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The Challenge of Primary CNS Lymphoma

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Abstract

Primary central nervous system lymphoma (PCNSL) represents one of the most challenging subtypes of aggressive non-Hodgkin's lymphoma, not only with respect to establishing the diagnosis, but also with respect to therapeutic resistance and treatment-related complications. Emerging clinical data suggest that optimized outcomes are achieved with dose-intensive central nervous system (CNS)-penetrant chemotherapy and the avoidance of whole brain radiotherapy. There is also increasing evidence that anti-CD20 antibody-based immunotherapy, incorporated as a component of high-dose methotrexate-based induction programs, may also contribute to improved outcomes. One of the interesting clinical questions in the present era is the determination of the optimal consolidative approach in the management of patients after remission induction therapy, with high-dose chemotherapy, minus or plus autologous stem cell transplantion, as well as reduced-dose whole brain radiotherapy representing the dominant therapeutic options currently under investigation. Additionally, an accumulation of insights into the molecular and cellular basis of disease pathogenesis is providing a foundation for the generation of molecular tools to facilitate diagnosis as well as a roadmap for integration of targeted therapy within the developing therapeutic armamentarium for this challenging brain tumor.

Keywords

Aggressive Lymphoma; Primary CNS Lymphoma; Brain Tumor; NF-kB; High-Dose Chemotherapy

Introduction

While PCNSL remains a rare neoplasm, representing only 2–3% of all cases of non-Hodgkin's lymphoma (NHL), the incidence of PCNSL among immunocompetent patients appears to be been increasing, particularly among persons age sixty-five years and older.[1] The chararacteristic pathobiology of PCNSL is that of an aggressive lymphoma, localized

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within the central nervous system and often disseminated within brain, cranial nerves, leptomeninges, cerebrospinal fluid (CSF), intraocular structures and spinal cord, without overt systemic disease. [2,3].

PCNSL has long been recognized to be an aggressive brain tumor associated with a poor prognosis.[4] Historically known as reticulum cell sarcoma or microglioma, management principles for this disease have emerged slowly. Beginning in the 1960's, in the absence of prospective data, whole brain radiotherapy (WBRT) was employed as the first-line intervention as a means to elicit immediate responses in patients faced with a rapidly deteriorating course; WBRT alone typically resulted in median survival of 12 months. To date, the most significant advance in PCNSL has been the recognition, in the 1970's, of the efficacy of high-dose methotrexate (HD-MTX). [5,6] Several recent prospective trials have demonstrated markedly improved outcomes in PCNSL. Our goal is to highlight significant advances in our understanding of disease biology, diagnosis, staging and therapeutic management. [7–12]

Etiology

Risk factors for PCNSL include acquired and/or congenital immunodeficiency states. PCNSL is an AIDS-defining illness associated with a low CD4 cell count (< 50 cells/ml) and Epstein Barr Virus (EBV) infection. In systemic AIDS-related lymphomas, EBV infection of the lymphoma may be predictive of secondary CNS involvement.[13] Congential immunodeficiency states such as Wiskott-Aldrich syndrome, severe-combined or common-variable immunodeficiency, or ataxia-telangiectasia carry a ~ 4% risk of PCNSL. Post-transplant lymphoproliferative disorder (PTLD) involving central nervous system develops in 1–2% of renal transplant recipients and 2–7% recipients of liver, cardiac, and lung transplants. CNS PTLD is associated with EBV in the setting of iatrogenic T-cell immunodeficiency induced by immunosuppressives such as mycophenolate mofetil (Cell Cept).[14] Among patients with PCNSL without clinically overt immunosuppression, EBV infection of lymphoma is rare.[15]

Clinical Features and Pathogenesis

PCNSL is typically a highly infiltrative neoplasm that has been characterized as a "whole brain disease," particularly at relapse. [16] For this reason, its radiographic appearance typically underestimates disease extent, and like malignant gliomas, PCNSL is not amenable to curative resection..[16] One of the archetypical histologic features of PCNSL is angiotropism; the accumulation of lymphoma cells around tumor vessels, a phenotype that likely disrupts the blood-brain barrier and enables radiographic detection of lesions via pathologic contrast enhancement. PCNSL commonly is diagnosed as a solitary mass, typically with vasogenic edema and mass effect. The frequency of multiple lesions is increased among the immunosuppressed. [17] (Figure 1).

While NHL presenting in the brain is typically classified as PCNSL, subclinical tumor-related clones are often detectable in the blood and bone marrow of PCNSL patients, suggesting that the brain microenvironment might promote malignant progression. [18,19]

Intraocular disease is a common manifestation: 20% of PCNSL patients present with involvement of the retina, uvea and vitreous. An important principle is that apparently localized intraocular lymphoma (IOL) will disseminate within brain in >80% of cases; therefore, detection of IOL mandates staging of the neuroaxis. Therapies for IOL that address this risk should be strongly considered.[20]

Approximately 95% of PCNSL are large B-cell lymphoma; other include T-cell (2%)[21], Burkitt, lymphoblastic, and marginal zone lymphomas. PCNSL is distinguished from dural-based marginal zone lymphomas as these rarely invade brain parenchyma and typically these share overlapping radiographic features on MRI with meningioma. [22]

Molecular Pathogenesis of PCNSL

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 the paucity of material available for investigational studies. Most diagnostic specimens are obtained by stereotactic biopsy or via analysis of cerebrospinal fluid (CSF). Most investigations have focused on the elucidation of PCNSL, large cell type. Between 50% to 80% of PCNSL express BCL6 by immunohistochemistry; [23] 95% stain positive for MUM-1; therefore the majority of PCNSL cases are of a late germinal center or an activated B-cell immunophenotype.[15] Immunohistochemical characterization of tumors from patients that participated in CALGB 50202 demonstrated that high BCL6 correlated with refractory disease and shorter progression-free and overall survival (Rubenstein *et al.,* 2013b), thus representing a potentially useful molecular prognostic biomarker. While the adverse prognostic significance of high BCL-6 in PCNSL was recently confirmed in an independent large prospective trial,[24] several small *retrospective* studies provided a conflicting result - *that BCL-6 correlates with a better prognosis*. This discrepancy raises the possibility that the prognostic significance of BCL-6 may be dependent upon treatment-related factors, such as rituximab or whole-brain radiotherapy. Between 56–93% of PCNSL express BCL2. [15,23]

Transcriptional analyses of PCNSL identified several candidate mediators of disease pathogenesis, including expression of Pim 1 and *MYC*.[2526] Increased MYC in PCNSL was confirmed in the recent CALGB 50202 study. [12] Upregulation of miRNA's associated with MYC pathway (miR-17-5p, miR-20a, miR-9) has also been demonstrated.[27] Circulating extracellular microRNA's in CSF such as miR-21 were also recently described in PCNSL, suggesting utility as clinical biomarkers.[28]

Given that aberrant somatic hypermutation contributes to the pathobiology of DLBCL, Montesinos-Rongen *et al*. evaluated the potential role of this mechanism in PCNSL. Somatic hypermutation of four proto-oncogenes was identified – *PAX5*, *PIM1*, *c-MYC*, and *RhoH/TTF*, genes that regulate B cell development, proliferation and apoptosis [29]. Mutational frequencies for these were 2- to 5-fold higher in PCNSL compared to extraneural DLBCL [29]. Such high mutation frequencies suggest a prolonged interaction of the tumor cell in the GC microenvironment [30]. Whole exome sequencing studies of PCNSL identified protein-coding mutations involving mediators of cell signaling, CARD14, CD79A/B, TLR2,

TLR6, and TLR10, regulators of cell cycle, CCND3, and CDK20, and chromatin structure CREBBP, MLL2, ARID1A/B, and SMARCA4..[31]

The *p16*^{INK4a} gene is commonly inactivated by either homozygous deletion (40–50%) or 5′-CpG hypermethylation (15–30%) in PCNSL. [32] Inactivation of *p14*^{ARF} and *p16*^{INK4a} genes by homozygous deletion or promoter hypermethylation may represent an important step in the molecular pathogenesis of PCNSL. The *p14*^{ARF} gene normally induces growth arrest and stabilizes p53 protein in the nucleus. Both *p14*^{ARF} and *p16*^{INK4a} genes are frequently co-deleted; moreover, mice lacking the murine homologue of *p14*^{ARF} develop a variety of tumors, including lymphomas, sarcomas and gliomas. [20,33,34,35] In contrast, mutations in the *TP53* gene have been observed in only a small proportion of PCNSL.

Comparative genomic hybridization has identified other genetic lesions in PCNSL. Recurrent gains have been detected on chromosome 12 as well as on the long arms of chromosomes 1, 7, and 18; gain on chromosome 12 appears to be the most common chromosomal alteration, specifically in the 12q region harboring STAT6, MDM2, CDK4 and GLI1 [20,34,36].

Another common genomic aberrational hotspot in PCNSL involves losses on chromosome 6p21 that harbor loci for HLA [37–39] as well as broad deletions involving chromosome 6q. Chromosome 6q deletions, in particular 6q21–23 may be most frequent and occur in 40%–60% of PCNSL.[40] Candidate tumor suppressors linked to chromosome 6q include *PRDM1*, a tumor suppressor and regulator of B-cell differentiation,[41] *PTPRK*, a protein tyrosine phosphatase that participates in cell adhesion signaling events,[42] and *A20* (*TNFAIP3*), a negative regulator of NFkB signaling. [43]

Further evidence for the aberrant activation of NFkB pathways in PCNSL is supported by a gain in DNA copy number for *MALT1* [44] as well as activating mutations of *CARD11* [45] and *MyD88*. The activating exchange of leucine to proline at position 265 of *MyD88* may be enriched in PCNSL and has been demonstrated to occur in between 38% to 50% of cases. [46,47] (Figure 2).

Several lines of investigation support a role for JAK/STAT signaling pathway as a mediator of pro-survival signals in PCNSL. Interleukin-4, a B-cell growth factor that mediates intracellular signals via JAK/STAT, is upregulated at the transcript and protein level within the vascular microenvironment in PCNSL tumors.[25] Increased concentration of IL-10 (another activator of JAK/STAT) is detectable in the vitreous and CSF in PCNSL and, in independent studies, correlated with adverse prognosis.[48,49] A recent analysis demonstrated upregulated IL-10 transcripts in primary CNS lymphoma tumors compared to secondary CNS lymphomas and nodal lymphomas, with concomitant upregulated IL-10 protein in CSF from cases of PCNSL. In addition, CSF concentration of IL-10 correlated with tumor response and progression in patients treated with rituximab and methotrexate.[50] Finally, intratumoral *JAK1* transcripts are upregulated in PCNSL.[25,51] *Importantly, elevated IL-10 expression plus activation of JAK/STAT signaling in PCNSL are manifestations of aberrant activation of the MyD88 pathway.*[52] (Figure 2–4).

In addition, *CD79B*, a component of the B-cell receptor signaling pathway, is mutated in approximately 20% of cases, providing further data that dysregulation of the B-cell receptor and the NFkB signaling pathway contribute to pathogenesis of PCNSL.[53] (Figure 2) Silencing of *CDKN2A,* a cell cycle regulator, occurs in 50% of cases and is linked to inferior outcome.[44,46]

Tumor Microenvironment in PCNSL

The molecular basis for tropism and selective dissemination of lymphoma within the brain are problems that are fundamental to the pathogenesis of PCNSL. *In vitro* chemotactic responses by large B-cell lymphoma cells isolated from brain lesions have been demonstrated in response to chemokines CXCL12 (SDF-1) and CXCL-13 (B-lymphocyte chemoattractant) have been demonstrated [54–56] providing evidence for their role as neurotropic factors. Moreover, high CXCL-13 concentration in CSF from CNS lymphoma patients correlates with adverse prognosis, supporting its role as a pro-survival factor in PCNSL. In addition, determination of the CSF concentration of CXCL-13, as well as IL-10, facilitate diagnosis of CNS lymphoma in that bivariate expression of each molecule has diagnostic sensitivity at least two-fold greater than cytology or flow-cytometry. In a multicenter investigation, the positive predictive value of bivariate elevation of IL-10 plus CXCL-13 in CSF was 95% in the identification of untreated PCNSL. [50]

Given that expression of B-cell chemokines CXCL13 and SDF-1 by retinal pigment epithelium has also been demonstrated in primary intraocular lymphomas, these chemokines may also contribute to lymphoma cell homing to the retinal pigment epithelium from choroidal circulation [57]

While under physiologic conditions, the brain is believed to be immunologically quiescent, diagnostic specimens of PCNSL often reveal a robust inflammatory response, with infiltrating reactive T-cells and activated macrophages. Notably, perivascular T-cell infiltrates in PCNSL may predict a favorable outcome, suggesting that immunotherapeutic interventions that potentiate T-cell-mediated immune surveillance may be effective.[58]

Diagnostic Evaluation of the Patient with a Focal Brain Lesion

Because patients with PCNSL/IOL commonly present with a variety of nonspecific and/or subtle neurologic symptoms, the diagnostic process may be protracted and extend for months-to-years. (Figure 5). The cornerstone of diagnostic testing in suspected PCNSL is MRI of the brain, with gadolinium contrast. In 95% of PCNSL, pathologic enhancement localizes homogeneously to dominant lesions. Among the immunocompetent, lesions are solitary in 65% of PCNSL patients and multifocal in 35%. Involvement of the cerebral hemispheres is most common (38%) followed by thalamus and basal ganglia (16%), corpus callosum (14%) periventricular loci (12%) and cerebellum (9%).[59].

While there is insufficient data to recommend newer techniques such as quantitative diffusion-weighted and perfusion MRI as “standard of care,” an accumulation of recent data demonstrates the utility of these metrics in prognostication as well as diagnosis of CNS lymphomas and related inflammatory and malignant conditions.[10,60–65] Given the

quantitative nature of these techniques, and their universal availability in standard MR-neuroimaging packages, it is possible that these will be incorporated in future studies.

Although glucocorticoids typically induce radiographic regressions in > 40% of patients, steroid-induced responses also increase risk of a non-diagnostic vitreal or brain biopsy.[66] Steroid-induced diagnostic delays may extend for months, and on occasion, steroid-induced regressions of sentinel lesions may delay diagnosis of PCNSL or IOL for years.[67] It is therefore important to emphasize that empiric glucocorticoids such as dexamethasone be tapered rapidly, or not administered until a diagnosis is established.

The standard diagnostic approach for PCNSL is stereotactic brain biopsy; in selected cases, a subtotal resection may be appropriate if deemed to be safe. Flow-cytometric or cytologic analysis of meningeal lymphoma cells isolated from CSF or vitrectomy may also yield the diagnosis. Notably, while flow-cytometry has increased diagnostic yield relative to cytology, CSF needs to be efficiently processed for studies designed to identify, in most cases, a kappa or lambda-restricted B-cell lymphoma. Repeat CSF cytological or flow-cytometric studies infrequently improve diagnostic yield, supporting development of innovative diagnostic methods based upon detection of genomic aberrations such as detection of oncogenic alleles of MYD88.[68]

Given that approximately 80% of patients with IOL will exhibit CNS dissemination, MRI of the brain with gadolinium may be indicated in the work-up of idiopathic uveitis in which lymphoma is a diagnostic consideration. Additional staging tests for IOL include fluorescence angiography and optical coherent tomography, as well as evaluation of mutant L265P MYD88[68]; intraocular concentrations of the cytokines IL-10 and IL-6 may also be useful adjuncts to diagnosis.[69]

Staging evaluation for the patient with presumptive PCNSL includes complete ophthalmologic examination plus systemic staging via computed tomography of chest, abdomen and pelvis plus bone marrow biopsy; the value of positron emission tomography in staging of PCNSL is not established. [70] but may be useful in possible concomitant testicular involvement in men older than 60.

Clinical Prognostic Determinants in PCNSL

The International Extranodal Lymphoma Study Group (IELSG) identified five clinical variables that correlate with prognosis in PCNSL, three are shared with systemic NHL: elevated LDH, age > 60, and performance status > 1; parameters specific to PCNSL include elevated CSF protein as well as tumor location within the deep regions of the brain (periventricular, basal ganglia, brainstem and/or cerebellum). The presence of 0 – 1, 2 – 3, or 4 – 5 adverse risk factors respectively correlates with 2-year survival rates of 80%, 48% or 15%.[71] Historically, age has been the most reliable clinical prognostic factor, however there is disagreement regarding the age cut-point at which prognosis declines. While IELSG considers age 60 years to be the cutpoint above which prognosis declines, the Memorial Sloan-Kettering (MSK) prognostic index uses a cutpoint of age 50. [72] Notably, in CALGB 50202, which evaluated intensive immunochemotherapy followed by high-dose

consolidation, without WBRT, outcomes for PCNSL patients older than 60 was similar to younger patients, a result that suggests that the optimal cutpoint for age as a prognostic variable is strongly linked to the effects of delayed neurotoxicity. [12; 10] (Figure 6).

Principles of Management in PCNSL

Surgery: Biopsy vs. Resection

Many authorities recommend against neurosurgical resection of PCNSL, given the scant evidence that surgical cytoreduction provides no survival benefit and increases risk of post-operative neurologic deficit.[73,74] On the other hand, data extracted from the German PCNSL SG-1 Trial provided evidence that aggressive resection of PCNSL correlated with improved PFS. [75] In many cases, maximum safe resection of lesions provides immediate relief of mass effect, facilitates glucocorticoid taper, and theoretically eliminates drug-resistant tumor clones, without contributing to neurologic deficits, particularly when performed using modern neurosurgical mapping techniques.

Whole Brain Irradiation (WBRT) in PCNSL

The positive impact of WBRT in PCNSL is compromised by at least three important short-comings: (1) Inadequate local control of lymphoma; (2) Subclinical dissemination of radiographically-occult lymphoma cells outside of the radiation field; (3) Deleterious delayed effects of radiation on normal brain function. In one study, the use of WBRT as the sole intervention in PCNSL yielded a median survival of only 11.6 months, and greater than 60% of patients experienced lymphoma progression within the irradiated field.[76] The archetypical features of the delayed neurotoxicity of WBRT in PCNSL include incontinence, gait and memory disturbances - toxicities that are most evident in patients older than 60; PCNSL survivors that experience late-delayed neurotoxicity of WBRT may ultimately require custodial care.[77] While lower doses of WBRT were associated with neurotoxicity that is barely discernable in preliminary studies,[78] additional validation of these results are necessary, and need to be reconciled with the established deleterious neurocognitive effects of prophylactic cranial irradiation at 30 Gy,[79]. It seems plausible that the neurotoxicity of WBRT is a continuous variable in terms of its relationship to dose. Importantly, it was recently noted that PCNSL patients older than 60 that received consolidative low-dose WBRT (23.4 Gy) experienced inferior outcome in terms of progression-free survival (PFS) compared to patients younger than 60. [80] Given the rising incidence in PCNSL in older patients, these results substantiate the need for innovative strategies that defer or eliminate WBRT as therapy in PCNSL.

Induction Chemotherapeutic Strategies in PCNSL

The feasibility and efficacy of high-dose methotrexate in CNS lymphomas was established in the 1970's [5,6] and led to its incorporation more broadly in induction and salvage regimens. High-dose methotrexate has been identified in multivariate analysis as the most important treatment-related prognostic variable related to survival in CNS lymphomas. [81].

While the optimal dose of methotrexate has not been defined, systemic doses ≥ 1 gm/m^2 mediate lymphocytotoxic effects within brain parenchyma. [6]. In a landmark study, Glantz

and colleagues demonstrated that intravenous methotrexate administered at 8 g/m^2 over four hours yielded higher cytotoxic levels of methotrexate in serum and CSF compared to intrathecal methotrexate (12 mg) at 48 and 72 hours. [82] Also, investigators at Memorial Sloan-Kettering Cancer Center demonstrated that elimination of intrathecal methotrexate during initial therapy for PCNSL did not affect outcome in patients receiving high-dose methotrexate at doses of at least 3.5 gm/m^2.[83] In summary, these studies indicate that high-dose intravenous methotrexate, administered every two weeks for a minimum of six cycles, can be used to treat large cell lymphoma within brain and leptomeningeal compartments, without intrathecal therapy. [10]

Prevention and Management of High-Dose Methotrexate Toxicity

The principal toxicity of high-dose methotrexate is nephropathy, caused by precipitation of methotrexate and its metabolite 7-OH methotrexate within renal tubules. Measures to prevent this life-threatening complication include hydration, urine alkalinization and avoidance of drugs that interact with MTX such as pencilillins, as well as drainage of third space effusions. Additional interventions for delayed methotrexate clearance include carboxypeptidase–G2 (CPDG2, glucarpidase) a recombinant enzyme that rapidly reduces toxic serum methotrexate, via direct hydrolysis of methotrexate;[84] glucarpidase was approved by the FDA in 2012.

Combined-Modality Regimens

Combined modality therapy was pioneered at Memorial Sloan-Kettering Cancer Center and consisted of HD-MTX plus procarbazine and vincristine, followed by WBRT and high-dose cytarabine. Evaluation of this approach in a multicenter RTOG trial demonstrated median PFS of 24 months.[85]. Because of this encouraging efficacy, combined-modality therapy became a widely adopted approach for PCNSL. [86,87] In a multicenter randomized phase II study, Ferreri evaluated HD-MTX-based induction, minus or plus high-dose cytarabine followed by consolidative WBRT: the median failure-free survival in patients receiving HD-Ara-C in combination with HD-MTX was eight months; in contrast, median failure-free survival for patients treated with HD-MTX without cytarabine was only four months (Ferreri et al., 2009). In the SG-1 randomized trial involving 551 PCNSL patients in which half received WBRT as first-line consolidation, Thiel and colleagues provided evidence that omission of WBRT from first-line treatment did not impact overall survival. While the study revealed a modest effect of WBRT on PFS after methotrexate-based induction, this did not translate into improved overall survival, possibly attributable to the neurotoxicity detected in the radiotherapy arm.[88]

Alternatives to WBRT Consolidation: High-Dose Chemotherapy

Given the recognition of inadequate efficacy as well as neurotoxicity associated with WBRT, there has been interest in development of strategies that eliminate radiotherapy. One approach has been high-dose chemotherapeutic consolidation, including autologous stem cell transplant (ASCT). Regimens that contain CNS penetrant agents such as carmustine, thiotepa, cyclophosphamide, busulfan, high-dose cytarabine and etoposide are associated with the best results. However, in one early trial, results using the BEAM combination (carmustine, etoposide, cytarabine and melphalan) followed by autologous stem cell rescue

were not encouraging, possibly because a major proportion of patients enrolled in the study had inadequate disease control before myeloablative therapy, likely because of the abbreviated course of high-dose methotrexate administered.[89]

Soussain and colleagues evaluated dose-intensive chemotherapy and autologous stem cell transplant in recurrent CNS lymphomas and IOL. These investigators noted that combination high-dose cytarabine plus etoposide constituted a highly potent salvage regimen for relapsed/refractory CNS lymphomas: 12 of 14 patients attained responses, 8 of which were complete. Responding patients received a myeloablative regimen consisting of thiotepa, busulfan and cyclophosphamide (TBC) followed by stem cell rescue.[90]

Beginning in 2001, investigators at the University of California, San Francisco (UCSF), began to evaluate dose-intensive chemotherapy in first-line consolidation, without WBRT, after induction immunochemotherapy with rituximab in newly-diagnosed PCNSL. The strategy involved a two-step regimen: the induction phase uses HD-MTX given every two weeks with temozolomide and rituximab (MT-R). Intravenous rituximab is administered starting day 3, and weekly for six infusions, an interval during which the blood-brain barrier may be most compromised by angiotropic lymphoma. [91] Temozolomide is a lipophilic alkylating agent with activity at relapse in CNS lymphoma, alone and in combination with rituximab [92–94]. Temozolomide yields superior health-related quality of life and toxicity characteristics compared to procarbazine in brain tumor patients [95,96]. To consolidate response after induction MT-R, PCNSL patients received intensive consolidation with non-cross-resistant agents with combination “EA”: 96-hour infusional etoposide plus eight doses of cytarabine at 2 gm/m^2. [97–99]. Notably, infusional etoposide is incorporated within the EPOCH regimen (etoposide, doxorubicin, cyclophosphamide, vincristine and prednisone), highly effective in large B-cell lymphoma [100,101]. Etoposide has demonstrated efficacy in brain tumours, including CNS lymphoid leukemia [102]. Notably, when given with CHOP in patients with aggressive lymphoma, etoposide was associated with a reduced risk of secondary CNS lymphoma. [103]

A key goal of the two-step MT-R EA program was to develop an induction regimen that incorporates an alkylator, temozolomide [93] as well as rituximab [104], and yet causes minimal myelosuppression, to enable minimal treatment delays during the first weeks of treatment, the interval at which maximal lymphoma cytoreduction is achieved. Long-term follow-up of the first cohort of PCNSL patients treated with this regimen demonstrates that combination EA is highly effective as consolidation after MT-R in newly diagnosed PCNSL.[10] Based on phase I data, the MT-R plus EA regimen was evaluated in CALGB 50202, demonstrating for the first time the feasibility of high-dose chemotherapy in a multicenter study in newly-diagnosed PCNSL. The rate of complete response to MT-R in CALGB 50202 was 66% and the two-year PFS was 59%. 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 WBRT and may be similar to or favorable to results of reduced-dose WBRT in patients older than 60. [85,88] Other key findings from CALGB 50202 were that outcomes were similar for PCNSL patients older than 60 compared to younger patients and the observation that the PFS curves reached a stable plateau, supporting the hypothesis that long-term survival can be achieved in PCNSL without brain irradiation.

Given the encouraging results of CALGB 50202, a successor, randomized phase II trial, CALGB 51101, has been activated in the United States, endorsed by the major cooperative groups: Alliance, ECOG and SWOG. In CALGB 51101 after randomization and remission induction therapy with MT-R, patients receive either consolidation with EA or myeloablative therapy with carmustine plus thiotepa.[7]

The myeloablative approach pioneered by Soussain *et al.* using the TBC conditioning regimen in relapsed CNS lymphoma was also recently evaluated in a phase II investigation performed at Memorial Sloan-Kettering for PCNSL in which newly-diagnosed PCNSL patients that responded to induction chemotherapy consisting of rituximab, high-dose methotrexate plus procarbazine and vincristine received consolidative TBC chemotherapy. Results of this investigation were highly promising with a two-year PFS of 79%, however treatment-related mortality among transplanted patients that received the TBC conditioning regimen was substantial: 11.5%. [105]

Alternatives to WBRT: Induction HD-MTX Therapy without Consolidation in Elderly Patients with PCNSL

Given the established toxicities of WBRT, as well as concerns regarding the feasibility of high-dose chemotherapy consolidation in patients older than 60, one approach has been to apply methotrexate-based induction regimens for newly-diagnosed elderly patients and to withhold consolidation, reserving salvage chemotherapy or radiation for disease progression. Results of a recent European intergroup, randomized phase II trial evaluated two promising methotrexate-based regimens – high-dose methotrexate (3.5 gm/m2) plus temozolomide vs. high-dose methotrexate (3.5 gm/m2) plus procarbazine, vincristine and high-dose cytarabine; neither regimen included radiotherapy. Remarkably the 1-year PFS, (the primary endpoint) was the same with both regimens, 36% there was however, a small, but statistically insignificant, trend for improved overall survival in patients that received the four drug regimen that contains high-dose cytarabine. [106]

Neurocognitive Function

Given the recent progress in outcomes in PCNSL, the consequences of treatment-related neurotoxicity among survivors has emerged as an increasingly important question. While reduced-dose brain radiotherapy may be associated with milder cognitive dysfunction among PCNSL survivors compared to standard-dose WBRT,[78], even reduced doses of WBRT as consolidation are associated with impairments of Verbal Memory and Motor Speed. By contrast, PCNSL patients treated with HD-MTX without consolidative WBRT do not exhibit severe cognitive dysfunction as determined by neuropsychological testing; PCNSL patients treated with HD-MTX without WBRT nevertheless score lower than normative control subjects in several domains including motor speed and executive function. [107] Given that PCNSL is an infiltrative brain tumor associated with a spectrum of neurologic symptoms, determination of whether impairments of neurologic function are the consequence of lymphoma versus neurotoxicity of agents such as methotrexate remains a challenge.

Treatment of Recurrent PCNSL

Several studies have demonstrated that dose-intensive chemotherapy with stem cell rescue can be an effective option in the treatment of relapsed CNS lymphomas and IOL.[8,90,108] In the setting of recurrent disease that is methotrexate-sensitive, one approach is to administer additional cycles of HD-MTX, to achieve maximal cytoreduction, followed by dose-intensive chemotherapy consolidation using non-cross-resistant, CNS penetrant agents such as thiotepa [9,109,110] High-dose carmustine-based therapy without thiotepa has also been studied.[111] (Table 1) For CNS lymphomas that have progressed within six months of dose-intensive chemotherapeutic consolidation, salvage high-dose chemotherapy may not be an effective option. Such patients may be managed with additional HD-MTX, pemetrexed,[112], WBRT or investigational agents in CNS lymphoma such as lenalidomide or ibrutinib.

Rituximab in CNS lymphomas

While rituximab has become a cornerstone of therapy in systemic B-cell NHL, a number of studies demonstrated that the addition of rituximab to CHOP may not significantly decrease the rate of CNS recurrence of systemic large B-cell lymphoma compared to CHOP alone. [113–115] Nevertheless, intravenous rituximab can induce responses of contrast-enhancing lesions in CNS lymphoma, likely in lesions in which there is substantial disruption of the blood-brain barrier. [104] Further data substantiating the role for rituximab in PCNSL has recently been provided in a randomized phase II study led by Ferreri that evaluated the MATRIX regimen, comprised of a methotrexate/cytarabine backbone plus thiotepa and rituximab. Results presented at the 13th International Conference on Malignant Lymphoma, in June 2015 in Lugano, confirm significantly improved outcomes in PCNSL patients that received rituximab.

Intraventricular Rituximab in CNS Lymphomas

The safety and efficacy of intraventricular rituximab, both as monotherapy and in combination with intraventricular methotrexate was recently evaluated in the setting of two phase I multicenter trials involving patients with recurrent primary and secondary CNS lymphomas.[26,116] These studies demonstrated that, when diluted in preservative-free normal saline and administered into ventricular CSF, 10 and 25 mg doses of rituximab are well-tolerated and elicited responses within leptomeninges, intraocular compartments and in small parenchymal lesions. The efficacy of intraventricular rituximab was additive or synergistic with methotrexate. One of the key findings was that intraventricular rituximab/methotrexate was particularly active in patients with a high burden of leptomeningeal lymphoma. These studies also suggested that intraventricular rituximab overcomes the problem of the blood-brain barrier, in that CSF responses were documented in patients with baseline serum rituximab concentrations greater than 15 μg/ml. [26,116] A potential mechanistic explanation for the rapid efficacy of intraventricular rituximab is provided by activation of the complement cascade at C3 as well as the C5b-9 membrane attack complex within CSF upon intra-CSF rituximab administration. [117]

Given the evidence for activity of intravenous rituximab in CNS lymphomas, as monotherapy and in combination with methotrexate-based induction,[118] a number of protocols now incorporate this anti-CD20 monoclonal antibody as a component of induction

in PCNSL. While several studies demonstrate its activity at relapse, intraventricular rituximab remains investigational and the combination of intraventricular plus intravenous rituximab with lenalidomide for recurrent CNS lymphomas is currently being studied in phase I investigation (NCT01542918).

Treatment of Intraocular Lymphoma (IOL)

Most cases of IOL involve large B-cell NHL, and are classified as either primary vitreoretinal lymphoma or uveal lymphomas; these are divided into primary neoplasms of the choroid, iris and ciliary body, or secondary choroidal lymphomas in patients with systemic NHL. Importantly, between 65% to 90% of patients with primary vitreoretinal lymphoma (PVRL) ultimately disseminate throughout the neuroaxis, typically within 30 months. Conversely, IOL impacts 15–25% of patients with PCNSL.

Therapies for PVRL can be divided into local approaches such as ocular radiation or intravitreal therapy vs. systemic chemotherapy. External beam radiotherapy using opposed lateral beams to the eyes is well tolerated, and associated with low rates of local recurrence. Typical complications of ocular radiotherapy are mild and include dry eye, cataracts and radiation retinopathy [119] Intravitreal methotrexate and rituximab may be of value in management of unilateral disease or in the setting of prior ocular radiation.[120,121] Treatment-related complications of intravitreal methotrexate include hemorrhage, endophthalmitis, hypotnony and retinal detachment.[122] Systemic therapeutic options for IOL include HD-MTX,[123] high-dose cytarabine or trofasfamide.[124125]Notably, in PVRL, systemic HD-MTX plus binocular irradiation provides local disease control and addresses the probability of subclinical disease throughout the neuroaxis.[126] Our approach to patients with primary IOL and/or concomitant PCNSL with IOL typically involves 3 steps: (1) HD-MTX--based induction (with rituximab, if disease is CD20+); (2) dose-intensive chemotherapeutic consolidation with EA or ASCT (3) Binocular radiotherapy, but not WBRT if there is persistence and/or recurrence of isolated IOL after completion of dose-intensive consolidation.

PCNSL in the Immunocompromised Host

While the incidence of HIV-associated PCNSL declined in incidence with advent of combination anti-retroviral therapy (cART), PCNSL remains a significant AIDS-defining illness that represents a major therapeutic challenge. Feasibility and efficacy of HD-MTX in HIV-associated PCNSL has been demonstrated. [127] Similarly, in the setting of CNS post-transplant lymphoproliferative disorder (PTLD), reconstitution of immune function is a first principle, and is achieved by reduction in immunosuppression. HD-MTX is usually effective but its implementation needs to be balanced with risk of allograft failure.[128] Rituximab is also active in the CNS complications of PTLD, via intravenous as well as intrathecal administration.[129]

Conclusions and Future Directions

Over the past 50 years, significant progress has been achieved in the treatment of PCNSL, an aggressive variant of large B-cell lymphoma. Between 40–50% of PCNSL patients are now

likely to exhibit long-term survival and a significant proportion may be cured. However given that at least 50% of patients develop disease refractory to the established armentarium of agents, it is now imperative that additional studies explore the potential efficacy of selective agents that target candidate resistance mechanisms in high-risk PCNSL patients.[130] For example, pharmacologic agents that evaluate disruption of NF-kB activating pathways involving the B-cell receptor, toll-like receptor, and PIM kinases are high priority in early phase investigation in PCNSL. Another key target is MUM-1/IRF-4, targeted by IMiD small molecule agents such as lenalidomide, or CC-122,[131] currently under evaluation in relapsed PCNSL [132,133] Transformative advances are needed given the predilection of PCNSL for an aging population that often cannot tolerate dose-intensive chemotherapy or WBRT.

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Key Points

1. Long-term survival and cure is feasible in primary CNS lymphoma (PCNSL) without whole brain radiotherapy.
2. Whole brain radiotherapy consolidation is associated with severe neurotoxicity, particularly in patients older than 60.
3. High-dose chemotherapy is currently under investigation as first-line consolidation.
4. There is a need for novel therapies that target key survival pathways in PCNSL, including activation of NF-kB survival signaling.

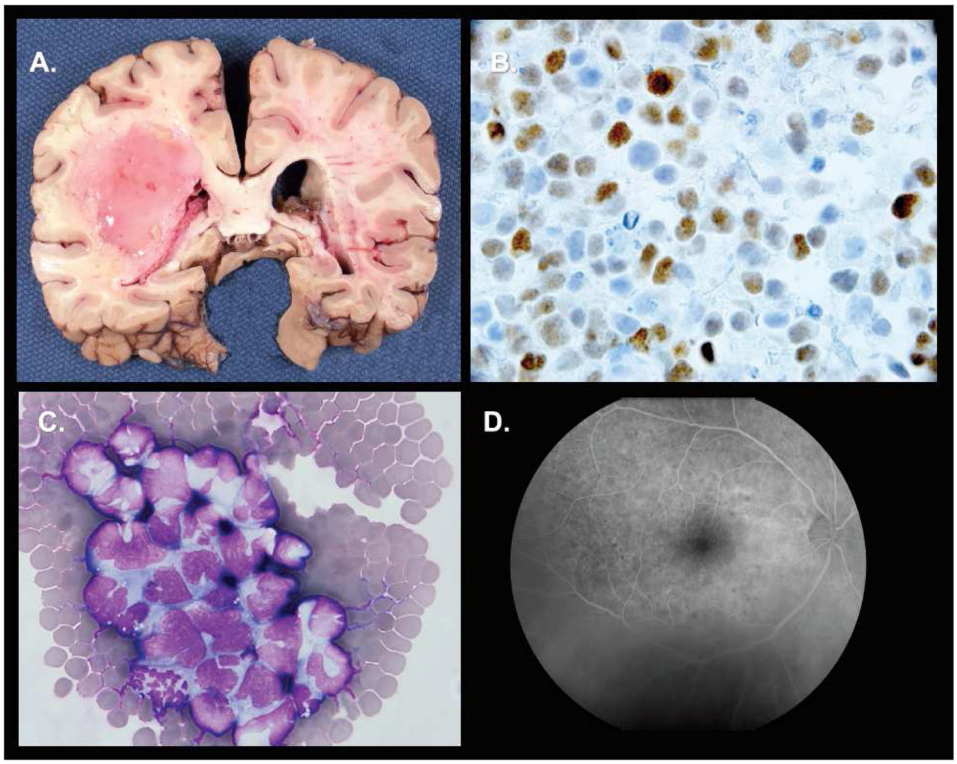

Figure 1.

Pathologic features of PCNSL. (A) Diffuse, large B-cell lymphoma (DLBCL) involving the left parietal lobe and basal ganglia with significant mass effect, subependymal spread, and invasion of the lateral ventricle, upon progression with HD-MTX and rituximab-based chemotherapy. (B) High expression of MUM1 by diffuse large B-cell lymphoma cells in a diagnostic specimen of PCNSL, as demonstrated by immunohistochemistry (B) Cytology of diffuse large B-cell lymphoma in cerebrospinal fluid in recurrent PCNSL. (C) Fluorescein angiography demonstrates classic ‘leopard spots’ in intraocular lymphoma. (Courtesy of Ray Sobel, MD, Stanford University School of Medicine, Stanford, CA.)

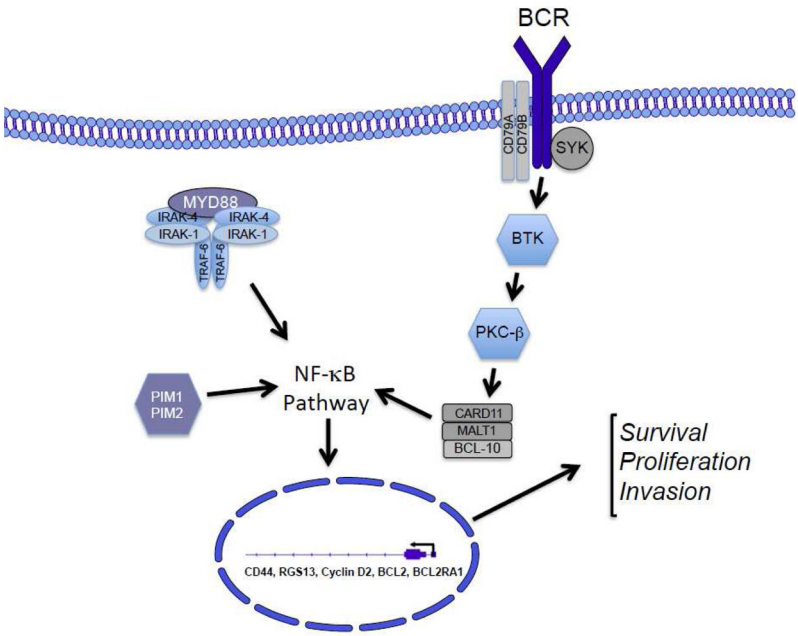

Figure 2. NF-kB Activation in Primary CNS Lymphoma

NF-kB transcriptional activation is regulated by multiple signals in PCNSL, including the MYD88/IRAK1/4 complex and the B cell receptor (BCR) complex consisting of CD79A and B and SYK tyrosine kinase. Activation of IRAK1 and 4 kinases via the oncogenic mutation of MYD88 at L265P impacts ~50% of PCNSL cases. MYD88 is an adapter protein that mediates toll-like receptor (TLR) and interleukin-1 receptor signaling. In addition, chronic active signaling via the BCR involving SYK and BTK also potentiates NF-kB activation. Activating mutations involving CD79B, a component of the BCR, as well as CARD11, a mediator of BCR signaling, are each present in ~15% of cases and result in NF-kB activation.

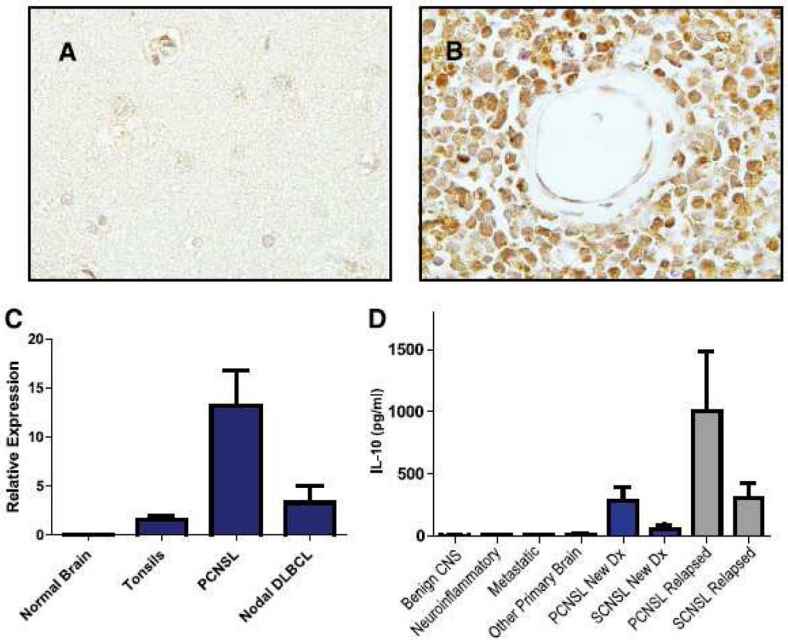

Figure 3.

IL-10 Expression in CNS Lymphomas. Absent expression in normal brain (A) with strong expression of IL-10 by lymphoma cells in PCNSL (B), as demonstrated by immunohistochemistry. (X1000). (C) Quantitative RT-PCR demonstrates markedly increased expression of IL-10 in diagnostic specimens of PCNSL (N=23) compared with reactive tonsils and normal brain. The average IL-10 expression was higher in PCNSL compared to 9 cases of nodal DLBCL of which 7 were of germinal center phenotype. (D) Mean CSF IL-10 protein is 70-fold higher in patients with PCNSL and SCNSL compared to neuro-inflammatory conditions and other brain tumors ($p < 2.3 \times 10^{-5}$). CSF concentration of IL-10 was highest in relapsed cases.

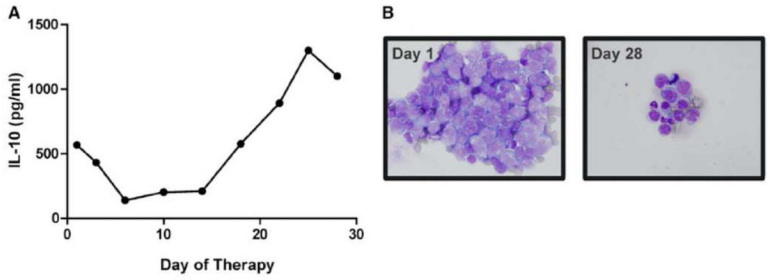

Figure 4.

(A) IL-10 concentration in CSF correlates with disease course in patients with recurrent CNS lymphomas that are treated with rituximab plus methotrexate (representative of six consecutive cases). (B) Cytological appearance of lymphoma cells in CSF at baseline and persistent disease at completion of intraventricular therapy with rituximab plus methotrexate. (From Rubenstein, J.L., *et al.* CXCL13 plus interleukin 10 is highly specific for the diagnosis of CNS lymphoma. *Blood* 2013;**121**:4740–4748; with permission.)

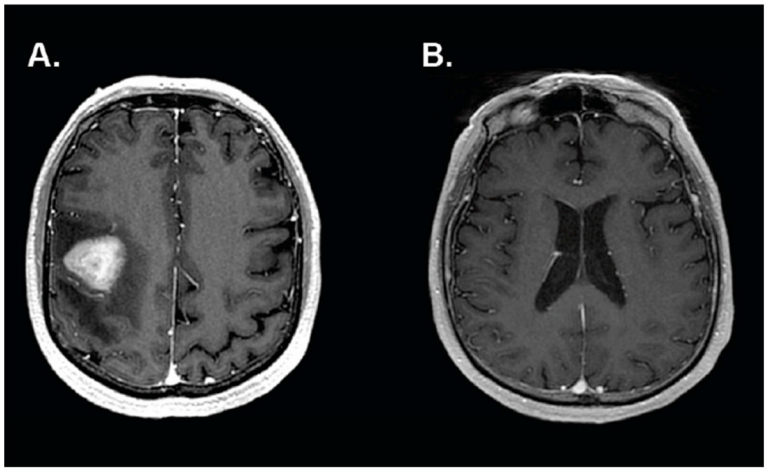

Figure 5.

MRI features of PCNSL in two patients at diagnosis (A). MRI depicts homogeneously enhancing mass with vasogeneic edema. (B). Normal appearing MRI of patient with progressive neurologic symptoms who was aggressively treated with steroids before a diagnosis could be elicited. Four repeat CSF collections and one brain biopsy were non-diagnostic and the diagnosis of disseminated PCNSL was made at autopsy. Notably, the CSF of each patient contained elevated concentrations of CXCL13 and IL-10, highly specific biomarkers that facilitate diagnosis of PCNSL. (From Rubenstein, J.L., *et al.* CXCL13 plus interleukin 10 is highly specific for the diagnosis of CNS lymphoma. *Blood* 2013;**121**:4740–4748; with permission.)

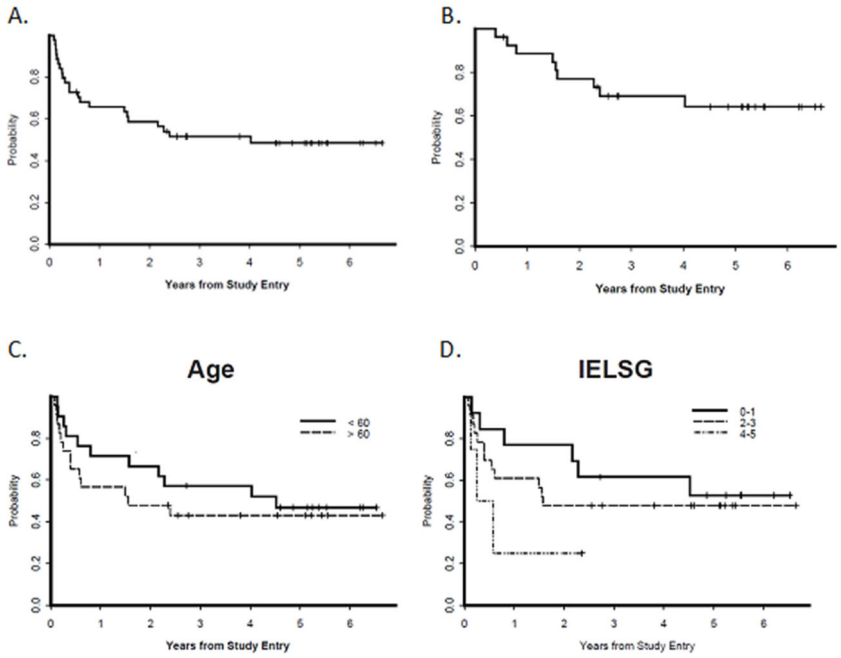

Figure 6. Outcomes with intensive chemotherapy and immunotherapy in newly-diagnosed primary central nervous system lymphoma, without whole brain radiotherapy: CALGB (Alliance) 50202)

Outcome for all CALGB 50202 patients; y-axis refers to cumulative probability of event. (A) Progression-free survival (PFS) for all patients. The 2-year PFS was 59%. (B) PFS for those patients who attained a complete response with MT- R (high-dose methotrexate, temozolomide, rituximab) induction and received EA (etoposide cytararbine) consolidation (n = 27). (C) PFS was similar for patients aged >60 years (n = 23) and for younger patients (n = 21; P = 0_48). (D) There was a trend between shorter PFS and highest International Extranodal Lymphoma Study Group (IELSG) risk score of 4–5 (P = 0_16). (From Rubenstein JL, Hsi ED, Johnson JL, Jung SH, Nakashima MO, Grant B, Cheson BD & Kaplan LD. Intensive Chemotherapy and Immunotherapy in Patients With Newly Diagnosed Primary CNS Lymphoma: CALGB 50202 (Alliance 50202). J Clin Oncol 31 (2013), 3061–3068; with permission.)

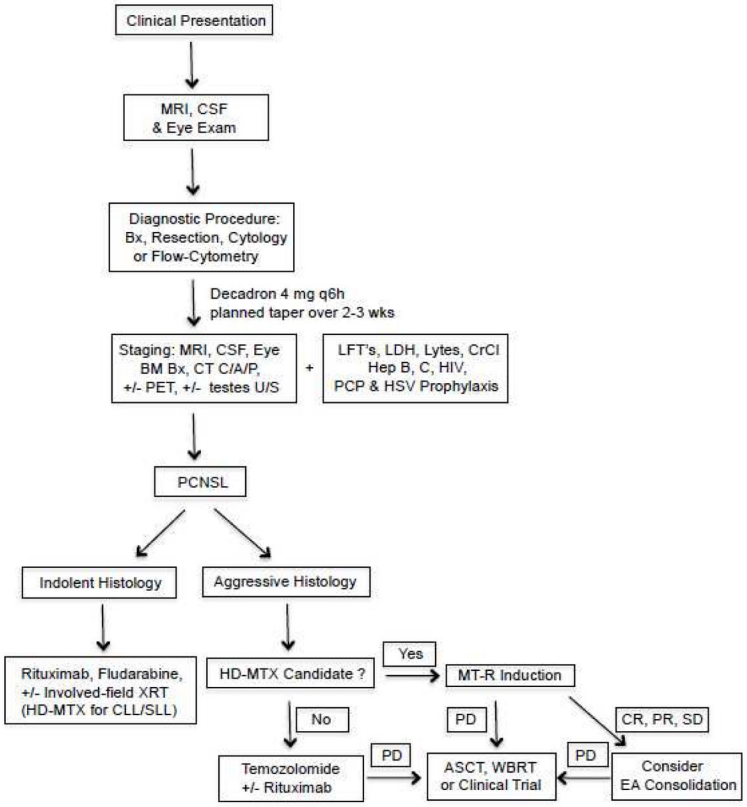

Figure 7. Approach to Treatment of Newly Diagnosed Primary CNS Lymphoma

In the diagnostic work-up, an MRI of the spine may be useful if warranted by neurologic symptoms or if CSF analysis is contraindicated. Ultrasonography of the testes is indicated for older male patients with CNS involvement of lymphoma in which testes coinvolvement is suspected on clinical and/or radiographic grounds. The value of a positron emission tomography scan in this setting is not established. Although the schedule of Decadron taper should be **i**ndividualized, we recommend a planned taper to be completed within 2 to 3 weeks of diagnosis, between the first and second courses of HD-MTX. Therapeutic options for indolent lymphomas that involve the CNS or dura include rituximab, fludarabine, involved-field irradiation, and HD-MTX for CNS involvement of chronic **l**ymphocytic leukemia/small lymphocytic leukemia. For newly diagnosed patients who are not candidates for HD-MTX, in most cases we recommend a trial of temozolomide and rituximab and/or strategies that use high-dose chemotherapy, before consideration of using whole-brain irradiation. ASCT, autologous stem cell transplant; CR, complete response; EA, etoposide-cytarabine; HSV, herpes simplex virus; MT-R, combination HD-MTX, temozolomide, and rituximab (rituximab is omitted for T-cell lymphomas); PCP, Pneumocytis jiroveci pneumonia; PD, progressive disease; PR, partial response; SD, stable disease; WBRT, whole-brain radiotherapy. (Originally published by the American Society of Hematology. (From Rubenstein *et al.*, How I treat CNS lymphomas. *Blood* 20134;**122**:2318–2330; with permission.)

Table 1

Regimens that are active in Dose Intensive Consolidation and Myeloablative Therapy in CNS Lymphomas.

Intensive Consolidation/Preparative Regimen	Reference
Carmustine, Thiotepa, Etoposide	Korfel (2013)
Infusional Etoposide, High-Dose Cytarabine	Wieduwilt (2012); Rubenstein (2013b)
Thiotepa, Busulfan, Cyclophosphamide	Soussain (2002, 2008); Cote (2012), Omuro (2015)
Carmustine, Thiotepa	Illerhaus (2008)
Cyclophosphamide, Carmustine, Etoposide	Alvarnas (2000)