5 ■ PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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QUICK HIT ■ PCNSL accounts for about 4% of primary brain tumors with common occurrence in the immunosuppressed population. Treatment options include MTX-based CHT ± consolidation with WBRT, Ara-C ± etoposide, or high-dose CHT followed by autologous SCT. Careful patient selection and clinical trial availability often determine therapy (Table 5.1).

Table 5.1: General Treatment Paradigm for Primary CNS Lymphoma

Induction Phase	Consolidation Phase After Complete Response
MTX-based CHT	Observation
	WBRT to 23.4 Gy/13 fx (higher dose or boost if <CR)
	Ara-C ± etoposide
	High-dose CHT + ASCT

EPIDEMIOLOGY: PCNSL accounts for about 4% of primary brain tumors, with a yearly age-adjusted incidence of 4 per million.[1] In the mid-1990s, the incidence rose significantly but since then has declined due to improvements in the management and incidence of HIV/AIDS. However, the incidence rate within immunocompetent older adults has risen in the past decade.[2] The median age of diagnosis is in the 60s.[3] It is considered an AIDS-defining illness, and those with an HIV infection have a 3,600-fold increased risk of developing PCNSL.[2] In this population, EBV infection is associated with PCNSL development.

RISK FACTORS: Congenital or acquired immunodeficiency: HIV infection, iatrogenic immunosuppression, severe combined immunodeficiency, Wiskott–Aldrich syndrome, ataxia–telangiectasia, or common variable immunodeficiency. In immunocompetent patients, the risk factors are less established. It is unclear if autoimmune disease is considered a true risk factor.[4]

ANATOMY: Presentations include intracranial, leptomeningeal, periventricular, vitreous, and/or spinal lesions. Location in order of decreasing frequency: frontal lobe, parietal lobe, temporal lobe, basal ganglia, corpus callosum, cerebellum, brainstem, insula, occipital lobe, and fornix.[3] Twenty percent of cases involve the eyes (commonly bilateral) and about 1% have isolated spinal cord involvement, typically involving the lower cervical or upper thoracic regions.[5]

PATHOLOGY: The large majority (90%–95%) of PCNSL are diffuse large B-cell lymphomas, with the other 5% to 10% composed of Burkitt, lymphoblastic, marginal zone, or T-cell lymphoma. Neoplastic B lymphocytes are classically described by "perivascular cuffing" with expression of CD20, CD19, CD22, BCL-6, and IRF4/MUM1; markers of B-cells, germinal center B-cells, and late germinal center B-cells, respectively.[5]

CLINICAL PRESENTATION: The clinical presentation is highly variable depending on location of disease (see Table 5.2). The majority of patients present with a single lesion (66%). Nonspecific symptoms include confusion, lethargy, headaches, focal neurologic deficits, neuropsychiatric symptoms, increased intracranial pressure, or seizures.[5] In a small percentage of patients (10%–15%), gastrointestinal symptoms or respiratory illness may be seen before manifestation of neurological symptoms.[3]

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Table 5.2: Presentation of Primary CNS Lymphoma by Location	
Primary cerebral lymphoma	Focal deficits (70%), neuropsychiatric symptoms (43%), increased intracranial pressure (33%), seizures (14%)[3]
Primary leptomeningeal lymphoma	Cranial neuropathies (58%), spinal symptoms (48%), headache (44%), leg weakness (35%), ataxia (25%), encephalopathy (25%), bowel and bladder dysfunction (21%)[6]
Primary intraocular lymphoma	Ocular complaints (62%), behavioral/cognitive changes (27%), hemiparesis (14%), headache (14%), seizures (5%), ataxia (4%), visual field deficit (2%)[7]
Primary spinal lymphoma	Myelopathies[8]
Neurolymphomatosis	Painful neuropathies including sensorimotor or pure sensory neuropathy, and pure motor neuropathy[9]

WORKUP: The International PCNSL Collaborative Group[10] recommends the following: H&P with complete neurologic and lymphatic exam including peripheral lymph nodes and testicular exam. Mini-Mental State Exam. Document performance status. Ophthalmologic and slit-lamp exam.

Labs: LDH, liver function tests, renal function tests, HIV status. Lumbar puncture (at least 1 week after surgery) with assessment of CSF cytology, total protein, cell count, glucose, beta-2 microglobulin, immunoglobulin heavy gene rearrangement, and flow cytometry.[6]

Imaging: Contrast-enhanced MRI brain; if spinal symptoms are present, MRI spine. CT chest, abdomen, pelvis with IV contrast or whole body PET/CT scan. Consider testicular ultrasound in men over age 60 or patients who have positive findings on physical exam.

Biopsy: Stereotactic needle biopsy is standard. Needle biopsy is preferred to surgical resection due to less risk and no clinical benefit with surgical resection. An ocular biopsy or CSF cytology can also be used for diagnosis.[7] Bone marrow biopsy is also indicated. If biopsy is nondiagnostic in the context of steroids, discontinue steroids and rebiopsy or repeat CSF evaluation at progression.[11]

PROGNOSTIC FACTORS: No formal staging system exists for PCNSL, but multiple prognostic systems have been described, as in the following tables (Tables 5.3 & 5.4).

Table 5.3: IELSG Score for Primary CNS Lymphoma[12]			
Number of Risk Factors	**2-Yr OS: All Patients**	**2-Yr OS (With High-Dose MTX)**	Risk factors: age >60, ECOG PS >1, elevated LDH, elevated CSF protein concentration (45 mg/dL in patients ≤60 years old; 60 mg/dL if >60 years old), and involvement of deep structures of the brain (e.g., periventricular regions, basal ganglia, corpus callosum, brainstem, cerebellum)
0–1	80% ± 8%	85% ± 8%	
2–3	48% ± 7%	57% ± 8%	
4–5	15% ± 7%	24% ± 11%	

Table 5.4: MSKCC Prognostic Classification[13]		
Class 1: ≤50 yrs	MS 8.5 yrs	FFS 2 yrs
Class 2: >50 yrs, KPS ≥70	MS 3.2 yrs	FFS 1.8 yrs
Class 3: patients ≥50 yrs, KPS <70	MS 1.1 yrs	FFS 0.6 yrs

TREATMENT PARADIGM

Surgery: Biopsy alone is sufficient for diagnosis. Surgical resection is not indicated. PCNSL involvement is classically widespread and involves deep brain structures. Therefore, surgical resection is potentially risky and has not been shown to increase OS.[5]

Chemotherapy: CHT is considered the mainstay of treatment. High-dose MTX (3.5–8 g/m^2) is standard and can be administered as monotherapy (older adults) or more commonly as multidrug therapy. The ideal combination regimen has yet to be defined but may include MTX, rituximab, and various

combinations of temozolomide, cytarabine, ifosfamide, procarbazine, and vincristine. After a complete response, consolidation therapy with Ara-C ± etoposide and ASCT are options.

Radiation

Indications: WBRT is used for consolidation after MTX-based CHT or for palliation. Historically, high-dose WBRT alone was the mainstay of treatment but is no longer considered the best long-term option for disease control. The utility of low-dose WBRT to 23.4 Gy/13 fx as consolidation approximately 3 to 5 weeks after CR remains controversial.[14] In patients >60 years old, WBRT in combination with MTX is concerning for neurotoxicity. It has yet to be determined if RT should be withheld in this patient population. Ocular RT can be considered for ocular involvement not responding to CHT. Consider WBRT for palliation in patients ineligible for CHT.

Dose: If WBRT is delivered after CR to CHT, standard is 23.4 Gy/13 fx. If PR, consider WBRT 30 to 36 Gy with boost to 45 Gy/25 fx.[11]

Toxicity: Acute: fatigue, headache, nausea, alopecia, skin erythema, high-frequency hearing loss, changes to hearing and taste, dry mouth. For ocular irradiation: dry eyes, less commonly retinal injury and cataracts. Late: Neurotoxicity changes such as short-term memory loss, verbal fluency/recall, gait changes, ataxia, Parkinson-like features, behavioral changes, and leukoencephalopathy.

Procedure: See *Handbook of Treatment Planning in Radiation Oncology,* Chapter 3.[15]

Medical: Traditionally, corticosteroids are held prior to biopsy unless medically necessary.[16] After biopsy, steroids can be used for quick alleviation of neurologic symptoms. Radiologic regression can be transiently seen with steroids in about 40%, which is suggestive but not diagnostic of PCNSL.

■ EVIDENCE-BASED Q&A

■ What is the role for radiation therapy alone for PCNSL?

Historically, RT alone was the initial treatment for PCNSL. However, WBRT alone has shown little success in long-term disease control with high rates of local recurrence.

Nelson, RTOG 8315 (*IJROBP* 1992, PMID 1572835): Single-arm phase II of 41 patients treated with 40 Gy WBRT plus 20 Gy boost to tumor bed plus 2 cm margin. MS 12.2 months. 62% CR. The main location of relapse was at the local site of disease. High KPS and CR were associated with increased OS. **Conclusion: PCNSL shows a good response to WBRT alone, but local recurrence is common.**

■ Can combination CHT with WBRT improve outcomes when compared to WBRT alone?

DeAngelis, RTOG 9310 (*JCO* 2002, PMID 12488408): Multicenter, single-arm phase II prospective study evaluating upfront MPV (methotrexate, procarbazine, vincristine) CHT combination with RT; 102 immunocompetent patients were enrolled; 5 cycles of MTX 2.5 g/m^2, vincristine, intra-Ommaya MTX, procarbazine, and consolidation WBRT followed by Ara-C. WBRT was 45 Gy (1.8 Gy/fx) in 63 patients, but due to late neurotoxicity seen with this dose, 16 patients who achieved CR after induction received 36 Gy (1.2 Gy/fx BID) for 15 days instead; 34% relapsed during follow-up period. Median PFS 24 months, MS 36.9 months. Between 45 Gy WBRT and 36 Gy hyperfractionated RT (1.2 Gy BID); there was no difference noted in PFS (24.5 months vs. 23.3 months; $p = .81$) and OS (37 months vs. 47.9 months; $p = .65$). Side effects of RT included the following: myelosuppression (63%) and delayed neurologic toxicities classified mostly as leukoencephalopathy (15%); 8 cases of the neurologic toxicities progressed to fatalities. **Conclusion: HD-MTX in combination with other agents improved survival compared to historical rates of RT alone. This CHT combination provides a high response rate, but in conjunction with WBRT there is a significant late risk of neurotoxicity.**

■ Is consolidation WBRT superior to CHT alone?

Thiel (*Lancet Oncol* 2010, PMID 20970380): Phase III PRT to compare HD-MTX vs. HD-MTX plus WBRT; 551 patients received 6 cycles of HD-MTX and HD-MTX plus ifosfamide and were randomly assigned to immediate WBRT (45 Gy/30 fx of 1.5 Gy) or delayed WBRT. For patients with PR after

CHT, they received high-dose Ara-C or WBRT; 13% died during initial CHT. In addition, there was a high dropout rate, leaving 318 patients to be analyzed. In HD-MTX + WBRT patients, MS was 32.4 months and median PFS was 18.3 months. In patients who received CHT alone, the MS was 37.1 months and median PFS was 11.9 months. Neurotoxicity was higher in the WBRT group vs. the non-WBRT group in both clinical (49% vs. 26%) and neuroradiology (71% vs. 46%) assessment. **Conclusion: No statistically significant difference was found in OS or PFS between the WBRT + CHT and CHT alone, but the noninferiority end point of 0.9 was not met. Therefore, the study was unable to conclude if WBRT has an impact on OS when added to CHT. In addition, the neurotoxicity rates were greater in the WBRT cohort.** *Comment: A small percentage of patients were treated per protocol.*

■ Can the dose of WBRT be reduced to avoid neurotoxicity but still maintain benefit?

Morris, MSKCC Multi-Center Trial (*JCO* 2013, PMID 24101038): Single-arm phase II trial assessing consolidation with rd-WBRT 23.4 Gy and addition of rituximab to MPV; 45 Gy was delivered for those with PR. Of 52 patients, 31 achieved CR postinduction. Both CR and PR received Ara-C as consolidation after RT. In the rd-WBRT group, median PFS was 7.7 years, 5-year OS was 80%, and MS was not reached with an MFU of 5.9 years. For the entire cohort, median PFS was 3.3 years and MS was 6.6 years. No evidence of cognitive decline was observed, with the exception of motor speed. **Conclusion: rd-WBRT and Ara-C following R-MPV demonstrated good control with minimal neurotoxicity.**

■ What is the role of temozolomide?

Glass, RTOG 0227 (*JCO* 2016, PMID 27022122): Single-arm phase I/II trial of induction CHT (rituximab, TMZ, and MTX) followed by WBRT (36 Gy/30 fx at 1.2 Gy BID), followed by adjuvant TMZ. 53 patients treated in phase II portion. Primary end point 2-year OS. 2-year OS was 80.8% and PFS was 63.6%, significantly improved from historical controls; 66% of patients experienced grade 3 to 4 toxicities prior to WBRT, and 45% experienced grade 3 to 4 toxicities attributable to post-WBRT CHT. **Conclusion: Induction with rituximab, TMZ, and MTX followed by hyperfractionated WBRT is safe, with 2-year OS superior to that of historical controls.**

■ Does low-dose WBRT improve PFS as compared to CHT alone?

This is a question on the completed but not yet reported trial RTOG 1114. This trial delivers rituximab, methotrexate, procarbazine, vincristine, and cytarabine; randomizes to low-dose WBRT (23.4 Gy/13 fx) or no RT; and then delivers two additional cycles of cytarabine. The addition of WBRT is hypothesized to improve PFS, but this remains an open question.

■ Is there a role for stem cell transplant with high-dose CHT?

High-dose CHT plus autologous SCT has a role in both initial and salvage therapy for patients with PCNSL.[17,18] *However, more trials are needed to fully evaluate its potential. Two randomized trials have been designed to further test HCT + ASCT, CALGB 51101, and IELSG 32. CALGB 51101 examined consolidation HCT + ASCT vs. nonmyeloablative CHT; results are not yet reported.*

Ferreri, IELSG-32 (*Lancet Haematol* 2016, PMID 27132696 and *Lancet Haematol* 2017, PMID 29054815): International phase II study with double randomization investigating both MTX-based initial CHT and WBRT vs. HDT + ASCT as consolidation. For the first randomization, 227 HIV-negative patients with newly diagnosed PCNSL were randomized to MTX + cytarabine, MTX + cytarabine + rituximab, or MTX + cytarabine + rituximab + thiotepa; 219 patients were assessable with an MFU 30 months. CR rates for the 3 arms were 23%, 30%, and 49%, respectively, with arms 2 and 3 statistically significantly improved vs. arm 1, at the cost of greater hematologic toxicity in arm 3. For the second randomization, 118 patients with responsive or stable disease were randomized to WBRT 36 Gy (with a 9-Gy boost in patients with PR) or carmustine–thiotepa followed by ASCT. The primary end point was 2-year PFS. There were no significant differences in PFS between WBRT and ASCT (80% vs. 69%, $p = .17$). Hematologic toxicity was more common in the ASCT arm, and two patients died of infection. **Conclusion: WBRT and ASCT are both feasible and effective consolidation therapies following high-dose MTX-based induction therapy.**

How is response assessed in PCNSL?

According to the International PCNSL Collaborative group guidelines,[10] in order to assess response, MRI must be completed within 2 months of finishing treatment. LP and/or ophthalmologic exam must be completed if initially positive (Table 5.5).

Table 5.5: Response Criteria in PCNSL per International PCNSL Collaborative Guidelines[10]

Response	Steroid Use	Eye Exam	CSF	MRI
CR	None	Normal	Negative	No enhancement
Unconfirmed CR	Any	Normal or minor abnormality	Negative	No enhancement or minor abnormality
PR	N/A	Decrease in vitreous cells/ retinal infiltrate	Persistent or suspicious	≥50% decrease in enhancement
PD	N/A	New ocular disease	Recurrent or positive	≥25% increase or new lesion/site

What is the role of WBRT as salvage therapy?

WBRT provides an adequate option as salvage therapy for recurrent or refractory PCNSL. Other options include additional CHT or HDT + ASCT.

Nguyen (*JCO* 2005, PMID 15735126): Evaluation of 27 patients with tumor relapse or progression of a refractory tumor after primary CHT with HD-MTX. Salvage WBRT ± boost was delivered, with the majority (67%) of patients remaining on steroids. Median WBRT dose was 36 Gy (1.5 Gy/fx was most prevalent); 5 patients received a boost to a median dose of 10 Gy and 2 patients received an SRS boost of 12 or 16 Gy; 74% had either a CR (n = 10) or a PR (n = 10) to WBRT; 8 patients later progressed or recurred at a median 18.8 months post-WBRT. Delayed neurotoxicity was diagnosed in 3 patients, at a median of 25 months, with none resulting in death. **Conclusion: WBRT is an effective option in the salvage setting. For older patients, withholding WBRT until the time of progression may decrease neurotoxicity rates.**

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