Management of Primary Central Nervous System Lymphoma

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Key Words
Lymphoma, brain, methotrexate, radiotherapy

Abstract
Primary central nervous system lymphoma (PCNSL) is a unique subtype of non-Hodgkin’s lymphoma (NHL). Although PCNSL is both chemosensitive and radiosensitive, it is very difficult to treat and outcomes are substantially inferior when compared with similar extranodal NHL. Furthermore, as a subtype of brain tumors and NHL, the overall incidence has been increasing over the past several decades. This review summarizes the salient clinical features and approach to management of the immunocompetent patient with PCNSL. (JNCCN 2004;2:341–349).

Primary central nervous system lymphomas (PCNSL) are a group of high- or intermediate-grade extranodal lymphomas arising in and confined to the central nervous system (CNS).1,2 This definition excludes angiotropic lymphomas and metastatic lymphomas.3 PCNSL was described as early as 1929 by Bailey in his description of the “perivascular sarcomatous tumour,”4 but modern immunohistochemical techniques allowed the definitive identification as a B-cell type of non-Hodgkin’s lymphoma (NHL).

The incidence of PCNSL in the immunocompetent population has increased significantly over the past 3 decades.5 However, despite a threefold increase, the absolute risk remains very low, and the incidence approximates 0.3/100,000/yr.6 PCNSL represents 2.7% of all CNS tumors and 1% to 2% of all lymphomas.7 It has a slight male predominance, with a gender ratio of 1.5 and a peak incidence at 60 years of age. It is regarded as a highly treatable disease, but overall prognosis is poor, with a 5-year overall survival rate of 25%.8,9

Clinical Presentation
Symptomatology in PCNSL is dictated primarily by the location of the tumor within the CNS as well as by the rapidity of disease progression. Personality changes and cognitive dysfunction are the most common presenting symptoms, followed by symptoms of increased intracranial pressure such as headaches and nausea. Focal neurologic symptoms (sensory or motor) can be present and vary according to the location of the disease. To a lesser degree, psychomotor slowing, disorientation, and seizures may be present.10,11 The average time to diagnosis from the beginning of symptoms is 2 to 3 months.10,11

Imaging
Magnetic resonance imaging (MRI) is the gold standard and typically shows a solitary (60% to 70%) hypointense nodular lesion with indistinct borders on T1-weighted images. Dense and homogeneous enhancement can be seen after injection of gadolinium. On T2-weighted images, lesions are hyperintense with moderate if any surrounding vasogenic edema.12 In AIDS patients, ring enhancement caused by central tumor necrosis may be seen. Perifocal edema can be seen, which is less prominent than the edema seen with malignant glioma or metastases.13 PCNSL is usually supratentorial rather than infratentorial, and is localized to the cerebral hemispheres, frontal lobes, corpus callosum, basal ganglia, or thalamus, often in a periventricular location. Spinal cord involvement is rare.14 The high cell density and metabolic rate of PCNSL may make discriminating it from other
high-grade brain tumors on $^{18}$fluorodeoxyglucose positron emission tomography possible.\textsuperscript{14,15}

Pathology
More than 90\% of cases are B-cell lymphomas CD19+ CD20+, monoclonal with either $\kappa$ or $\lambda$ light chain restriction, and morphologically indistinguishable from systemic lymphoma. The pattern of expression of adhesion molecules is identical to NHL.\textsuperscript{16,17} According to the Revised European American Classification (REAL) system for extranodal lymphomas, most are diffuse large cell, immunoblastic, or lymphoblastic cell type. Approximately 3\% are T-cell lymphomas, which are more commonly infratentorial.\textsuperscript{2,18,19} The growth pattern shows angiocentric, infiltrating lesions forming cuffs around the arterioles and venules, sometimes invading the vessel walls, and a centrifugal infiltration of the surrounding parenchyma.\textsuperscript{2}

Prognostic Factors
The most important and widely recognized prognostic factors are age 60 years or younger and Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2.\textsuperscript{20,21} More recently, the International Extranodal Lymphoma Study Group identified age, performance status, lactate dehydrogenase (LDH) serum level, cerebrospinal fluid (CSF) protein concentration, and involvement of the deep structures of the brain as independent prognostic variables. They were able to use these variables to construct a prognostic index in which each variable was assigned a value of 0 if favorable and 1 if not. The 2-year overall survival was 80\% for patients with a score of 0 to 1, 48\% for a score of 2 to 3, and 15\% for a score of 4 to 5.\textsuperscript{21}

Diagnosis and Staging

Biopsy
When the diagnosis of PCNSL is suspected, steroids should be avoided if possible because their potent cytolytic effect on the lymphoma cells may obscure the diagnosis. Stereotactic or open biopsy of the contrast-enhancing lesions is the most appropriate diagnostic procedure.\textsuperscript{22} Resection is rarely performed because it provides no therapeutic benefit, and the risk of surgical complications is high.\textsuperscript{23}

Staging
After the diagnosis is made, disease work-up is critical to evaluate ocular or leptomeningeal involvement and to rule out systemic dissemination (Table 1). Ocular involvement is present in 20\% to 25\%, and a slit lamp ophthalmologic examination for ocular involvement is always required. Cytologic examination of vitreal aspirates may be necessary in patients with isolated ocular lymphoma (PIOL).\textsuperscript{18–20} CSF cytology reveals tumor cells in about 15\% and nonspecific abnormalities in up to 75\%.\textsuperscript{24,27} $\beta_{2}$-microglobulin levels, immunophenotyping, and clonal immunoglobulin gene rearrangement can be performed to increase the yield of the CSF analysis.\textsuperscript{24} The rest of the work up comprises a computed tomography (CT) scan of the chest, abdomen, and pelvis, and a bone marrow aspiration. Systemic lymphoma is found in fewer than 4\% of cases.\textsuperscript{24} Serology for HIV is imperative to rule out AIDS.

Therapy
NHLs are exquisitely chemosensitive and radiosensitive malignancies, with an initial response in excess of 90\% for each modality. This is also true for PCNSL, but PCNSL has lower response rates of 60\% per modality and a high risk of early relapse if radiotherapy is used as a single modality. Therefore, numerous clinical trials have sought to improve outcome with various combinations of chemotherapy and radiotherapy.

### Table 1  Recommended Baseline Evaluation

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Brain MRI with and without gadolinium</td>
<td>Tumor detection and staging are performed.</td>
</tr>
<tr>
<td>Clinical examination including a baseline performance status</td>
<td>Life-threatening complications.</td>
</tr>
<tr>
<td>Serum LDH levels</td>
<td>Detects systemic disease.</td>
</tr>
<tr>
<td>LP for CSF analysis; protein, cytology, $\beta_{2}$-microglobulin</td>
<td>Detects systemic disease.</td>
</tr>
<tr>
<td>Ophthalmologic examination including a slit lamp examination</td>
<td>Detects ocular involvement.</td>
</tr>
<tr>
<td>CT Scan with IV contrast of the chest, abdomen and pelvis</td>
<td>Detects ocular involvement.</td>
</tr>
<tr>
<td>Bilateral bone marrow biopsy</td>
<td>Detects systemic disease.</td>
</tr>
<tr>
<td>Testicular examination and ultrasound examination in males older than 65 years</td>
<td>Prevents potential systemic spread.</td>
</tr>
<tr>
<td>MRI of the spine with and without gadolinium if symptomatic</td>
<td>Detects leptomeningeal involvement.</td>
</tr>
</tbody>
</table>

Abbreviations: MRI, magnetic resonance imaging; LDH, lactate dehydrogenase; LP, lumbar puncture; CSF, cerebrospinal fluid; CT, computed tomography; IV, intravenous.
Corticosteroids
Corticosteroids induce apoptosis via a direct cytotoxic effect in lymphoid cells. Dexamethasone may lead to complete remission in 15% or partial remissions in 25% of PCNSL patients (Fig. 1). This correlates with clinical and radiologic improvement that may occasionally last long after discontinuation of the corticosteroid. More commonly, this is temporary, and relapse typically occurs shortly after discontinuation of dexamethasone. Resistance may develop after re-exposure to corticosteroids in previously documented sensitive disease or during withdrawal therapy. Therefore, the corticosteroid may be restarted after biopsy to prevent symptom recurrence and to decrease associated vasogenic edema. Long-term steroid therapy should be avoided to minimize secondary complications.

Radiotherapy
Whole brain radiotherapy (WBRT) has a response rate close to 65%, but median survival is only 12 to 18 months, and 5-year survival is 4%. In comparison, radiotherapy alone for equivalent stages IE or IIE extranodal systemic NHL has a local control rate in excess of 90%, and a 5-year survival of 43% to 77%. Thus, WBRT is unacceptable as a single modality treatment for PCNSL.

Furthermore, there is no role for dose intensification, as was shown by the prospective RTOG 8315 trial, in which a total dose of 40 Gy to the whole brain with a boost of 20 Gy to the tumor bed did not yield improved disease control (39%) or median survival (12.2 months). In this study, 79% of the recurrences occurred in the boosted field.

In cases of primary ocular lymphoma or ocular dissemination, treatment should include radiotherapy to the globe, with doses of 35 to 40 Gy fractionated over 5 weeks. Both eyes should be treated even in cases with only evidence of monocular involvement. Most patients will experience a symptomatic improvement and vitreal clearing. However, some patients show vitreal clearing without improved vision and others may not respond to radiotherapy. Accelerated cataract, optic neuropathy, conjunctivitis, dry eyes, corneal epithelial defects, retinal atrophy, and vitreous hemorrhage are possible complications of ocular irradiation.

Chemotherapy
The addition of chemotherapy to WBRT has generally resulted in improved response rates and survival; however, the optimal chemotherapy regimen has yet to be identified, and numerous agents have shown activity in PCNSL (Table 2). A standard NHL regimen such as CHOP or the slightly modified CHOD (cyclophosphamide, Adriamycin, vincristine, and Decadron) combined with WBRT has a very short-lived response, with distant CNS treatment failure or florid leptomeningeal
recurrences. Randomized studies failed to show any survival advantage when compared with WBRT alone.\textsuperscript{38–42} MACOP and MACOP-B combined with WBRT PC-NSL showed excellent initial responses that were comparable to the responses in systemic NHL. However, no survival advantage was seen over WBRT alone.\textsuperscript{43} Methotrexate is the most effective and extensively used drug in PCNSL (Fig. 2). Its activity against CNS lymphoma was recognized with the observation that NHL patients treated with methotrexate experienced fewer

<table>
<thead>
<tr>
<th>Agent</th>
<th>Properties and use in PCNSL</th>
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<tbody>
<tr>
<td>Methotrexate</td>
<td>Antimetabolite, intravenous high dose single agent or in combination. Intrathecal, intravitreous or intraarterial administration possible. Requires aggressive hydration and alkalinization with leucovorin rescue.</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Antimetabolite, prolonged intra-CSF activity, intravenous and intrathecal administration as a single agent or in combination.</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Steroid hormones, oral or intravenous, single agent or in combination rapid response as trigger oncolytic response, numerous side effects.</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>Oral methyl-hydrazine derivative in conjunction with HD-MTX, neurotoxicities usually reversible.</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Mitotic spindle inhibitor, intravenous administration in combination regimen, has cumulative neurotoxicity.</td>
</tr>
<tr>
<td>Thiotepa</td>
<td>Alkylating agent, IV in combination regimen or HD intensification prior to stem cell transplant, also intrathecal and intravitreal administration.</td>
</tr>
<tr>
<td>Temozolomide</td>
<td>Oral imidazotetrazines single agent or in combination regimen.</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Human/murine chimeric anti-CD-20 monoclonal antibody, IV, intrathecal or ventricular administration in combination regimen, may prolong post chemotherapy granulocytic recovery.</td>
</tr>
<tr>
<td>Topotecan</td>
<td>Oral or IV topoisomerase I inhibitor, few reports of activity in PCNSL and dose limiting myelosuppression.</td>
</tr>
<tr>
<td>Lomustine</td>
<td>Oral nitrosourea used in combination regimen, has cumulative pulmonary and renal toxicities.</td>
</tr>
</tbody>
</table>

Abbreviations: PCNSL, primary central nervous system lymphoma; CSF, cerebrospinal fluid; HD-MTX, high dose methotrexate; HD, high dose.

Figure 2 Sagittal MRI of the brain with gadolinium before (left) and after (right) completion of 5 cycles of HD-methotrexate show a complete radiographic response.
CNS relapses. This efficacy of MTX in improving survival outcomes was first noted by Loeffler et al. In a group of 5 patients who received intravenous or intrathecal methotrexate followed by WBRT, the median survival rate seen was 44 months. Similar observations by other investigators led to a wide range of reported methotrexate-based regimens with varying degrees of success (Table 3). A prospective trial by the RTOG confirmed the observation that methotrexate-based chemotherapy in combination with WBRT improves disease control and overall survival.

The role of intrathecal chemotherapy in treating PCNSL is controversial. Rapid intravenous administration of both methotrexate and cytarabine produce tumoricidal levels within the CSF and may obviate intrathecal administration of drug. Furthermore, at least two retrospective studies have failed to show any advantage in terms of disease control or survival for patients treated with intrathecal chemotherapy.

However, disease recurrence is common, and treatment-related neurotoxicity is a recognized complication of the combination of high-dose methotrexate and WBRT. Therefore, current efforts to improve outcomes have focused on strategies that seek to intensify the chemotherapy regimen and minimize or defer WBRT. Administration of chemotherapy after disruption of the blood-brain barrier in 111 patients

Table 3: Survival and Response Rates to Various Methotrexate Based Chemotherapy for PCNSL

<table>
<thead>
<tr>
<th>Author year published</th>
<th>N</th>
<th>Regimen</th>
<th>IT CHT</th>
<th>RT and dose</th>
<th>Response</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabbai et al. 1989</td>
<td>13</td>
<td>MTX 3.5 g/m²</td>
<td>—</td>
<td>30-44 Gy</td>
<td>92%</td>
<td>9.5 months</td>
</tr>
<tr>
<td>Glass et al. 1994</td>
<td>25</td>
<td>MTX 3.5 g/m²</td>
<td>—</td>
<td>30-44 Gy</td>
<td>88%</td>
<td>33 months</td>
</tr>
<tr>
<td>DeAngelis et al. 1992</td>
<td>31</td>
<td>MTX 1 g/m²</td>
<td>MTX 12 mg × 6</td>
<td>40 Gy + 14.4 Gy boost</td>
<td>64%</td>
<td>41 months</td>
</tr>
<tr>
<td>Sandor et al. 1998</td>
<td>14</td>
<td>MTV (MTX 8.4 g/m²) IT Ara-C</td>
<td>MTX 12 mg × 2 and Ara-C 15mg/d × 2</td>
<td>—</td>
<td>100%</td>
<td>16.5 months PFS</td>
</tr>
<tr>
<td>Cheng et al. 1998</td>
<td>19</td>
<td>BOMES (MTX 1.5 g/m²)</td>
<td>MTX 12 mg × 4</td>
<td>If CSF involved</td>
<td>—</td>
<td>84%</td>
</tr>
<tr>
<td>Guha-Thakurta et al. 1999</td>
<td>31</td>
<td>MTX 8 g/m² and consolidation with 3.5 g/m² every 3rd month.</td>
<td>—</td>
<td>—</td>
<td>100%</td>
<td>30+ months</td>
</tr>
<tr>
<td>Abrey et al. 2000</td>
<td>52</td>
<td>MPV (MTX 3.5 g/m²) Ara-C</td>
<td>MTX 12 mg × 3</td>
<td>45 Gy in 35 Patients</td>
<td>90%</td>
<td>60 months</td>
</tr>
<tr>
<td>McAllister et al. 2000</td>
<td>74</td>
<td>IA MTX (2.5 g) + cyclophosphamide and etoposide</td>
<td>—</td>
<td>—</td>
<td>65% complete</td>
<td>40.7 months</td>
</tr>
<tr>
<td>Ferreri et al. 2001</td>
<td>13</td>
<td>MPV (MTX 3 g/m²)</td>
<td>—</td>
<td>39.6 Gy</td>
<td>92%</td>
<td>25+ months</td>
</tr>
<tr>
<td>DeAngelis et al. 2002</td>
<td>102</td>
<td>MPV (MTX 2.5 g/m²)</td>
<td>MTX 12 mg × 5</td>
<td>45 Gy</td>
<td>94%</td>
<td>30+ months</td>
</tr>
<tr>
<td>Batchelor et al. 2003</td>
<td>25</td>
<td>MTX 8 g/m²</td>
<td>—</td>
<td>—</td>
<td>74%</td>
<td>22.8+</td>
</tr>
<tr>
<td>Poortmans et al. 2003 - EORTC 20962</td>
<td>52</td>
<td>MBVP (MTX 3 g/m²)</td>
<td>MTX 15 mg – ARA-C40 mg and hydrocortisone 25mg × 2</td>
<td>30 Gy + 10 Gy boost</td>
<td>81%</td>
<td>46 months</td>
</tr>
<tr>
<td>Pels et al. 2003</td>
<td>65</td>
<td>MTX 5 g/m² and ARA-C 3 g/m² with ifosfamide VCR cyclophosphamide and dexamethasone</td>
<td>MTX 3 mg, ARA-C 30 mg and prednisolone and 2.5 mg × 3</td>
<td>—</td>
<td>71%</td>
<td>&gt;60 year old MS 34 months. &lt;60-year-old MS NR 5-year survival 75%</td>
</tr>
</tbody>
</table>

Abbreviations: MTX, methotrexate; VCR, vincristine; Ara-C, cytarabine; IA, intra-arterial; MTV, methotrexate, thiotepa, vincristine; IT, intra-thecal; BOMES, BCNU, vincristine, etoposide, methylprednisolone; MPV, methotrexate, procarbazine, vincristine; MTV, methotrexate, thiotepa, vincristine; MBVP, methotrexate, teniposide, Carmustine, prednisolone.
yielded a 65% response rate with an overall median survival of 40.7 months; detailed neurocognitive testing has shown no evidence of treatment-related neurotoxicity.\textsuperscript{14} High-dose chemotherapy with autologous stem cell rescue and maintenance high-dose methotrexate for nearly 1 year after initial complete response are other strategies that have been used in an effort to optimize the efficacy of single-modality chemotherapy.\textsuperscript{52,63}

**Recurrent PCNSL**

More than half of the patients attaining a remission will experience relapse. At relapse, all patients should undergo complete restaging; it is worth noting that up to 10% of recurrent disease is seen outside the CNS. Treatment must be individualized and based primarily on site of recurrence, prior therapy, and the patient’s overall clinical and neurologic condition. Patients who deferred initial radiotherapy may derive palliative benefit at relapse. Most recurrent PCNSL remains chemosensitive, with responses reported using re-induction with methotrexate, temozolomide, topotecan, rituximab, thiopeta, and other single- or multi-agent regimens.\textsuperscript{64-66}

**Primary Intraocular Lymphoma**

Primary intraocular lymphoma is a subset of the PCNSL involving the vitreous or the retina, and it should be approached in an identical manner to PCNSL. The risk of subsequent recurrence elsewhere in the CNS is as high as 80%.\textsuperscript{67} Diagnosis is made with a slit lamp examination, but vitreal aspirates or vitrectomies are sometimes required. Although radiotherapy to the globes is almost always successful, relapse is common. Treatment with high-dose methotrexate or cytarabine in combination with ocular radiotherapy is the best approach. Alternatively, intra-vitreal injections of methotrexate or thiopeta have been successfully used in some patients.\textsuperscript{26,35,36}

**HIV-Related PCNSL**

Since the advent of highly active antiretroviral therapy (HAART), the incidence of HIV-related PCNSL has substantially declined, and therapeutic options for affected patients have improved. Low CD4 count and elevated peripheral viral load are the most important risk factors. The patient population tends to be younger (median 37 years) and predominantly male. Most HIV-related PCNSL is of the B-cell phenotype. However, in distinction to PCNSL in the immunocompetent population, the majority of HIV-related PCNSL has associated EBV DNA. Single-photon emission CT (SPECT) scanning using thallium-201 may be used to distinguish between CNS toxoplasmosis in the AIDS patient and PCNSL. It has both a sensitivity and a specificity approaching 95%.\textsuperscript{68,69} In combination with positive CSF EBV titers, sensitivity and specificity of SPECT to diagnose PCNSL is 100%.\textsuperscript{70} Treatment should include initiation or optimization of HAART and aggressive antiviral therapy in addition to methotrexate-based chemotherapy.\textsuperscript{51,72}
Conclusions
Given the lack of an optimal therapeutic approach and the rarity of patients, it is critical that every patient diagnosed with PCNSL be considered for enrollment in a prospective trial (Table 5). Efforts are currently underway to foster international collaboration to enhance the understanding and treatment of this unique primary brain tumor.

References


