Table 1**).[13]

Resection is not part of the standard treatment approach for PCNSL given the multifocal, deep, and invasive nature of this cancer and brain biopsy is favored.[16] There have been some recent reports that indicate that gross total resection in PCNSL patients may be associated with better prognosis.[17] However, given the chemosensitivity of the disease and the retrospective or post hoc nature of the reports, resection is not favored unless to help with neurologic symptoms and mass effect.

Table 1
International PCNSL Collaborative Group Consensus Guidelines for the Assessment of Response in PCNSL (adapted from reference[9])

Response	Brain Imaging	Steroid Dose	Ophthalmologic Examination	CSF Cytology
Complete response	No contrast-enhancing disease	None	Normal	Negative
Unconfirmed complete response	No contrast-enhancing disease	Any	Normal	Negative
	Minimal enhancing disease	Any	Minor RPE abnormality	Negative
Partial response	50% decrease in enhancement	NA	Normal or minor RPE abnormality	Negative
	No contrast-enhancing disease	NA	Decrease in vitreous cells or retinal infiltrate	Persistent or suspicious
Progressive disease	25% increase in enhancing disease	NA	Recurrent or new disease	Recurrent or positive
	Any new site of disease			
Stable disease	All scenarios not covered by responses above			

Abbreviations: CSF, cerebrospinal fluid; NA, not applicable; PCNSL, primary central nervous system lymphoma; RPE, retinal pigment epithelium.

Modified from 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;23:5034-5043.

Standard of care induction and consolidation treatment of PCNSL has yet to be defined. Historically, PCNSL was treated only with WBRT at doses ranging from 36 to 45 Gy, which resulted in a high proportion of radiographic responses but also early relapses within less than a year. Given the lack of durable responses to radiation and the risk of neurotoxicity associated with this modality of therapy, WBRT alone is no longer a recommended treatment of patients with newly diagnosed PCNSL and is considered for consolidation or salvage. Additionally, PCNSL is an infiltrative, multifocal disease, so focal radiation or radiosurgery is not recommended. The most effective treatment of PCNSL is intravenous, high-dose methotrexate (HD-MTX) in combination with other chemotherapeutic agents. Variable doses and schedules of HD-MTX have been used, but in general, doses of 3 g/m^2 or greater delivered as an initial bolus followed by an infusion over 3 hours, administered every 10 to 21 days, is recommended for adequate brain and CSF penetration.[18] Additionally, it has been shown that longer duration of induction chemotherapy with HD-MTX (>6 cycles) results in higher proportion of complete responses.[19,20] The role of additional chemotherapeutic agents has been studied in the context of several single-arm and randomized phase 2 trials.[20,21] In a phase 2 trial conducted by IELSG (IELSG20), 79 PCNSL patients were randomized to receive induction therapy with either HD-MTX or HD-MTX in combination with cytarabine followed by consolidative WBRT in all. The HD-MTX and cytarabine arm demonstrated a higher number of complete responses (46% vs 18%) and a superior 3-year OS.[22] The IELSG conducted a follow-up, randomized, phase 2 trial in 219 newly diagnosed PCNSL patients using the HD-MTX and cytarabine combination from the IELSG20 study as a control arm. In this study (IELSG32), 3 different induction chemotherapy regimens were compared: HD-MTX and cytarabine (arm A), HD-MTX, cytarabine, and rituximab (arm B), and HD-MTX, cytarabine (Ara-C), thiotepa, and rituximab (MATRix) (arm C). In this study, the combination of the 4 drugs (MATRix) in arm C was superior to the other arms in terms of complete response (49% in arm C than 23% in arm A and 30% in arm B) and overall response (87% in arm C than 40% in arm A and 51% in arm B) proportions.[23] Other induction chemotherapy regimens that have been studied in the context of multicenter trials include the HD-MTX, temozolomide, and rituximab (MTR) regimen[21]; the rituximab, HD-MTX, procarbazine, and vincristine (R-MPV) regimen[19]; and the rituximab, HD-MTX, carmustine (BCNU), teniposide (Vumon), and prednisolone (R-MBVP) regimen.[24] In addition to different chemotherapeutic agents, these different induction regimens also include different doses and schedules of MTX. Because there have been no head-to-head comparisons of these induction chemotherapy regimens in randomized trials for newly diagnosed PCNSL patients, there is no compelling rationale at this time to select one over the other.

The role of rituximab which is an anti-CD20 monoclonal antibody is controversial in newly diagnosed PCNSL. Despite being a large molecular and its limited CSF penetration, radiographic responses have been observed in relapsed/refractory PCNSL patients treated with rituximab.[25] Also, historical comparisons have indicated that the complete response rates are higher with induction regimens that include rituximab than those that don't.[26] The IESLG32 trial demonstrated in a prospective, randomized phase 2 setting that the addition of rituximab to HD-MTX and cytarabine led to improved complete and overall response rates although this did not meet criteria for statistical significance. Regardless, there was a significant improvement in progression-free and overall survival.[23] A randomized phase 3 trial did not meet the primary endpoint of improvement in event-free survival with rituximab at 1 year (49% vs 52%), although younger patients seemed to benefit.[27] Here, the authors defined "event" as not achieving a complete response, or progression or death. A

meta-analysis including data from the 343 patients enrolled in both randomized trials suggested the benefit of rituximab on progression-free survival.[28] A retrospective review of 1002 patients showed longer overall survival in patients receiving rituximab on a univariate analysis.[29] Most patients receiving rituximab were significantly younger with higher performance status, and the association was not confirmed in multivariate analysis. For these reasons, the precise role of rituximab in the management of newly diagnosed PCNSL remains undefined.

The options for consolidation include WBRT, chemotherapy alone, or high-dose chemotherapy followed by autologous stem cell transplantation (HDT/ASCT). There is increasing data on the risk of delayed neurotoxicity particularly with combined-modality treatment that includes HD-MTX and WBRT, especially in elderly patients.[30] Several trials have assessed whether WBRT can be eliminated from the management of PCNSL. In a multicenter, phase 3 trial, 318 patients were randomized to receive HD-MTX–based chemotherapy with or without consolidative WBRT.[31,32] Intent-to-treat analysis revealed that patients treated with chemoradiation achieved prolonged progression-free survival (PFS) but no improvement in OS, demonstrating that the elimination of WBRT from the treatment regimen did not compromise OS. Another approach studied is using lower doses of consolidative WBRT to determine if it is as effective and less toxic. In a multicenter phase 2 study, no significant neurocognitive decline was observed after consolidative reduced-dose WBRT (23.4 Gy) in patients who had achieved a complete response to induction chemotherapy including HD-MTX.[19] The promising results from this study led to a randomized phase 2 trial conducted by the NRG of R-MPV-A (rituximab, HD-MTX, procarbazine, vincristine, cytarabine) with or without reduced dose WBRT. This study met its primary endpoint and demonstrated improved 2 year PFS on the reduced dose WBRT arm (NCT1399372) although the data for long-term neurotoxicity and overall survival are yet to mature.[33] High dose chemotherapy and autologous stem cell transplant (HDT-ASCT) is being increasingly used for consolidation in appropriate patients with newly diagnosed PCNSL.[34,35] Conditioning regimens including thiotepa have demonstrated the most encouraging results. In a multicenter phase 2 study, 79 patients were treated with induction therapy with MATRix, followed by carmustine and thiotepa conditioning before ASCT in whom the overall response rate was 91% with a 2-year OS of 87%. Toxicities were manageable and treatment-related deaths occurred in less than 10% of patients. Two randomized, multicenter, phase 2 trials compared WBRT and HDT/ASCT for consolidation in newly diagnosed PCNSL patients. The IESLG32 demonstrated that both modalities are equally effective in patients $\leq$ 70 years of age with 2-year-progression-free survival of 80% in the WBRT arm and 69% in the HDT/ASCT arm.[36] The PRECIS study conducted by the ANOCEF-GOELAMS in patients $\leq$60 years of age demonstrated favorable 2-year-progression-free survival rate on the HDT/ASCT arm at 87% than 63% on the WBRT arm, although the HDT/ASCT-associated mortality in this study was slightly higher at 11%.[37] Both trials prospectively evaluated neurocognitive function over time, and at 2 to 3 years of follow-up, objective cognitive decline was noted in patients receiving WBRT and improvement in those undergoing HDT/ASCT. These results demonstrated at least comparable if not better results with HDT/ASCT to WBRT. The risk-benefit ratio of neurocognitive worsening from WBRT versus the treatment-associated mortality with HDT/ASCT should be weighed in making the decision regarding consolidative treatment.

Nonmyeloablative chemotherapy is also being studied for consolidation especially to concerns of HDT/ASCT related morbidity and mortality, and the fact that this approach is more suited for young and fit patients. A phase 2 study (CALGB 50202)

including 44 patients treated with MT-R followed by high-dose infusional etoposide and cytarabine (EA) demonstrated an encouraging 2 year PFS rate of 57%.[20] Based on these results, the Alliance cooperative group conducted a randomized study of patients receiving MTR-A for induction followed by consolidative thiotepa-based ASCT versus nonmyeloablative chemotherapy with EA. In this study, the median PFS was superior on the ASCT arm, although there was a statistically higher number of progressors on the EA arm with induction chemotherapy before consolidation.

In general, due to the impact of WBRT on cognition and quality of life, full-dose WBRT is not preferred for newly diagnosed PCNSL patients. Consolidation with HCT-ASCT is considered in the appropriate patient.

ELDERLY PATIENTS WITH PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

Elderly patients account for more than half of all the subjects diagnosed with PCNSL.[2] The risk of neurotoxicity is highest in this population and survival is also poor in this population than younger patients. In fact, despite optimization of treatment regimens over the last few decades, these efforts have not resulted in an improvement in overall survival for most elderly patients, particularly those over 70 years of age.[38] Most of the PCNSL patients over 60 years of age develop clinical neurotoxicity after treatment with a WBRT-containing regimen, and some of these patients die of treatment-related complications rather than recurrent disease.[39] Several studies have indicated that HD-MTX at doses of 3.5 to 8 g/m^2 is well tolerated in elderly patients with manageable World Health Organization grade 3 or 4 renal and hematologic toxicity.[40] A meta-analysis of 783 PCNSL patients greater than 60 years of age demonstrated that regimens including HD-MTX are associated with improved survival.[41] Another retrospective study of 244 elderly PCNSL patients demonstrated that higher relative dose-intensity of HD-MTX was associated with improved progression-free and overall survival.[42] Here, the authors also showed that older patients receiving HD-MTX-based induction and consolidation had outcomes similar to younger patients. In a multicenter phase 2 trial of chemotherapy alone in 98 elderly patients with PCNSL randomized to receive three 28-day cycles of either MPV-A (HD-MTX, procarbazine, vincristine, and cytarabine [Ara-C]) or MT (MTX and temozolomide), trends favored the MPV-A regimen over the simpler, less toxic MT regimen with respect to complete response rate, PFS, and OS, although none of these differences were statistically significant.[43] Subsequent studies suggest that the addition of rituximab to both MPV and MT could increase the radiographic response rate. Other nonrandomized studies have demonstrated the feasibility of HD-MTX (8 g/m^2) and multiagent immunochemotherapy consisting of rituximab, MTX, procarbazine, and lomustine for elderly patients with newly diagnosed PCNSL.[44,45] Aggressive treatments and consolidation are typically not feasible in most elderly patients, but these can be carefully considered in a select subgroup. A retrospective review of 52 elderly ($\geq$65 years) patients treated with HDT/ASCT demonstrated 2-year progression-free survival and overall survival rates of 62% and 71%, respectively, with 4% HDT/ASCT-related mortality.[46] In a pilot prospective study of HDT/ASCT in 14 patients, there were no treatment-related deaths. There is an ongoing phase 2 trial of the safety, feasibility, and efficacy of age-adjusted HDT/ASCT in elderly (>65 years of age) and fit PCNSL patients in a multicenter setting.[47] Given the multiple factors in consideration including performance status, concurrent medical comorbidities, organ, and bone marrow function as well as a neurocognitive baseline, there is no standard of care established for elderly patients (>60 years of age) with newly diagnosed PCNSL, but deferral of WBRT and utilization of chemotherapeutic approaches is the primary approach recommended by most experts.

REFRACTORY AND RELAPSED PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

Despite high initial response rates with HD-MTX-based induction therapy, approximately 50% of patients with PCNSL relapse particularly within the first 2 years. Additionally, 15% to 25% of PCNSL patients have HD-MTX refractory disease. Prognosis of relapsed/refractory PCNSL is poor, with a limited number of prospective phase 2 studies for guidance on the management of this patient population. In a study of 256 patients with relapsed/refractory PCNSL, relapse was asymptomatic in 25% of patients and was identified on serial surveillance imaging,[48] which highlights the importance of surveillance imaging as recommended by the IPCG. Although relapses in PCNSL are predominantly within the CNS, relapses in extraneural organs are reported in up to 17% of patients. Late relapses also appear to occur more commonly in primary CNS DLBCL versus systemic DLBCL.[49] Rechallenge with HD-MTX is effective in patients who had previously responded to this agent. In a multicenter, retrospective study of 22 relapsed PCNSL patients with a history of prior response to HD-MTX, 91% had a radiographic response to the first salvage treatment with HD-MTX, and 100% to second salvage treatment. The median OS from the first salvage treatment was 61.9 months.[50]

In patients who have not previously been treated with HDT/ASCT, this is also an option at the time of relapse. In a phase 2 trial of 43 patients with relapsed/refractory PCNSL, salvage therapy with high-dose cytarabine and etoposide was followed by HDT/ASCT with a conditioning regimen consisting of thiotepa, busulfan, and cyclophosphamide. Twenty-six of the 27 patients who proceeded to ASCT had a complete response, and the median PFS and median OS in this group were 41.1 and 58.6 months, respectively.[51] It is noteworthy that, in a small series of patients with relapsed PCNSL after initial HDT/ASCT, a second autotransplantation was successful as salvage treatment.[52]

WBRT in patients who have not received radiation as a part of their initial treatment may be an effective option in the relapsed PCNSL setting, although the risk of neurotoxicity remains high.[53,54] Many clinicians reserve WBRT for those patients with chemotherapy-refractory disease or at the time of relapse. In a series of 27 relapsed or refractory PCNSL patients treated with WBRT (median dose, 36 Gy), 74% achieved an overall radiographic response and the median OS was 10.6 months. Delayed neurotoxicity rates of 15% were noted at doses greater than 36 Gy even in this set of short survival.

Novel therapeutics currently under study for primary CNS DLBCL include BTK (Bruton's tyrosine kinase) inhibitors, IMiDs (immunomodulatory imide drugs), mTOR (mammalian target of rapamycin) inhibitors, pI3K (phosphoinositide 3-kinase) inhibitors, immune checkpoint inhibitors, and CD19-directed chimeric antigen receptor (CAR) T cells.[4] In light of the fact that more than 90% of primary CNS DLBCL cases are of the poor-prognosis ABC subtype and the importance of BCR signaling in these tumors, a treatment regimen designed to target BCR signal transduction using ibrutinib, the BTK inhibitor, is noteworthy. Phase 1 and 2 studies of single-agent ibrutinib demonstrated high overall response rates of 52% to 77% in relapsed and refractory PCNSL patients, although the durability of the responses was short-lived.[55,56] Ibrutinib has been investigated in combination with chemotherapy such as rituximab and HD-MTX, as well with temozolomide, etoposide, doxil, dexamethasone, ibrutinib, and rituximab (TEDDI-R) in phase I studies yielding longer progression-free survival.[57,58] Second-generation BTK inhibitor, tirabrutinib has demonstrated similar results in R/R PCNSL in the context of a phase 1/2 trial, and is now approved for this indication in Japan. Lenalidomide, an immunomodulatory agent, has antiproliferative properties

and is the subject of several ongoing, prospective clinical trials in relapsed and refractory PCNSL. In phase 1 and 2 studies of lenalidomide with rituximab, the overall response rate was 64% to 67% with median progression-free survival of 6 to 7.8 months.[59,60] Lenalidomide is also being investigated as maintenance or consolidative therapy after induction chemotherapy in elderly patients (FIORELLA trial). The National Comprehensive Cancer Network (NCCN) guidelines list both lenalidomide and ibrutinib as considerations for salvage therapy in PCNSL. Various other next-generation BTK inhibitors, mTOR/PI3K inhibitors, BCL2 inhibitors, and IMiDs are being studied are single agents or in combination in phase 1 and 2 trials. Clinical trials of checkpoint inhibitors (nivolumab and pembrolizumab) and CD-19 directed CAR T cell therapy are also ongoing based on encouraging responses in case series with these agents.[61,62] The precise role of novel agents in PCNSL including specific combinations and their introduction in first-line treatment is currently under investigation, but they hold tremendous promise to improve response rates and overall outcomes.

MONITORING AND FOLLOW-UP

As treatment improves for PCNSL, more patients are living longer, emphasizing the need to optimize neurocognitive function and quality of life. The IPCG recommends a schedule of follow-up neuroimaging studies and cognitive assessment in PCNSL survivors.[13]

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CLINICS CARE POINT

- Early brain biopsy is preferred to make the diagnosis of primary CNS lymphoma. It is recommended to withhold corticosteroids before histopathologic confirmation. High dose methotrexate dose of 3g/m^2 is recommended for adequate brain and CSF penetration. Renalfunction should be closely monitored during high-dose methotrexate treatment. Whole brain radiotherapy can increase the risk of neurocognitive decline particularly in combination with high-dose methotrexate in older patients and so preferable to use in salvage.

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