HHS Public Access

Author manuscript

Neurotherapeutics. Author manuscript; available in PMC 2016 July 12.

Published in final edited form as:

Neurotherapeutics. 2009 July ; 6(3): 587–597. doi:10.1016/j.nurt.2009.04.013.

Biology and Treatment of Primary Central Nervous System Lymphoma

Alain P. Algazi, **Cigall Kadoch**, and **James L. Rubenstein**

Division of Hematology and Oncology; University of California, San Francisco; 505 Parnassus Avenue, Suite M1286; Box 1270; San Francisco, CA 94143

Summary

Primary central nervous system lymphoma (PCNSL) is a rare variant of extranodal non-Hodgkin lymphoma that is restricted in distribution to the brain, leptomeninges, spinal cord and intraocular compartments. While PCNSL shares overlapping features of systemic lymphoma, recent studies also reveal a unique pattern of gene and protein expression in PCNSL. These findings have yielded new insights into the pathophysiology of the disease as well as the identification of novel prognostic biomarkers. Immune system compromise such as that seen in the acquired immune deficiency syndrome is the best established known risk factor for PCNSL. Like other lesions of the brain, meninges, and eye, the presenting symptoms associated with PCNSL typically include focal neurological deficits related to the site of disease or more global consequences of increased intracranial pressure. Diagnosis of PCNSL typically includes gadolinium-enhanced magnetic resonance imaging and pathological tissue analysis as well as additional studies aimed at excluding concurrent systemic disease. PCNSL is typically associated with a worse overall prognosis than systemic lymphoma. High dose chemotherapy, particularly with methotrexate-based regimens, is the backbone of therapy for most patients and chemotherapy is associated with much lower rates of treatment-related morbidity and mortality than whole brain irradiation. Autologous stem cell transplantation is an emerging treatment modality, particularly in younger patients with relapsed disease, but high rates of treatment related mortality are observed in older patients. Immunotherapy, including treatment with intrathecal rituximab, is another area of active research that may have promise in refractory or relapsed disease. Treatment options for intraocular lymphoma parallel those for PCNSL elsewhere in the brain and they included systemic chemotherapy, radiation, and local delivery of cytotoxic and immunologically-active agents such as anti-CD20 antibody.

Introduction

Primary central nervous system lymphoma (PCNSL) is a rare variant of extranodal non-Hodgkin lymphoma (NHL) that is restricted in distribution to the brain, meninges, spinal cord, and eye. It represents 1-2% of all cases of NHL[1] and 3.1% of primary brain tumors.[2] Immune system compromise is the only known risk factor for the disease and the incidence

of PCNSL rose dramatically during the peak of the acquired immune deficiency syndrome (AIDS) epidemic in the late 1980s.[3, 4] Ninety percent of PCNSL lesions in patients with normal immune function exhibit diffuse large B-cell histologies with the remainder exhibiting other B or T-cell phenotypes, but outcomes are generally worse in PCNSL than in systemic lymphoma given the same histology. Furthermore, the major chemotherapeutic agents that are active in systemic NHL, such as adriamycin and cyclophosphamide are ineffective in PCNSL. While new treatment approaches are emerging that are more effective and less toxic whole brain radiation, the historical cornerstone of treatment for this disease. A substantial proportion of PCNSL patients ultimately develop refractory, or recurrent disease. This review addresses progress to date in the diagnosis and treatment of PCNSL. A focus is on the identification of novel prognostic biomarkers as well as biological clues illuminate the pathophysiology of PCNSL and which may lead to potentially significant therapeutic leads.

Pathological Features and Prognostic Biomarkers

It is clear that, on the cellular and molecular level, PCNSL is different from systemic lymphoma. Immunophenotypic findings in B-cell lymphoma in the CNS show that these tumors share molecular features with multiple systemic B-cell lymphoma subtypes, but these molecular features do not necessarily suggest that these tumors will exhibit similar clinical behavior. It has been proposed that systemic large cell lymphomas can be classified into two major distinct subtypes: germinal center and activated B-cell.[5] In the systemic setting, germinal B-cell lymphomas express BCL-6 and they tend to confer a more favorable prognosis than the other subtypes. In the CNS, large B-cell lymphoma also tends to express BCL-6. Furthermore sequencing of the immunoglobulin variable regions in these tumors reveals a pattern of frequent somatic mutation that suggests that they are derived from mature B-cells that have undergone T-cell dependent affinity maturation in a germinal center microenvironment.[6] However, PCNSL is associated a poorer prognosis in contrast to systemic germinal cell lymphoma. In addition, large B-cell lymphoma in the CNS usually also express activated B-cell type markers such as MUM-1 that are typically absent in systemic germinal B-cell lymphoma.[7, 8] This also suggests that these tumors are biologically distinct from their systemic counterparts.

Molecular data have also revealed distinct patterns of gene expression of CNS B-cell lymphoma in comparison with systemic B-cell lymphoma. In one microarray study from our group, at least 100 genes were upregulated in PCNSL when compared to systemic disease.[9] These included MYC and PIM1, protooncogenes that have also been shown to exhibit somatic mutations in PCNSL.[10] Our data also suggested that IL-4 signaling promotes tumor progression. IL-4 was expressed both by PCNSL tumor cells and by the tumor vasculature. In addition, increased tumor or endothelial expression of STAT6, a downstream mediator of IL-4 signaling, predicted early progression and short survival in an independent set of patients all treated with high-dose methotrexate-based chemotherapy.

Comparison of two recent microarray studies of PCNSL, one performed by our group,[11] the other by Tun et al.,[12] revealed an overlapping set of genes which are differentially expressed in CNS lymphoma compared to systemic lymphomas (Table 1). A significant subset of these

genes appear to constitute components of the extracellular matrix which are distinct in the brain vs nodal microenvironments: for example, osteopontin, chitinase-3-like 1, Collagen, type VI. alpha 1 and laminin, alpha 4. The differential upregulation of RGS-13 in PCNSL is also notable given that this protein may have a role in the modulation of responses to chemokines.[13]

Prior data also demonstrated distinct genetic alterations in PCNSL. For example, deletions of CDKN2A, a gene that produces P14ARF, were noted in 40% of PCNSL lesions.[14] P14ARF, in turn, inhibits cell cycling by promoting p53 stabilization and inactivation of certain cyclin-dependent kinases. The importance of P14ARF is supported by the finding that TP53 gene activation is detected in 20-40% of PCNSL tumors while mutations of TP53 itself are rare.[15] Alterations in the long arm of chromosome12, which contains cell cycle genes MDM2 and CDK4 as well as the oncogene GLI1, are also observed in PCNSL.[16] Sixty six percent of PCNSL lesions have deletions in the long arm of chromosome 6, which correlates with reduced expression of PTPRK, a candidate tumor suppressor protein, and, based on loss of heterozygosity analysis, 6q aberrations may predict short survival in PCNSL.[17]

One interesting paradox in PCNSL is the question of how malignant B-cell arise in or are introduced to the CNS. BCA-1 (CXCL13) is a B-cell attracting chemokine that promotes B-cell homing to secondary lymphoid organs and that was recent shown to be widely expressed in PCNSL tumors.[18] It appears that lymphoma cells within the brain as well as the eye have the capacity to respond to BCA-1 signals given their co-expression of CXCR5.[19] In addition, there is evidence that CNS lymphomas also express the chemokine SDF-1 (CXCL-12) and its cognate receptor at high levels.[15] While it has also been hypothesized that systemic B-cells may express specific adhesion molecules that facilitate homing to the CNS where these cells undergo transformation, to date no adhesion molecules specific to PCNSL have been identified to date.[5]

In AIDS patients, primary CNS lymphoma is strongly associated with Epstein Barr Virus (EBV),[20, 21] and EBV-associated PCNSL has also been reported in patients who are chronically exposed to immunosuppressive medications.[22] In immunocompetent individuals, EBV infection may lead to the immortalization of otherwise normal B-cells. In AIDS, the proliferation of infected B-cells that would be suppressed by normal T-cells is left unchecked and this is thought to allow proliferation and malignant transformation of the infected clone.[23] EBV may also play a role in CNS trophism for PCNSL in the setting of AIDS since AIDS patients with EBV positive systemic NHL have been shown to be more likely to have CNS involvement than patients whose tumors are EBV negative.[24] PCNSL is not associated with EBV in immunocompetent patients.

Recent proteomic analysis of CSF from CNS lymphoma patient identified approximately 80 CSF proteins that were present in increased quantities in PCNSL compared with controls.[25] Increased levels of one of these proteins, antithrombin III, a serine protease inhibitor best known for its role in the regulation of blood clotting, was strongly associated with poor overall survival in patients with relapsed disease.

Epidemiology and Risk Factors

The best established risk factor for primary CNS lymphoma is immunodeficiency. The importance of this risk factor was borne out by a 1996 retrospective study that demonstrated several thousand times the incidence of CNS lymphoma in patients with AIDS than in the general population;[3] AIDS patients had an approximately 20% lifetime risk of developing the disease. The advent of highly-active antiretroviral therapy, which lead to immune recovery in many AIDS patients, was associated with a decreased incidence of primary CNS lymphoma as demonstrated in a 2005 study that found a marked decrease in the incidence of primary CNS lymphoma from 8.6 per 1000 patients between 1988 and 1995 to 1.1 per 1000 patients between 1996 and 2000.[4] Following the peak of the AIDS epidemic, a net decrease in the overall incidence of primary CNS lymphoma was noted in study based on a systematic review of the Surveillance, Epidemiology, and End Results (SEER) database.[26] Although this review did not separate primary CNS lymphoma patients with and without co-morbid HIV infections, the decreasing incidence of primary CNS lymphoma was not observed in women who had a substantially lower incidence of HIV than men at the peak of the HIV epidemic in the 1980s. Primary CNS lymphoma has also been observed in other settings of immunodeficiency such as in patients with rheumatologic conditions[22, 27] and in transplant recipients [27, 28] who are managed chronically with immunosuppressive medications.

Several authors have suggested that there has been a dramatic increase in the incidence of primary CNS lymphoma in immunocompetent patients. Two studies based on the SEER database demonstrated a net increase in the incidence of primary CNS lymphoma between then 1970s and the 1990s in a population that excluded never married persons or persons of unknown marital status.[29] This strategy was presumed to deplete the population of homosexual men, who comprised a substantial majority of HIV infected persons during the time period of the study. Another group linked AIDS and cancer registries in a number of states to identify primary CNS lymphoma patient with and without concurrent AIDS diagnoses. They found that the incidence of patients with non-AIDS patients CNS lymphoma increased seven-fold between 1982 and 1989.[3]

Primary CNS lymphoma can afflict patient of both genders over a wide age range, although there are notable demographic differences between immunocompetent and immunocompromised individuals. In patients with no detectable immune deficiency, the ratio of male patients to females is 3:2 and the mean age at diagnosis is fifth decade.[27] In contrast, perhaps due in significant part to the AIDS epidemic, the male to female ratio in immunocompromsed patients is 10:1 and the mean age at diagnosis is the third decade.

Clinical Features

The onset of symptoms in PCNSL tends to be insidious and clinical presentation depends to a substantial extent on the location of the disease. Immunocompetent patients are more likely to present with a single mass lesion on the cerebrum,[30] while nearly all patients with AIDS present with multifocal disease. Immunocompetent patients present less commonly with tumors in the basal ganglia and cerebellum. Patients with PCNSL tumors in the

cerebrum may present with focal neurological deficits, manifestations of increased intracranial pressure, cognitive deficits, or neuropsychiatric changes. Focal neurological deficits are noted in over half of patients and may include aphasia, motor, or visual deficits. Signs and symptoms of increased intracranial pressure are seen in about a third of patients and may include headaches, nausea, vomiting, papilledema, and lethargy. Cognitive, behavioral, mood, and personality changes are also seen in about a third of patients, often in the setting of frontal lobe, callosal, or white matter lesions. These symptoms may include depression, changes in executive function, memory impairment, and confusion. Approximately eleven percent of all patients present with seizures.

Sites of disease outside the brain parenchyma lead to unique constellations of symptoms. Patient with leptomeningeal lymphoma, with or without mass lesions in the brain parenchyma, may develop meningismus, cranial nerve palsies, headaches, and/or signs and symptoms of hydrocephalus and increased intracranial pressure. Approximately 10%-20% of patients present with intraocular lymphoma (IOL). Patients with isolated ocular disease may present with an insidious decrease in visual acuity and because this symptom is non-specific, there can be a long time lag between the onset of symptoms and diagnosis.[30, 31] Patients may also note vitreal opacities that increase over time[32] and visual hallucinations have been described. Spinal lesions are uncommon in PCNSL and they are typically manifest as discrete intramedullary nodules.[30] These may be associated with motor or sensory levels similar to other mass lesions affecting the spinal cord.

PCNSL is diagnosed in patients over a large range of ages. The peak incidence differs markedly between immunocompetent patients, with a median age at diagnosis in the sixth decade, and immunocompromised patients, with a median age at diagnosis of 30 years.

Diagnosis

The vast majority of patients with PCNSL present with a mass lesion in brain parenchyma; definitive diagnosis typically involves high resolution imaging of the brain, exclusion of systemic disease through additional imaging and staging procedures, and the pathological analysis of tumor specimens most commonly obtained via stereotactic surgical brain biopsy although diagnosis may be established by cerebrospinal fluid analysis using either cytology or flow-cytometry; pathologic analysis of vitreal biopsies is also feasible to establish the diagnosis of intraocular lymphoma.

Imaging

Gadolinium contrast enhanced magnetic resonance imaging (MRI) is the imaging modality of choice for evaluation of PCNSL. The most common finding on MRI for immunocompetent patients with PCNSL is a contrast-enhancing solitary tumor located in one of the cerebral hemispheres.[2, 33] For example, in one series, 55% of patients had lesions in the cerebral hemispheres, 27.5% had lesions in the basal ganglia and 27.5% had lesions in the corpus callosum. Leptomeningeal involvement was found in 12.5%, but nearly all (97.5%) had lesions adjacent to the subarachnoid space.[33] Only a quarter of patients with normal immune systems have more than one lesion, while over 50 percent of AIDS patients have multifocal disease.[2] The pattern of contrast enhancement is uniform in 55-60% of

cases[2] while, T2 signal intensity may be heterogeneous (55%), uniformly hyperintense (15%), or uniformly hypointense (32.5%).[33] Moderate to extensive vasogenic edema surrounding PCNSL lesions has been described in the majority of cases, but significant peritumoral edema is observed less frequently in PCNSL than in gliomas and in solid tumor brain metastases of the same size.[2] Necrosis is more common in patients previously treated with corticosteroids. Positron emission tomography (PET) is thought to be of limited utility in the diagnosis of PCNSL due to the high background metabolic activity of the brain.

Newer imaging techniques may confer additional diagnostic and even prognostic information. Histologically, PCNSL often exhibits an angiocentric growth pattern. While conventional MRI findings in PCNSL may be similar to those found with other tumors, there is evidence that perfusion MRI may be able to exploit this unique growth pattern to differentiate PCNSL lesions from other tumors, such as glioblastoma multiforme tumors and infectious lesions such as those seen in toxoplasmosis.[34] Other investigators seek to exploit differences in a tumor's cellular density to determine tumor grade based on imaging alone. For example, the apparent diffusion coefficient (ADC), a measure of the diffusion of water molecules in cerebral tissue, has been correlated with cellular density in human subjects with PCNSL and astrocytoma and ADC values were significantly different between the two groups.[35] Changes in ADC are correlated with treatment associated changes in tumor cell density, proliferation, and therapeutic response in murine models non-Hodgkin Lymphoma.[36] Increased cellular density has been inversely correlated with overall survival in PCNSL[9] and recent data suggest that pre-therapeutic ADC, as a possible surrogate marker for cellular density, predicts clinical outcome in PCNSL patients treated with methotrexate-based chemotherapy regimens.

Biopsy and Diagnosis

While surgical biopsy is usually required to diagnose PCNSL, under special circumstances it may be possible to diagnose PCNSL through imaging and CSF examination. CSF cytology is diagnostic in a minority of patients with estimates ranging from 15-31%,[37-39] although it has been suggested that repeat CSF cytological examinations may facilitate diagnosis.[37] MRI of brain and spine, with and without gadolinium, is useful for complete staging of the neuroaxis. A recent proteomic study of CSF in PCNSL patients revealed a distinct protein profile in association with the disease, and it has been suggested that a panel of CSF protein biomarkers proteins including antithrombin III may ultimately facilitate non-invasive diagnosis as well as risk stratification.[25] In the setting of AIDS, there is a close association between PCNSL and infection with the Epstein-Barr Virus (EBV) and EBV PCR has a high positive predictive value for the disease.[20] Since single photon emission computed tomography (SPECT) and PET imaging[40] can distinguish PCNSL from infectious causes such as cerebral toxoplasmosis in AIDS patients, it has been suggested that patients with positive EBV PCR results and findings on PET or SPECT that are consistent with PCNSL do not require brain biopsies. Of note, stereotactic brain biopsy is associated with up to a four percent risk of significant intracranial hemorrhage[41] and biopsy is non-diagnostic in 8-9% percent of patients with intraaxial mass lesions.[42, 43] In addition, because corticosteroids induce transient treatment responses in PCNSL,[44] prior exposure to systemic corticosteroids is expected to decrease the diagnostic yield of stereotactic biopsy.

Differential Diagnosis and Staging

The vast majority (90%) of patients with lymphomatous involvement of the CNS will not have systemic disease. However, a thorough assessment for systemic disease is crucial because of the obvious treatment implications. Patients with both systemic and CNS disease should be assigned a diagnosis of stage IV non-Hodgkin lymphoma with CNS involvement. The National Clinical Cancer Network[45] recommends CT imaging of the chest, abdomen and pelvis with consideration of PET imaging. Additional tests for systemic disease include a bone marrow biopsy and there is recent evidence suggesting that identification of clonally-rearranged immunoglobulin-heavy chain (IgH) genes suggests subclinical bone marrow involvement.[46] A testicular ultrasound should also be considered given that approximately 30% of testicular lymphomas metastasize to the brain. A complete blood count with a platelet count and white cell differential is indicated as are liver function tests. It is also important to screen patient for the human immunodeficiency virus (HIV) given the associated between PCNSL and HIV as well as the treatment implications of this comorbidity. Serum lactate dehydrogenase (LDH) levels should be assessed because LDH are independently associated with a worse overall prognosis.[47] 10-20 percent of patient's with lymphoma in the brain also have intraocular disease and a slit lamp examination is recommended. PCNSL tumors are avascular on angiography and their tendency to develop adjacent to ventricles and cortical convexities suggests dissemination via the CSF and 10-20% of patient with PCNSL present with overt leptomeningeal lymphoma. Thus, all patient should undergo a lumbar puncture unless increased intracranial pressure prohibits this this procedure. Key clinical prognostic markers include Eastern Cooperative Oncology Group performance status (<1) and Age >60.

Treatment

Left untreated, the median life expectance for a patient with newly diagnosed PCNSL is 3 months. However, PCNSL will respond to a number of therapeutic interventions including systemic corticosteroid therapy, external beam radiation, chemotherapy, and immunotherapy. With the advent of new therapies, 5-year overall survival rate of up to 30 to 40% have now been reported.[48] Indeed, the revolution over the past several decades has been the development of therapeutic approaches that can lead to durable remissions with acceptable toxicities which obviate the neurotoxicity of whole brain irradiation.

Clinical Stabilization

Because mass lesions in the brain and spinal cord can have devastating consequences patients with PCNSL may require timely medical or surgical decompression even before they are formally diagnosed. PCNSL lesions are quite sensitive to corticosteroids, which kill tumor cells and decrease tumor associated edema, with response rates as high as 70% reported.[44] However, responses to corticosteroids are transient and corticosteroids can decrease the diagnostic yield of surgical biopsies delaying diagnosis and definitive therapies. Therefore, it is recommended that surgical biopsies be obtained prior to the initiation of corticosteroid therapy if medically feasible. Surgical intervention may also be required when PCNSL mass lesions lead to increased intracranial pressure, actual or impending herniation, or other neurosurgical emergencies and a surgical biopsy is often required for diagnosis.

However, surgical resection or debulking do not confer survival benefits, and reported median overall survival durations with surgery alone[38, 49-51] are similar to overall survival durations in untreated patients.

First-Line Therapy

Radiation Therapy—In the past, whole brain external beam radiation, without systemic chemotherapy, was the mainstay of definitive treatment for PCNSL. External beam radiation yields overall response rates in PCNSL of 90% with complete response rates of approximately 60%. Median overall survival in PCNSL patient treated with external beam radiation alone has been estimated at 12-18 months.[52] Based the infiltrative and multifocal nature of PCNSL, whole brain irradiation has been the preferred radiation modality. There is no evidence that irradiating the spine is advantageous in the absence of detectable disease in the spine and the majority of patients with intracranial disease relapse in the irradiated field[38, 53] suggesting that treatment failure stem from inherent limitations of irradiation rather than inadequate treatment fields. In addition to limitations in efficacy, whole brain irradiation frequently leads to neurocognitive deficits. Up to two thirds of patients who were treated with whole brain irradiation suffer from delayed neurotoxicity that may include cerebellar dysfunction, progressive dementia, and urinary incontinence.[48, 54] Lower doses of whole brain radiation appear to be associated with decreased anti-tumor efficacy. For example, one group found that decreasing the dose from 45 Gy to 30.6 Gy decreased both progression free and overall survival.[55]

Chemoradiation—To increase response and survival rates in PCNSL lymphoma, a number of treatment regimens have developed that combine whole brain irradiation with systemic chemotherapy, but treatment with these regimens is also associated with high rates of treatment-related neurotoxicity. By the 1980s, combined modality regimens showed promise of improved overall survival as first line therapy. One regimen combined induction chemotherapy with systemic and intrathecal methotrexate followed by cranial irradiation and then two cycles of systemic cytarabine in a non-AIDS population with PCNSL.[56] The median overall survival was 42.5 months, substantially longer than historical overall survival estimates seen in patients treated with radiation alone. The same group subsequently published a number of studies on the long term adverse neurological effects of treatment with combined modality therapy. In one retrospective, a 24% incidence of neurotoxicity with increasing incidence noted over time. In this study, the medical records of patients with primary CNS lymphoma were reviewed for documentation of neurologic deterioration that could not be attributed to tumor progression or other causes and it was noted that many patients died before delayed neurotoxicity, if present, would be anticipated.[57] A European study of PCNSL patient treated with methotrexate and WBRT found a much higher rate of cognitive impairment with 63% of patients treated with methotrexate and WBRT impaired despite a complete tumor response.[54]

More aggressive chemotherapy regimens have subsequently been used in conjunction with WBRT in attempts to increase survival and decrease WBRT doses in hopes of reducing toxicity. Another regimen evaluated by the Radiation Therapy Oncology Group (RTOG) combined induction chemotherapy using five cycles of high-dose methotrexate with

vincristine, procarbazine, and intrathecal methotrexate followed by WBRT with a total dose of 45 Gy. 36% of patient's had a complete response after induction chemotherapy and 94% responded overall. The median progression-free survival with this regimen was 24 months and the overall survival was 36.9 months (N=102). The authors noted a significantly longer overall survival in patients under 60 years of age (median OS 50.4 months) and a 15% rate of delayed neurological toxicity that was often fatal.[58] In a later study by the same group, patients were treated with five to seven cycles of rituximab, methotrexate, procarbazine, and vincristine (R-MPV) followed by reduced dose WBRT (23.4 Gy) in patients achieving a complete response to chemotherapy and standard dose WBRT (45 Gy) in all others.[59] Patients were then treated with two cycles of high dose cytarabine. The overall response rate in the study was 93% with 78% complete response after chemotherapy and the two-year overall survival rates were 67 and 57 percent in patients with and without a CR following induction chemotherapy respectively. A small prospective case series of the patients treated with the lower dose (23.4 Gy) of WBRT showed improving executive function over the two-year study period with persistent deficits overall in verbal memory and motor speed at two years.[60] Other chemoradiation regimens have included an intensive induction regimen consisting of a combination of systemic and intrathecal methotrexate, teniposide, carmustine, methylprednisolone, and cytarabine followed by 40 Gy of WBRT. This regimen yielded an overall response rate of 81% and a median overall survival of 46 month at the expense of a 10% treatment-related mortality rate.[61]

Chemotherapy Alone—The use of cytotoxic chemotherapy alone in PCNSL has been studied for over 30 years and the findings of these studies highlight the unique biology and treatment challenges surrounding PCNSL. As early as the mid 1970s, case reports described patients who were successfully treated with methotrexate after unsuccessful treatment with whole brain radiation.[62, 63] Although PCNSL may share many pathological characteristics with systemic non-Hodgkin lymphoma, responses may differ markedly between systemic and CNS lymphoma to a given chemotherapeutic agent. For example, the combination of systemic cyclophosphamide, doxorubicin, vincristine and corticosteroids that can be highly effective is systemic large B-cell lymphoma, is ineffective in PCNSL, adding no survival benefit when combined with WBRT.[64, 65] This has been attributed the poor penetration of many chemotherapy agents into the CNS due to the blood-brain barrier although there are also data suggesting that molecular differences exist between PCNSL and its systemic counterparts.[11] Among pharmacologically active agents, distribution of a drug and its pharmacokinetics is of particular important. This is certainly true of methotrexate, which forms the backbone of most systemic cytotoxic therapy regimens for PCNSL. In patients with meningeal leukemia or carcinomatosis, CNS methotrexate levels have been shown to be one thirtieth of systemic levels.[66] Several approaches to overcome this obstacle have been attempted including the administration of intrathecal methotrexate and the use of high-dose systemic methotrexate. Overall, pharmacokinetic and clinical data favor the superiority of high-dose systemic therapy. For example, one study of patients with solid-tumor neoplastic meningitis demonstrated that, compared to intrathecal methotrexate, high doses systemic methotrexate therapy yielded much more sustained cytotoxic drug concentrations in the CSF.[67] Retrospective studies have also demonstrated that there is no additional benefit derived from administering intrathecal methotrexate to patients with PCNSL who have

received adequate doses of systemic, high-dose methotrexate.[68] Another approach for attaining adequate CSF chemotherapy concentrations in PCNSL has been to alter the permeability of the blood-brain barrier using intra-arterial or intravenous osmotic agents. In one study, 53 patients with PCNSL were treated with mannitol followed by high dose intra-arterial methotrexate, cyclophosphamide, and etoposide.[69] The overall and complete response rates were 86 and 71% respectively. Another study from the same group examining the efficacy of disruption of the tight junctions of the CNS endothelium with mannitol but with oral procarbazine substituted for parenteral etoposide in some patients yielded a CR rate of 65%, an estimated 5-year survival rate of 42% and a median survival of 40.7 months.[70] Acute adverse effects in theses studies included seizures, strokes and venous thrombolic disease, but there was no evidence of treatment-related neuropsychological deficits in patients who had not been exposed to whole brain irradiation.

In the 1990s, more formal evaluation of methotrexate-based chemotherapy regimens without WBRT suggested that these regimens could be highly effective with a substantially better side effect profile than WBRT containing regimens. One case series, expanding on data from a small cohort of patients who refused WBRT, demonstrated durable treatment responses in the majority of patients with little or no significant treatment-associated toxicity.[71] Another group based at the Memorial Sloan-Kettering Cancer Center in New York examined methotrexate-based chemotherapy regimens in 13 elderly patients (median age 74 years) and found responses in 12 of 13. Performance scores improved in 11 of 13 patients, cognitive function improved in 8 of 9 patients with pretreatment cognitive deficits, and only one patient developed new cognitive deficits in the setting of progressive disease and possible methotrexate-induced leukoencephalopathy. A 1999 consortium study lead by Dr. Fred Hochberg's group at Massachusetts General Hospital of 31 non-immunosuppressed PCNSL patients examined the treatment efficacy, toxicity, and quality of life after treatment with high-dose methotrexate alone.[72] Standard treatment dosing for methotrexate was 8 grams per meter squared every two weeks with dose reductions for sub-optimal renal function. All patients responded to treatment and 65% of patients had a complete response. Performance status also improved dramatically with treatment. The median Karnofsky Performance Scale score improved from 40 to 90 with treatment. The median overall survival was over 30 months and 90% of patients who had a complete response to therapy were alive at 2 years. Treatment toxicities were infrequent and included leucopenia, non-oliguric acute renal failure, and mucositis. A cohort of 11 patients who achieved a complete response to chemotherapy was monitored for two years with cognitive and quality of life assessments and all had preserved cognitive function and memory. A subsequent, multicenter trial of intensive high-dose methotrexate conducted in the New Approaches to Brain Tumor Therapy CNS Consortium demonstrated a 52% complete response rate and a 74% overall response rate in 25 patients studied.[73] Median progression free survival was 12.8 months and median overall survival had not been reached at over 22 months. Again, no delayed neurotoxicity was observed. One European trial of intensive, high-dose methotrexate for PCNSL yielded more modest benefits with only a 30% CR rate in 37 patients and refractory disease in 38%.[74] Consistent with prior results, however, delayed neurotoxicity rates in surviving patients were much lower (10%) in patients who were never treated with WBRT salvage therapy compared to those who were (58%).

Given the favorable toxicity profile of high-dose methotrexate based chemotherapy regimens, new regimens are being developed that integrate high-dose methotrexate and additional agents. Our group initiated a trial of the combination of high-dose methotrexate, temozolomide, and rituximab (MTR) followed by consolidation with cytarabine and etoposide, a regimen currently under study nationally as CALGB trial 50202. Temozolomide is a congener of dacarbazine that is taken orally with excellent bioavailability in the CSF and a favorable toxicity profile. The agent is approved for use in malignant gliomas and it has demonstrated efficacy as monotherapy in PCNSL[75, 76] as salvage therapy in patients previously treated with high-dose methotrexate with recent data suggesting a 31% overall response rate and 31% one-year survival in 36 patients. Rituximab is a monoclonal antibody directed toward CD20, a cell-surface protein expressed exclusively on mature B-cells and not on neurons or glia. The efficacy of rituximab in systemic B-cell lymphoma is now well established based on clinical trials including a large randomized trial in Europe in which complete response rates to CHOP chemotherapy increased from 63 to 76% with the addition of rituximab to the therapeutic regimen.[77] In addition, patients treated with R-CHOP had fewer relapses and longer overall survival. A major problem with using rituximab for primary CNS lymphoma has been poor bioavailability of the drug in the central nervous system with CSF levels of the drug approximately 0.1% of the serum levels that are achieved.[78] However, it has been suggested that higher CSF levels may be attained in the setting of leptomeningeal inflammation as suggested by recent data showing that CSF:serum rituximab ratios correlated with CSF:serum albumin ratios in patients with neurological autoimmune disorders. Similar changes have been seen after WBRT in CSF concentrations of systemically-administered trastuzumab,[79] a monoclonal antibody directed against the cell surface antigen HER2 that is overexpressed in many breast cancer patients.

Preliminary data from a pilot trial at UCSF which evaluated the MTR regimen, which is currently being studied in the CALGB 50202 protocol, showed a 56.5% CR rate. The median progression free and overall survival had not been reached at 33 months. In generally, the regimen was well tolerated with no treatment-related mortality and no patients developed significant treatment-related neurotoxicity.[80] Another aggressive chemotherapy regimen developed in Bonn, Germany, involving high doses systemic methotrexate, intrathecal methotrexate, ifosfamide, cyclophosphamide, cytarabine, prednisone and vinca alkaloids yielded a 71% overall response rate with 61% complete responses in 65 patients. The median progression free and overall survival times were 21 and 50 months respectively. However, 9% of patients died from treatment related complications and 19% suffered from Ommaya reservoir infections.[81] A subsequent study by the same group examined a similar regimen without intraventricular methotrexate in an effort to circumvent Ommaya reservoir-related complications.[82] The found a high rate of early relapses with a mean response duration of only 10 months in responding patients. Based upon their experience these investigators concluded that intraventricular therapy was an essential part of the therapeutic regimen in contrast to earlier retrospective studies suggesting that there was no benefit of administering intrathecal methotrexate to PCNSL patients receiving high dose methotrexate systemically.[68]

Stem-Cell Transplantation—Autologous stem cell transplantation, a therapy that has shown efficacy in relapsed and high-risk systemic lymphoma, has also been used in PCNSL. Several different regimens have been examined in the first-line setting. Abrey and colleagues treated 28 patients with induction chemotherapy with methotrexate at 3.5 g/m2 and cytarabine at 3 g/m2 for 2 days, conditioning with carmustine, etoposide, cytarabine, and melphalan, and then autologous stem-cell rescue. The objective response rate with this regimen was a modest 57% and median event-free survival was only 9.3 months. There was one treatment-related death. Several groups have examined salvage and transplantation regimens in the first-line setting that call for whole brain irradiation for patients with incomplete treatment responses. One recent example of this is a 2008 study that examined tandem high-dose methotrexate induction followed by conditioning with busulfan and thiotepa and autologous stem-cell rescue.[83] Patients without a response to induction or without a complete remission after transplantation received whole brain radiotherapy. Out of 23 patients treated, three died during therapy and three died of delayed neurotoxicity following WBRT. The 2-year overall survival rate for all patients was 48% and for transplanted patients it was 61%.

Salvage regimens

Chemotherapy, Radiation, and Transplantation—Soussain and her colleagues have had success treating refractory or relapsed PCNSL with intensive salvage chemotherapy followed by autologous stem-cell transplantation.[84] Their regimen includes two cycles of high dose cytarabine and etoposide with chemosensitive patients subsequently receiving conditioning with thiotepa, busulfan, and cyclophosphamide followed by autologous stem-cell rescue. Fourty-three patients were enrolled in a stud, and 27 proceeded to conditioning and transplantation. Twenty-six of 27 patients who underwent transplantation entered complete remission. The median overall survival was 18.3 months in all patients and 58.6 months in patients who completed intensive chemotherapy with stem cell rescue. Three patients died from treatment-related toxicity after salvage therapy, two died from sepsis, one died from CNS toxicity, and one died from hemorrhage after a brain biopsy that followed salvage chemotherapy. This regimen does not appear to be a viable alternative for patients over 60 years of age since, in an earlier study five of seven patients over 60 years of age died of treatment-related causes.

Other approaches to salvage therapy for relapse or refractory PCNSL have included retreatment with methotrexate, whole brain irradiation, and combination chemotherapy. In a study at Massachusetts General Hospital, retreatment with high-dose methotrexate yielded a high response rate, durable remissions, and acceptable levels of toxicity.[85] Of 22 patients (median age 58 years) receiving high-dose methotrexate after a first relapse, twenty achieved a complete remission. The median overall survival in this group was 61.9 months. Combination chemotherapy approaches have included procarbazine, lomustine, with vincristine,[86] which yielded an 86% overall response rate in seven patients, four of whom remained disease free one year after relapse. Salvage therapy with temozolomide[75, 76] yielded a 31% overall response rate and 31% one-year survival in 36 patients. In patients who fail initial induction with high-dose methotrexate, WBRT with a median dose of 36Gy yielded an overall response rate of 74% and a median overall survival of 10.9 months.[87]

Stereotactic radiosurgery has also been examined in a small series of nine patients in which five had recurrences distant to the site of radioablation and four survived for one year.[88]

Immunotherapy—Immunotherapy directed toward the CNS is a promising approach to treating patients with relapsed or refractory disease that may also provide insights into the mechanisms of immune response and resistance in PCNSL. Rituximab is a monoclonal antibody directed toward CD20, a cell surface protein expressed on mature B-cells but not neurons or glia. Rituximab has well-documented efficacy in systemic B-cell lymphoma and rituximab-containing regimens have become the standard of care in this setting. However, as above, systemically-administered rituximab yields poor bioavailability in the CSF with levels of estimated at 0.1% of those measured in the serum.[78] In a phase one study of intrathecal rituximab in nine patients with relapsed PCNSL, four achieved complete cytological responses and two achieved partial responses.[89] Dose-limiting toxicities included grade 3 hypertension observed in two patients treated at a 50 mg dose level. In addition, the combination of intrathecal rituximab plus liposomal ara-C has recently been evaluated in fourteen patients with recurrent lymphomatous meningitis. Preliminary evidence suggests that this combination has no additive toxicity and is associated with moderate activity in this setting.[90]

Intraocular lymphoma—Many of the therapeutic modalities employed in intraocular lymphoma parallel those used in PCNSL that is restricted to the brain. Twenty-four-hour continuous intravenous administration of high dose methotrexate yields cytotoxic levels in the anterior chamber of the eye within seven hours[91] and both methotrexate and cytarabine have activity in intraocular lymphoma (IOL).[92, 93] In a study of systemic methotrexate for IOL, seven of nine patients had objective responses and four of these responses were sustained after eight to 36 months of follow up. Ocular radiation is also effective[31] but, as in PCNSL in the brain, treatment associated morbidity, including cataracts, retinal damage and vision loss, is common. Furthermore, sustained responses to ocular radiation, systemic chemotherapy, and the two modalities combined are seen in only a minority of patients with IOL.[31] Serial intravitreal injections of methotrexate lead to clinical remissions in nearly all of 36 patients treated in one series and none of these patients were noted to have had an intraocular recurrence.[94] Intravitreal injections of rituximab yields concentrations of this antibody of greater than 10 ng/mL for 72 days,[95, 96] and anecdotal evidence suggests that the drug may be effective in this setting. For example, one group used rituximab alone in patients who could no longer tolerate intravitreal methotrexate. Both patients had objective responses.[97]

New Approaches and Future Directions—Given the evidence for neurotoxicity associated with standard genotoxic agents in primary CNS lymphoma, in particular whole brain irradiation, there is considerable interest in the evaluation of new genotoxic and targeted strategies to treat this disease. Approaches under consideration include the analysis of pemetrexed disodium, a recently-approved folate antagonist, the up-front utilization of rituximab in combination with the standard methotrexate, procarbazine and vincristine, as well as ongoing evaluation of blood-brain barrier disruption.

References

1. Hochberg FH, Baehring JM, Hochberg EP. Primary CNS lymphoma. Nat Clin Pract Neurol. 2007; 3:24–35. [PubMed: 17205072]
2. Fine HA, Mayer RJ. Primary central nervous system lymphoma. Ann Intern Med. 1993; 119:1093–1104. [PubMed: 8239229]
3. Cote TR, Manns A, Hardy CR, Yellin FJ, Hartge P. Epidemiology of brain lymphoma among people with or without acquired immunodeficiency syndrome. AIDS/Cancer Study Group. J Natl Cancer Inst. 1996; 88:675–679. [PubMed: 8627644]
4. Diamond C, Taylor TH, Aboumrad T, Anton-Culver H. Changes in acquired immunodeficiency syndrome-related non-Hodgkin lymphoma in the era of highly active antiretroviral therapy: incidence, presentation, treatment, and survival. Cancer. 2006; 106:128–135. [PubMed: 16329140]
5. Kadoch C, Treseler P, Rubenstein JL. Molecular pathogenesis of primary central nervous system lymphoma. Neurosurg Focus. 2006; 21:E1. [PubMed: 17134111]
6. Montesinos-Rongen M, Kuppers R, Schluter D, et al. Primary central nervous system lymphomas are derived from germinal-center B cells and show a preferential usage of the V4-34 gene segment. Am J Pathol. 1999; 155:2077–2086. [PubMed: 10595937]
7. Camilleri-Broet S, Criniere E, Broet P, et al. A uniform activated B-cell-like immunophenotype might explain the poor prognosis of primary central nervous system lymphomas: analysis of 83 cases. Blood. 2006; 107:190–196. [PubMed: 16150948]
8. Lin CH, Kuo KT, Chuang SS, et al. Comparison of the expression and prognostic significance of differentiation markers between diffuse large B-cell lymphoma of central nervous system origin and peripheral nodal origin. Clin Cancer Res. 2006; 12:1152–1156. [PubMed: 16489068]
9. Rubenstein JL, Fridlyand J, Shen A, et al. Gene expression and angiotropism in primary CNS lymphoma. Blood. 2006; 107:3716–3723. [PubMed: 16418334]
10. Montesinos-Rongen M, Van Roost D, Schaller C, Wiestler OD, Deckert M. Primary diffuse large B-cell lymphomas of the central nervous system are targeted by aberrant somatic hypermutation. Blood. 2004; 103:1869–1875. [PubMed: 14592832]
11. Rubenstein JL, Shen A, Fridlyand J, et al. Gene expression profile analysis of primary CNS lymphoma: Class distinction and outcome prediction. Proc Amer Assoc Cancer Res. 2004:45. Abstract 4433.
12. Tun HW, Personett D, Baskerville KA, et al. Pathway analysis of primary central nervous system lymphoma. Blood. 2008; 111:3200–3210. [PubMed: 18184868]
13. Han JI, Huang NN, Kim DU, Kehrl JH. RGS1 and RGS13 mRNA silencing in a human B lymphoma line enhances responsiveness to chemoattractants and impairs desensitization. J Leukoc Biol. 2006; 79:1357–1368. [PubMed: 16565322]
14. Cobbers JM, Wolter M, Reifenberger J, et al. Frequent inactivation of CDKN2A and rare mutation of TP53 in PCNSL. Brain Pathol. 1998; 8:263–276. [PubMed: 9546285]
15. Rubenstein JL, Treseler P, O'Brien JM. Pathology and genetics of primary central nervous system and intraocular lymphoma. Hematol Oncol Clin North Am. 2005; 19:705–717, vii. [PubMed: 16083831]
16. Harada K, Nishizaki T, Kubota H, et al. Distinct primary central nervous system lymphoma defined by comparative genomic hybridization and laser scanning cytometry. Cancer Genet Cytogenet. 2001; 125:147–150. [PubMed: 11369058]
17. Nakamura M, Kishi M, Sakaki T, et al. Novel tumor suppressor loci on 6q22-23 in primary central nervous system lymphomas. Cancer Res. 2003; 63:737–741. [PubMed: 12591717]
18. Mazzucchelli L, Blaser A, Kappeler A, et al. BCA-1 is highly expressed in Helicobacter pylori-induced mucosa-associated lymphoid tissue and gastric lymphoma. J Clin Invest. 1999; 104:R49–54. [PubMed: 10562310]
19. Smith JR, Braziel RM, Paoletti S, et al. Expression of B-cell-attracting chemokine 1 (CXCL13) by malignant lymphocytes and vascular endothelium in primary central nervous system lymphoma. Blood. 2003; 101:815–821. [PubMed: 12393412]
20. Antinori A, De Rossi G, Ammassari A, et al. Value of combined approach with thallium-201 single-photon emission computed tomography and Epstein-Barr virus DNA polymerase chain

reaction in CSF for the diagnosis of AIDS-related primary CNS lymphoma. J Clin Oncol. 1999; 17:554–560. [PubMed: 10080599]

21. Bossolasco S, Cinque P, Ponzoni M, et al. Epstein-Barr virus DNA load in cerebrospinal fluid and plasma of patients with AIDS-related lymphoma. J Neurovirol. 2002; 8:432–438. [PubMed: 12402169]
22. Kleinschmidt-DeMasters BK, Damek DM, Lillehei KO, Dogan A, Giannini C. Epstein Barr virus-associated primary CNS lymphomas in elderly patients on immunosuppressive medications. J Neuropathol Exp Neurol. 2008; 67:1103–1111. [PubMed: 18957891]
23. Penn I. The role of immunosuppression in lymphoma formation. Springer Semin Immunopathol. 1998; 20:343–355. [PubMed: 9870250]
24. Cingolani A, Gastaldi R, Fassone L, et al. Epstein-Barr virus infection is predictive of CNS involvement in systemic AIDS-related non-Hodgkin's lymphomas. J Clin Oncol. 2000; 18:3325–3330. [PubMed: 11013271]
25. Roy S, Josephson SA, Fridlyand J, et al. Protein biomarker identification in the CSF of patients with CNS lymphoma. J Clin Oncol. 2008; 26:96–105. [PubMed: 18056677]
26. Kadan-Lottick NS, Skluzacek MC, Gurney JG. Decreasing incidence rates of primary central nervous system lymphoma. Cancer. 2002; 95:193–202. [PubMed: 12115333]
27. Schabet M. Epidemiology of primary CNS lymphoma. J Neurooncol. 1999; 43:199–201. [PubMed: 10563423]
28. Penn I, Porat G. Central nervous system lymphomas in organ allograft recipients. Transplantation. 1995; 59:240–244. [PubMed: 7839447]
29. Olson JE, Janney CA, Rao RD, et al. The continuing increase in the incidence of primary central nervous system non-Hodgkin lymphoma: a surveillance, epidemiology, and end results analysis. Cancer. 2002; 95:1504–1510. [PubMed: 12237919]
30. Hochberg, FH.; Batchelor, T.; Loeffler, JS. [April 24, 2009] Clinical presentation, pathologic features, and diagnosis of primary central nervous system lymphoma. Available at: www.uptodate.com.
31. Hormigo A, Abrey L, Heinemann MH, DeAngelis LM. Ocular presentation of primary central nervous system lymphoma: diagnosis and treatment. Br J Haematol. 2004; 126:202–208. [PubMed: 15238140]
32. Park S, Abad S, Tulliez M, et al. Pseudouveitis: a clue to the diagnosis of primary central nervous system lymphoma in immunocompetent patients. Medicine (Baltimore). 2004; 83:223–232. [PubMed: 15232310]
33. Buhring U, Herrlinger U, Krings T, et al. MRI features of primary central nervous system lymphomas at presentation. Neurology. 2001; 57:393–396. [PubMed: 11515505]
34. Cha S, Knopp EA, Johnson G, et al. Intracranial mass lesions: dynamic contrast-enhanced susceptibility-weighted echo-planar perfusion MR imaging. Radiology. 2002; 223:11–29. [PubMed: 11930044]
35. Guo AC, Cummings TJ, Dash RC, Provenzale JM. Lymphomas and high-grade astrocytomas: comparison of water diffusibility and histologic characteristics. Radiology. 2002; 224:177–183. [PubMed: 12091680]
36. Huang MQ, Pickup S, Nelson DS, et al. Monitoring response to chemotherapy of non-Hodgkin's lymphoma xenografts by T(2)-weighted and diffusion-weighted MRI. NMR Biomed. 2008; 21:1021–1029. [PubMed: 18988250]
37. Balmaceda C, Gaynor JJ, Sun M, Gluck JT, DeAngelis LM. Leptomeningeal tumor in primary central nervous system lymphoma: recognition, significance, and implications. Ann Neurol. 1995; 38:202–209. [PubMed: 7654067]
38. Batchelor T, Loeffler JS. Primary CNS lymphoma. J Clin Oncol. 2006; 24:1281–1288. [PubMed: 16525183]
39. Fitzsimmons A, Upchurch K, Batchelor T. Clinical features and diagnosis of primary central nervous system lymphoma. Hematol Oncol Clin North Am. 2005; 19:689–703, vii. [PubMed: 16083830]

40. Pierce MA, Johnson MD, Maciunas RJ, et al. Evaluating contrast-enhancing brain lesions in patients with AIDS by using positron emission tomography. Ann Intern Med. 1995; 123:594–598. [PubMed: 7677300]
41. Kulkarni AV, Guha A, Lozano A, Bernstein M. Incidence of silent hemorrhage and delayed deterioration after stereotactic brain biopsy. J Neurosurg. 1998; 89:31–35. [PubMed: 9647169]
42. Boviatsis EJ, Kouyialis AT, Stranjalis G, Korfias S, Sakas DE. CT-guided stereotactic biopsies of brain stem lesions: personal experience and literature review. Neurol Sci. 2003; 24:97–102. [PubMed: 14600819]
43. Soo TM, Bernstein M, Provias J, et al. Failed stereotactic biopsy in a series of 518 cases. Stereotact Funct Neurosurg. 1995; 64:183–196. [PubMed: 8817805]
44. Weller M. Glucocorticoid treatment of primary CNS lymphoma. J Neurooncol. 1999; 43:237–239. [PubMed: 10563429]
45. Network, NCC. [April 24, 2009] NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.
46. Jahnke K, Hummel M, Korfel A, et al. Detection of subclinical systemic disease in primary CNS lymphoma by polymerase chain reaction of the rearranged immunoglobulin heavy-chain genes. J Clin Oncol. 2006; 24:4754–4757. [PubMed: 16966685]
47. Ferreri AJ, Blay JY, Reni M, et al. Prognostic scoring system for primary CNS lymphomas: the International Extranodal Lymphoma Study Group experience. J Clin Oncol. 2003; 21:266–272. [PubMed: 12525518]
48. Abrey LE, DeAngelis LM, Yahalom J. Long-term survival in primary CNS lymphoma. J Clin Oncol. 1998; 16:859–863. [PubMed: 9508166]
49. Bellinzona M, Roser F, Ostertag H, Gaab RM, Saini M. Surgical removal of primary central nervous system lymphomas (PCNSL) presenting as space occupying lesions: a series of 33 cases. Eur J Surg Oncol. 2005; 31:100–105. [PubMed: 15642434]
50. Henry JM, Heffner RR Jr. Dillard SH, Earle KM, Davis RL. Primary malignant lymphomas of the central nervous system. Cancer. 1974; 34:1293–1302. [PubMed: 4607602]
51. Murray K, Kun L, Cox J. Primary malignant lymphoma of the central nervous system. Results of treatment of 11 cases and review of the literature. J Neurosurg. 1986; 65:600–607. [PubMed: 3772445]
52. Deangelis LM. Current management of primary central nervous system lymphoma. Oncology (Williston Park). 1995; 9:63–71. discussion 71, 75-66, 78. [PubMed: 7718442]
53. Nelson DF, Martz KL, Bonner H, et al. Non-Hodgkin's lymphoma of the brain: can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG): RTOG 8315. Int J Radiat Oncol Biol Phys. 1992; 23:9–17. [PubMed: 1572835]
54. Harder H, Holtel H, Bromberg JE, et al. Cognitive status and quality of life after treatment for primary CNS lymphoma. Neurology. 2004; 62:544–547. [PubMed: 14981168]
55. Bessell EM, Lopez-Guillermo A, Villa S, et al. Importance of radiotherapy in the outcome of patients with primary CNS lymphoma: an analysis of the CHOD/BVAM regimen followed by two different radiotherapy treatments. J Clin Oncol. 2002; 20:231–236. [PubMed: 11773174]
56. DeAngelis LM, Yahalom J, Thaler HT, Kher U. Combined modality therapy for primary CNS lymphoma. J Clin Oncol. 1992; 10:635–643. [PubMed: 1548527]
57. Omuro AM, Ben-Porat LS, Panageas KS, et al. Delayed neurotoxicity in primary central nervous system lymphoma. Arch Neurol. 2005; 62:1595–1600. [PubMed: 16216945]
58. DeAngelis LM, Seiferheld W, Schold SC, Fisher B, Schultz CJ. Combination chemotherapy and radiotherapy for primary central nervous system lymphoma: Radiation Therapy Oncology Group Study 93-10. J Clin Oncol. 2002; 20:4643–4648. [PubMed: 12488408]
59. Shah GD, Yahalom J, Correa DD, et al. Combined immunochemotherapy with reduced whole-brain radiotherapy for newly diagnosed primary CNS lymphoma. J Clin Oncol. 2007; 25:4730–4735. [PubMed: 17947720]

60. Correa DD, Rocco-Donovan M, DeAngelis LM, et al. Prospective cognitive follow-up in primary CNS lymphoma patients treated with chemotherapy and reduced-dose radiotherapy. J Neurooncol. 2009; 91:315–321. [PubMed: 18974934]

61. Poortmans PM, Kluin-Nelemans HC, Haaxma-Reiche H, et al. High-dose methotrexate-based chemotherapy followed by consolidating radiotherapy in non- AIDS-related primary central nervous system lymphoma: European Organization for Research and Treatment of Cancer Lymphoma Group Phase II Trial 20962. J Clin Oncol. 2003; 21:4483–4488. [PubMed: 14597741]

62. Ervin T, Canellos GP. Successful treatment of recurrent primary central nervous system lymphoma with high-dose methotrexate. Cancer. 1980; 45:1556–1557. [PubMed: 7370915]

63. Herbst KD, Corder MP, Justice GR. Successful therapy with methotrexate of a multicentric mixed lymphoma of the central nervous system. Cancer. 1976; 38:1476–1478. [PubMed: 1036465]

64. O'Neill BP, O'Fallon JR, Earle JD, et al. Primary central nervous system non-Hodgkin's lymphoma: survival advantages with combined initial therapy? Int J Radiat Oncol Biol Phys. 1995; 33:663–673. [PubMed: 7558957]

65. Schultz C, Scott C, Sherman W, et al. Preirradiation chemotherapy with cyclophosphamide, doxorubicin, vincristine, and dexamethasone for primary CNS lymphomas: initial report of radiation therapy oncology group protocol 88-06. J Clin Oncol. 1996; 14:556–564. [PubMed: 8636771]

66. Shapiro WR, Young DF, Mehta BM. Methotrexate: distribution in cerebrospinal fluid after intravenous, ventricular and lumbar injections. N Engl J Med. 1975; 293:161–166. [PubMed: 806016]

67. Glantz MJ, Cole BF, Recht L, et al. High-dose intravenous methotrexate for patients with nonleukemic leptomeningeal cancer: is intrathecal chemotherapy necessary? J Clin Oncol. 1998; 16:1561–1567. [PubMed: 9552066]

68. Khan RB, Shi W, Thaler HT, DeAngelis LM, Abrey LE. Is intrathecal methotrexate necessary in the treatment of primary CNS lymphoma? J Neurooncol. 2002; 58:175–178. [PubMed: 12164690]

69. Doolittle ND, Miner ME, Hall WA, et al. Safety and efficacy of a multicenter study using intraarterial chemotherapy in conjunction with osmotic opening of the blood-brain barrier for the treatment of patients with malignant brain tumors. Cancer. 2000; 88:637–647. [PubMed: 10649259]

70. McAllister LD, Doolittle ND, Guastadisegni PE, et al. Cognitive outcomes and long-term follow-up results after enhanced chemotherapy delivery for primary central nervous system lymphoma. Neurosurgery. 2000; 46:51–60. discussion 60-51. [PubMed: 10626935]

71. Cher L, Glass J, Harsh GR, Hochberg FH. Therapy of primary CNS lymphoma with methotrexate-based chemotherapy and deferred radiotherapy: preliminary results. Neurology. 1996; 46:1757–1759. [PubMed: 8649588]

72. Guha-Thakurta N, Damek D, Pollack C, Hochberg FH. Intravenous methotrexate as initial treatment for primary central nervous system lymphoma: response to therapy and quality of life of patients. J Neurooncol. 1999; 43:259–268. [PubMed: 10563432]

73. Batchelor T, Carson K, O'Neill A, et al. Treatment of primary CNS lymphoma with methotrexate and deferred radiotherapy: a report of NABTT 96-07. J Clin Oncol. 2003; 21:1044–1049. [PubMed: 12637469]

74. Herrlinger U, Kuker W, Uhl M, et al. NOA-03 trial of high-dose methotrexate in primary central nervous system lymphoma: final report. Ann Neurol. 2005; 57:843–847. [PubMed: 15929034]

75. Reni M, Mason W, Zaja F, et al. Salvage chemotherapy with temozolomide in primary CNS lymphomas: preliminary results of a phase II trial. Eur J Cancer. 2004; 40:1682–1688. [PubMed: 15251157]

76. Reni M, Zaja F, Mason W, et al. Temozolomide as salvage treatment in primary brain lymphomas. Br J Cancer. 2007; 96:864–867. [PubMed: 17325700]

77. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med. 2002; 346:235–242. [PubMed: 11807147]

78. Rubenstein JL, Combs D, Rosenberg J, et al. Rituximab therapy for CNS lymphomas: targeting the leptomeningeal compartment. Blood. 2003; 101:466–468. [PubMed: 12393404]

79. Stemmler HJ, Schmitt M, Willems A, et al. Ratio of trastuzumab levels in serum and cerebrospinal fluid is altered in HER2-positive breast cancer patients with brain metastases and impairment of blood-brain barrier. Anticancer Drugs. 2007; 18:23–28. [PubMed: 17159499]
80. Issa, S.; Shen, A.; Karch, J., et al. Treatment of Primary CNS Lymphoma with Induction High-Dose Methotrexate, Temozolomide, Rituximab Followed by Consolidation Cytarabine/Etoposide: A Pilot Study with Biomarker Analysis.. Presented at the American Society of Hematology 2007 Annual Meeting; Atlanta, GA. December 8, 2008; Abstract 1364
81. Pels H, Schmidt-Wolf IG, Glasmacher A, et al. Primary central nervous system lymphoma: results of a pilot and phase II study of systemic and intraventricular chemotherapy with deferred radiotherapy. J Clin Oncol. 2003; 21:4489–4495. [PubMed: 14597744]
82. Pels H, Juergens A, Glasmacher A, et al. Early relapses in primary CNS lymphoma after response to polychemotherapy without intraventricular treatment: results of a phase II study. J Neurooncol. 2009; 91:299–305. [PubMed: 18931887]
83. Montemurro M, Kiefer T, Schuler F, et al. Primary central nervous system lymphoma treated with high-dose methotrexate, high-dose busulfan/thiotepa, autologous stem-cell transplantation and response-adapted whole-brain radiotherapy: results of the multicenter Ostdeutsche Studiengruppe Hamato-Onkologie OSHO-53 phase II study. Ann Oncol. 2007; 18:665–671. [PubMed: 17185743]
84. Soussain C, Hoang-Xuan K, Taillandier L, et al. Intensive chemotherapy followed by hematopoietic stem-cell rescue for refractory and recurrent primary CNS and intraocular lymphoma: Societe Francaise de Greffe de Moelle Osseuse-Therapie Cellulaire. J Clin Oncol. 2008; 26:2512–2518. [PubMed: 18413641]
85. Plotkin SR, Betensky RA, Hochberg FH, et al. Treatment of relapsed central nervous system lymphoma with high-dose methotrexate. Clin Cancer Res. 2004; 10:5643–5646. [PubMed: 15355887]
86. Herrlinger U, Brugger W, Bamberg M, et al. PCV salvage chemotherapy for recurrent primary CNS lymphoma. Neurology. 2000; 54:1707–1708. [PubMed: 10762527]
87. Nguyen PL, Chakravarti A, Finkelstein DM, et al. Results of whole-brain radiation as salvage of methotrexate failure for immunocompetent patients with primary CNS lymphoma. J Clin Oncol. 2005; 23:1507–1513. [PubMed: 15735126]
88. Sakamoto M, Oya N, Mizowaki T, et al. Initial experiences of palliative stereotactic radiosurgery for recurrent brain lymphomas. J Neurooncol. 2006; 77:53–58. [PubMed: 16283435]
89. Rubenstein JL, Fridlyand J, Abrey L, et al. Phase I study of intraventricular administration of rituximab in patients with recurrent CNS and intraocular lymphoma. J Clin Oncol. 2007; 25:1350–1356. [PubMed: 17312328]
90. Chamberlain MC, Johnston SK, Van Horn A, Glantz MJ. Recurrent lymphomatous meningitis treated with intra-CSF rituximab and liposomal ara-C. J Neurooncol. 2009; 91:271–277. [PubMed: 18820836]
91. de Smet MD, Stark-Vancs V, Kohler DR, et al. Intraocular levels of methotrexate after intravenous administration. Am J Ophthalmol. 1996; 121:442–444. [PubMed: 8604740]
92. Batchelor TT, Kolak G, Ciordia R, Foster CS, Henson JW. High-dose methotrexate for intraocular lymphoma. Clin Cancer Res. 2003; 9:711–715. [PubMed: 12576439]
93. Baumann MA, Ritch PS, Hande KR, et al. Treatment of intraocular lymphoma with high-dose Ara-C. Cancer. 1986; 57:1273–1275. [PubMed: 2418934]
94. Grimm SA, McCannel CA, Omuro AM, et al. Primary CNS lymphoma with intraocular involvement: International PCNSL Collaborative Group Report. Neurology. 2008; 71:1355–1360. [PubMed: 18936428]
95. Itty S, Pulido JS. Rituximab for intraocular lymphoma. Retina. 2009; 29:129–132. [PubMed: 19202422]
96. Kim H, Csaky KG, Chan CC, et al. The pharmacokinetics of rituximab following an intravitreal injection. Exp Eye Res. 2006; 82:760–766. [PubMed: 16289160]
97. Ohguro N, Hashida N, Tano Y. Effect of intravitreous rituximab injections in patients with recurrent ocular lesions associated with central nervous system lymphoma. Arch Ophthalmol. 2008; 126:1002–1003. [PubMed: 18625954]

Table 1

Differential Gene Expression in Primary CNS Lymphoma

Genes Whose Expression is Upregulated in Primary CNS Lymphoma
Osteopontin
Complement component 1, q, subcomponent C1QB
Hemoglobin, alpha2
Regulator of G-protein signaling 13
Chitinase 3-like 1
T-cell leukemia/lymphoma 1A
Genes Whose Expression in Downregulated in Primary CNS Lymphoma
Nicotinamide N-methyltransferase
Vascular endothelial growth factor C
Collagen, type VI. alpha 1
Latexin
Lumican
Laminin, alpha 4

Table 1 (*adapted from* Rubenstein JL, Shen A, Batchelor TT, Kadoch C, Treseler P, Shuman MA. Differential gene expression in central nervous system lymphoma. Blood 2009;113:266-267.)