

Current management of primary central nervous system lymphoma

Jon Glass

Neurology and Neurological Surgery, Thomas Jefferson University, Philadelphia, PA, USA

Correspondence to: Jon Glass, MD. Associate Professor of Neurology and Neurological Surgery, Thomas Jefferson University, Philadelphia, PA, USA.

Email: Jon.glass@jefferson.edu.

Abstract: Primary central nervous system lymphoma (PCNSL) is a rare but treatable disease. The hallmark therapy is based on the use of high-dose intravenous methotrexate (HDMTX), with clinical trial data suggesting that a more aggressive and targeted chemoimmunotherapeutic approach, to include the use of targeted therapy with rituximab (RTX) and the addition of other chemotherapeutic agents, may improve prognosis and reduce or defer the need for radiation therapy. Understanding of the molecular basis of tumor growth and proliferation may allow for the use of new targeted agents.

Keywords: Brain tumor, primary; diffuse large B-cell lymphoma (DLBCL); non-Hodgkin lymphoma

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Introduction

Primary central nervous system lymphoma (PCNSL) is an extranodal non-Hodgkin's lymphoma, usually diffuse large B-cell lymphoma (DLBCL), confined to the brain or spinal cord parenchyma, leptomeninges or intraocular contents without evidence of systemic disease.

In the USA, its incidence is 0.47 per 100,000 people per year. It accounts for approximately 1% of all lymphomas and 2% to 5% of all primary brain tumors. The incidence is higher in patients with congenital or acquired immunosuppression, and may be seen up to 7% of patients with human immunodeficiency virus (HIV) infection.

In immunocompetent patients, the median age at diagnosis is 56 and there is a male predominance. Its incidence is increasing in the elderly population. The age of onset is younger in patients with immunosuppression (1).

In patients with immunosuppression, PCNSL is associated with Epstein Barr virus, whereas an association is rare in immunocompetent patients, though it may be seen in the elderly (2).

Pathology and pathogenesis

PCNSL is characterized pathologically by an angiocentric

appearance, with lymphoma and inflammatory cells surrounding small blood vessels. The vast majority, approximately 95%, of PCNSLs are DLBCL. However, T cell lymphomas constitute approximately 2%, with the remainder reported as being of other histologies, including lymphoblastic and small cell lymphomas (3).

DLBCL PCNSL contains unique genetic aberrations that may serve as targets for therapy. These support a late germinal origin and are most consistent with a late germinal cell exit B-cell. *BCL6* is seen in 60% of tumors, and has been associated with a worse prognosis. Interferon regulatory factor 4 (*IRF4/MUM1*) is positive in 95% of tumors. *BCL2* expression is likewise detectable in 95% of tumors. Increased *MYC* expression is also common (4).

Most mutations are common in the DLBCL and are not unique to primary CNS lymphoma. The B cell receptor (BCR) is frequently activated and may serve as a therapeutic target. Activation of other pathways including toll-like receptor and nuclear factor κ B are also found. These promote tumor cell proliferation and survival, and are related to mutations in one or more genes including *BCL2*, *BLNK*, *CARD11*, *CBL*, *CD79B*, *MALT1*, *MYD88*, *PAX5*, *PIM1*, *SHIP* and *TTF* genes (4,5).

However, PCNSL is unique given its central nervous

system tropism. The mechanism by which PCNSL cells are attracted exclusively to the central nervous system has not been fully elucidated. These cells are known to express a variety of adhesion molecules, and a number of chemokines, in particular CXCL-12 and CXCL-13 may be expressed by endothelium and microglia resulting in interactions with tumor cells that lead to extravasation and local infiltration. Additional interactions with the microenvironments may also have a role in tumor proliferation. However, the mechanism of CNS homing and tumor proliferation remains under investigation (4).

Diagnosis and approach to patient

Typically, PCNSL presents with progressive neurological signs and symptoms. The onset is usually rapid and progressive. One or more focal neurological deficits representing location of the neoplasm is the most common presentation, seen in approximately 60% of patients. Other common presentations are changes in mental status, signs of increased intracranial pressure, seizures and visual changes (that may reflect intra-ocular involvement). Seizures are less common. Primary presentation in the spinal cord is uncommon.

Typically, patients who presented with a focal neurological deficit for an encephalopathy will undergo a head computed tomography (CT) scan, which will often show a mass-like area and vasogenic edema. Magnetic resonance imaging (MRI) without and with contrast will provide further information into the etiology of any abnormality seen on MRI. In immunocompetent patients, MRI typically shows diffuse homogeneous contrast enhancement with T2 hypointensity and surrounding vasogenic edema. Most tumors are single (approximately 60%) and supratentorial. Tumors are typically found at the gray white junction or in the periventricular region. Frank meningeal involvement is seen in a small percentage of patients, though it is typically asymptomatic.

If PCNSL is suspected based on radiographic findings, glucocorticoids should be avoided for symptom control unless required for management of severe focal deficits or encephalopathy. These have a cytotoxic effect on primary CNS lymphoma, particularly at the time of presentation, which may lead to a false-negative biopsy.

A CT scan of the chest, abdomen and pelvis and a bone marrow biopsy should be performed to evaluate for systemic lymphoma. Positron emission tomography (PET) may be performed if necessary to clarify findings on CT scan (6).

A scrotal ultrasound should be performed in older males as there is an association between testicular lymphoma and brain lymphomas (6).

If feasible, all patients should undergo a lumbar puncture and a slit-lamp examination to determine the presence of meningeal and intra-ocular disease. A diagnosis made by cerebrospinal fluid (CSF) or vitreous cytology or flow cytometry may eliminate the need for brain biopsy. At the time of lumbar puncture, interleukin 10 (IL10) level should also be measured and followed in subsequent studies as the presence of a detectable IL10 level at the completion of therapy portends an early recurrence (7).

If central nervous system tissue is needed, a stereotactic or open biopsy may be performed for diagnosis. There is no need for tumor resection unless it is for symptom management. The amount of resection will not affect the outcome. In patients who have a significant response to corticosteroids prior to obtaining diagnostic tissue, steroids should be tapered and discontinued and biopsy deferred until the time of tumor regrowth. Likewise, a negative biopsy in this setting should be repeated on tumor recurrence. Pretreatment diagnostic evaluations should include testing for HIV, hepatitis B virus and hepatitis C virus (2,8).

Prognostic factors

In determining prognosis, age and performance status are highly relevant. Additional prognostic factors include the presence of an elevated LDH, elevated CSF protein and involvement of the brain structures. Ferreri *et al.* performed a retrospective review of 378 patients, scoring each of the following with one point: age greater than 60 years, performance status 2–4, elevated LDH, elevated CSF protein and involvement of the brain structures. Patients with a score of 0–1 had a two-year overall survival (OS) of 80%±8% those with a score of 2–3 had a 2-year OS of 48%±7%, and those with a score of 4–5 had a 2-year OS of 15%±7% ($P=0.00001$) (9).

The G-PCNSL-SG-1 trial (10) identified age (<60 *vs.* over 60 years), Karnofsky Performance Score (70 or above *vs.* less than 70), and body mass index over 25 were strongly associated with improved OS.

Treatment

Until the late 1980s, PCNSL were routinely treated with whole-brain radiation therapy (WBRT). A prospective

Table 1 Chemotherapeutic regimen for newly diagnosed PCNSL

Reference [year]	Regimen	N	PFS (months)	Median OS (months)
Abrey [2000] (18)	MTX 3.5 g/m ² , PCB, VCR, IT MTX, ARA-C, WBRT	52	129	51
Batchelor [2003] (19)	MTX 8 g/m ²	25	13	55
Bessell [2001] (20)	MTX 1.5, CTX, DOX, VCR, dexamethasone, BCNU, ARA-C, WBRT	57	N/A	40
DeAngelis [1992] (5)	MTX 1 g/m ² , IT MTX, ARA-C, dexamethasone, WBRT	31	41	43
DeAngelis [2002] (16)	MTX 2.5, PCB, VCR, IT MTX, WBRT	98	24	37
Ferreri [2006] (21)	MTX 3.5 g/m ² , ARA-C, idarubicin, thiotepa, WBRT	41	13	15
Ferreri [2009] (22)	MTX 3.5 g/m ² WBRT or MTX 3.5, ARA-C, WBRT	40/39	5/9	10/31
Glass [1994] (15)	MTX 3.5 g/m ² , WBRT	25	32	33
Glass [2016] (23)	MTX 3.5 g/m ² , RTX, TMZ, hyperfractionated WBRT	53	65	90 (Est)
Herrlinger [2002] (24)	MTX 8 g/m ²	37	10	25
Morris [2013] (25)	MTX 3.5 g/m ² , RTX, VCR, PCB, ARA-C, reduced dose WBRT	52	4	79
Omuro [2005] (26)	MTX 1 g/m ² , PCB, thiotepa, ITMTX, WBRT	17	18	32
Pels [2003; 2009] (27,28)	MTX 5 g/m ² , VCR, IFOS, cyclophosphamide, vindesine, dexamethasone, IT MTX, ARA-C, prednisolone or MTX 5, VCR, IFOS, CTX, vindesine, dexamethasone	65/17	21/9	54/30
Poortmans [2003] (29)	MTX 3 g/m ² , teniposide, BCNU, methylprednisolone, IT MTX, ARA-C, hydrocortisone, WBRT	52	N/A	46
Thiel [2010] (10)	MTX 4 g/m ² +/- IFOS 1.5 g/m ² with or without WBRT	164 (WBRT);154 (no RT)	18/12	32/37
Wieduwilt [2012] (30)	MTX 8 g/m ² , RTX, TMZ, etoposide, ARA-C	31	24	66

ARA-C, cytarabine; BCNU, carmustine; CTX, cyclophosphamide; DOX, doxorubicin; IFOS, ifosfamide; IT MTX, intrathecal methotrexate; MTX, methotrexate; OS, overall survival; PCB, procarbazine; PFS, progression-free survival; RTX, rituximab; VCR, vincristine; WBRT, whole brain radiation therapy; N/A, not addressed in study.

clinical trial from the radiation therapy oncology group (RTOG) treated patients with 40 Gy of WBRT with a 20 Gy boost to the tumor. The median OS was 12.2 months (11). A follow-up trial from RTOG treated patients with cyclophosphamide, doxorubicin, vincristine and dexamethasone (CHOD) prior to radiation therapy with a similar regimen. While there were objective radiographic responses to treatment, the median survival was not much improved (16.1 months) (12).

Anecdotal reports in the 1970s led to high-dose intravenous methotrexate (HDMTX) being identified as highly active in obtaining objective radiographic responses in patients with newly diagnosed PCNSL (13). DeAngelis and colleagues at Memorial Sloan Kettering Medical Center treated a series of patients with HDMTX and intrathecal (IT) methotrexate followed by WBRT, with a

resulting improvement in progression free survival (PFS) and OS (14). These findings were subsequently reproduced (15), and a prospective clinical trial (RTOG 93–10) confirmed the efficacy of HDMTX followed by radiation therapy (16). Methotrexate based chemotherapy is now the basis and standard of care for the treatment of PCNSL.

Since that time, there have been many single institution, multi institution and cooperative group trials that have sought to define optimal treatment for PCNSL. Strategies have included the addition of different antineoplastic agents to methotrexate, the escalation of chemotherapy dosing (high dose chemotherapy with stem cell support), the addition of a targeted agent [rituximab (RTX)] to treatment and evaluation of strategies to eliminate radiation therapy (17). A sampling of these trials is detailed in *Table 1*. There has,

thus far, been no clear evidence that the intensification of chemotherapy with the use of additional cytotoxic agents provides any survival advantage, though objective response rates and PFS may be improved (31).

The role of radiation therapy in the treatment of PCNSL is pertinent, as improved survival allows for the emergence of late neurological effects of radiation therapy, in particular leukoencephalopathy, resulting in cognitive decline and dementia (32).

Neurotoxicity as a result of whole brain radiation therapy has been a driving factor in the reduction in radiation dose or in the elimination of radiation altogether. Late neurotoxicity, in most cases leukoencephalopathy, were seen in 20% to 50% of patients, especially in those older than 60 (33,34).

In 1991, Neuwelt *et al.* demonstrated that intensive chemotherapy with osmotic blood brain barrier opening and no initial WBRT resulted in prolonged median OS without cognitive decline (35).

Batchelor *et al.* published results of a clinical trial in which patients received methotrexate-based chemotherapy with deferred radiation therapy. While PFS was not affected, OS was similar to that of other clinical trials (19).

The German PCNSL study group performed a randomized clinical trial in which patients were randomized to receive whole brain radiotherapy immediately after initial methotrexate based chemotherapy or deferred radiotherapy (at relapse). Patients randomized to deferred therapy received no treatment with a complete response and cytarabine without a complete response after completion of initial chemotherapy. Of the 208 patients in the deferred radiation arm, 112 did not have a complete response. Of these, 68 were treated with cytarabine per protocol, 33 received radiation therapy and 11 no treatment. There was no statistically significant difference in median OS or PFS between the two groups (10).

Reductions in WBRT dosing have also been investigated. In RTOG 93-10, patients were initially treated with WBRT to a dose of 45 Gy. Evidence of late radiation effect (leukoencephalopathy) prompted a change in dosing during this study to 36 Gy in twice daily fractions (16). There was an apparent reduction in leukoencephalopathy in patients receiving this dose. The subsequent RTOG trial, 02-27, used this protocol in all patients and had a low rate of delayed neurotoxicity (23).

Rubenstein *et al.* provided patients with high-dose methotrexate, temozolomide and RTX followed by consolidation chemotherapy with intravenous etoposide and

cytarabine (CALGB/Alliance 50202). The time to tumor progression was 4.0 years with median OS not reached at the time of provocation (36).

RTOG 11-14 randomized patients between low-dose radiation therapy (23.4 Gy) and no initial radiation therapy (immediate consolidation with cytarabine). The results of this clinical trial are still pending.

The inclusion of a targeted therapy, RTX, has become standard in initial treatment regimens. While there is evidence that RTX improves radiographic response rates (37) there is no evidence that it improves PFS or OS (38).

High-dose chemotherapy with stem cell support can provide effective treatment at relapse. It has been used in a limited fashion as initial therapy in a number of academic centers, though it is overall improving outcomes has not been fully elucidated in this population (39-43).

Treatment at relapse

The optimal treatment of recurrent disease has not been fully elucidated. Patients not previously receiving radiation therapy may be rechallenged with methotrexate. The use of methotrexate in patients previously treated with radiation therapy increases the risk of leukoencephalopathy. Options for treatment at relapse are detailed in *Table 2*. Systemic treatment at relapses includes temozolomide monotherapy, RTX, RTX combined with temozolomide and other forms of chemotherapy.

Intrathecal therapy

While meningeal dissemination of disease is frequency PCNSL at presentation, there is no evidence that its addition to initial treatment improves outcomes (58). Methotrexate enters the CSF in amounts sufficient to have a cytotoxic effect on meningeal lymphoma. Patient's to have refractory or relapsed disease may benefit from intrathecal chemotherapy. Intrathecal therapy can include methotrexate, cytarabine or liposomal cytarabine (59).

Primary vitreoretinal lymphoma (PVRL)

PVRL is a DLBCL involving the contents of the eyes in the absence of evidence of systemic disease. It will typically present as visual loss including blurred vision, loss of visual acuity and floaters. Disease is most often present in both eyes, though may be symptomatic in only one eye. Diagnosis may be made by vitrectomy and cytologic examinations.

Table 2 Treatment of recurrent disease

Reference [year]	Regimen	N	Median PFS (months)	Median OS (months)
Arellano-Rodrigo [2003] (44)	Etoposide, IFOS, ARA-C	16	3	7
Chamberlain [2014] (45)	Bendamustine	12	3.5	5.5
Chamberlain [2016] (46)	ARA-C	14	5	12
Enting [2004] (47)	RTX + TMZ	15	2	14
Fischer [2006] (48)	Topotecan	27	2.0	8.4
Herrlinger [2000] (49)	PCV	7	N/A	16
Hottinger [2007] (50)	WBRT	48	10	16
Mappa [2013] (51)	RTX, IFOS, etoposide	5	21%±12% (2-year PFS)	25%±9% (2-year OS)
Pentsova [2014] (52)	MTX	39	16	41
Raizer [2012] (53)	Pemetrexed	11	5.7	10.1
Reni [2007] (54)	TMZ	36	3	4
Rubenstein [2007] (55)	IT RTX	5	N/A	5
Soussain [2008] (56)	ARA-C, etoposide, thiotepa, busulfan, cyclophosphamide	43	11.6	18.3
Welch [2015] (57)	Thiotepa, busulfan, cyclophosphamide	17	Not reached	Not reached

ARA-C, cytarabine; IFOS, ifosfamide; IT RTX, intrathecal rituximab; MTX, methotrexate; RTX, rituximab; OS, overall survival; PCV, procarbazine, lomustine, vincristine; PFS, progression-free survival; WBRT, whole brain radiation therapy.

Measurement of IL10 is also helpful (60,61). All patients with PVRL should be screened at the time of presentation and subsequently for central nervous system disease. Intra-ocular involvement is present in approximately 15 percent of all patients with PCNSL at initial presentation. In patients presenting with PVRL without central nervous system involvement, there is a 65% to 90% chance of progression to PCNSL (60). The optimum treatment for PVRL has not been determined. Treatment options include ocular radiation with or without systemic chemotherapy or intravitreal chemotherapy (methotrexate, RTX). Systemic chemotherapy produces temporary responses with a high recurrence rate.

Other targeted therapies

The use of targeted therapies has attracted attention in the treatment of PCNSL. RTX, and anti CD20 monoclonal antibody, is the only targeted therapy that is currently use. However, large molecules such as RTX have limitations owing to their inability to cross an attack blood brain barrier. While objective responses can be obtained with RTX, this occurs in the setting of a blood brain barrier

breakdown and the ability of RTX to enter the brain parenchyma and effectively treat the lymphoma. However, treatment including corticosteroids and chemotherapy may result in reconstitution of the blood-brain barrier, eliminating its efficacy. Smaller molecules that are able to cross the blood brain barrier. The BCR transduction cascade has a potential target in Bruton's tyrosine kinase, which is a target for a commercially available agent, ibrutinib. Another driver in CNS lymphoma is BCL6, which a number of targeted agents are undergoing clinical trials. Another commercially available targeted therapy, lenalidomide, targets IRF4/MUM1. The JAK/STAT signaling pathway is also implicated in tumor proliferation and targeted agents are under investigation in other cancers (62).

Conclusions

PCNSL is a lymphoma isolated to the central nervous system and intra-ocular contents that is sensitive to cytotoxic chemotherapies. The optimum treatment has not yet been determined, but treatment is methotrexate based, often in association with other forms of chemotherapy or

with RTX. The early use of radiation therapy does not ultimately affect outcomes, and may be deferred until tumor recurrence. Investigations are ongoing into the optimum treatment for this disorder, including optimum chemotherapeutic and radial therapeutic approaches and targeted therapies.

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Footnote

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