Update on the Management of Primary CNS Lymphoma

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Primary central nervous system (CNS) lymphoma is a non-Hodgkin’s lymphoma restricted to the nervous system. The incidence of this lymphoma is rising in the immunocompetent population but may be decreasing in patients with AIDS. Because the clinical and therapeutic issues differ greatly when primary CNS lymphoma occurs in AIDS vs non-AIDS patients, we will discuss these populations separately.

Introduction

Although uncommon, primary CNS lymphoma has generated great interest due to its rising incidence in the immunocompetent host and its responsiveness to systemic chemotherapy.[1,2] Primary CNS lymphoma also occurs with a markedly increased incidence in immunosuppressed patients, especially those with the acquired immune deficiency syndrome (AIDS); 2% to 10% of AIDS patients may develop this lymphoma during their illness.[3] However, the frequency of primary CNS lymphoma is decreasing among AIDS patients who are receiving highly active antiretroviral therapy. Because the clinical and therapeutic issues differ greatly when primary CNS lymphoma occurs in AIDS vs non-AIDS patients, we will discuss these populations separately.

Primary CNS Lymphoma in Immunocompetent Patients

Establishing the Diagnosis

The approach to managing a patient with suspected primary CNS lymphoma begins with confirmation of the diagnosis. Diagnosis is usually established by stereotactic biopsy because the lesions are typically deep-seated in the brain and are not amenable to extirpation. Furthermore, unlike all other primary brain tumors, control of and survival from primary CNS lymphoma does not improve with surgical resection.[2]

The diagnosis of primary CNS lymphoma is often suggested by its radiographic appearance. Lesions are often periventricular and diffusely enhancing, lack central necrosis, and may lack marked mass effect on neurologic imaging. Magnetic resonance imaging (MRI) with gadolinium enhancement clearly visualizes primary CNS lymphoma and is the best imaging technique to assess the full extent of intracranial involvement. Lesions are multiple in about 30% of patients.[4] Corticosteroids are frequently administered immediately after the diagnosis of an intracranial mass is made based on neurologic imaging. However, in 40% to 85% of patients with primary CNS lymphoma, corticosteroids can cause cell lysis and regression of tumor.[2] The speed of regression is variable, but a complete disappearance may occur in 1 to 2 days. Even patients with a partial response can have enough tumor lysis that nondiagnostic tissue is obtained at biopsy. Consequently, when the radiographic features suggest primary CNS lymphoma as a diagnostic possibility, corticosteroids should be withheld until tissue is obtained and the diagnosis is confirmed. Failure to withhold steroids will often put the physician in a clinical dilemma of how to proceed in the absence of a definitive diagnosis.

Although most patients with primary CNS lymphoma have neurologic symptoms and signs, they can usually clinically tolerate deferral of steroid administration if biopsy proceeds in a timely fashion. The rare patient with rapid neurologic deterioration or herniation must receive immediate corticosteroids; subsequent biopsy should be performed as soon as possible.

Is a lesion that rapidly diminishes or disappears after a few doses of corticosteroids pathognomonic for primary CNS lymphoma? Unfortunately not, as other intracranial processes, such as multiple sclerosis and neurosarcoidosis, not only can mimic primary CNS lymphoma radiographically but also respond to steroids. Therefore, steroids should not intentionally be used as a diagnostic test. If corticosteroids were administered inadvertently and the lesions resolved, however, one must decide how to proceed. When the lesions are clearly large masses on MRI with radiographic features suggestive of primary CNS lymphoma, biopsy should be performed with corticosteroid withdrawal. However, when lesions are small and do not demonstate the expected mass effect, biopsies can be performed under steroid cover because the results may be less diagnostic. When large residual masses are left in the brain, they may be safely resected with no evidence of recurrence.
characteristics typical of primary CNS lymphoma and alternative diagnoses can be ruled out, we have occasionally proceeded with empiric treatment for primary CNS lymphoma. Although therapy should be based on pathologic confirmation, in our experience, withdrawal of steroids with a plan to biopsy lesions when they reappear has resulted in fulminant tumor growth and rapid death in some patients even before treatment can begin.

Assessing the Extent of CNS Disease

Once the diagnosis has been established, it is important to assess the extent of the disease in the nervous system (Table 1). Active systemic lymphoma can be identified in only 2% to 3% of patients at diagnosis after an extensive systemic evaluation. In all of these patients, systemic disease was identified on an abdominopelvic CT scan or bone marrow biopsy and subsequently confirmed pathologically. In none of these few patients did the systemic disease determine the patient's course or outcome.

In the nervous system, primary CNS lymphoma can involve multiple compartments; it primarily affects the brain but can also involve the cerebrospinal fluid (CSF), eyes, and spinal cord parenchyma. These areas must be evaluated with a cranial MRI, an ophthalmologic evaluation (including slit-lamp examination), and lumbar puncture; spinal MRI with gadolinium is performed if the patient has signs and symptoms of spinal cord or cauda equina disease. The extent of CNS involvement is essential for guiding treatment and has prognostic importance. Primary CNS lymphoma is primarily a brain tumor, and multifocal gross disease is present in about 30% of patients. However, extensive microscopic infiltration of the brain can be found in most patients at autopsy. Neurologic imaging performed close to death will delineate areas of bulky disease but usually underestimates the tumor burden in the CNS, where extensive disease can be seen microscopically. This is likely true at diagnosis as well, and is exemplified by the occasional patient who has a nonenhancing tumor at diagnosis. Such patients typically have radiographic abnormalities identified on T2-weighted MRI scans that do not enhance after gadolinium administration. However, we also have seen patients in whom widely infiltrative disease is identified at autopsy even in areas that were completely normal on an MRI obtained close to death.

Prognostic Factors

Age at diagnosis is the most important prognostic factor in patients with primary CNS lymphoma (Table 2). Several studies have demonstrated that patients older than 60 years tend to fare worse. This is an important issue in a disease with a median age at onset of 58 years. Youth confers a survival benefit, while old age increases the risk of relapse and treatment-related neurologic sequelae.

Recently, Corry et al looked at 62 patients diagnosed with primary CNS lymphoma between 1982 and 1994 and found age to be an independent prognostic factor. These researchers also identified gender and performance status as important prognostic factors; they reported that men do better than women, but others have not found gender to affect outcome.

Blay et al divided the prognostic factors into classic and specific factors. Classic factors include age, performance status, and serum lactic acid dehydrogenase. These well-documented prognostic factors for systemic lymphoma also were found to be important for primary CNS lymphoma. With respect to specific factors, Blay et al determined that involvement of the corpus callosum, deep gray nuclei, brainstem, basal ganglia, and meninges predicted a poor outcome. Ocular involvement and multifocality on neurologic imaging did not affect survival in their study. A CSF protein level of ≥ 60 mg/dL was associated with better survival in the reviews of both Blay et al and Corry et al. However, on multivariate analysis, only age, performance status, and CSF protein level were independent predictors of overall survival.

Treatment

Great progress has been made in the treatment of primary CNS lymphoma. However, improvements are still necessary, as some patients do not respond to initial treatment and others relapse after a complete response.

Resection does not increase survival and, in some cases, causes neurologic deterioration due to the deep location of most lesions. Furthermore, there is a theoretical concern that craniotomy may cause spillage of tumor cells into the subarachnoid space, possibly seeding the leptomeninges.

At present, the best surgical technique to obtain tissue for definitive diagnosis is stereotactic biopsy. Radiotherapy rapidly became one of the mainstays of treatment and remained the focal point of therapy for many years. Whole-brain radiotherapy alone increases survival from 4 months with surgery to 15 to 18 months. Data support the use of at least 4,000 cGy to the whole brain.
cGy of whole-brain radiation therapy followed by a 2,000-cGy focal boost.[13] A response was seen in 62% of patients and a complete response in 19%. Median survival duration, however, was only 12.2 months. The addition of a boost to the area of bulky disease did not improve intracranial disease control or survival. We also found that a boost did not decrease relapse within the boosted field, demonstrating that radiotherapy doses above 4,000 to 5,000 cGy do not improve disease control.[14]

Recently, Reni et al analyzed 50 papers on the management of primary CNS lymphoma published in English between 1980 and 1995.[15] This literature review demonstrated that whole-brain irradiation improves survival compared to focal radiation. Although most authors who have prospectively studied radiotherapy as a treatment for primary CNS lymphoma found a plateau in local tumor control at a dose of 4,500 to 5,000 cGy, the retrospective analysis by Reni et al showed that a dose of > 5,000 cGy to the whole brain prolongs survival. Craniospinal irradiation has been advocated by some because of the high incidence of leptomeningeal involvement; however, it has not increased survival.[16] Furthermore, craniospinal irradiation may compromise the subsequent administration of systemic chemotherapy due to bone marrow suppression.

Chemotherapy Added to Radiation Therapy—

Since primary CNS lymphoma is histologically similar to systemic lymphoma, it was reasonable to try systemic lymphoma regimens for primary CNS lymphoma.

Two multicenter, prospective trials randomized patients with primary CNS lymphoma to receive either cyclophosphamide HCl, doxorubicin, Oncovin, and either prednisone (CHOP) or dexamethasone (CHOD) followed by whole-brain irradiation or whole-brain irradiation alone.[17,18] The CHOP regimen is the optimal combination for the treatment of advanced systemic NHL. However, CHOP/CHOD failed to produce sustained remissions in patients with primary CNS lymphoma, and median survival times were no better than with whole-brain radiotherapy alone. Typically, large lesions regressed initially, but new disease appeared in other sites of the brain, often between the second and third cycle. In addition, one trial had significant chemotherapy-related toxicity and only 54% of patients actually proceeded to radiotherapy.[18] Brada et al combined methotrexate (400 mg/m²), Adriamycin, cyclophosphamide, Oncovin, prednisone, and bleomycin (MACOP-B) with whole-brain radiotherapy and achieved a median survival of 16 months, which was no better than results with whole-brain irradiation alone.[16] To date, no conventional systemic lymphoma regimen has proved effective against primary CNS lymphoma.

The initial response of bulky disease to systemic lymphoma regimens suggests that primary CNS lymphoma has some intrinsic sensitivity to these standard chemotherapy protocols. However, the appearance of disease between chemotherapy cycles in areas of the brain not initially involved on MRI suggests that drug access may be a limiting factor. None of the drugs in standard lymphoma regimens can penetrate an intact blood-brain barrier. The drugs reach bulky disease because the blood-brain barrier is disrupted, but they cannot reach areas of microscopic disease situated behind an intact barrier.[19] Thus, while bulky disease may be regressing, microscopic disease continues to grow, resulting in the formation of new tumors.

High-Dose Methotrexate—

Regimens containing high-dose methotrexate clearly increase survival when added to radiotherapy.[20] In 1992, DeAngelis et al used high-dose methotrexate along with intrathecal methotrexate, followed by whole-brain radiation therapy and high-dose cytarabine, to treat 31 patients with primary CNS lymphoma.[14] Median survival was 41 months. Further follow-up of these patients has shown the same median survival, and 7 of the 31 patients are still alive.[8] Recently, Blay et al retrospectively analyzed 226 patients with primary CNS lymphoma.[4] Their analysis showed that patients who received chemotherapy with high-dose methotrexate (≥ 1.5 g/m²) or cytarabine did significantly better than those treated with radiotherapy alone or radiotherapy plus other chemotherapy. This benefit was not seen with nitrosourea therapy. Furthermore, after adjustment for age, performance status and CSF protein level, high-dose methotrexate was found to be the only independent treatment-related factor with prognostic value.

Intrathecal Methotrexate—

Primary CNS lymphoma is often a disseminated disease in the nervous system at diagnosis. Approximately 20% of patients have ocular involvement at diagnosis and at least 42% have documented leptomeningeal seeding.[2,21] Furthermore, biopsy specimens often reveal focal leptomeningeal infiltration without widespread CSF involvement or a positive CSF cytologic examination. Several regimens have incorporated intrathecal methotrexate into treatment. Systemic high-dose methotrexate can penetrate into the CSF but achieves a therapeutic concentration for 2 to 24 hours,
depending on the dose. Intrathecal methotrexate, on the other hand, provides a higher concentration for at least 24 hours, particularly when given through an Ommaya reservoir. The literature review of Reni et al has shown that the addition of intrathecal methotrexate to systemic chemotherapy increases survival on multivariate analysis. Balmaceda et al also demonstrated improved disease control with the addition of intrathecal methotrexate. However, a direct comparison of systemic high-dose methotrexate with and without intrathecal methotrexate has not been made.

It is possible that systemic high-dose therapy may be sufficient to treat the subarachnoid space and that placement of a reservoir is unnecessary. Furthermore, the addition of intrathecal methotrexate to systemic chemotherapy may enhance the potential for delayed neurotoxicity (see below).

**Neurotoxicity**

High-dose methotrexate is well tolerated acutely by most patients. The addition of leucovorin minimizes gastrointestinal and myelosuppressive side effects. Renal toxicity with delayed clearance of the drug is the most frequently encountered problem, especially in the elderly. This is partially prevented by prior hydration. Uncommon side effects include non-oliguric renal failure, drug-induced hepatitis, pneumonitis, and transient stroke-like episodes that resolve completely.

The most frequent and troublesome toxicity of combined-modality treatment with methotrexate and radiotherapy is leukoencephalopathy. Whole-brain radiotherapy often causes diffuse white matter changes seen on MRI. Cognitive dysfunction correlates poorly with the degree of white matter abnormalities, but significant dementia can occur from whole-brain irradiation alone.

Methotrexate also causes leukoencephalopathy, and, when combined with radiation, the effect is synergistic. This was initially shown by Bleyer in children with leukemia who were treated with CNS prophylactic regimens. Methotrexate given intravenously, intrathecally, or together with cranial irradiation had a synergistic toxic effect on the brain. This synergistic toxicity was observed at doses of whole-brain irradiation (eg, 2,400 cGy) and systemic methotrexate (40 to 80 mg/m²) that are substantially lower than those used to treat primary CNS lymphoma.

The sequence of therapies also proved to be important. Methotrexate administered prior to cranial irradiation reduced the risk of leukoencephalopathy, as compared with methotrexate and irradiation given concurrently or methotrexate given following radiation therapy. The effect of modality sequence is thought to be due to enhanced capillary permeability induced by cranial irradiation that permits increased drug concentrations to reach normal brain, thus amplifying the toxic synergistic effects of chemotherapy and cranial radiation therapy. These data provide the rationale for administering all methotrexate prior to whole-brain radiotherapy in current studies of primary CNS lymphoma.

Late neurotoxicity has become increasingly important as survival from primary CNS lymphoma has improved. Long-term follow-up of our population has shown that a large percentage develops neurotoxicity, with risk directly related to increasing age. Patients ≥ 60 years of age at diagnosis had a 100% incidence of late neurotoxicity 24 months after diagnosis, whereas those under age 60 years had a maximal risk of 30% at 96 months. This high incidence of late neurotoxicity was seen even though methotrexate was administered prior to whole-brain irradiation. Many of our older patients died from neurotoxicity without any evidence of primary CNS lymphoma.

This observation is particularly important in a disease in which the median age at diagnosis is about 58 years old. Thus, at least half of patients would be vulnerable to leukoencephalopathy after successful combined-modality therapy.

With a median follow-up of 76 months, Blay et al projected the incidence of late neurotoxicity to be 26% at 6 years. They observed a median survival of 12 months after the diagnosis of neurotoxicity. The frequency of neurotoxicity was projected to be 4% at 12 months and 26% at 68 months, confirming that prevalence rises with prolonged follow-up. Blay et al found a radiation dose > 5,000 cGy (on univariate analysis) and the sequence of cranial irradiation followed by chemotherapy (on multivariate analysis) to be the only significant risk factors. Age was not a significant risk factor in their analysis.

**Chemotherapy Alone**

Because the combination of chemotherapy and radiation is so toxic, and whole-brain irradiation alone is so ineffective, alternative approaches are being sought. Currently, there is a major focus on the use of chemotherapy alone.

In designing such an approach, there are several lessons to be learned from the experience with systemic non-Hodgkin’s lymphoma. Single-agent therapy has never produced durable or sustained remissions in a significant number of patients with systemic lymphoma. The development of complementary multidrug regimens was the key to the first true cures of non-Hodgkin’s lymphoma. To date, there is no reason to believe that the biology of primary CNS lymphoma differs markedly.
from comparable systemic lymphoma. Therefore, a combination chemotherapy approach is most likely to succeed by using non-cross-resistant agents to avoid drug resistance.

Experience with primary CNS lymphoma demonstrates that drugs that penetrate the blood-brain barrier are essential. The failure of the standard lymphoma regimens to improve outcome in primary CNS lymphoma must be attributed, at least in part, to the inability of the drugs contained in these regimens to penetrate a relatively intact blood-brain barrier. Adequate drug concentrations must reach the CSF and penetrate into regions of the brain that harbor microscopic disease. These requirements are restrictive, however, as the best drugs against non-Hodgkin's lymphoma, such as doxorubicin and cyclophosphamide (Cytoxan, Neosar), cannot penetrate the blood-brain barrier, and those drugs capable of penetrating this barrier do not have the most potent antilymphoma activity. This dilemma has led to experimentation with different regimens, none of which has been studied in sufficient detail to determine an optimal approach. However, there are indications that chemotherapy alone can produce sustained remissions in a number of patients, including the elderly (Figure 1). Using high-dose methotrexate combined with vincristine and procarbazine (Matulane) or thiotepa in patients with CNS lymphoma, Freilich et al reported a response rate of 92% and median survival of 30 months.[29] No neurotoxicity was observed in these patients.

Sandor et al used methotrexate-based combination chemotherapy regimen without radiation therapy to treat 14 patients.[30] Median disease-free survival was 16.5 months, and median overall survival has not been reached despite follow-up of more than 3 years. Of the 14 patients, 7 required salvage radiation therapy with or without additional chemotherapy. These findings suggest that relapse occurs more rapidly with chemotherapy alone than with chemotherapy plus radiotherapy, but the data are preliminary and patient numbers are small. Three older patients developed severe neurotoxicity after the administration of whole-brain irradiation, whereas neurotoxicity was not seen in the patients who received chemotherapy alone.

Intraarterial Chemotherapy—Dahlborg et al have taken an alternative approach.[31] They disrupt the blood-brain barrier with intraarterial mannitol and then administer intraarterial methotrexate and systemic cyclophosphamide and procarbazine without radiation therapy. The cyclophosphamide is administered 10 minutes before the mannitol so that it can be converted to the active agent and reach the brain when the blood-brain barrier is perturbed. The procarbazine is given after the intraarterial procedure because it can reach the brain by virtue of its lipophilic structure. Median survival was 40 months, which is comparable to survival obtained with combined-modality treatment and clearly superior to that achieved with whole-brain irradiation alone. Intraarterial chemotherapy was associated with acute toxicities, including seizures, raised intracranial pressure, and arterial trauma. The authors reported no late neurotoxicity, except in patients who received whole-brain radiotherapy for progression or relapse. However, intra-arterial chemotherapy has substantial, well-documented neurotoxicities, particularly with use of a known neurotoxin, such as methotrexate.

Primary CNS Lymphoma in Immunosuppressed Patients

Primary CNS lymphoma is a late complication of AIDS.[32] Like primary CNS lymphoma in the immunocompetent patient, AIDS-related disease is a B-cell lymphoma, usually of large-cell or large-cell-immunoblastic subtypes. However, unlike primary CNS lymphoma in the immunocompetent patient, AIDS-related primary CNS lymphoma is triggered by Epstein-Barr virus infection; it is comprised of infected B-cells that proliferate uncontrollably because they have escaped T-cell surveillance.[3,33]

Establishing the Diagnosis

Primary CNS lymphoma usually develops in AIDS patients with a CD4 count of < 100/mm³ and is second to toxoplasmosis as a cause of intracranial mass lesions. Unlike primary CNS lymphoma in the immunocompetent host, the disease in AIDS patients does not have a characteristic radiographic appearance.[34] It is frequently ring enhancing, where contrast is evident only at the periphery of a spherical lesion, and can occur in the cortex or deep periventricular structures. Therefore, it is indistinguishable from toxoplasmosis or other CNS processes on CT or MRI. This makes the diagnosis especially challenging.

The only definitive means of establishing the diagnosis is brain biopsy. However, biopsy often is avoided in AIDS patients. Positron emission tomography (PET) or single-photon emission computed tomography (SPECT) has been used successfully to distinguish lymphoma, which is hypermetabolic, or [hot, from infection, which is hypometabolic, or [cold.[35,36] Another diagnostic technique, the identification of Epstein-Barr virus DNA in the CSF, has been shown to be very sensitive and specific
for primary CNS lymphoma.[35,37]
These noninvasive techniques should be performed immediately after an intracranial mass is identified in an AIDS patient. The prior approach of instituting antitoxoplasmosis treatment and then treating for primary CNS lymphoma when antimicrobials fail often leads to severe neurologic debilitation by the time appropriate therapy is started.[38]

**Treatment**
The choice of treatment is usually dictated by the patient's clinical condition. Whole-brain radiation in a dose of 4,000 to 5000 cGy often produces tumor regression, but median survival with this therapy is only 2 to 5 months.[3,39] Survival is short because patients die of other AIDS-related illnesses, especially infection.

Traditionally, chemotherapy was withheld in AIDS patients because of their underlying immunosuppression and poor performance status. However, several studies have shown a benefit from chemotherapy in a subset of affected patients. Forsyth et al treated 10 patients with systemic and intrathecal methotrexate, thiotepa, and procarbazine prior to irradiation.[40] Six patients had a complete response at the end of treatment, while one had a partial response, one had stable disease, and two died. Two patients survived for 1 year or longer.

A recent study demonstrated the efficacy of high-dose methotrexate in patients with AIDS-related primary CNS lymphoma.[41] Patients not only responded to this therapy but also had an improved quality of life.

The most exciting advance in the management of AIDS is highly active antiretroviral therapy. McGowan et al described a HIV-seropositive patient with primary CNS lymphoma who was treated with highly active antiretroviral therapy, including zidovudine (Retrovir), lamivudine (Epivir), and saquinavir (Invirase, Fortovase).[42] No other antineoplastic treatment was administered. Regression of the CNS lymphoma was shown on neurologic imaging and the CD4 count increased to $10^6$ cells/L. The patient remained asymptomatic for 26 months.

**Conclusions**
Exciting advances have been made in the management of primary CNS lymphoma. It is one of the few primary brain tumors responsive to systemic chemotherapy. A marked improvement in survival has been observed with combined-modality therapy and the use of systemic chemotherapy. Prolonged survival comes at the expense of a significant risk for delayed cognitive impairment, however, particularly in older patients. To effectively treat this brain tumor without damaging the brain itself is essential, because severe cognitive neurotoxicity is an unacceptable consequence of successful treatment. The challenge for the future is to further improve therapy so that more patients respond and experience prolonged disease-free survival without incurring significant neurologic sequelae.

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