

Primary Central Nervous System Lymphoma

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Primarily central nervous system (CNS) lymphoma (PCNSL), an uncommon variant of extranodal non-Hodgkin lymphoma (NHL), can affect any part of the neuraxis including the eyes, brain, leptomeninges, or spinal cord. It accounts for approximately 3% of all the primary CNS tumors diagnosed each year in the United States. Congenital or acquired immunodeficiency is the only established risk factor for PCNSL, and individuals with human immunodeficiency virus (HIV) infection are at greater risk for developing this tumor. Infection with HIV likely accounted for the increased incidence in PCNSL observed from 1970 to 2000, but over the last decade the number of cases of PCNSL has stabilized or decreased to about 0.47 cases per 100 000 persons. Owing to the rarity of PCNSL, the disease has been challenging to study and an effective standard of care has been difficult to establish. Unfortunately, although durable remissions may be achieved for some patients with PCNSL, the tumor relapses in most cases. In this review, we will focus on PCNSL in the immunocompetent host.

PATHOBIOLOGY

Ninety percent of non-HIV-associated PCNSL cases are of the diffuse large B-cell type, with the remaining 10% being poorly characterized low-grade lymphomas, Burkitt lymphomas, or T-cell lymphomas.¹ The diffuse large B-cell type of PCNSL is composed of immunoblasts or centroblasts that have a predilection for blood vessels, resulting in a characteristic lymphoid clustering around small cerebral vessels.

Primary CNS lymphoma is thought to arise from late-germinal center or post-germinal center lymphoid cells and localizes to the CNS because of a poorly understood neurotropism. Systematic studies of the molecular pathology of PCNSL have been challenging to perform because most cases of PCNSL are diagnosed by stereotactic needle biopsy. Despite this limitation, gene expression studies have dem-

onstrated 3 gene “signatures” associated with PCNSL: germinal center B-cell, activated B-cell, and type 3 large B-cell lymphoma.² While these 3 gene expression patterns parallel systemic diffuse large B-cell lymphoma, there are unique molecular features of PCNSL. For example, extracellular matrix-related genes are upregulated in PCNSL compared with systemic diffuse large B-cell lymphoma.³ Interaction between tumor cells and extracellular matrix proteins specific to the CNS may offer an explanation for the neurotropism of PCNSL.

Several genes associated with interleukin-4 (IL-4), a B-cell growth factor expressed by both tumor vessels and tumor cells, are highly expressed in PCNSL including X-box binding protein 1 (XBP-1), a regulator of the unfolded protein response signaling pathway. The expression of unfolded protein response-related genes is important for cell survival under stressful conditions such as hypoxia. Signal transducer and activator of transcription 6 (STAT6), a mediator of IL-4 signaling, is expressed by tumor cells and tumor endothelia in PCNSL. High expres-

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Table 1. International PCNSL Collaborative Group Guidelines for Baseline Evaluation for Clinical Trials^a

Pathology	Clinical	Laboratory	Imaging
Centralized review of pathological findings	Complete medical and neurological examination	HIV serology	Contrast-enhanced cranial MRI ^b
Immunophenotyping	Dilated eye examination, including slitlamp evaluation	Serum LDH level	CT of chest, abdomen, and pelvis
	Recording of prognostic factors (age, performance status)	CSF cytology, flow cytometry, immunoglobulin heavy-chain PCR	Bone marrow biopsy with aspirate
	Serial evaluation of cognitive function ^c	24-h urine collection for creatinine clearance ^d	Testicular ultrasonography in elderly men

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PCNSL, primary central nervous system lymphoma; PCR, polymerase chain reaction.

^aAdapted from the article by Abrey et al.⁶

^bContrast-enhanced cranial CT should be obtained in patients who have a contraindication for MRI (eg, those with a pacemaker) or who cannot tolerate MRI (eg, those with claustrophobia).

^cThe Mini-Mental State Examination is used commonly, although improved instruments are being developed.

^dFor patients who will receive high-dose methotrexate.

sion levels of STAT6 are associated with short survival in patients with PCNSL treated with methotrexate (MTX).² Recently, the first mouse model of PCNSL was developed; it could potentially be used to test new therapeutic agents that target these molecular abnormalities including the IL-4 signaling pathway.⁴

CLINICAL FEATURES

Primary CNS lymphoma typically presents with a focal mass lesion in more than 50% of cases. In 248 immunocompetent patients, 43% had neuropsychiatric signs, 33% had increased intracranial pressure, 14% had seizures, and 4% had ocular symptoms at the time of presentation.⁵ Seizures are less common than with other types of brain tumors, probably because PCNSL involves predominantly subcortical white matter rather than epileptogenic gray matter. Patients rarely present with B symptoms such as fever, weight loss, or night sweats that are commonly associated with other forms of NHL.

DIAGNOSTIC EVALUATION

The International PCNSL Collaborative Group has established guidelines for the diagnostic evaluation of a patient with suspected PCNSL (**Table 1**).⁶ The goals of these guidelines are to establish the baseline extent of disease and to confirm that the disease is restricted to the CNS. Physical examination should include palpation for enlarged lymph nodes as well as testicular examination in males because testicular lymphoma has a predilection to disseminate to the brain parenchyma. Contrast-enhanced cranial magnetic resonance imaging (MRI) (postcontrast cranial computed tomography if MRI is contraindicated), lumbar puncture if not contraindicated (for cell count, protein and glucose measurement, cytology, immunoglobulin heavy-chain gene rearrangement studies, and flow cytometry studies), ophthalmologic examination including slitlamp evaluation, computed tomography of the chest, abdomen, and pelvis, and bone marrow biopsy should be performed. Blood tests for HIV, complete blood cell count, basic metabolic profile, and lactate dehydrogenase level are also recommended. Testicular ultrasonography should be considered in men.

Searching for occult systemic disease has become increasingly important as recent evidence suggests that lymphoma may not be restricted to the nervous system in a subpopulation of patients with CNS lymphoma. Identical polymerase chain reaction products of clonally rearranged immunoglobulin heavy-chain genes were identified in the bone marrow aspirates, blood samples, and brain tumor biopsy specimens in 2 of 24 patients with “primary” CNS lymphoma in one study.⁷ In 1 of these patients, follow-up immunoglobulin heavy-chain polymerase chain reaction 24 months after diagnosis yielded a persistent monoclonal blood product despite a complete radiographic response in the CNS.⁷ In a retrospective study of 49 patients with PCNSL evaluated with body fludeoxyglucose F 18–positron emission tomography studies, extraneural hypermetabolic lesions were identified in 15% of subjects. Subsequent tissue biopsy was performed; 11% of the lesions were found to be lymphoma, while 4% were other types of cancer. Prospective, long-term follow-up studies will be necessary to further elucidate the frequency and importance of subclinical systemic disease in patients with CNS lymphoma and whether the presence of these monoclonal cell populations increases the risk of relapse—either in the CNS or elsewhere in the body.

NEUROIMAGING

Contrast-enhanced cranial MRI is the imaging modality of choice in evaluating a patient with suspected PCNSL. If MRI is not possible or is contraindicated, a contrast-enhanced cranial computed tomographic scan is recommended. Primary CNS lymphoma tends to enhance homogeneously on both MRI and computed tomography, although in HIV-associated PCNSL, lesions are often ring enhancing (**Figure**). In immunocompetent patients with PCNSL, lesions are solitary in 65% of cases and are located in a cerebral hemisphere (38%), thalamus/basal ganglia (16%), corpus callosum (14%), periventricular region (12%), and cerebellum (9%).⁸ Isolated spinal cord involvement is rare and observed in less than 1% of cases, so spinal imaging is only necessary if warranted based on clinical suspicion or to screen for leptomeningeal involvement if lumbar puncture cannot be performed.

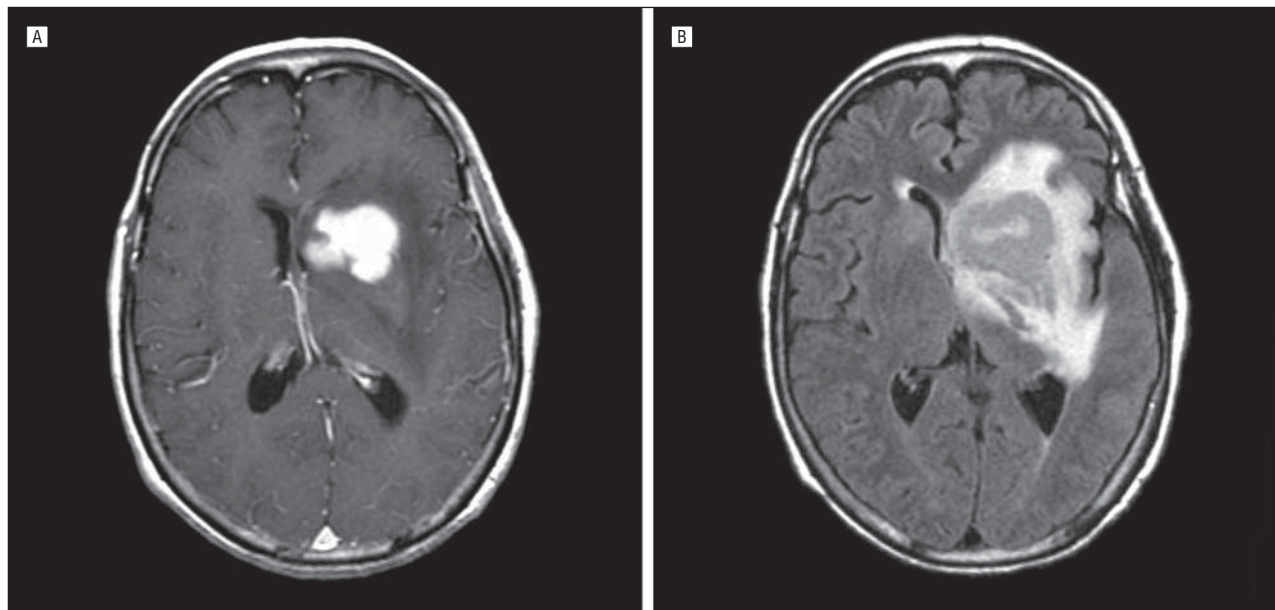


Figure. Magnetic resonance imaging. A, Postcontrast T1-weighted magnetic resonance image from a patient with primary central nervous system lymphoma. Note the homogeneous enhancement and periventricular location. B, Fluid-attenuated inversion recovery sequence demonstrating extensive peritumoral edema with mass effect on the lateral ventricle.

PROGNOSTIC MARKERS

The identification of prognostic markers in PCNSL enables physicians to discuss prognosis with individual patients and may eventually allow the application of risk-adjusted therapeutic strategies. In addition, the knowledge of important prognostic markers is critical for prospective study designs. Different prognostic scoring systems have been proposed. One proposed prognostic model divides patients with PCNSL into 3 groups based on age and performance status: those younger than 50 years; those older than 50 years with a Karnofsky Performance Scale score higher than 70; and those older than 50 years with a Karnofsky Performance Scale score lower than 70.⁹ Based on these divisions, significant differences in overall and failure-free survival were observed. As these variables are easily obtained, this model may prove useful in future prospective clinical trials for risk stratification.

The search for tissue biomarkers of prognosis for patients with PCNSL is an active area of investigation. *BCL-6*, a proto-oncogene expressed in 22% to 100% of patients, has been associated with improved prognosis. Both progression-free survival and overall survival are longer in patients who have PCNSL with *BCL-6* expression.¹⁰ These findings are consistent with the observation that *BCL-6* expression is a favorable prognostic marker in patients with systemic NHL.

TREATMENT

As with systemic forms of NHL, the available treatment options for PCNSL include corticosteroids, chemotherapy, and radiation. Resection of PCNSL is not a viable treatment option except in the rare patient experiencing brain herniation due to mass effect. The infiltrative nature of lymphoma and its multifocality involving the

leptomeninges, the eyes, or the deep regions of the brain make complete tumor removal unfeasible. Median survival following surgery alone is only 1 to 4 months. Consequently, once the diagnosis is achieved after a stereotactic biopsy, further surgery is not useful. The optimal treatment plan following histological diagnosis has not been defined and the International PCNSL Collaborative Group has established guidelines for assessing response in clinical trials to help determine optimal treatment (**Table 2**).

CORTICOSTEROIDS

Although corticosteroids can work rapidly to cause tumor regression and decrease peritumoral edema, these medications should be withheld prior to diagnostic biopsy in clinically stable patients. Corticosteroids have a direct lymphocytolytic effect that may disrupt cellular morphology and lead to diagnostic inaccuracy at the time of microscopical analysis. Despite an initial response to corticosteroids, most patients quickly relapse and require alternate treatment strategies. Nevertheless, initial radiographic response to corticosteroids in patients with newly diagnosed PCNSL is a favorable prognostic marker, with survival of 117 months in responders vs 5.5 months in nonresponders.¹¹

RADIATION THERAPY

Whole-brain radiation therapy (WBRT) was historically the modality of choice to treat PCNSL given the multifocal and infiltrative nature of the tumor. However, WBRT alone is inadequate therapy for patients with PCNSL, particularly those with cerebrospinal fluid dissemination of their tumor. Initial radiographic response to WBRT is observed in 90% of patients with PCNSL but relapse usually occurs within a few months.¹² In pa-

Table 2. International PCNSL Collaborative Group Guidelines for Response Assessment for Clinical Trials^a

Response	Brain Imaging	Corticosteroid Dose	Eye Examination Results	CSF Cytology Results
Complete	No enhancing disease	None	Normal	Negative
Unconfirmed complete	No enhancing disease	Any	Normal	Negative
	Minimal enhancing disease	Any	Minor RPE abnormality	Negative
Partial	50% Decrease in enhancement	NA	Minor RPE abnormality or normal	Negative
	No enhancing disease	NA	Decrease in vitreous cells or retinal infiltrate	Persistent or suspicious
Progressive disease	25% Increase in enhancement	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.

^aAdapted from the article by Abrey et al.⁵

tients receiving WBRT alone without chemotherapy, median survival varies from 12 to 18 months and 5-year survival ranges from 18% to 35%. While WBRT is effective for initial control of disease, it produces delayed neurotoxic effects, especially in those older than 60 years. For this reason, WBRT is often deferred in patients with newly diagnosed PCNSL who are older than 60 years.

COMBINED-MODALITY THERAPY

Given the disappointing outcomes with surgery or radiation alone, chemotherapy was added to WBRT in an attempt to improve survival (combined-modality therapy). Several different chemotherapy agents have been studied, but MTX, a folate antagonist, is the backbone for any combination regimen. However, MTX has limited penetration into the CNS because of a high degree of ionization at physiologic pH. This low penetration is an important reason why high doses (≥ 3.5 g/m²) of intravenous MTX are necessary to achieve cytotoxic intratumoral concentrations.

Combination regimens including MTX and WBRT are associated with a radiographic response in more than 50% of patients and a 2-year survival of 43% to 73%.¹³ Most MTX-based regimens are associated with similar survival rates, but the toxic effects vary depending on the regimen. One commonly used combination regimen is MTX, vincristine sulfate, and procarbazine hydrochloride followed by WBRT and cytarabine in the postradiation setting. This regimen is associated with an overall response rate of 91%, a progression-free survival of 24 months, and an overall survival of 36.9 months.¹⁴ Toxic effects associated with this regimen were notable and included 8 patient deaths and 12 cases of clinically significant neurotoxic effects in the 98 patients studied. A subsequent study tested rituximab with MTX, vincristine, and procarbazine followed by lower-dose WBRT (23.4 Gy [to convert gray to rad, multiply by 100]) if the patient achieved a complete response (CR) to chemotherapy or by 45 Gy of WBRT if a CR was not achieved.¹⁵ The overall response rate was 93% and the 2-year median progression-free survival was 57%. At a median follow-up of 37 months, no patients had experienced treatment-related neurotoxic effects but most patients required growth factor support. Other selected combined-modality regimens are listed in **Table 3**. While the overall response rate reported in these studies is encouraging, long-term survival is uncommon and the high

frequency of treatment-related toxic effects is a significant concern.

A common observation from these trials is that patients who respond to initial chemotherapy have improved outcomes. In one study,²⁵ patients who could not tolerate MTX or failed to achieve a CR had a median survival of 1.5 months vs 56 months in those patients who did achieve a radiographic response. Forty percent of patients in this study did not complete chemotherapy because of toxic effects or disease progression, so more tolerable and effective agents are needed in this patient population.

CHEMOTHERAPY

The combined-modality protocols just described are often associated with delayed cognitive neurotoxic effects, particularly in those patients older than 60 years or with vascular risk factors. To avoid this high frequency of toxic effects, other studies have explored the use of chemotherapy alone, reserving WBRT for patients who subsequently relapse.

In a phase 2 multicenter study of 25 patients using intravenous MTX (8 g/m²) alone, the outcomes included a CR proportion of 52%, a median progression-free survival of 12.8 months, and a median overall survival of 55.4 months, but median disease-specific survival had not been reached at 72.3 months.^{22,23} In this study, 5 of the 25 patients treated with MTX alone achieved a CR and had not relapsed after a median follow-up of 6.8 years. Duration and timing of maintenance MTX therapy after a patient achieves a CR remain unclear. Toxic effects were modest and manageable.

While MTX monotherapy may be effective for a subset of patients, most patients will likely need combination chemotherapy to achieve a durable response. There have been a large number of phase 2 trials involving MTX-based, multiple-agent chemotherapy regimens without WBRT (Table 3). A number of different intravenous and intrathecal cytotoxic drugs have been advocated, and encouraging radiographic response proportions and survival have been reported.^{20,21} Rituximab, a humanized monoclonal antibody against the CD20 antigen on B-lymphoma cells, has been incorporated in some combination regimens, although it is not yet known whether this agent will improve outcomes in patients with PCNSL to the extent that it has for patients with systemic B-cell lymphomas.

Table 3. Selected Treatment Studies

Source	Chemotherapy Regimen	Patients, No.	Intrathecal Chemotherapy	WBRT	CR, % (No./Total No.)	PR, % (No./Total No.)	OS, mo ^a	PFS, mo ^a
Chemotherapy With RT								
Poortmans et al, ¹⁶ 2003	MTX (3 g/m ²), teniposide, carmustine	52	Cytarabine, MTX	30 Gy with 10-Gy boost	69 (36/52)	12 (6/52)	46	NA
Gavrilovic et al, ¹⁷ 2006; Abrey et al, ¹⁸ 2000	MTX (3.5 g/m ²), procarbazine, vincristine, cytarabine	57	MTX	45 Gy in those aged <60 y	56 (27/48)	33 (16/48)	51	129
Shah et al, ¹⁵ 2007	MTX (3.5 g/m ²), rituximab, procarbazine, vincristine, cytarabine	30	None	23.4 Gy if CR; 45 Gy if not CR	77 (23/30)	NA	2-y OS, 67% ^b	40 ^b
Ferreri et al, ¹⁹ 2009	MTX (3.5 g/m ²) with or without cytarabine	MTX alone, 40; MTX plus cytarabine, 39	None	Added based on response and age	MTX alone, 18; MTX plus cytarabine, 46	MTX alone, 23; MTX plus cytarabine, 23	3-y survival: MTX alone, 32%; MTX plus cytarabine, 46%	3-y survival: MTX alone, 21%; MTX plus cytarabine, 38%
Chemotherapy Without RT								
Pels et al, ²⁰ 2003	MTX (5 g/m ²), vincristine, ifosfamide, dexamethasone, cyclophosphamide, cytarabine, vindesine	65	Prednisolone, MTX, cytarabine	None	61 (37/61)	10 (6/65)	50	21
Hoang-Xuan et al, ²¹ 2003	MTX (1 g/m ²), lomustine, procarbazine, methylprednisolone	50	Cytarabine, MTX	None	42 (21/50)	6 (3/50)	14.3	10.6
Gerstner et al, ²² 2008; Batchelor et al, ²³ 2003	MTX (8 g/m ²)	25	None	None	52 (12/25)	NA	55.4	12.8
Intra-arterial Chemotherapy								
Angelov et al, ²⁴ 2009	Intra-arterial MTX	149	None	None	57.8	24.2	3.1 y; 8.5-y OS, 25%	1.8 y; 5-y PFS, 31%

Abbreviations: CR, complete response; MTX, methotrexate; NA, not applicable; OS, overall survival; PFS, progression-free survival; PR, partial response; RT, radiation therapy; WBRT, whole-brain RT.

Conversion factor: To convert gray to rad, multiply by 100.

^aValues are expressed as medians unless otherwise indicated.

^bEstimated.

Blood-brain barrier disruption is an alternate strategy aimed at circumventing the blood-brain barrier to deliver higher concentrations of chemotherapeutics directly to the CNS and tumor. In a pooled analysis of 149 patients treated with intra-arterial MTX, the CR proportion was 57.8% with a median overall survival of 3.1 years.²⁴ However, blood-brain barrier disruption is technically complex and should only be performed in centers with expertise and experience in the technique.

INTRATHECAL CHEMOTHERAPY

A controversial issue in the management of PCNSL is the role of intrathecal chemotherapy. Historical comparisons have determined that there appears to be no survival advantage when intrathecal MTX is added to regimens that already include high doses of intravenous MTX. By administering MTX systemically, the risk of Ommaya reservoir placement, extra-cerebrospinal fluid drug

delivery, chemical meningitis, and infection can be avoided. As mentioned earlier, the intravenous dose must be high enough, though, and administered often and quickly enough for MTX to penetrate into the cerebrospinal fluid and tumor. For patients with concurrent brain and leptomeningeal lymphoma, intrathecal chemotherapy is often recommended. Ommaya reservoir placement is the most efficient and safest way to deliver intrathecal chemotherapy.

HIGH-DOSE CHEMOTHERAPY WITH STEM CELL RESCUE

Initial studies of high-dose chemotherapy followed by autologous stem cell transplantation for patients with newly diagnosed PCNSL have involved limited numbers of highly selected patients and have yielded mixed results. The heterogeneous therapies used and variable outcome measures reported make comparison between trials

difficult. However, preliminary results from these small studies are encouraging, and it is likely that high-dose chemotherapy with autologous stem cell transplantation will assume an increasingly important role in younger patients with PCNSL in the newly diagnosed and relapsed settings.

SALVAGE THERAPY

Despite aggressive treatment, most patients with PCNSL will progress or relapse and require salvage therapy. Optimal management of relapsed or refractory PCNSL has yet to be determined and has only been studied in small patient series or case reports using heterogeneous therapies. In general, prognosis for patients with relapsed or progressive PCNSL is poor, with a median survival of approximately 4.5 months. For patients who initially achieve a CR to a chemotherapy regimen that included MTX, re-treatment with MTX alone may be effective. The following have been studied in patients with relapsed or refractory PCNSL with varying results: temozolomide; topotecan hydrochloride; etoposide, ifosfamide, and cytarabine; high-dose chemotherapy followed by autologous stem cell transplantation; and procarbazine, lomustine, and vincristine.

Rituximab may be useful in relapsed patients who have not received it as first-line therapy. Intraventricular rituximab (10-25 mg) was determined to be feasible in a phase 1 study of patients with relapsed or refractory lymphomatous meningitis.²⁶ Unexpected observations in this study were a radiographic response of brain parenchymal lymphoma in 1 case and 2 patients with intraocular lymphoma who experienced disease resolution and/or clinical improvement in vision. A clinical trial is currently under way to test intrathecal rituximab and intrathecal MTX for patients with relapsed CNS lymphoma and includes patients with brain parenchymal lymphoma.

Whole-brain radiation therapy alone is associated with a radiographic response in 74% to 79% of patients with relapsed or refractory PCNSL. Median survival after radiation treatment is 10.9 to 16 months, with patients younger than 60 years faring better.

NEUROTOXIC EFFECTS

Neurotoxic effects are a well-known, delayed consequence of treatment of PCNSL with WBRT plus chemotherapy or with WBRT alone. They are more common in patients older than 60 years and those with underlying vascular risk factors. Patients typically present with subcortical dementia, gait ataxia, and incontinence. Less severely affected patients have problems with attention, executive function, memory (particularly verbal), and psychomotor speed. The MRI may show periventricular white matter abnormalities, cortical atrophy, and ventricular enlargement, but these radiographic changes do not always correlate with clinical symptoms. Pathological studies have demonstrated demyelination, neuronal loss, gliosis, and rarefaction of the white matter. Large-vessel atherosclerosis has been observed as well, implicating vascular injury and resultant tissue ischemia as one possible mechanism for neurotoxic effects. Although the pathophysiology of treatment-related neurotoxic ef-

fects is multifactorial, toxic effects to neural progenitor cells are hypothesized to have a central role.

Studies examining the cognitive effects of treatment have several methodological limitations, including lack of baseline evaluations, different definitions of cognitive impairment, and small patient sample sizes. In one study²⁷ of patients with PCNSL, the 5-year cumulative incidence of neurotoxic effects was 24% and the use of WBRT was the only significant predictor of the development of neurotoxic effects on multivariate analysis. This is in contrast to chemotherapy alone, in which less decline in cognitive function is observed despite evidence of white matter changes on MRI. One treatment strategy has been to decrease the dose of WBRT to 23.4 Gy in patients who achieved a CR to induction chemotherapy. In a small study of 12 patients with PCNSL who had serial neuropsychological testing up to 24 months after chemotherapy with rituximab, MTX, vincristine, and procarbazine followed by low-dose WBRT, there was no significant decline in cognitive function compared with baseline.²⁸ However, the small sample size and high attrition rate may have limited the ability of the investigators to detect more subtle cognitive changes.

Unfortunately, there is no effective treatment for neurotoxic effects, and patients often die of complications of neurotoxic effects without evidence of recurrent lymphoma. To better assess cognitive function as an end point in this patient population, the International PCNSL Collaborative Group has proposed a single battery of psychometric tests for inclusion in all prospective PCNSL clinical trials.

CONCLUSIONS

Primary CNS lymphoma is a distinct and rare type of NHL that may involve multiple compartments within the CNS. Evaluation requires proper assessment of the brain, eyes, cerebrospinal fluid, and body to confirm that the tumor is confined to the CNS. The rarity of PCNSL and the difficulty in obtaining tissue for molecular studies have limited our biological understanding of this disease and impeded development of novel therapeutics. There is no consensus regarding the optimal management strategy for patients with PCNSL. Methotrexate is the most effective drug against PCNSL, but it is unclear which drugs should be added to MTX to improve survival and whether low-dose radiation with chemotherapy can avoid delayed neurotoxic effects.

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