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Progress in Central Nervous System Lymphomas

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Abstract

Until recently, primary central nervous system lymphoma (PCNSL) was associated with a uniformly dismal prognosis. It is now reasonable to anticipate long-term survival and possibly cure for a significant proportion of patients diagnosed with PCNSL. Accumulated data generated over the past ten years has provided evidence that long-term progression-free survival (PFS) can reproducibly be attained in a significant fraction of PCNSL patients that receive dose-intensive chemotherapy consolidation, without whole brain radiotherapy. One consolidative regimen that has reproducibly demonstrated promise is the combination of infusional etoposide plus high-dose cytarabine (EA), administered in first complete remission after methotrexate, temozolomide and rituximab-based induction. Given evolving principles of management and the mounting evidence for reproducible improvements in survival rates in prospective clinical series, our goal in this review is to highlight and update principles in diagnosis, staging and management as well as to review data regarding the pathogenesis of central nervous system lymphomas, information that is likely to constitute a basis for the implementation of novel therapies that are requisite for further progress in this unique phenotype of non-Hodgkin lymphoma.

Keywords

Primary CNS Lymphoma; High-Dose Chemotherapy; Rituximab; Tumour Microenvironment

Introduction

Primary central nervous system lymphoma (PCNSL) is characterized by dissemination of aggressive non-Hodgkin lymphoma (NHL) within the brain, cranial nerves, leptomeninges, cerebrospinal fluid (CSF), intraocular structures and spinal cord. (Hochberg & Miller, 1988; Batchelor & Loeffler, 2006) In secondary central nervous system (CNS) lymphomas, CNS localization of lymphoma is accompanied by either concomitant or a history of systemic involvement. While PCNSL constitutes approximately 3% of all brain tumours, and 2–3% of all cases of NHL, according to the Surveillance, Epidemiology and End Results database

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(http://seer.cancer.gov/), its incidence appears to be increasing among persons age sixty-five years and older. (Villano *et al.*, 2011)

Historically, PCNSL, known previously as reticulum cell sarcoma or microglioma, was associated with an extremely grave prognosis. (Norden *et al.*, 2011) During the 1960's, physicians lacked prospective data to guide management and whole brain irradiation (WBRT) was usually implemented as a first-line intervention, given its activity in yielding immediate responses in patients faced with a rapidly deteriorating course, resulting in median survival of 12 months. Treatment of CNS lymphomas became more effective in the 1970's with recognition of the efficacy of high-dose methotrexate (HD-MTX). (Skarin *et al.*, 1977; Ervin & Canellos, 1980)

Given that several recent phase I/II studies have demonstrated improvements in outcomes for patients with PCNSL, our goal is to review current information regarding disease biology, diagnosis, staging and strategies in therapeutic management. (Illerhaus *et al.*, 2008; Wieduwilt *et al.*, 2012; Bromberg *et al.*, 2013; Korfel *et al.*, 2013; Rubenstein *et al.*, 2013a; Rubenstein *et al.*, 2013b)

Aetiology

The best established risk factors for CNS involvement of NHL are acquired or congenital immunodeficiency states. PCNSL is an acquired immunodeficiency syndrome (AIDS)-defining illness associated with a low CD4 count ($< 0.05 \times 10^9$ cells/l) and almost 100% association with Epstein Barr Virus (EBV). While only 20% of systemic AIDS-related lymphomas are associated with EBV, EBV infection of the malignant clone correlates with increased risk for CNS involvement. (Cingolani *et al.*, 2000) Patients with severe-combined or common-variable immunodeficiency, ataxia-telangiectasia or Wiskott-Aldrich syndrome have about a 4% risk of PCNSL. Post-transplant lymphoproliferative disorder (PTLD) involving the brain develops in 1–2% of renal transplant recipients and 2–7% recipients of cardiac, lung and liver transplants. CNS PTLD is strongly associated with EBV in the setting of T-cell immunodeficiency caused by agents such as mycophenolate mofetil. (Schabet, 1999) By contrast, among patients without overt immunosuppression, EBV infection of CNS lymphoma is rarely detected. (Camilleri-Broet *et al.*, 2006)

Molecular Pathogenesis and the Microenvironment

Like glioblastoma, PCNSL is a highly infiltrative neoplasm, particularly at relapse, prompting its description as a "whole brain disease." (Lai *et al.*, 2002) It is generally appreciated that the radiographic appearance of the tumour underestimates disease extent and, like malignant gliomas, PCNSL is essentially impossible to completely resect. (Lai *et al.*, 2002) One of the characteristic histological features of PCNSL is that of angiotropism, in which lymphoma cells accumulate around small and medium-sized blood vessels, contributing to disruption of the blood-brain barrier, and enabling their detection by virtue of pathological contrast enhancement. PCNSL usually presents as a solitary mass with vasogenic oedema and mass effect. (Figures 1–3). The frequency of multiple lesions is increased two-fold among immunosuppressed patients. (Fine & Mayer, 1993)

Approximately 95% of PCNSL tumours are large B-cell lymphoma; other histologies include T-cell (2%)(Shenkier *et al.*, 2005), lymphoblastic, Burkitt, and marginal zone lymphoma. PCNSL is distinguished from dural-based marginal zone lymphomas as these have a distinct pathogenesis, are typically devoid of intraparenchymal extent and share radiographic features with meningioma. (Tu *et al.*, 2005)

Nearly 20% of PCNSL cases present with intraocular disease with involvement of the retina, vitreous and uveal tract. It is important for the clinician to recognize that intraocular lymphoma (IOL) disseminates within CNS in greater than 80% of cases, and therefore, suspicion or detection of IOL mandates staging of the neuroaxis, including brain magnetic resonance imaging (MRI) and CSF evaluation. (Rubenstein *et al.*, 2005) Between 50% to 80% of tumours express BCL6 by immunohistochemistry (Braaten *et al.*, 2003) and greater than 95% stain positive for MUM1; thus the majority of PCNSL express an immunophenotype consistent with the activated B-cell subclass of large-cell lymphoma. (Camilleri-Broet *et al.*, 2006) Between 56–93% of PCNSL cases express BCL2. (Braaten *et al.*, 2003; Camilleri-Broet *et al.*, 2006) In addition, there is reproducible evidence for distinct transcriptional features in PCNSL (Jordanova *et al.*, 2002; Rubenstein *et al.*, 2006; Booman *et al.*, 2008; Tun *et al.*, 2008) and, given that the disease requires a unique therapy, PCNSL is recognized as a distinct subtype of large B-cell lymphoma by the World Health Organization(Campo *et al.*, 2011).

Genomic aberrations in PCNSL include losses on chromosome 6p21 containing human leucocyte antigen (HLA) loci. (Harada *et al.*, 2001; Boonstra *et al.*, 2003; Cady *et al.*, 2008) Candidate tumour suppressor genes linked to deleted loci on chromosome 6q include *PRDM1*, a regulator of B-cell differentiation and tumour suppressor,(Courts *et al.*, 2008) *PTPRK*, a protein tyrosine phosphatase involved in cell adhesion,(Nakamura *et al.*, 2003) and *TNFAIP3* (*A20*), a regulator of nuclear factor (NF)κB signalling. (Braggio *et al.*, 2011) Aberrant activation of NFκB is supported by gain in DNA copy number for *MALT1* (Schwindt *et al.*, 2009) activating mutations of *CARD11* (Montesinos-Rongen *et al.*, 2010) 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% and 50% of cases. (Montesinos-Rongen *et al.*, 2011; Gonzalez-Aguilar *et al.*, 2012) In addition, *CD79B*, a component of the B-cell receptor signalling pathway, contains mutations in 20% of cases, suggesting that dysregulation of the B-cell receptor and NFκB pathways contribute to pathogenesis of PCNSL. (Montesinos-Rongen *et al.*, 2012) Silencing of the cell cycle regulator *CDKN2A* occurs in 50% of CNS lymphoma and correlates with inferior outcome. (Schwindt *et al.*, 2009; Gonzalez-Aguilar *et al.*, 2012)

The basis for selective tropism and dissemination of lymphoma within the brain are problems fundamental to the pathogenesis of PCNSL. Expression of chemokine (C-X-C motif) ligand (CXCL)12 and CXCL13 within PCNSL has been documented (Smith *et al.*, 2003; Smith *et al.*, 2007; Fischer *et al.*, 2009) and chemotactic responsiveness to these peptides by CNS lymphoma recently demonstrated, supporting their role as neurotropic factors. In addition, elevated CXCL13 concentration in CSF correlates with adverse prognosis, supporting its role as a survival factor in PCNSL. Measurement of CSF concentration of CXCL13, as well as interleukin 10 (IL10), may be useful in facilitating

diagnosis of CNS lymphoma; bivariate upregulated expression of each peptide in CSF has diagnostic sensitivity at least two-fold greater than cytology and/or flow-cytometry. (Rubenstein *et al.*, 2013c) In a multicentre study, the positive predictive value of bivariate elevation of IL10 plus CXCL13 in CSF was 95% in identification of newly diagnosed human immunodeficiency virus (HIV)-negative PCNSL (Rubenstein *et al.*, 2013c).

While it has been established that flow-cytometry is more sensitive than cytology in the detection of CNS lymphomas, (Quijano *et al.*, 2009) recent evidence demonstrates that quantification of soluble CD19 in CSF may augment flow-cytometry in detection of secondary CNS lymphoma associated with diffuse large B-cell lymphoma or Burkitt lymphoma. (Muniz *et al.*, 2014)

Transcriptional profile studies of PCNSL identified several potential mediators of disease pathogenesis, including upregulated MYC expression. (Rubenstein *et al.*, 2006) Increased MYC in PCNSL was confirmed in the recent CALGB 50202 study. (Rubenstein *et al.*, 2013b) High expression of miRNA's involved in the MYC pathway, (Fischer *et al.*, 2011) as well as MYC translocations (Cady *et al.*, 2008) have also been demonstrated.

The JAK/STAT system is a candidate pro-survival pathway in PCNSL. Interleukin 4 (IL4), a B-cell growth factor that signals via the JAK/STAT pathway, is upregulated at the transcript and protein level within the vascular microenvironment in CNS lymphoma. (Rubenstein *et al.*, 2006) Increased concentration of IL10 protein in the vitreous and CSF is associated with PCNSL and, in independent studies, correlated with adverse prognosis. (Roy *et al.*, 2008; Sasayama *et al.*, 2012) Intratumoural *JAK1* transcripts are upregulated in PCNSL with demonstration of JAK1 activation. (Rubenstein *et al.*, 2006; Sung *et al.*, 2011) Elevated IL10 expression plus activation of JAK/STAT signalling in PCNSL are consistent with aberrant activation of the MYD88 pathway (Ngo *et al.*, 2011).

While the brain is typically assumed to be an immunologically privileged site, histopathological evaluation of diagnostic specimens demonstrates a robust inflammatory response within PCNSL, with infiltrating activated macrophages and reactive T-cells. Importantly, there is evidence that reactive, perivascular T-cell infiltrates in PCNSL are associated with favourable outcome, perhaps supporting development of immunotherapies that potentiate T-cell-mediated immune surveillance. (Ponzoni *et al.*, 2007)

Clinical Presentation

Among the immunocompetent, the median age of the PCNSL patient at diagnosis is 56 years with a male-to-female ratio of 1.2–1.7:1. Neurological symptoms of PCNSL typically reflect the neuroanatomical location of the lesion(s). Greater than 60% of patients present with constitutional, cognitive or motor symptoms; 20% present with seizures and 30% have visual symptoms. (Josephson *et al.*, 2007) Leptomeningeal disease occurs in 15–20% of patients at presentation. (Fischer *et al.*, 2008) IOL is manifest by non-specific symptoms of blurred vision, decreased visual acuity, eye pain, floaters and photophobia, usually with involvement of both eyes. The pace of neurological decline at presentation is variable; some patients exhibit chronic visual symptoms that antedate the diagnosis by years, while for others, disease progression is highly aggressive. Notably, in a recent retrospective series of

patients with rapidly progressive neurological deterioration who presented for diagnostic brain biopsy, the most common aetiology was PCNSL (20%). (Josephson *et al.*, 2007)

Diagnostic and Staging Evaluation of the Patient with Neurological Symptoms

As CNS and IOL patients typically present with nonspecific symptoms, establishing a diagnosis may be difficult and it is not uncommon for the interval between first onset of disease signs to extend from months to years before the diagnosis is established. The first-line test in diagnostic evaluation of suspected PCNSL is MRI-based examination of the brain, with gadolinium contrast. In 95% of cases, there is pathological enhancement that homogenously localizes to dominant tumour masses. Lesional necrosis is rare and is one of the radiographic features that may distinguish CNS lymphoma from glioblastoma. Among immunocompetent patients with newly-diagnosed PCNSL, lesions are solitary in 65% and multifocal in 35%. Cerebral hemisphere disease is the most common localization of lesions (38%) followed by the basal ganglia and thalamus (16%), corpus callosum (14%) ventricular region (12%) and cerebellum (9%).(Kuker *et al.*, 2005) (Figure 3).

While glucocorticoids may produce rapid symptomatic improvement, with dramatic radiographic responses in 40% of patients, steroid-induced responses may increase the risk of a non-diagnostic brain or vitreal biopsy. (Porter *et al.*, 2008) Steroid-induced diagnostic delays may extend for weeks to months, although on occasion, steroid-induced regressions of sentinel lesions may delay the diagnosis of PCNSL for years. (Pirotte *et al.*, 1997) It is important to emphasize that, if possible, empiric dexamethasone be rapidly tapered or not administered until a diagnosis is established. If CNS lymphoma is confirmed, steroids should be tapered and discontinued as quickly as possible, unless there is symptomatic tumour-associated mass effect that can be mitigated by glucocorticoids.

The standard diagnostic approach for PCNSL is stereotactic brain biopsy, however in selected cases, subtotal or gross total resections, if safe, may be appropriate. Cytological and/or flow-cytometric analysis of meningeal lymphoma cells isolated from CSF or vitrectomy may also yield diagnostic material. In the setting of tumour-associated mass-effect, particularly in the posterior fossa, consultation with neurosurgery is advised to assess the safety of a diagnostic or staging lumbar puncture. CSF should be efficiently processed for cytology and flow-cytometric studies designed to identify, in most cases, a kappa or lambda-restricted B-cell lymphoma. Repeated CSF cytological or flow-cytometric studies infrequently improve diagnostic yield in PCNSL, supporting further development of innovative molecular diagnostic methods based upon proteomics or analysis of non-coding RNA's. (Roy *et al.*, 2008; Baraniskin *et al.*, 2011; Rubenstein *et al.*, 2013c)

Staging evaluation for the patient with presumptive PCNSL includes complete ophthalmological examination with slit lamp. Systemic staging is also indicated, given that between 4–12% of patients with presumptive PCNSL ultimately manifest extra-CNS disease. (Ferreri *et al.*, 1996) Therefore, contrast-enhanced computerized tomography (CT) of the chest, abdomen and pelvis, as well as bone marrow biopsy are requisite; the value of positron emission tomography (PET) imaging has not been established. (Mohile *et al.*, 2008) but may be useful in evaluation of possible concomitant testicular involvement. Serological

testing for HIV, hepatitis B and C, plus quantification of serum lactate dehydrogenase (LDH) are standard-of-care at baseline. (Abrey *et al.*, 2005)

Diagnostic and Staging Evaluation of Intraocular Lymphoma (IOL)

Given that nearly 80% of patients with IOL ultimately progress to CNS dissemination, MRI of the brain with gadolinium should be performed to evaluate idiopathic uveitis, in which lymphoma is a consideration. Additional diagnostic and staging tests for IOL include fluorescence angiography (Figure 1C) and optical coherent tomography. (Chan *et al.*, 2011) Processing of diagnostic specimens from ocular lesions must be expedited to achieve the highest diagnostic yield by flow-cytometry or cytology. (Rubenstein *et al.*, 2005) Identification of immunoglobulin gene rearrangements and/or quantitative determination of intraocular cytokine concentration of IL10 and IL6 may also be a useful adjunct to diagnosis. (Chan *et al.*, 2002)

Prognostic Assessment in PCNSL

The International Extranodal Lymphoma Study Group (IELSG) identified five variables that correlate with prognosis in PCNSL, three are shared with systemic NHL: elevated LDH, age greater than 60 years, and Eastern Cooperative Oncology Group (ECOG) performance status greater than 1; CNS lymphoma-specific parameters include high CSF protein concentration and tumour 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 of adverse risk factors correlate with two-year survival rates of 80%, 48% or 15%.(Ferreri *et al.*, 2003) Historically, age has been considered the most reproducible clinical prognostic factor, however there is a discrepancy regarding the cut-off point at which prognosis declines. While the IELSG considered age 60 years as the cut-off point above which prognosis declines, the Memorial Sloan-Kettering (MSK) prognostic index uses age 50 years. (Abrey *et al.*, 2006) Notably, in the Cancer and Leukemia Group B (CALGB) 50202 trial, which evaluated intensive immunochemotherapy with dose-intensive consolidation without WBRT, patients older than 60 years did similarly well as younger patients,(Rubenstein *et al.*, 2013b) an observation that suggests that the optimal cut-off point for age as a prognostic variable is largely treatment-dependent. (Wieduwilt *et al.*, 2012)

Principles of Management

Surgery

Until recently, authorities have recommended against neurosurgical resection of CNS lymphoma based upon reports that surgical cytoreduction provides no survival benefit compared to biopsy alone and potentially increases risk of post-operative deficit. (DeAngelis *et al.*, 1990; Bataille *et al.*, 2000) Notably, retrospective analysis of the German PCNSL Study Group (SG)-1 Trial provided the first evidence that aggressive resection of CNS lymphoma correlated with improved PFS. (Weller *et al.*, 2012) In our experience, maximum safe resection of lesions may provide immediate relief of mass effect, facilitate glucocorticoid taper, potentially eliminate drug-resistant tumour clones and provide substantial clinical benefit without contributing to neurological deficits, particularly when performed with modern neurosurgical mapping techniques. (Figure 4).

Whole Brain Irradiation (WBRT)

WBRT is highly effective in the elicitation of immediate responses in CNS lymphoma and therefore brain radiotherapy has historically been of value. The impact of WBRT in the treatment of CNS lymphoma is however compromised by at least three important limitations: (1) Inadequate local control of lymphoma; (2) Dissemination of radiographically-occult lymphoma cells outside of the radiation field; (3) Deleterious effects of radiation on brain function. In one study, the use of WBRT as the sole treatment of PCNSL yielded a median survival of only 11.6 months with greater than 60% of patients experiencing lymphoma progression within the irradiated field. (Nelson *et al.*, 1992) The archetypical features of delayed neurotoxicity caused by WBRT, incontinence, gait and memory disturbances, are most common in patients aged greater than 60 years, and many PCNSL survivors who experience this complication ultimately require custodial care. (Abrey *et al.*, 1998) Whilst a preliminary analysis found that lower doses of WBRT were associated with neurotoxicity that is barely discernable (Correa *et al.*, 2009), additional validation of these results are necessary, and, given the established deleterious neurocognitive effects of prophylactic cranial irradiation at 30 Gy (Sun *et al.*, 2011), there is reason to be concerned that delayed neurotoxicity secondary to WBRT may be a continuous variable in terms of its relationship to dose. Finally, recent updates demonstrate that long-term outcomes of PCNSL patients treated with low-dose WBRT (23.4 Gy) in consolidation revealed significantly inferior outcome in the subgroup of patients older than 60 years. (Morris *et al.*, 2013) For these reasons, there has been progressive interest in innovative strategies that defer or eliminate WBRT as a component of induction therapy.

Induction Chemotherapeutic Strategies

Studies performed by Canellos and colleagues demonstrated the feasibility and efficacy of systemic HD-MTX in recurrent CNS lymphomas. (Skarin *et al.*, 1977; Ervin & Canellos, 1980) Subsequently, HD-MTX was incorporated more broadly in induction and salvage regimens and identified in a multivariate analysis as the most significant treatment-related prognostic variable related to survival for CNS lymphomas. (Blay *et al.*, 1998).

The optimal dose of MTX during induction has not been defined. It is clear from our experience that systemic doses ≥ 1 g/m^2 mediate lymphocytotoxic effects within brain parenchyma, in agreement with others. (Skarin *et al.*, 1977). In an important study, Glantz *et al* (1998) demonstrated that intravenous MTX administered at 8 g/m^2 over 4 h yields higher cytotoxic levels of MTX (greater than 1 μM) in serum and CSF than intrathecal MTX (12 mg) at 48 and 72 h post-infusion. In another influential analysis, investigators at MSK demonstrated that elimination of intrathecal MTX from induction therapy for PCNSL did not affect outcome if patients received HD-MTX at doses of 3.5 gm/m^2.(Khan *et al.*, 2002) These results indicate that high-dose intravenous MTX administered every two weeks for a minimum of six cycles can be used to treat aggressive lymphoma within the brain and leptomeningeal compartment, without intrathecal therapy. (Wieduwilt *et al.*, 2012) One of the many therapeutic issues in PCNSL yet to be resolved is the optimal number of cycles of HD-MTX administered during induction. Given data that greater than four cycles of MTX may be necessary to obtain an effective remission before consideration of dose-intensive

consolidation (Abrey *et al.*, 2003), our approach has been to administer eight cycles of HD-MTX during induction, assuming a complete remission is attained by cycle six.

Prevention and Management of HD-MTX Toxicity

It is important for the haematologist to be skilled in the management of the toxicities of HD-MTX, in particular MTX nephropathy, caused by precipitation of MTX and 7-OH-MTX within renal tubules. Basic principles to prevent this life-threatening complication, which occurs in up to 5% of patients, include vigorous hydration, urine alkalinization, and avoidance of agents that interact with HD-MTX, such as penicillin derivatives. Third-space effusions must be drained before MTX administration and leukovorin rescue started at 24 h, with serial monitoring of MTX serum concentrations. Delayed MTX excretion mandates continued alkalinization and hydration as well as escalated leukovorin dosing. Additional interventions for delayed MTX clearance include carboxypeptidase-G2 (CPDG2, glucarpidase), a recombinant enzyme. Glucarpidase reduces toxic serum MTX concentrations within 15 min, via direct hydrolysis of MTX. (Green, 2012) It is also important to be aware of the risk of superimposed iodine contrast nephropathy with that of MTX nephropathy, which can be mitigated by providing an interval of at least two days between CT imaging and HD-MTX.

Combined-Modality Regimens

DeAngelis and colleagues pioneered combined modality therapy for PCNSL, consisting of HD-MTX plus procarbazine and vincristine, followed by WBRT and high-dose cytarabine (HD-Ara-C); implementation of this regimen in the multicentre setting, coordinated by RTOG, yielded a median progression-free survival of 24 months. (DeAngelis *et al.*, 2002) (Table I). Because of this encouraging efficacy, combined-modality therapy became a widely adopted approach for PCNSL. (DeAngelis *et al.*, 1992; Glass *et al.*, 1994) In a large randomized phase II study that evaluated HD-MTX-based induction, with or without HD-Ara-C (2 g/m^2) followed by consolidative WBRT: 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 cytarabine, was only four months. (Ferreri *et al.*, 2009) In the SG-1 trial, a large randomized phase III trial involving 551 patients in which half the patients received WBRT as first-line consolidation, Thiel *et al* (2010) provided evidence that omission of WBRT from first-line chemotherapy does not compromise survival. While WBRT resulted in a modest improvement in PFS after MTX-based induction, this did not translate into improved overall survival, possibly because of severe neurotoxicity with WBRT, detected in nearly half of patients in the radiotherapy arm. (Thiel *et al.*, 2010)

Dose-Intensive Chemotherapy Consolidation

Given the increased recognition of the delayed neurotoxicity caused by WBRT in CNS lymphoma survivors, during the past two decades there has been significant interest in the role of high-dose consolidation, including autologous stem cell rescue, in PCNSL, both at diagnosis and in the setting of relapse. Regimens that contain agents with good CNS penetration, such as carmustine, thiotepa, cyclophosphamide, busulfan, HD-Ara-C and

etoposide, have been associated with the best results. (Alvarnas *et al.*, 2000; Soussain *et al.*, 2001; Illerhaus *et al.*, 2008; Korfel *et al.*, 2013) (Table II). Notably, results obtained using the BEAM regimen (carmustine, etoposide, cytarabine, melphalan) followed by autologous stem cell rescue were not promising, however in this trial a large proportion of patients had inadequate disease control before myeloablative therapy, possibly because of the abbreviated induction used in this trial. (Abrey *et al.*, 2003)

Soussain *et al* (2001) demonstrated the efficacy of dose-intensive chemotherapy and autologous stem cell transplant in recurrent CNS and IOL. Their data provided evidence that HD-Ara-C plus etoposide (EA) constitutes a highly potent salvage regimen when used in combination for recurrent/refractory CNS lymphomas: 12 of 14 patients attained responses, eight of which were complete responses (Soussain *et al.*, 2001). After stem cell collection, responding CNS lymphoma patients received a myeloablative regimen consisting of thiotepa, busulfan and cyclophosphamide.

Beginning in 2001, investigators at the University of California, San Francisco (UCSF), began to pursue dose-intensive chemotherapy as first-line consolidation, without WBRT, after induction immunochemotherapy in patients with newly-diagnosed PCNSL. We developed a two-step regimen: the induction phase uses HD-MTX given every two weeks with oral temozolomide and rituximab (MT-R). MTX is administered at 8 g/m^2 with dose reductions as appropriate and leucovorin rescue day 2. Intravenous rituximab is administered day 3, and weekly for six doses, an interval during which the blood-brain barrier may be most compromised. (Ott *et al.*, 1991) Temozolomide is an alkylating agent with lipophilic properties that has established efficacy at relapse in CNS lymphoma, alone and in combination with rituximab (Reni *et al.*, 2000; Wong *et al.*, 2004; Reni *et al.*, 2007). Importantly, temozolomide has a superior health-related quality of life and toxicity profile compared to procarbazine (Osoba *et al.*, 2000a; Osoba *et al.*, 2000b). Temozolomide is administered monthly in a five-day course at 150 mg/m^2, beginning days 7–11. To consolidate response after induction with MT-R, PCNSL patients received intensive consolidation with non-cross-resistant agents: 96-h infusional etoposide (40 mg/kg IV) plus eight doses of HD-Ara-C (EA) (2 g/m^2, every 12 h) (Damon *et al.*, 2008; Damon *et al.*, 2009; Linker *et al.*, 2009). Notably, infusional etoposide is incorporated within the EPOCH regimen (etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone), which is active against large B-cell lymphoma (Wilson *et al.*, 1993; Wilson *et al.*, 2008). A number of studies provide evidence for activity of etoposide in brain tumours, including CNS lymphoid leukaemia (Relling *et al.*, 1996). Notably, when given in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) in patients with aggressive lymphoma, etoposide was associated with a reduced risk of secondary CNS lymphoma (Boehme *et al.*, 2007)

While the impact of HD-Ara-C in PCNSL was demonstrated in a randomized phase II study (Ferreri *et al.*, 2009) the dose-intensity of cytarabine within EA is markedly greater than in previous studies in PCNSL and similar to schedules of HD-Ara-C used to treat Burkitt and mantle cell lymphoma and acute myeloid leukaemia. (Damon *et al.*, 2008; Damon *et al.*, 2009; Linker *et al.*, 2009; Schaich *et al.*, 2011; Schaich *et al.*, 2013). Notably, the dose-

intensity of EA is also approximately two-fold higher than doses of etoposide-cytarabine used as first-line salvage in the Soussain series. (Soussain *et al.*, 2001)

One of the goals of the two-step MT-R EA programme was to develop an induction regimen that incorporates an alkylator, temozolomide (Reni *et al.*, 2007) plus rituximab (Batchelor *et al.*, 2011), and yet causes minimal myelosuppression, resulting in few 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 patients treated with this regimen demonstrates that combination EA is highly effective as consolidation after MT-R in newly diagnosed PCNSL. (Wieduwilt *et al.*, 2012) Of the first 14 PCNSL patients who received MT-R followed by EA consolidation, 12 remain in remission, with a median follow-up of greater than 72 months. Based on promising institutional pilot data, the MT-R plus EA regimen was evaluated in CALGB 50202, which, for the first time, demonstrated the multicentre feasibility of high-dose chemotherapy in newly-diagnosed PCNSL. The rate of complete response to MT-R induction in CALGB 50202 was 0.66 and the two-year PFS was 0.57, exceeding other chemotherapy-alone studies thus far. Moreover, the median time to progression of all 50202 patients, four years, is two-times longer than achieved with combined-modality therapy in multicentre trials using standard-dose WBRT and appears to compare favourably to reduced-dose WBRT. (DeAngelis *et al.*, 2002; Thiel *et al.*, 2010) Also encouraging is the fact that the PFS curves reached a stable plateau, and outcome data was similar in patients older than 60 compared to younger patients. (Table I; Figure 5).

Based upon the promising results of CALGB 50202, a successor randomized phase II trial, CALGB 51101, has been initiated and endorsed by major cooperative groups in the United States: Alliance, Southwestern Oncology Group (SWOG), and Eastern Cooperative Group (ECOG). In CALGB 51101, after remission induction therapy with MT-R, patients receive either consolidation with EA or myeloablative therapy and stem cell transplant with carmustine plus thiotepa, a regimen evaluated by the Freiburg group. (Illerhaus *et al.*, 2008) Recently completed randomized control studies are comparing outcomes of high-dose chemotherapy versus WBRT, and, like CALGB 51101, the MATRIX/IELSG43 trial compares high-dose consolidation chemotherapy with conventional consolidative chemotherapy (dexamethasone, etoposide, ifosfamide and carboplatin) (Table III).

Neurocognitive Function

Given recent progress in outcomes in PCNSL, the issue of treatment-related neurotoxicity among survivors is receiving significant attention. Delayed cognitive dysfunction is recognized as a major complication of combined-modality therapy that includes WBRT. As above, while there is preliminary data that reduced-dose WBRT is associated with milder cognitive dysfunction among PCNSL survivors compared to standard-dose WBRT,(Correa *et al.*, 2009) reduced doses of WBRT as consolidation may be associated with impairments of verbal memory and motor speed. PCNSL patients treated with HD-MTX-based therapies without consolidative WBRT do not appear to exhibit severe cognitive dysfunction as determined by post-treatment neuropsychological testing but nevertheless score lower than normative control subjects in evaluations of selective attention, motor speed, executive function, verbal learning and delayed recall. (Correa *et al.*, 2012) Given that PCNSL is a

highly infiltrative neoplasm associated with a spectrum of neurological symptoms, discernment of whether impairments of neurological function are caused by lymphoma or the consequence of the delayed neurotoxicity of agents, such as MTX, is a major challenge.

Management of Secondary CNS Lymphoma

CNS dissemination is one of the most devastating complications of relapsed aggressive systemic NHL. The natural history of secondary CNS lymphoma was defined in a retrospective analysis of SWOG 8516. Here it was recognized that CNS relapses occurred earlier than systemic relapses and median survival after diagnosis of secondary CNS lymphoma was only 2.2 months compared to 9 months with non-CNS relapse. Risk factors for CNS localization at recurrence of aggressive lymphomas include extranodal involvement, with testes a site of particular high-risk, as well as high International Prognostic Index score. The efficacy of intrathecal chemotherapy in prophylaxis of secondary CNS lymphoma could not be demonstrated in this analysis. (Bernstein *et al.*, 2009)

Given the demonstration that higher sustained cytotoxic MTX levels in CSF are achieved after high-dose intravenous dosing compared to intrathecal administration,(Glantz *et al.*, 1998) there is increasing interest in HD-MTX as prophylaxis for patients with systemic NHL with high-risk features of CNS relapse. Recent data substantiates evidence for the efficacy of this approach in preventing CNS relapse in patients at high-risk. (Abramson *et al.*, 2010), and taken together, these data support our recommendation that HD-MTX be administered as prophylaxis of secondary CNS lymphoma in patients with aggressive lymphomas at high risk for CNS dissemination.

Therapeutic Options in Recurrent CNS Lymphomas

Dose-intensive chemotherapy with autologous stem cell transplant has become an attractive option in the management of relapsed CNS and IOL. (Soussain *et al.*, 2001; Soussain *et al.*, 2008; Bromberg *et al.*, 2013) Recently, the Berlin group presented their experience using a salvage regimen consisting of HD-MTX-based chemotherapy plus other CNS-penetrant agents (ifosfamide, thiotepa, cytarabine and depocyt), followed by myeloablative therapy (carmustine, thiotepa, etoposide) and stem cell transplant. This approach yielded a PFS rate of 0.49 at two-years. (Korfel *et al.*, 2013) An important consideration in the treatment of relapsed CNS lymphomas is whether the lymphoma is MTX-sensitive. In the setting of recurrent disease that is sensitive to HD-MTX, our approach is to administer repetitive cycles of HD-MTX, to achieve maximal cytoreduction, (six-to-eight cycles), followed by dose-intensive consolidation using non cross-resistant, CNS penetrant agents such as thiotepa. (Cote *et al.*, 2012; Falzetti *et al.*, 2012; Korfel *et al.*, 2013) High-dose carmustine-based therapy without thiotepa has also been studied. (Alvarnas *et al.*, 2000) (Table I)

For CNS lymphomas that have progressed within six months of dose-intensive consolidation, second-line high-dose chemotherapeutic salvage may not be a reasonable option. Such patients may be managed with additional HD-MTX, pemetrexed,(Raizer *et al.*, 2012) WBRT or investigational agents.

Rituximab in CNS lymphomas

Because the blood-brain barrier normally excludes molecules that exceed 400 daltons, it is not surprising that most studies report that less than 1% of systemic rituximab penetrates the leptomeningeal compartment. (Rubenstein *et al.*, 2003) While rituximab has become a cornerstone of therapy in systemic B-cell NHL, several 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. (Feugier *et al.*, 2004; Yamamoto *et al.*, 2010; Tai *et al.*, 2011) Nevertheless, intravenous rituximab may induce responses of contrast-enhancing lesions in CNS lymphoma, probably in foci in which there is disruption of the blood-brain barrier. (Batchelor *et al.*, 2011)

Intraventricular Rituximab

We recently evaluated the safety and activity of intraventricular rituximab, both as monotherapy and in combination with intraventricular MTX in the setting of two phase I multicentre trials. 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 can elicit responses within leptomeninges, intraocular compartments and in small parenchymal lesions. The efficacy of intraventricular rituximab was additive or synergistic with MTX. One of the key findings was that intraventricular rituximab/MTX appeared particularly useful in high burden leptomeningeal lymphoma. These studies also suggested that intraventricular rituximab overcomes resistance caused by the blood-brain barrier, in that CSF responses were documented in patients with baseline serum rituximab concentrations greater than 15 μg/ml. Notably, two patients achieved a first complete response of CNS lymphoma with intraventricular rituximab/MTX, including one with disease refractory to high-dose systemic and intrathecal MTX plus 20 previous intravenous infusions of rituximab. (Rubenstein *et al.*, 2007; Rubenstein *et al.*, 2013d) One mechanistic explanation for the efficacy of intraventricular rituximab is provided by the demonstration of activation of the complement cascade within CSF upon intra-CSF rituximab administration as well as pharmacokinetic evidence for penetration of rituximab into neural tissue. (Kadoch *et al.*, 2013)

Given the evidence for activity of rituximab in CNS lymphomas, as monotherapy and in combination with MTX-based induction,(Shah *et al.*, 2007) a number of protocols incorporate rituximab for this disease. While several studies demonstrate its activity at relapse, intraventricular rituximab should be considered investigational and the combination of intraventricular plus intravenous rituximab for recurrent CNS lymphoma is currently being studied in a phase I investigation (NCT01542918).

Therapy of Intraocular Lymphoma (IOL)

Most cases of IOL involve large B-cell NHL, either primary vitreoretinal lymphoma or uveal lymphomas, which are divided into primary neoplasms of the choroid, iris and ciliary body, or secondary choroidal lymphomas in patients with disseminated systemic NHL. Notably, between 65% and 90% of patients with primary vitreoretinal lymphoma ultimately develop CNS lymphoma, usually within 30 months. Conversely, IOL impacts between 15–25% of patients with PCNSL.

Therapy for primary vitreoretinal lymphoma can be divided into local approaches, such as ocular radiation and intravitreal therapy vs. systemic chemotherapy. External beam radiotherapy to the eyes using opposed lateral beams, is well tolerated, and associated with low rates of local recurrence. Complications of ocular radiotherapy are typically mild, including dry eye, cataract and mild radiation retinopathy (Berenbom *et al.*, 2007) Intravitreal MTX and rituximab may be indicated in the setting of unilateral disease or prior ocular radiation. (Kitzmann *et al.*, 2007; Itty & Pulido, 2009) Treatment-related complications of intravitreal MTX include vitreous haemorrhage, endophthalmitis, retinal detachment and hypotony. (Chan *et al.*, 2011) Systemic therapeutic options for IOL are HD-MTX, (Batchelor *et al.*, 2003) HD-Ara-C or trofasfamide. (Jahnke *et al.*, 2009) Notably, in primary vitreoretinal lymphoma, implementation of HD-MTX plus binocular irradiation as induction provides local disease control and addresses the possibility of subclinical disease throughout the neuroaxis. (Stefanovic *et al.*, 2010) Our approach to patients with primary IOL and/or concomitant PCNSL with IOL usually involves three steps: (1) HD-MTX-based induction (MT-R); (2) dose-intensive consolidation as used in CALGB 50202 (EA); (3) Binocular but not WBRT if there is persistence and/or recurrence of isolated IOL after completion of dose-intensive chemotherapy consolidation.

CNS Lymphoma in the Immunocompromised Host

While HIV-associated PCNSL declined in incidence with advent of highly-active antiretroviral therapy (HAART), PCNSL continues to be a significant AIDS-defining illness that is aggressive and a major therapeutic challenge. The feasibility and efficacy of HD-MTX in HIV-associated PCNSL has been demonstrated. (Jacomet *et al.*, 1997) Similarly, in the setting of CNS PTLD, reconstitution of immune function is a first principle in management, and can be achieved by reductions or cessation of immunosuppression. HD-MTX may be effective but its implementation needs to be balanced with risk of allograft failure. (Elstrom *et al.*, 2006) Rituximab is also active in CNS complications of PTLD, via intravenous as well as intrathecal administration. (van de Glind *et al.*, 2008)

Conclusions and Future Directions

Over the course of the past half-century, the haematology/oncology community has made significant progress in the treatment of PCNSL, a highly malignant brain tumour. Based upon the results of recent series that evaluate novel therapeutic approaches, approximately 40–50% of patients will exhibit long-term survival and a significant proportion may be cured. The vast majority of this progress has been achieved in the absence of randomized data. It is likely that the next five years of clinical trials will continue to focus on optimization of interventions based upon high-dose chemotherapy.

However, given that at least 40–50% of PCNSL patients develop disease refractory to the established armamentarium of agents, it is imperative that additional studies explore the potential efficacy of selective agents that target candidate resistance mechanisms for high-risk patients. For example, pharmacological agents that evaluate disruption of pathways involving the B-cell receptor, JAK-STAT, toll-like receptor, mTOR, and PIM kinases should be considered high priority in early phase investigation in CNS lymphomas. Another key target is MUM1/IRF4, targeted by the immunomodulatory class of agents, such as

lenalidomide or pomalidomide, that are under evaluation in PCNSL. (Ponzoni *et al.*, 2013) Transformative advances are needed in CNS lymphomas given its increasing predilection for an aging population among whom a major proportion cannot tolerate dose-intensive chemotherapy or WBRT.

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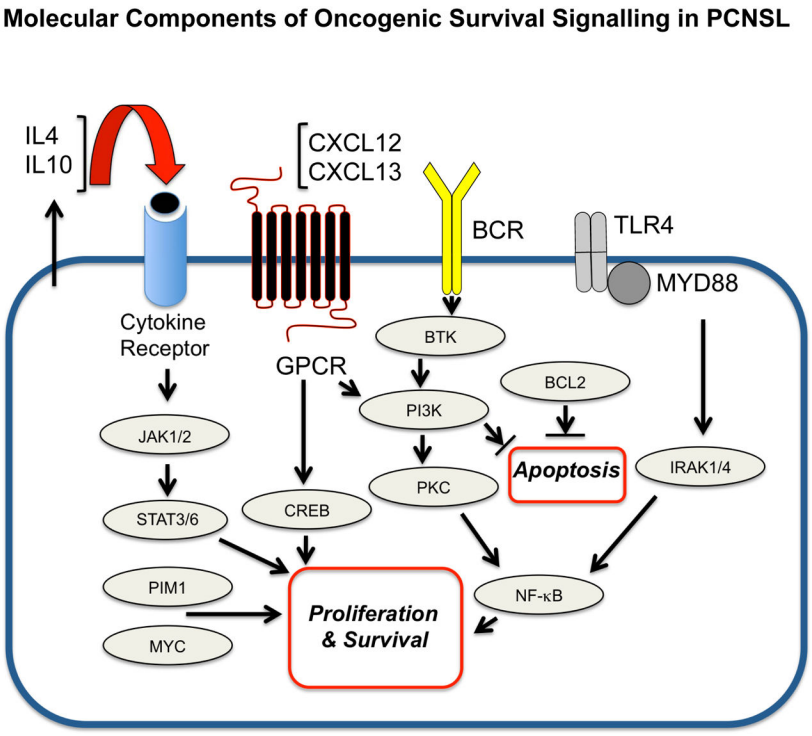

Figure 1. Molecular components of oncogenic survival signalling in primary central nervous system lymphoma

Notably, activation of the TLR/MYD88 pathway may directly contribute to pro-survival signalling via NFκB as well as via enhanced secretion of IL10, which probably promotes pro-survival signals via the JAK/STAT pathway. GPCR, G protein-coupled receptor.

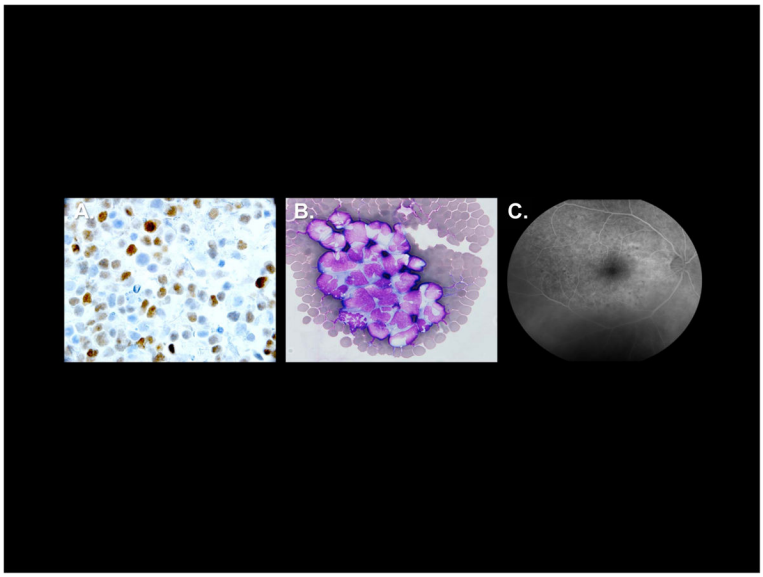

Figure 2. Pathological features of primary central nervous system lymphoma and intraocular lymphoma

A. High expression of MUM1 by diffuse large B-cell lymphoma cells in a diagnostic specimen of primary central nervous system lymphoma, as demonstrated by immunohistochemistry 1000x). **B.** Cytological appearance of malignant diffuse large B-cell lymphoma in cerebrospinal fluid from recurrent central nervous system lymphoma. **C.** Fluorescein angiography showing classic “leopard spots” in Intraocular Lymphoma.

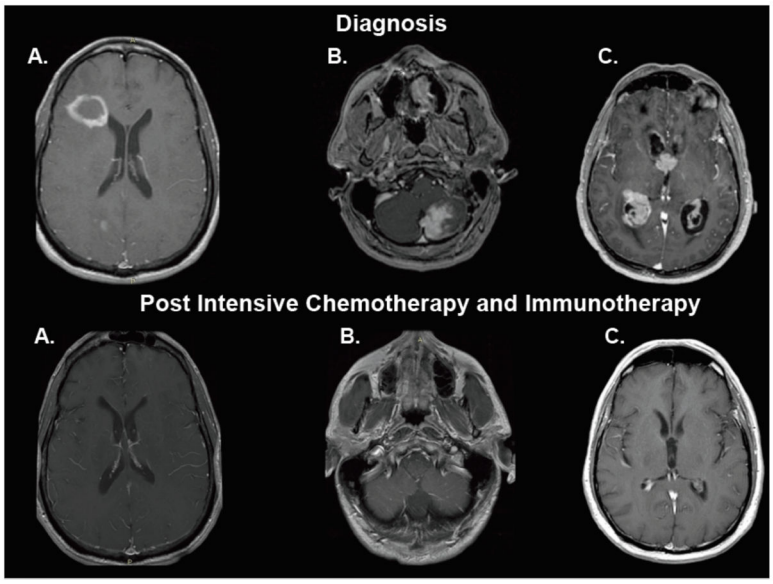

Figure 3. Distinct radiographic presentations of central nrvous system lymphomas and durable responses to intensive chemotherapy and immunotherapy, Without whole brain radiotherapy (T1 axial, post-gadolinium magnetic resonance imaging, at diagnosis and at restaging, at least two months after completion of therapy)

3A. Ring enhancing lesion in the right frontal lobe, adjacent to the lateral ventricle. 3B. Solid enhancing infiltrative mass involving the left cerebellum with evidence of dural attachment. 3C. Diffuse involvement of the ventricular system by nodular, avidly enhancing masses with extension into the surrounding parenchyma.

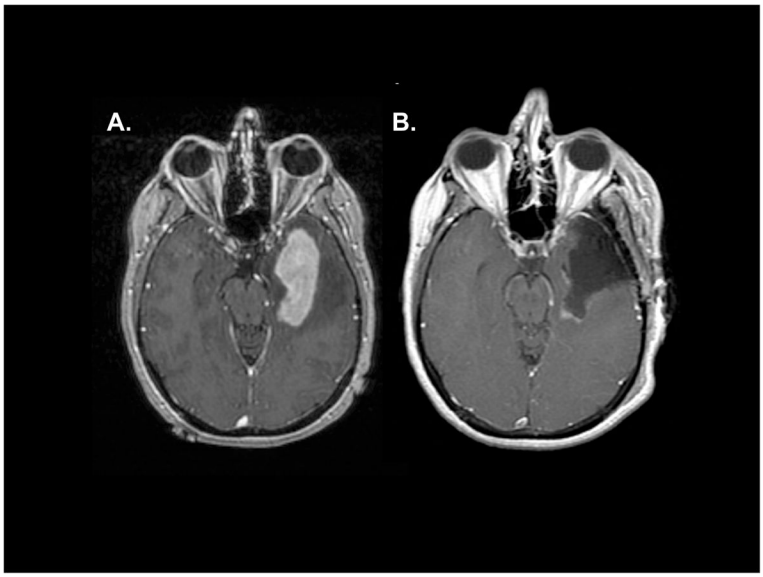

Figure 4. Example of safe surgical resection of primary central nervous system lymphoma

A 54-year-old right-handed patient presented with a generalized seizure and a magnetic resonance imaging scan that demonstrated a homogeneous contrast-enhancing lesion involving the left temporal lobe with significant vasogenic oedema. (3A). Safe resection of the contrast-enhancing mass was performed with assistance of awake speech mapping, without a post-operative neurological deficit. The diagnosis was large B-cell lymphoma and staging revealed primary central nervous system lymphoma (PCNSL). (3B). Subsequently, the patient was treated with MT-R (high-dose methotrexate, temozolomide, rituximab) induction immuno-chemotherapy followed by EA (etoposide cytarabine) dose-intensive consolidation, without whole brain radiotherapy. She regained her pre-PCNSL functional and neurological status and continues to work full-time, seven years later, without evidence of disease. (Courtesy of Mitchel Berger, M.D. and Michael McDermott, M.D., UCSF).

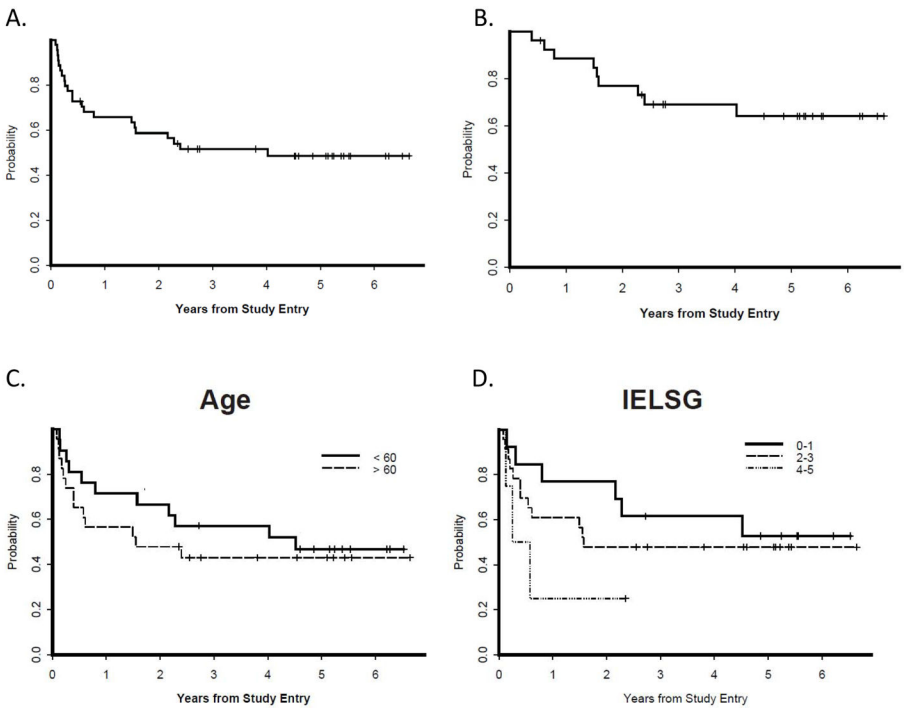

Figure 5. Outcomes with intensive chemotherapy and immunotherapy in newly-diagnosed primary central nervous system lymphoma, without whole brain radiotherapy: CALGB (Alliance) 50202)

Outcome for all CALGB 50202 patients; y-axis refers to cumulative probability of event. **4A.** Progression-free survival (PFS) for all patients. The 2-year PFS was 59%. **4B**. 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). **4C.** PFS was similar for patients aged> 60 years (n=23) and for younger patients (n=21; p=0.48). **4D.** There was a trend between shorter PFS and highest International Extranodal Lymphoma Study Group (IELSG) risk score of 4–5 (p=0.16).

Table I

High-dose methotrexate-based trials in PCNSL that yielded median progression-free survival ≥ 2-years.

Regimen	Reference	Patients (n)	Median PFS	Median OS
MTX 2.5 g/m^2, PCB, vincristine, IT-MTX, WBRT	DeAngelis *et al* (2002)	98	24	37
MTX 8 g/m^2, TMZ, rituximab, etoposide, ARA-C	Wieduwilt *et al* (2012)	31	24	66
MTX 3.5 g/m^2, rituximab, vincristine, PCB, ARA-C, rd-WBRT	Morris *et al* (2013)	52	39	79
MTX 8 g/m^2, TMZ, Ritux, Etop, ARA-C	Rubenstein *et al* (2013b)	44	48	NR

PCNSL, primary central nervous system lymphoma; PFS, progression-free survival; OS, overall survival; MTX, methotrexate; PCB, procarbazine; IT-MTX, intrathecal methotrexate; WBRT, whole brain radiotherapy; TMZ, temozolomide; ARA-C, cytarabine; rd-WBRT, reduced dose whole brain radiotherapy. NR, not reached. (Response criteria according to Abrey et al., 2005).

Table II

Chemotherapy regimens used in dose-intensive consolidative and preparative regimens that are effective in central nervous system lymphoma.

Intensive Consolidation/Preparative Regimen	Reference
Carmustine, thiotepa, etoposide	Korfel *et al* (2013)
Infusional etoposide, high-dose cytarabine	Wieduwilt *et al* (2012); Rubenstein *et al* (2013b)
Thiotepa, busulfan, cyclophosphamide	Soussain *et al* (2001, 2008); Cote *et al* (2012)
Carmustine, thiotepa	Illerhaus *et al* (2008)
Cyclophosphamide, carmustine, etoposide	Alvarnas *et al* (2000)

Table III

Recently completed and ongoing randomized controlled trials for primary central nervous system lymphoma.

Trial	Regimen	Status
G-PCNSL-SG1	HD-MTX-based induction +/− WBRT consolidation	Thiel *et al* (2010)
IELSG-20	HD-MTX +/− Ara-C - > WBRT consolidation	Ferreri *et al* (2009)
IELSG-32	Myeloablative vs. WBRT consolidation	Accrual Complete
PRECIS	Myeloablative vs. WBRT consolidation	Active
Alliance 51101	Intensive vs. Myeloablative consolidation (ASCT)	Active
MATRIX/IELSG43	Intensive vs. Myeloablative consolidation (ASCT)	Active

CALGB (Alliance) 51101 is comparing dose-intensive consolidation with infusional etoposide plus high-dose cytarabine (EA)(Rubenstein *et al.*, 2013b) with high-dose chemotherapy (carmustine plus thiotepa) supported by autologous stem cell transplant. (Illerhaus *et al.*, 2008) The MATRIX/IELSG43 is comparing high-dose chemotherapy (carmustine plus thiotepa) (Illerhaus *et al.*, 2008) supported by autologous stem cell transplant with dose-intensive consolidation (dexamethasone, etoposide, Ifosfamide and carboplatin).

G-PCNSL-SG-1, German Primary Central Nervous System Lymphoma Study Group 1; IELSG, International Extranodal Lymphoma Study Group; PRECIS, Cranial Radiotherapy or Intensive Chemotherapy With Haematopoietic Stem Cell Rescue for Primary Central Nervous System Lymphoma in Young Patients; CALGB, Cancer and Leukemia Group B; HD-MTX, high-dose methotrexate; WBRT, whole brain radiotherapy, Ara-C, cytarabine; ASCT, autologous stem cell transplantation.