How I Treat CNS Lymphomas

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Abstract

The pathogenesis of primary and secondary CNS lymphoma poses a unique set of diagnostic, prognostic and therapeutic challenges. During the past ten years there has been significant progress in the elucidation of the molecular properties of CNS lymphomas and their microenvironment as well as evolution in the development of novel treatment strategies. Once assumed to be uniformly associated with a dismal prognosis, it is now reasonable to anticipate long-term survival and possibly cure for a significant fraction of CNS lymphoma patients. The pathogenesis of CNS lymphomas impacts multiple compartments within the neuroaxis and proper management of the CNS lymphoma patient requires a multidisciplinary team with expertise not only in Hematology/Oncology but also in Neurology, Neuroradiology, Neurosurgery, Clinical Neuropsychology, Ophthalmology, Pathology and Radiation Oncology. Given the evolving principles of management and the evidence for improvements in survival, our goal is to provide an overview of current knowledge regarding the pathogenesis of CNS lymphomas, and to highlight promising strategies that we believe to be most effective in establishing diagnosis, staging, as well as therapeutic management.
Introduction

Central nervous system (CNS) involvement of non-Hodgkin's lymphoma (NHL) occurs in two patterns: (1) primary CNS lymphoma (PCNSL) which is limited to the brain parenchyma, intraocular compartment, cranial nerves, leptomeninges, and rarely spinal cord; (1, 2) (2) secondary CNS lymphoma (SCNSL) in which there is concomitant systemic as well as CNS localization of lymphoma, often within the leptomeningeal compartment.

PCNSL is a rare brain tumor with an annual incidence in the United States of approximately 1,900 new cases year. While PCNSL constitutes approximately 3% of all newly-diagnosed brain tumors, and 2-3% of all cases of non-Hodgkin's lymphoma (NHL), the Surveillance, Epidemiology and End Results (SEER) database suggests that the incidence of this neoplasm may be increasing among patients age sixty-five and older, with patients older than seventy-five having the highest incidental risk. (3)

Because CNS complications of NHL are relatively rare, there is limited prospective and/or randomized data to guide therapy. Historically, CNS lymphomas have been associated with a very poor prognosis. (4) On the other hand, an accumulation of recent prospective phase I/II results as well as retrospective series demonstrate reproducible improvements in outcomes for patients with primary and secondary CNS lymphoma. (5-9) Because published evidence for therapeutic advances may not be uniformly reflected in population-based data, there is a possibility that patients in the community may not routinely receive optimal therapy. Our goal in this review is to highlight areas of progress and to provide an overview of current knowledge regarding the pathogenesis of primary and secondary CNS lymphomas. In addition, we will illuminate strategies that we believe to be most effective in establishing diagnosis, staging, as well as in therapeutic management.
Etiology of CNS Lymphomas

As for most other types of non-Hodgkin’s lymphomas, the etiology of CNS lymphomagenesis is largely undefined and the mechanistic basis for brain tropism is not understood. The most significant risk factors for CNS involvement of lymphoma are acquired or congenital immunodeficiency states. Patients with Wiskott-Aldrich syndrome, ataxia-telangiectasia and severe-combined or common-variable immunodeficiency have a 4% lifetime risk for developing PCNSL. The lifetime risk for development of CNS post-transplant lymphoproliferative disorder is 1-2% for renal transplant patients and 2-7% for cardiac, lung and liver transplant recipients with a probable etiologic relationship between PCNSL and T-cell specific immunodeficiency caused by agents such as mycophenolate mofetil. PCNSL is also an AIDS-defining illness associated with a very low CD4 T-cell count (below 50 cells/μl) and, like post-transplant lymphoproliferative disorder shares a near 100% association with Epstein Barr Virus (EBV). While only 20% of systemic AIDS-related lymphomas are associated with EBV, infection of the tumor clone by EBV appears to significantly increase the risk of CNS involvement. By contrast, EBV infection is rarely detected in CNS lymphomas that develop in immune-competent patients, consistent with a distinct pathogenesis.

Histology and Molecular Pathogenesis

Among immunocompetent patients, PCNSL usually presents as a solitary supratentorial mass within periventricular white matter, often with subependymal spread and significant vasogenic edema and mass effect: the displacement of normal brain structures. The frequency of multiple lesions is increased two-fold in the immune suppressed. It is well-established that the radiographic as well as gross appearance of the tumor underestimates the extent of disease as PCNSL can be highly-infiltrative,
particularly at relapse, prompting its designation as "a whole brain disease."(12) A
unique histopathologic feature of most CNS lymphomas is that of angiotropism in which
lymphoma cells preferentially accumulate around small blood vessels, likely disrupting
the integrity of the blood-brain barrier. (Figure 1).

Approximately 95% of PCNSL tumors are CD20+ diffuse large B-cell lymphoma;
less common histologies include T-cell PCNSL (2%)(13), Burkitt, lymphoblastic, and
intraparenchymal marginal zone lymphoma. Notably, dural-based marginal zone
lymphomas, devoid of intraparenchymal extent, share overlapping radiographic features
with meningioma and are not protected by the blood-brain barrier.

Nearly twenty percent of PCNSL cases present with intraocular involvement with
cellular infiltrates in the vitreous, retina and with lymphoid hyperplasia of the uveal tract.
In some cases, thickened choroid invested with lymphoma may extend into the orbit. It
is important to recognize that intraocular lymphoma progresses to clinically-evident CNS
lymphoma in at least 80% of cases, and thus mandates staging procedures
commensurate with this risk.(14)

Montesinos-Rongen and colleagues demonstrated that PCNSL exhibits somatic
hypermutilation of genes such as BCL6, MYC, PIM1, PAX5, suggesting that the
neoplastic cells of PCNSL DLBCL are derived from antigen-selected B-cells exposed to
the germinal center,(15) and while only 10-20% are CD10 positive, between 50% to 80%
of tumors express significant levels of BCL-6.(16) Nevertheless, these tumors exhibit a
near-uniform activated B-cell like immunophenotype in that 95% stain positive for MUM-
1, consistent with overlapping features of germinal center and activated B-cell
phenotypes.(17)

Determination of the unique genetic features of PCNSL poses a greater
challenge than for systemic DLBCL, both because of the rarity of this neoplasm and
because of the paucity of material available for investigational studies after the diagnosis
is established. Most specimens are obtained by stereotactic needle biopsy or via cytologic analysis of cerebrospinal fluid. Based upon the fact that PCNSL tumors require distinct therapeutic protocols and display unique transcriptional features by gene expression profiling, (18-21) PCNSL is recognized as a distinct subtype of large B-cell lymphoma by the WHO Working Group.(22)

Frequent genomic aberrations in PCNSL include focal losses on chromosome 6p21 containing the HLA locus, as well as deletions on chromosome 6q21-6q25. (23-25) Silencing of CDKN2A, a cell cycle regulator, by deletion or by DNA methylation, occurs in approximately half of CNS lymphoma cases and may correlate with adverse prognosis.(26, 27) Several candidate tumor suppressor genes are linked to deleted loci on chromosome 6q including PRDM1, a regulator of B-cell differentiation and tumor suppressor,(28) PTPRK, a protein tyrosine phosphatase which regulates cell adhesion,(29) and A20 (TNFAIP3), a regulator of NFκB signaling. (30) Aberrant activation of the NFκB pathway in PCNSL,(31) is supported by increased DNA copy number for MALT1,(26) activating mutations of CARD11(32) as well as of MyD88 (toll-like receptor pathway). The activating exchange of leucine to proline at position 265 of MyD88, noted to occur in between 38% (11/29) to 50% (7/14) of patients, is the most frequent mutation thus far identified in PCNSL. (27, 33) In addition, the coding region of CD79B, a component of the B-cell receptor signaling pathway, appears to contain mutations in 20% of cases, suggesting that dysregulation of the B-cell receptor and NFκB pathways contribute to the pathogenesis of PCNSL. (34)

Elucidation of mechanisms responsible for the selective tropism of lymphoma to the brain microenvironment is a question central to the pathogenesis of PCNSL. Expression of the B-cell chemokines CXCL12 and CXCL-13 by intraocular and CNS lymphomas has been documented.(35-37) Each of these peptides promote chemotaxis
of cells isolated from CNS lymphoma lesions, consistent with neurotropic factors in CNS lymphoma. Moreover, elevated concentrations of CXCL13 in CSF correlates with adverse prognosis, supporting its role as a potential survival factor. Measurement of CSF concentration of CXCL13 as well as IL-10 may also be useful in facilitating the diagnosis of CNS lymphoma, both at diagnosis as well as relapse.(38)

Transcriptional profile studies of PCNSL have identified a number of potential mediators of disease pathogenesis including upregulated expression of MYC.(19) Evidence for increased MYC expression was also observed in an independent immunohistochemical analysis of diagnostic specimens of PCNSL patients enrolled in CALGB (Alliance) 50202.(5) Selective upregulation of miRNA's associated with the MYC pathway (miR-17-5p, miR-20a, miR-9) was also demonstrated in an analysis comparing microRNA's (miRNA's) between PCNSL and nodal DLBCL.(39)

The JAK/STAT pathway may also contribute to survival signaling in PCNSL. Expression of Interleukin-4 (IL-4), a B-cell growth factor which signals via the JAK/STAT pathway, is upregulated within the vascular microenvironment in CNS lymphoma.(19) Increased levels of Interleukin-10 (IL-10) protein in vitreous fluid and in CSF are associated with the pathogenesis of PCNSL and correlate with adverse prognosis.(40, 41) JAK1 transcripts are increased in PCNSL (19, 42) with evidence for intratumoral JAK1 activation. (40) Elevated expression of IL-10 as well as activation of JAK/STAT signaling in PCNSL are consistent with aberrant activation of the MyD88 pathway (43).

Clinical Presentation

In a recent retrospective series of patients with a history of rapidly progressive neurological deterioration who presented for diagnostic brain biopsy, the most common etiology was PCNSL (20%). Among immunocompetent patients, the median age at diagnosis of PCNSL is 56 years with a male-to-female ratio of 1.2-1.7:1. The clinical presentation of PCNSL usually reflects the neuroanatomical location of the lesion(s).
Greater than 60% of patients present with either cognitive, motor or constitutional symptoms; 30% have visual symptoms at presentation and 20% present with seizures.(44) Concomitant leptomeningeal disease, which occurs in approximately 15-20% of patients at presentation, is typically asymptomatic.(45) Isolated cranial nerve, spinal cord and/or cauda equine involvement at presentation is rare. Intraocular lymphoma is associated with blurred vision, decreased acuity, photophobia, eye pain and floaters, usually with involvement of both eyes.

**Diagnostic and Staging Evaluation**

Because CNS and intraocular lymphoma patients typically present with nonspecific signs and symptoms, establishing a diagnosis may be difficult. A magnetic resonance-based examination of the brain, with gadolinium contrast, is the recommended first imaging test in diagnostic evaluation. In 95% of cases, there is homogenous enhancement localized to the tumor with rare necrosis, one of the radiographic features that helps to distinguish CNS lymphomas from glioblastoma. Among immunocompetent patients with newly-diagnosed PCNSL, lesions are solitary in 65% and multifocal in 35%. Cerebral hemisphere disease is most common (38%) followed by lesions within the thalamus/basal/ganglia (16%), corpus callosum (14%) ventricular region (12%) and cerebellum (9%).(46) (Figure 2).

While initial treatment with glucocorticoids may produce rapid symptomatic improvement, with associated dramatic radiographic responses in approximately 40% of patients, steroid-induced responses may increase the risk of a non-diagnostic brain or vitreal biopsy.(47) Steroid-induced diagnostic delays may extend weeks to months, although we and others have noted rare cases in which steroid-induced regressions of sentinel lesions appear to delay a diagnosis of PCNSL for several years.(48) Notably however, after an initial exposure, re-challenge of PCNSL tumors with glucocorticoids sometimes yields a weaker lymphocytotoxic response. In any case, it is recommended
that if possible, empiric administration of dexamethasone or other glucocorticoids be delayed or tapered until a diagnosis is established. If CNS lymphoma is confirmed, steroids should be tapered as quickly as possible, unless there is symptomatic tumor-associated mass effect that is reversed by glucocorticoids.

The most commonly used diagnostic approach for PCNSL is stereotactic brain biopsy, in selected cases however, partial or gross total resections may be appropriate. Cytologic and/or flow-cytometric analysis of meningeal lymphoma cells isolated from CSF or via pars plana vitrectomy may also yield diagnostic material. In the setting of significant tumor-associated mass-effect, particularly in the posterior fossa, a neurosurgical consult may be indicated to evaluate the safety of a diagnostic or staging lumbar puncture. CSF should be efficiently processed for analyses which includes cell count, protein and glucose concentration, cytology and flow-cytometric studies designed to identify, in most cases a kappa or lambda-restricted B-cell neoplasm. Our experience has been that repeated CSF cytological or flow-cytometric studies infrequently improves diagnostic yield in PCNSL, supporting development and implementation of other types of molecular diagnostic methods using CSF.(38, 40, 49)

Additional standard pretreatment staging tests for PCNSL include complete ophthalmologic examination including slit lamp, contrast-enhanced computed tomography (CT) scan of the chest, abdomen and pelvis, as well as bone marrow biopsy. Systemic staging examinations are indicated, given that between 4-12 % of patients with presumptive PCNSL are ultimately found to have extra-CNS disease on evaluation.(50) Whether positron emission tomography imaging significantly improves yield in staging all PCNSL patients has yet to be defined.(51) On the other hand, clinical and/or ultrasound examination of the testes should be considered in older men in the work-up of presumptive PCNSL. Screening for HIV, hepatitis B and C serology, serum lactate dehydrogenase (LDH) as well as routine blood screening including baseline
electrolytes, renal and hepatic function tests are requisite in newly-diagnosed PCNSL.(52)

Because approximately 80% of intraocular lymphoma patients progress to CNS lymphoma, an MRI study of the brain with gadolinium should be performed in patients with idiopathic uveitis in which lymphoma is considered in the differential. Additional diagnostic tests for ocular lymphoma include fluorescence angiography and optical coherent tomography.(53) Flow-cytometric analysis of vitrectomy or biopsy material can be a highly accurate diagnostic modality, however again, rapid transportation of the specimen to the laboratory should be performed to achieve the greatest diagnostic yield.(14) Molecular analyses of immunoglobulin gene rearrangements and ocular cytokine levels demonstrating elevations in IL-10 with an IL-10/IL-6 ratio greater than 1.0 may be useful to aid in diagnosis.(54)

**Prognosis**

While PCNSL is classified as a stage IE form of non-Hodgkin’s lymphoma, clinical prognostication of this disease is based upon systems distinct from the Ann Arbor index. The International Extranodal Lymphoma Study Group described five parameters associated with poor prognosis in PCNSL, three of which are shared with systemic NHL: age older than 60 years, Eastern Cooperative Group performance status greater than 1, and elevated LDH; CNS lymphoma-specific parameters include high CSF protein concentration and tumor location within the deep regions of the brain (periventricular, basal ganglia, brainstem and/or cerebellum). Patient with 0 - 1, 2 - 3, or 4 - 5 of these adverse risk factors had two-year overall survival rates of 80%, 48% or 15% respectively.(55) While age is the most reproducible clinical prognostic factor cited in the literature, there is disagreement in regards to the specific age cut-point at which prognosis declines most reliably; while most studies specify an age of 60, the Memorial Sloan-Kettering prognostic index identified age 50 as the cutpoint at which prognosis
Notably, in a recent prospective multicenter study using an intensive immunochemotherapy regimen with dose-intensive consolidation, without whole brain irradiation, patients older than 60 did similarly well as younger patients, an observation that replicates the institutional experience with the same regimen, and suggests that the optimal cut-point for age as a prognostic variable may be dependent on type of treatment.

How I Treat CNS Lymphomas

Surgery

As above, the diagnosis of PCNSL is usually established by stereotactic brain biopsy and previously, authorities have recommended against planned resections of CNS lymphoma based upon evidence that aggressive surgery may increase risk of post-operative deficit and provides no survival benefit compared to biopsy alone. A recent retrospective analysis of the German PCNSL Study Group-1 (GPSG-1) Trial, a large randomized phase III study, has however, challenged this paradigm. According to their data, when controlled for the number of lesions, aggressive resection of CNS lymphoma correlated with improved progression-free survival with the regimen studied in this trial. We concur that in individualized cases, particularly in the setting of well-circumscribed lesions with significant mass effect and in which tumor debulking is deemed feasible with low risk of neurologic deficit, aggressive surgical cytoreductions may provide immediate relief of mass effect, facilitate the rapid tapering of glucocorticoids, and eliminate cell populations with drug resistance potential, and thus provide significant clinical benefit. Another key factor which may explain the discrepancy between the conclusions of previous studies and those of the GPSG-1 study, may relate to technical advances in neurosurgery that increase the safety of more aggressive resections. On the basis of this preliminary data, as well as our experience, we believe that in selected cases, aggressive resection of a CNS lymphoma
may be indicated, particularly in the setting of well-circumscribed lesions with significant mass effect in non-deep brain structures. The conclusions of the retrospective analysis of GPSG-1 trial are also not surprising considering previous evidence that extent of resection of newly-diagnosed as well as recurrent glioblastoma, another infiltrative brain tumor, positively correlates with improved survival.(60)

**Whole Brain Radiation**

In general, whole brain irradiation is highly effective in the generation of immediate responses to patients with CNS lymphoma and therefore this modality historically has been of value to patients who otherwise experienced a rapidly deteriorating course caused by an unusual type of brain tumor rarely encountered in community practice. The utility of whole brain radiotherapy in the treatment of CNS lymphoma is however limited by at least three factors: (1) Insufficient local control of lymphoma; (2) Dissemination of lymphoma cells within the CSF circulation, outside of the radiation field; (3) Detrimental effects of radiation on brain function. In one study, the use of whole brain radiation therapy as the sole treatment of PCNSL (36-40 Gy) yielded an overall response rate of 90% but a median overall survival of only 11.6 months with over 60% of patients experiencing progression of lymphoma within the irradiated field.(61)  There is also increasing recognition of the long-term neurotoxicity of whole brain radiotherapy which, as illustrated by Abrey and colleagues, is manifest by incontinence, gait and memory disturbances. In their series, patients age older than 60 years were most vulnerable to this complication and many required custodial care to manage this treatment-related toxicity.(62)  While there is evidence that lower doses of whole brain radiotherapy may cause less discernable neurotoxicity compared to standard doses, additional validation is necessary and based upon the evidence of deleterious neurocognitive effects of prophylactic cranial irradiation at 30 Gy,(63) it is logical to postulate that radiation-induced neurotoxicity may be a continuous variable.  Certainly
whole brain radiotherapy can be a highly effective first-line salvage for methotrexate resistance; nevertheless, during the past ten years there is increased interest in the development of strategies that defer or eliminate whole brain radiotherapy as induction therapy or as consolidation in patients in first complete remission.

**Induction Chemotherapeutic Strategies**

Studies by Canellos and colleagues in the late 1970's demonstrated unanticipated efficacy of systemic high-dose methotrexate plus leukovorin rescue as monotherapy in the treatment of selected patients with recurrent CNS lymphomas.\(^\text{64, 65}\) For pharmacologic and/or biological reasons that are unclear, it is now appreciated that large-cell lymphoma within the brain microenvironment has approximately two-fold greater sensitivity to high-dose methotrexate-based therapies compared to systemic lymphomas of the same histology.\(^\text{66}\) Blay and colleagues demonstrated that high-dose methotrexate is the most significant treatment-related prognostic variable relating to survival in PCNSL\(^\text{67}\) and currently high-dose methotrexate constitutes the backbone of the vast majority of induction regimens in this disease.

To date, however, the optimal high-dose regimen for methotrexate has not been firmly defined. In our experience, doses greater than or equal to 1 \(\frac{gm}{m^2}\) achieve tumoricidal levels of methotrexate in brain parenchyma, in agreement with the experience of Skarin et al.\(^\text{65}\). Importantly, Glantz and colleagues demonstrated that intravenous administration of methotrexate (8 \(\frac{g}{m^2}\) over four hours) produces higher cytotoxic levels of methotrexate (greater than 1 \(\mu\text{M}\)) in serum and CSF than intrathecal methotrexate (12 mg dose) at 48 and 72 hours. In addition, retrospective analysis of PCNSL outcomes at Memorial Sloan-Kettering Cancer Center demonstrated that the elimination of intrathecal methotrexate from induction therapy did not affect outcome in patients treated with high-dose methotrexate at a target dose of 3.5 \(\frac{gm}{m^2}\).\(^\text{68}\) Taken together these observations suggest that high-dose methotrexate is sufficient to treat
brain and leptomeningeal disease. Our experience confirms these observations, in
particular that combined intravenous plus intrathecal methotrexate is not necessary,
even with established lymphomatous meningitis at diagnosis, assuming that high-dose
methotrexate at doses in excess of 3 gm/m² can be administered every two weeks for a
minimum of six cycles. (5, 9)

At present, there are no evidence-based guidelines that dictate the optimal
number of high-dose methotrexate cycles to be administered at diagnosis. There is
however, evidence which suggests that greater than four cycles of methotrexate-based
therapy may be necessary to obtain a significant remission before using non-cross-
resistant agents in consolidative therapy.(69) Based upon our experience and the
prospective studies of Hochberg and Batchelor, (70, 71) we administer eight cycles of
high-dose methotrexate during induction in responding patients, assuming a complete
remission has been attained by completion of cycle six; in selected cases additional
cycles beyond eight may be appropriate and feasible if the disease is responsive but not
in radiographic and cytologic CR by cycle six. Remarkably, according to the data of
Batchelor et al., approximately 20% of PCNSL patients may have long-term progression-
free survival with methotrexate monotherapy using this approach. (72)

It is important to be aware of the acute toxicities of high-dose methotrexate which
include renal dysfunction caused by methotrexate nephropathy, the precipitation of
methotrexate and 7-OH-methotrexate within renal tubules, a potentially life-threatening
complication that occurs in up to 5% of patients. Safe administration of high-dose
methotrexate requires vigorous hydration, urine alkalinization, the avoidance of drug
interactions such as non-steroidal anti-inflammatory drugs, salicylic acid, fluoroquinolines,
penicillin derivatives and sulfonamides, etc. It is also important to minimize the risk of
superimposed iodine contrast nephropathy with that of methotrexate nephropathy by
providing an interval of at least two days between CT-based axial imaging during pre-
treatment staging and induction high-dose methotrexate. Third-space effusions need to be identified and drained and serum methotrexate monitored closely with leukovorin rescue at 24 hours. Delayed methotrexate excretion with renal dysfunction requires prompt increases in leukovorin dosing, continued alkalinization, hydration. Additional interventions for delayed methotrexate clearance due to impaired renal function include administration of carboxypeptidase-G2 (CPDG2, glucarpidase), a recombinant bacterial enzyme, approved by the FDA in 2012, that hydrolyzes methotrexate, reducing toxic serum methotrexate concentrations within 15 minutes of administration.(73)

**Combined-Modality Regimens**

DeAngelis and colleagues pioneered a combination regimen consisting of high-dose systemic methotrexate plus CNS penetrant agents such as procarbazine followed by whole brain irradiation and high-dose cytarabine; implementation of this regimen in the multicenter setting, coordinated by RTOG, yielded a median progression-free survival of 24 months.(74) Because of this encouraging efficacy, combined-modality therapy became a widely adopted approach for PCNSL.(75, 76) In a large randomized phase II study, Ferreri and colleagues evaluated a high-dose methotrexate-based induction, minus or plus high-dose cytarabine (2 gm/m²) followed by consolidative whole brain radiotherapy: the median failure-free survival in patients who received HD-MTX in combination with HD-Ara-C induction was eight months; by contrast, the median failure-free survival of patients who received HD-MTX without Ara-C was only four months.(77) (Table 1). However, in the SG-1 trial, a large randomized phase III trial in which half the patients received whole brain radiotherapy as first-line consolidation, Thiel and colleagues provided evidence that omission of whole brain radiotherapy from first-line chemotherapy does not compromise survival. While whole brain radiotherapy resulted in a modest improvement in progression-free survival after methotrexate-based induction, this did not translate into improved overall survival, possibly because of the
severe neurotoxicity caused by whole brain radiotherapy that was detected in nearly half of patients in the radiotherapy arm. (78)

High-Dose Chemotherapy Consolidation

During the past 15 years there has been increasing interest in the role of dose-intensive chemotherapeutic consolidation including autologous stem cell rescue in CNS lymphoma. Many of the most promising results are obtained with regimens that include CNS penetrant agents such as carmustine, thiotepa, cyclophosphamide, busulfan, high-dose cytarabine and etoposide. (6, 8, 79, 80) (Table 2). Notably, results obtained using the BEAM combination regimen followed by autologous stem cell rescue were not promising in a single institution study. (69)

Soussain and colleagues described one of the earliest series to demonstrate the efficacy of high-dose chemotherapy and autologous stem cell transplant in salvage of recurrent CNS and intraocular lymphoma. One of the key findings of this study was the observation that the combination of etoposide plus high-dose cytarabine was highly active as first-line salvage therapy in recurrent/refractory CNS lymphomas, with 12 of 14 patients exhibiting responses, eight of which were complete responses (79). After stem cell collection, responding patients on the trial were treated with a myeloablative regimen consisting of thiotepa, busulfan and cyclophosphamide.

In early 2001, our group at the University of California, San Francisco (UCSF), began to pursue high-dose chemotherapy as first-line consolidation in patients with newly-diagnosed PCNSL. We developed a two-step regimen, designed to be tolerated by the majority of PCNSL patients, particularly during the month post diagnosis when performance status and neurologic function are most compromised. The regimen involves 4 months of induction therapy using intravenous high-dose methotrexate given every two weeks with oral temozolomide and intravenous rituximab (MT-R) followed by high-dose consolidation, without WBRT. Methotrexate is administered at a target dose
of 8 g/m² over four hours, with appropriate dose reductions particularly for renal
drugs, and with leucovorin rescue starting day two every 6 hours. Intravenous
rituximab (375 mg/m²) is administered on day 3 of this regimen, weekly for six doses
during the first two months, a window in which the blood-brain barrier is compromised
and we hypothesized would therefore facilitate delivery of rituximab to the tumor.
Temozolomide is a brain penetrant alkylator with established activity at relapse in CNS
lymphoma, both as monotherapy and in combination with rituximab (82-84). Importantly,
temozolomide has a superior toxicity and health-related quality of life profile in brain
further, is administered
monthly in a five-day course at 150 mg/m², starting on days 7-11. To attempt to improve
progression-free survival after MT-R, responding PCNSL patients received intensive
consolidation with non-cross-resistant agents: 96-hour infusional etoposide (40 mg/kg IV
over 96 hours) plus eight doses of high-dose cytarabine (EA) at 2 gm/m² over two hours,
every 12 hours (87-89). Notably, infusional etoposide is incorporated within the EPOCH
regimen (infusional etoposide, vincristine, adriamycin plus bolus cyclophosphamide and
oral prednisone), which is highly active against large B-cell lymphoma (90, 91), the most
common histologic subtype to cause CNS lymphomas. Several studies have
demonstrated the activity of etoposide in brain tumors, including lymphoid leukemia
involving the CNS (92). Etoposide is also associated with a reduced risk of secondary
CNS lymphoma, when given in combination with CHOP in patients with aggressive
lymphoma (93). The contribution of high-dose cytarabine in PCNSL was demonstrated
in a randomized phase II study by Ferreri and colleagues (77).

The relative effectiveness of this two-step program may be attributed to the fact
that there is very little significant myelosuppression with combination MT-R, despite the
addition of an alkylator, temozolomide (83) and rituximab (94), resulting in few treatment
delays during induction. Malignant CSF cytology at diagnosis did not impact outcome or
pattern of recurrence. With long-term follow-up, our findings suggest that combination high-dose infusional etoposide plus cytarabine (EA) is highly effective as consolidation after MT-R in newly diagnosed patients with PCNSL. Notably, the dose-intensity of EA used in this regimen is approximately two-fold higher than the doses of etoposide-cytarabine used as first-line salvage in the Soussain series. With a median follow-up of greater than seventy-two months, of the first fourteen PCNSL patients who received MT-R followed by EA consolidation, twelve remain in remission. Similar promising results have been observed in newly-diagnosed patients with stage IV large B-cell lymphoma with synchronous brain parenchymal and systemic lymphoma treated with induction high-dose methotrexate plus R-CHOP followed by consolidation with EA.

When the MT-R plus EA regimen was evaluated in the multicenter setting, nearly identical results were obtained. CALGB (Alliance) 50202 demonstrated for the first time the feasibility of high-dose chemotherapy in the multicenter setting in newly-diagnosed PCNSL patients. The two-year rate of progression-free survival in this multicenter study, 0.57, exceeds those of other chemotherapy-alone studies and the median time to progression of all 50202 patients, four years, is two-times longer than achieved with combined-modality therapy in multicenter trials using standard-dose whole brain radiotherapy. In addition, for the first time in a multicenter trial in PCNSL conducted by a cooperative group, the progression-free survival curves showed evidence of a stable plateau, and with a median follow-up of greater than five years, the median overall survival has not been reached. The overall survival for the cohort that completed dose-intensive consolidation with EA was particularly promising, and confirmed institutional data. (Figure 5) Moreover, the regimen was well-tolerated, with only 10% of patients experiencing grade 4 neutropenia during induction. As expected however, high-dose consolidation was associated with a greater than 80% rate of grade
4 neutropenia and thrombocytopenia and all patients received growth factor and antibiotic support during consolidation. The one treatment-related mortality in the study was a grade 5 septic event during a neutropenic nadir from intensive consolidation in a subject managed as an outpatient, underscoring our recommendation for detailed inpatient monitoring during the consolidation phase until count recovery. Importantly there were no reported cases of severe neurotoxicity in the trial, despite the high-doses of cytarabine administered, however detailed neurocognitive evaluations were not performed. A flow-chart, depicting our diagnostic and therapeutic approach, is presented in Figure 4.

The most significant clinical prognostic variable identified in 50202 was the timing of initiation of remission-induction therapy: delayed initiation of high-dose methotrexate beyond 30 days after diagnosis correlated with significantly shorter event-free survival.(5) This observation is in agreement with prior evidence that significant delays in the diagnosis of intraocular lymphoma correlates with adverse outcome (95, 96) and underscores our recommendation that PCNSL patients be efficiently staged and that methotrexate-based therapy promptly be started after diagnosis of this aggressive brain tumor.

Based upon the promising results of this regimen, a successor randomized phase II trial, CALGB 51101, has been initiated. After remission induction therapy with MT-R, patients receive either non-myeloablative consolidation with EA or myeloablative therapy and stem cell transplant with carmustine plus thiotepa, a regimen that has been studied by the Freiburg group.(6) This study, which has been endorsed by Alliance, SWOG and ECOG, represents the first randomized trial for PCNSL in which neither arm involves whole brain radiotherapy.

**Treatment of Synchronous Brain and Systemic Lymphoma at Diagnosis**

Our approach to the treatment of patients with synchronous brain parenchymal
and/or leptomeningeal plus systemic lymphoma (usually large cell or, more rarely, intravascular lymphoma) at diagnosis is, after staging of the body and neuroaxis, to proceed with high-dose methotrexate (between 3-8 grams/m²) with leucovorin rescue every two weeks for a total of 8 cycles plus standard dose R-CHOP (rituximab, cyclophosphamide, vincristine, adriamycin, and prednisone) every three weeks for a total of six cycles. When R-CHOP and high-dose methotrexate are given on the same week, we administer high-dose methotrexate on day one and R-CHOP on day 3. We recommend that patients who achieve complete responses with this M-R-CHOP induction, in both CNS and systemic compartments, and who have adequate organ function, receive EA consolidation. Our experience with this approach, while somewhat limited given its rarity, suggests that long-term survival can be achieved without whole brain radiotherapy consolidation for patients with this complex presentation.(9)

Secondary CNS Lymphoma

Brain and leptomeningeal dissemination is one of the most morbid complications of recurrent aggressive systemic non-Hodgkin lymphoma. The natural history of secondary CNS lymphoma was recently illustrated in a retrospective analysis of SWOG 8516 which illustrated the fact that CNS relapses tend to occur earlier than systemic relapses (p<0.003) (median onset of CNS relapse occurred within 5.4 months of initial therapy) and that the median survival after diagnosis of secondary CNS lymphoma was only 2.2 months compared to nine months for non-CNS relapse. Risk factors for CNS dissemination of systemic aggressive lymphomas include high IPI score and extranodal involvement at diagnosis, with testes being a site of notoriously high-risk. In addition, in this study, the efficacy of intrathecal chemotherapy intended to prophylax against secondary CNS lymphoma could not be demonstrated.(97)

Given the efficacy of high-dose methotrexate-based chemotherapy in the treatment of established PCNSL as well as data demonstrating higher sustained
cytotoxic methotrexate levels in CSF after high-dose intravenous dosing compared to CSF levels after intrathecal administration,(98) we selectively administer high-dose methotrexate, (3-8 grams/m²) typically for between two-to-four courses, in a sequence individualized for the patient, as prophylaxis for patients with systemic NHL with the above mentioned high-risk features of CNS relapse. A recent retrospective study performed by Abramson and colleagues provides the first evidence for the efficacy of this approach in preventing CNS relapse in patients with high-risk systemic disease.(99)

Treatment of Recurrent CNS Lymphomas

In the setting of established relapsed primary and/or secondary CNS and intraocular lymphoma, there is increasing data suggesting that high-dose chemotherapy with autologous stem cell transplant is feasible and effective. (7, 79, 100) Recently Korfel and colleagues described their phase II experience with systemic high-dose methotrexate-based therapy in combination with other CNS-penetrant agents, thiotepa, ifosfamide and cytarabine plus intrathecal depocyt as first line salvage. Responding patients went on to receive myeloablative therapy with carmustine, thiotepa and etoposide. The approach yielded an encouraging progression-free survival rate of 0.49 at two-years.(8) Our approach to the treatment of relapsed CNS lymphomas depends on whether the recurrent CNS lymphoma is methotrexate-resistant. In the setting of relapsed CNS lymphoma that is sensitive to high-dose methotrexate, we recommend repeat high-dose methotrexate administration in a manner analogous to the treatment of newly-diagnosed PCNSL, with the aim of achieving maximal cyto reduction, (six-to-eight cycles), followed by dose-intensive consolidation with non cross-resistant agents and stem cell transplant using one of several thiotepa-based regimens which are active in CNS lymphomas. (Figure 4). (8, 101, 102) High-dose carmustine-based therapy without thiotepa is also a consideration.(80) (Table 2).
Notably however, patients with disease that has relapsed within six months of EA or other dose-intensive regimens used to consolidate a first remission of PCNSL may not be good candidates for second-line high-dose chemotherapeutic salvage approaches. We offer investigational therapeutic trials or reserve whole brain radiotherapy primarily for such patients as well as for those with demonstrated methotrexate resistance.

**The role of rituximab in CNS lymphomas**

While rituximab consistently improves outcomes in systemic B-cell non-Hodgkin’s lymphoma (NHL), a number of reports suggest that the addition of rituximab to CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy may not significantly decrease the rate of central nervous system (CNS) relapse of systemic diffuse large B-cell lymphoma compared to CHOP alone.(103-105) These observations concur with data that less than 1% of systemic rituximab penetrates the leptomeningeal compartment.(106) Nevertheless, a number of studies demonstrate that intravenous rituximab may induce responses of contrast-enhancing lesions of CNS lymphoma, suggesting selective activity in the setting of a disrupted blood-brain barrier, (94) and supporting the rationale for incorporation of rituximab within induction regimens for PCNSL.

In two multicenter phase I trials, our group evaluated the safety and activity of intraventricular rituximab, both as monotherapy and in combination with intraventricular methotrexate. Our data suggests that, when diluted in preservative-free normal saline and administered via Ommaya reservoir, 10 mg and 25 mg doses of rituximab are well-tolerated and can elicit responses in CSF, intraocular compartments and in small lesions within the brain, in a steroid-independent manner. The activity of intraventricular rituximab was additive or synergistic with methotrexate; this combination appeared to be useful in the setting of a high burden of leptomeningeal disease, e.g. lymphoma cell...
counts greater than 20,000 cells/ml in CSF. Finally, we demonstrated that intraventricular rituximab may overcome resistance mediated by the blood-brain barrier in that several responses were noted in the CSF in patients with baseline serum rituximab concentrations in excess of 15 μg/ml. Notably, two patients achieved a first complete response of CNS lymphoma with intraventricular rituximab/MTX, including one with CNS lymphoma refractory to high-dose systemic and intrathecal MTX plus 20 previous infusions of IV rituximab. (107, 108)

In summary, given data from a number of prospective trials as well as clinical series that document activity of rituximab in the setting of CNS lymphomas, as monotherapy and in combination with methotrexate-based induction regimens,(109) as well as the overwhelming evidence that rituximab improves survival in systemic CD20+ NHL, we recommend the incorporation of intravenous rituximab in CD20+ CNS lymphoma-directed therapies. Notably, however randomized data evaluating the impact of rituximab as part of induction therapy have not yet been presented. While an accumulation of evidence suggests activity in recurrent disease, intraventricular rituximab remains investigational and the combination of intraventricular plus intravenous rituximab for recurrent CNS lymphoma is currently under evaluation in the phase I setting (NCT01542918).

Treatment of Intraocular Lymphoma

Most cases of intraocular lymphomas are of diffuse large B-cell type, either primary vitreoretinal lymphoma or uveal lymphomas, which themselves can be subdivided into primary neoplasms of the choroid, iris and ciliary body or secondary choroidal lymphomas in patients with disseminated NHL. These types of B-cell neoplasms are to be distinguished from marginal zone lymphomas that tend to present in the ocular adnexa, e.g. the conjunctiva, and which do not pose a high risk of CNS dissemination. Notably, intraocular lymphoma impacts between 15-25% of patients with
primary CNS lymphoma and between 65% to 90% of patients with primary vitreoretinal lymphoma ultimately develop CNS lymphoma, usually within 30 months.

Therapy for primary vitreoretinal lymphoma can be divided into systemic chemotherapy vs. local approaches such as ocular radiation and intravitreal therapy; here again, the optimal approach has not been defined. (Table 3). External beam radiotherapy involving 35-40 Gy using opposed lateral beams results is well tolerated with low rates of local recurrence and is favored in the setting of bilateral disease.(110) Intravitreal methotrexate and rituximab are also highly effective and may be preferred in the setting of unilateral disease or in patients previously treated with ocular radiation.(111, 112) Treatment-related complications of intravitreal methotrexate may be dose-related but can be significant, including vitreous hemorrhage, endophthalmitis, retinal detachment and hypotony.(53) Systemic treatments for intraocular lymphoma include high-dose systemic methotrexate, yielding cytotoxic levels in the aqueous and vitreous humor, (113) as well as high-dose cytarabine and ifosfamide or trofasfamide.(114) Notably, in primary vitreoretinal lymphoma, the up-front use of high-dose methotrexate plus binocular irradiation provides both local control and addresses the high probability of microscopic disease throughout the neuroaxis.(115) At our institution, we have observed favorable outcomes in patients who present with primary intraocular lymphoma and/or concomitant PCNSL with IOL with the two-stage program involving high-dose methotrexate-based induction followed by dose-intensive consolidation as used in CALGB 50202. Using this approach, the persistence and/or recurrence of isolated intraocular lymphoma after completion of dose-intensive consolidation is an indication for binocular but not whole brain irradiation.

**Treatment of CNS Lymphoma in the Immunocompromised Host**

While the incidence of HIV-associated PCNSL has declined markedly with the advent of highly-active antiretroviral therapy (HAART), PCNSL continues to be a
significant AIDS-defining illness that is difficult to treat. Jacomet and colleagues described the feasibility and efficacy of high-dose methotrexate monotherapy in HIV-associated PCNSL.(116) Our experience has been that reconstitution of immune function with HAART in combination with high-dose methotrexate can result in complete remissions and long-term survival in this EBV-related neoplasm, without whole brain radiotherapy.(117)

Similarly, in the setting of CNS post-transplant lymphoproliferative disorder (PTLD) reconstitution of immune function by downward titration and/or cessation of immunosuppressive agents such as prednisone, mycophenolate and tacrolimus is a requisite first principle in management. In this set of diseases, high-dose methotrexate may also be highly effective but its implementation and dosing needs to be balanced with the risk of allograft toxicity and failure.(118) Intravenous rituximab is also highly effective in CNS complications of post-transplant lymphoproliferative disorder and is frequently indicated given that these are nearly uniformly CD20-positive neoplasms. Intrathecal rituximab has also been shown to have activity in this setting.(119)

Conclusions and Future Directions

The past 20 years has witnessed remarkable changes in the incidence, epidemiology, natural history and prognosis for patients with PCNSL, an adult brain tumor previously considered to be incurable and closely linked to the HIV epidemic. It now appears that the incidence of PCNSL is increasing in a population age greater than 60 years, without clinically overt immunosuppression. Moreover, there is reproducible evidence that by judicious application of established agents and their empiric refinement within combination regimens, long-term survival and cure can be anticipated in approximately 50% of patients. In particular, an accumulation of studies show encouraging survival in newly-diagnosed patients treated without whole brain radiotherapy as consolidation. There is also evidence for progress in the treatment of
secondary CNS lymphomas, a complication long associated with a dismal prognosis.

The central questions in therapeutic management for CNS lymphoma patients have evolved significantly: instead of asking whether omission of whole brain radiotherapy as standard of care in consolidation will compromise survival, a relevant question now is whether there exists a subpopulation who may benefit from whole brain radiotherapy in first remission. Instead of whole brain radiotherapy, might radiosurgical approaches such as gamma knife or cyberknife be systematically applied in combination with chemotherapy or targeted small molecule therapies? What dose-intensive consolidation and/or preparative regimen is most effective and has the most acceptable toxicity profile in terms of myelosuppression, as well as gastrointestinal and neurotoxicity? (Table 2)

Nevertheless, it is highly likely that therapeutic outcomes have now achieved a plateau with existing genotoxic strategies and that further innovations are urgently needed to facilitate diagnosis, prevention and/or treatment of primary and secondary CNS lymphomas, especially given their predilection for an aging population among whom a significant proportion can not tolerate high-dose chemotherapy and/or whole brain radiotherapy. As patients with CNS lymphoma are living longer, there is also a greater need to begin to address quality-of-life issues including cognitive dysfunction that can occur as a result of disease and treatments.

There is also significant need for novel biomarkers that identify high-risk patient subpopulations, particularly the 20-25% of patients who exhibit primary refractory disease during the first six months and the additional 20% of patients who achieve complete response but later relapse. Candidates include biomarkers such as bcl-6 and XBP-1 which are detected by immunohistochemistry,(5, 120, 121) CSF peptides such as CXCL-13 and IL-10, quantified by ELISA, and imaging-based biomarkers such as the apparent diffusion coefficient.(122) Given the evidence that, like its systemic counterpart,
the most common form of PCNSL among immunocompetent patients represents a biologically heterogenous set of diseases, we suggest that the implementation of risk-adapted strategies that apply novel therapies for high-risk patients is now warranted in the next iteration of clinical trial design in PCNSL.

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**Authorship.** James L. Rubenstein conceived, performed research, and wrote the article. Neel Gupta, Gabriel Mannis, and Amanda LaMarre performed research. Patrick Treseler performed research and pathologic consultation.

**Conflicts of Interest Disclosure:** James L. Rubenstein receives research funding from Celgene and Genentech for a phase I clinical trial.
References


intraventricular administration of rituximab in patients with recurrent CNS and intraocular lymphoma. *J Clin Oncol* 25: 1350-6


Table Legends

Legend to Table 1. Treatment Regimens for Primary CNS Lymphoma.
WBRT, whole brain radiotherapy; MTX, methotrexate; HD-AC, high-dose cytarabine, TT, thiotepa, IT, intrathecal; MPV, methotrexate plus procarbazine and vincristine; MT-R, methotrexate plus temozolomide and rituximab. EA, infusional etoposide plus high-dose cytarabine; ASCT, autologous stem cell transplant. Note that for Ferreri et al., 2009, the median failure-free survival is represented in the table.

Legend to Table 2. Chemotherapy Agents and Combinations Used in High-Dose Chemotherapy Consolidative and Preparative Regimens that are Effective in CNS Lymphomas.

Legend to Table 3. Therapeutic Approaches for Intraocular Lymphoma.
TBC, thiotepa, busulfan, cyclophosphamide; VOD, venoocclusive disease.

Table 1.

<table>
<thead>
<tr>
<th>Study (# Pts)</th>
<th>Regimen</th>
<th>Response Rate</th>
<th>Median PFS</th>
<th>Median OS</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>WBRT</td>
<td></td>
<td></td>
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<tr>
<td>Nelson et al., 1992 (N=41)</td>
<td>WBRT 40 Gy + 20 Gy boost</td>
<td>100%</td>
<td>NA</td>
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<td>MTX Monotherapy</td>
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<tr>
<td>Batchelor et al., 2003 (N=23)</td>
<td>MTX 8 g/m²</td>
<td>74%</td>
<td>12.8</td>
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<td>Herrlinger et al., 2005 (N=37)</td>
<td>MTX 8 g/m²</td>
<td>35%</td>
<td>10</td>
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<tr>
<td>Combined-Modality Therapy</td>
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<tr>
<td>Ferreri et al., 2009 (N=40)</td>
<td>MTX 3.5 g/m² + WBRT (36-45 Gy)</td>
<td>41%</td>
<td>4</td>
<td>10</td>
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<td>Ferreri et al., 2009 (N=39)</td>
<td>MTX 3.5 g/m² + HD-AC + WBRT (36-45 Gy)</td>
<td>69%</td>
<td>8</td>
<td>32</td>
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<tr>
<td>DeAngelis et al., 2002 (N=102)</td>
<td>MPV + IT MTX + WBRT (45 Gy) + HD-AC</td>
<td>94%</td>
<td>24</td>
<td>37</td>
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<td>Shah et al., 2007 (N=30)</td>
<td>R-MPV+ HD-AC + WBRT (23 Gy)</td>
<td>93%</td>
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<td>40</td>
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<td>Intensive Chemotherapy</td>
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<tr>
<td>Illerhaus et al., 2008 (N=13)</td>
<td>MTX 8 g/m² + HD-AC/TT+ BCNU/TT (ASCT)</td>
<td>85%</td>
<td>NR</td>
<td>NR</td>
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<td>Rubenstein et al., 2013 (N=44)</td>
<td>MT-R + EA</td>
<td>77%</td>
<td>52</td>
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Table 2.

<table>
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<th>Reference</th>
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<tbody>
<tr>
<td>Cyclophosphamide, Carmustine, Etoposide</td>
<td>Alvarnas et al., 1999</td>
</tr>
<tr>
<td>Thiotepa, Busulfan, Cyclophosphamide</td>
<td>Soussain et al., 2001, 2008, Cote et al., 2012</td>
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<tr>
<td>Carmustine, Thiotepa</td>
<td>Illerhaus et al., 2008</td>
</tr>
<tr>
<td>Carmustine, Thiotepa, Etoposide</td>
<td>Korfel et al., 2013</td>
</tr>
<tr>
<td>Infusional Etoposide, High-Dose Cytarabine</td>
<td>Wieduwilt et al., 2012, Rubenstein et al., 2013</td>
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Table 3.

<table>
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<th>Therapy</th>
<th>Efficacy</th>
<th>Toxicity</th>
<th>Reference</th>
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<tr>
<td>Ocular XRT (30-40Gy) Wash U: Protocol = 35 Gy</td>
<td>Rare local recurrence 60-95% RR No impact on OS</td>
<td>Cataracts, Dry eyes, Retinopathy (Mild)</td>
<td>Berenbom et al., Eye 2007</td>
</tr>
<tr>
<td>HD-MTX</td>
<td>~ 50% sustained response, Poor vitreous penetration</td>
<td>Mild</td>
<td>Batchelor et al., Clinical Cancer Res. 2003</td>
</tr>
<tr>
<td>HD-MTX + Binocular XRT (+/overlap)</td>
<td>100% CR</td>
<td>Cataracts, Dry eyes, Retinopathy</td>
<td>Stefanovic et al. Br.J. Hematology 2010</td>
</tr>
<tr>
<td>Intensive Chemo (EA) + ASCT (TBC)</td>
<td>&gt;50% pts respond to EA 6/10 CR</td>
<td>Neurologic toxicity, Hemorrhage, VOD</td>
<td>Soussain et al. JCO 2001</td>
</tr>
<tr>
<td>Intravitreal rituximab (1 mg) or MTX (200 mcg) in 0.1 ml</td>
<td>Requires &gt; 6 injections to achieve CR, Investigational</td>
<td>Conjunctival Keratopathy, Cataracts, Optic atrophy, Endophthalmitis</td>
<td>Pulido et al. Retina 2009 Kim H. et al. Exp Eye Res. 2006</td>
</tr>
</tbody>
</table>
Figure Legends

Legend to Figure 1. Pathologic Features of Primary CNS Lymphoma (PCNSL).
1A. Diffuse large B-cell lymphoma (DLBCL) involving the left parietal lobe and basal ganglia exhibits marked mass effect, subependymal spread and invasion of the lateral ventricle at relapse, upon progression with high-dose methotrexate and rituximab-based chemotherapy. (Courtesy of Ray Sobel, M.D., Stanford University School of Medicine).
1B. DLBCL cells exhibiting angiotropic growth pattern in a diagnostic specimen of PCNSL (100x, H&E).
1C. Invasive growth of DLBCL cells along cerebral vasculature in PCNSL (200x, H&E).
1D. High expression of MYC by DLBCL cells in diagnostic specimen of PCNSL, as demonstrated by immunohistochemistry (400x). (Courtesy of Eric Hsi, M.D., Cleveland Clinic).

Legend to Figure 2. Characteristic Radiographic Features of Primary CNS Lymphoma on Magnetic Resonance Imaging.
2A. T1 axial, post-gadolinium image depicts a periventricular contrast-enhancing lesion with near uniform contrast-enhancement, vasogenic edema and mass effect, in displacement of the lateral ventricles. Lesional contrast-enhancement using MRI is used for response assessment. 2B. Flair signal abnormality demonstrates the extent of vasogenic edema. (Courtesy of Soonmee Cha, M.D., UCSF).

Legend to Figure 3. Features of Intraocular Lymphoma.
3A. Slit lamp evaluation demonstrating advanced intraocular lymphoma with optic disc swelling, vasculitis as well as subretinal and retinal infiltrates. 3B. Optical coherence tomography demonstrating nodular hyperreflective lesion (arrow) at the retinal pigment epithelium and subretinal space. (Courtesy of Paul Stewart, M.D., UCSF).

Legend to Figure 4. How I Treat Primary CNS Lymphoma.
In the diagnostic work-up, an MRI of the spine (+/- gadolinium) may be useful if warranted by neurologic symptoms or if CSF analysis is contraindicated. Testes ultrasound is indicated for older male patients with CNS involvement of lymphoma in which testes co-involvement is suspected on clinical and/or radiographic grounds. The value of PET scan in this setting is not established. While the schedule of decadron taper should be individualized for each patient, we recommend a planned taper to be completed within 2-3 weeks of diagnosis, between the first and second courses of HD-methotrexate. Therapeutic options for indolent lymphomas that involve the CNS or dura include rituximab, fludarabine, involved-field irradiation, and high-dose methotrexate for CNS involvement of CLL/SLL. For newly-diagnosed patients who are not candidates for HD-methotrexate, in most cases we recommend a trial of temozolomide and rituximab and/or strategies that employ high-dose chemotherapy, before consideration of whole brain irradiation. Abbreviations: PCP, pneumocytis carinii; HSV, herpes simplex virus; PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response; MT-R, combination high-dose methotrexate, temozolomide, and rituximab (rituximab is omitted for T-cell lymphomas); EA, etoposide-cytarabine; WBRT, whole brain radiotherapy; ASCT, autologous stem cell transplant.

Legend to Figure 5. Progress in the Treatment of Primary CNS Lymphoma.
Comparison of outcomes for newly-diagnosed primary CNS lymphoma in two multicenter cooperative group clinical trials. (A) Combined modality therapy with whole brain radiotherapy in RTOG-9310 resulted in median progression-free survival of two years with a significant rate of disease progression beyond two years. (B)
Immunochemotherapy with rituximab plus intensive consolidation, CALGB (Alliance) 50202, resulted in a median progression-free survival of four years with evidence for a stable plateau in the survival curve. (C) Progression-free survival was particularly encouraging for the 65% of patients who received both induction plus consolidation treatment modules of CALGB (Alliance) 50202.
Figure 1.
Figure 2.
Figure 3.
Figure 4.

Clinical Presentation

MRI, CSF & Eye Exam

Diagnostic Procedure: Bx, Resection, Cytology or Flow Cytometry

Decadron 4 mg q5h
planned taper over 2-3 wks

Staging: MRI, CSF, Eye
BM Bx, CT C/A/P,
+/- PET, +/- testes U/S + LFT’s, LDH, Lyses, CrCl
Hep B, C, HIV,
PCP & HSV Prophylaxis

PCNSL

Indolent Histology

Rituximab, Fludarabine,
+/- Involved field XRT (HD-MTX for CLL/SLL)

Aggressive Histology

HD-MTX Candidate?

Yes
MT-R Induction

No

PD

PD

PD

Temozolomide
+/- Rituximab

Consider EA Consolidation

ASCT, WBRT or Clinical Trial
Figure 5.

RTOG 9310 (2002)  
CALGB 50202 (2012)
How I treat CNS lymphomas

James L. Rubenstein, Neel K. Gupta, Gabriel N. Mannis, Amanda K. LaMarre and Patrick Treseler