Primary CNS lymphoma is rising in incidence in both the AIDS and non-AIDS populations. It is a non-Hodgkin's lymphoma that usually presents as a brain tumor, but the leptomeninges, eyes, and spinal cord also are.

Introduction

Primary central nervous system (CNS) lymphoma is a non-Hodgkin's lymphoma that arises within and is restricted to the nervous system. It usually presents as a brain tumor, but may also involve the leptomeninges, eyes, spinal cord, or any combination of these sites [1]. Formerly, the disease was rare, representing less than 1% of all intracranial tumors, but since 1974 there has been at least a threefold rise in incidence in apparently immunocompetent patients. It has also been recognized for decades that primary CNS lymphoma occurs with increased frequency in patients with congenital (eg, ataxia-telangiectasia) or acquired (eg, renal transplant recipients) immunodeficiencies. It is now most common in patients with the acquired immunodeficiency syndrome (AIDS), as many as 6% of whom develop primary CNS lymphoma during their illness. It is so characteristic of the immunosuppression associated with AIDS that it is classified as an AIDS-defining illness in HIV-infected individuals.

Historically, treatment of primary CNS lymphoma was surgery followed by cranial irradiation; the median survival was 12 to 18 months, and the 5-year survival rate, 3% to 4% in immunocompetent patients; immunosuppressed individuals fared worse. Survival figures with this treatment approach were consistent in numerous retrospective series evaluating small numbers of patients (20 to 30) collected over several decades. These studies also demonstrated the aggressive biologic behavior of primary CNS lymphoma, with untreated patients surviving only a few months. Furthermore, the collected series suggested that surgical resection had no significant therapeutic role in the treatment of this disease, because survival was not worsened if only biopsy for tissue diagnosis was performed. Because the disease was so infrequent, pursuit of more effective therapy seemed neither practical nor necessary.

In the early 1980s, physicians began to see a rising number of immunocompetent patients with primary CNS lymphoma, an increase later confirmed by epidemiologic data. During this time, the full force of the AIDS epidemic led to increased cases of AIDS-related primary CNS lymphoma, and recent studies demonstrate that the incidence continues to rise, as HIV-infected individuals survive longer [2,3]. These factors clearly highlighted the inadequacy of then-current therapy, and clinical trials were begun in an effort to improve treatment.

Biologic Behavior

To design an appropriate therapeutic approach, a number of issues concerning the biologic behavior of primary CNS lymphoma needed to be defined and incorporated into the treatment plan. Using the clinical staging criteria applied to systemic non-Hodgkin's lymphoma, primary CNS lymphoma is a stage IE lymphoma; that is, it involves a single extranodal site, the brain. Most patients with systemic stage IE non-Hodgkin's lymphoma can be treated effectively with involved field irradiation. Focal radiotherapy achieves a complete response rate of almost 100% and can yield 10-year survival or cure rates of 70% in patients with stage I disease [4]. Using involved field radiotherapy (whole brain radiotherapy) for the treatment of primary CNS lymphoma does not produce comparable control of disease. Two possible reasons are that (1) disease exists outside the radiotherapy field and that (2) pathologically, primary CNS lymphoma has more aggressive biology than identical systemic lymphomas.

The issue of dissemination of disease is more easily addressed than the question of a fundamental
biologic difference between primary CNS lymphoma and systemic lymphomas, but systemic and nervous system dissemination must be considered independently.

**Systemic Dissemination Not a Factor**

It has been hypothesized that an occult systemic lymphoma is the origin of primary CMS lymphoma, because the nervous system has no lymph nodes or lymphatics, and thus the source of malignant lymphocytes in the CNS must be from outside. If an occult systemic lymphoma accounts for disease in the nervous system, then primary CNS lymphoma would simply be a stage IV lymphoma with an unusual and rare pattern of metastasis to CNS only. However, the evidence argues strongly against this hypothesis.

First, when systemic lymphoma spreads to the nervous system, it spreads to meninges and affects the brain in only 1% of patients [5]. In those few patients with brain metastases, the lesions appear late in the course of their illness and are associated with recurrent or uncontrolled systemic disease, often specifically with bone marrow infiltration or retroperitoneal adenopathy.

Second, patients with primary CNS lymphoma have no evidence of systemic lymphoma, either at diagnosis or at autopsy. At Memorial Sloan-Kettering Cancer Center, more than 100 non-AIDS patients with primary CNS lymphoma had a complete systemic evaluation at diagnosis, including body computed tomography (CT) scans, bone marrow aspiration, and biopsy, and not one had evidence of systemic lymphoma. There are two case reports of patients who presented with apparent primary CNS lymphoma and had systemic lymphoma on evaluation, but one patient had two histologically different lymphomas, and the disease in the second patient likely represented systemic metastases from untreated primary CNS lymphoma [6,7].

Autopsy studies have found systemic lymphoma in only 7% to 8% of primary CNS lymphoma patients, and most of these patients have a single site of microscopic disease believed to be a metastasis from their uncontrolled CNS tumor. Rare patients with primary CNS lymphoma develop clinically obvious systemic lymphoma, which may even develop in the context of undetectable cerebral tumor. In some of these patients, the systemic lymphoma may be a second primary, as primary CNS lymphoma is seen occasionally in patients with a variety of prior systemic neoplasms [8]; however, the development of systemic lymphoma is very unusual and does not represent the typical clinical behavior of primary CNS lymphoma.

These data demonstrate that systemic lymphoma is not a factor in the natural history of primary CNS lymphoma, and that treatment need not include therapy designed to eradicate occult systemic disease.

**Nervous System Dissemination**

Although systemic dissemination is not a factor when considering treatment of primary CNS lymphoma, dissemination within the nervous system must be considered (Table 1). Primary CNS lymphoma is confined to a single extranodal site, the central nervous system, but is almost always disseminated within it. This dissemination can take many forms and involve different compartments of the CNS. The brain is the most important site of disease and is involved in more than 95% of patients [1]. By magnetic resonance (MR) scan, parenchymal brain lymphoma is multifocal in about half of patients at diagnosis. However, autopsy and some radiographic studies have demonstrated that the contrast-enhancing lesions seen on scan can significantly underestimate the extent of tumor present within the parenchyma [9]. At autopsy, all patients have microscopic infiltration involving regions of brain and occasionally spinal cord that were radiographically normal. Consequently, the tumor burden is always greater than initially appreciated, and if enhancement on CT or MR scan measures blood-brain barrier integrity, all patients have some disease behind a relatively intact blood-brain barrier.

**The Brain**—The brain is the most important area of involvement by primary CNS lymphoma, but dissemination within other CNS compartments, such as the leptomeninges, eyes, and spinal cord, may also be important, and appropriate neurologic staging, including lumbar puncture and ophthalmologic examination, is imperative (Table 2). Primary CNS lymphoma tends to form mass lesions in periventricular locations. It is a highly infiltrative neoplasm and will usually traverse the ependyma to involve the ventricular surface. Lesions more peripherally located grow into the overlying leptomeninges. Leptomeningeal infiltration is so characteristic of primary CNS lymphoma that Shibata10 has postulated that malignant lymphocytes from the subarachnoid space are the source of primary CNS lymphoma and grow into the brain to form parenchymal mass lesions.

**The Leptomeninges**—In many patients, leptomeningeal involvement remains localized to areas adjacent to the parenchymal lesions, accounting for the absence of clinical symptoms or signs
specifically suggestive of leptomeningeal tumor, such as cranial neuropathies or radiculopathies (Figure 1). In spite of the relatively localized leptomeningeal involvement seen pathologically, malignant cells are identified in the cerebrospinal fluid (CSF) of one third of patients at diagnosis; in an additional third, lymphocytes with a suspicious cytology are present [11]. Thus, there is a high incidence of at least microscopic CSF dissemination of primary CNS lymphoma at diagnosis. In occasional patients, widespread leptomeningeal lymphoma with clinical evidence of subarachnoid tumor may be the presenting problem, but these patients are a distinct minority. Nevertheless, most patients have tumor within the leptomeninges, at the gross or microscopic level, and thus specific therapy must be directed against the CSF.

The Eyes—In addition to the leptomeninges, the eye is another important site of primary CNS lymphoma [12-14]. Embryologically and functionally, the eye is an extension of the nervous system. Occasionally, ocular involvement (as opposed to orbital lymphoma, which always represents systemic disease) occurs by direct extension of brain disease through the optic nerve or meninges, but more commonly it arises as an independent site of this multifocal process [15]. Patients may present with blurred vision or floaters, but clinically this may be hard to distinguish from more common benign ocular conditions, particularly in an older population. In the AIDS population, these symptoms may be confused with ocular infections, particularly cytomegalovirus (CMV) retinitis. In addition, about half of patients with ocular lymphoma have no visual symptoms. About 12% to 18% of patients in whom primary CNS lymphoma began in the brain have ocular involvement at diagnosis [11]. Conversely, lymphoma can begin in the globe, and 50% to 80% of patients with ocular lymphoma develop cerebral involvement during the course of their disease. Frequently, the latency from onset of ocular lymphoma to the appearance of CNS disease is many years. Ocular lymphoma is detected by slit-lamp ophthalmologic examination. Vitrectomy may demonstrate malignant lymphocytes, but such a biopsy may yield a false negative if the patient has been taking corticosteroids [12]. While the relationship between ocular and cerebral lymphoma has been known for years, ophthalmologic examination has only recently become part of the staging evaluation of patients with primary CNS lymphoma, and, therefore, clinically silent ocular infiltration was not detected previously. This has important therapeutic implications, since ocular involvement necessitates specific therapy, which is not administered in the course of standard whole brain radiotherapy. Neglect of ocular lymphoma not only results in progressive ocular disease with visual loss but also can lead to CNS relapse and an apparent failure of standard treatment.

The Spinal Cord—Parenchymal spinal cord involvement is rare and usually clinically evident; however, we have encountered a few patients with spinal cord infiltration missed at diagnosis and not covered by the initial therapy. Complete imaging of the spinal cord is not necessary in every patient with primary CNS lymphoma, but patients with neck or back pain, and symptoms or signs suggestive of myelopathy should have an enhanced MR scan of the entire spine. Very rarely, primary CNS lymphoma originates within the spinal cord, but localization of the disease is usually straightforward, since patients present with progressive paraplegia [1]. In virtually all patients, primary CNS lymphoma is disseminated throughout the nervous system at diagnosis. While almost all patients present with brain tumor(s), many will have involvement of the eyes, leptomeninges, spinal cord, or some combination of these sites. These regions must be incorporated into a treatment regimen or they will serve as a potential reservoir of untreated disease that will lead to subsequent relapse. Nevertheless, failure to cover sites of dissemination accounts for treatment failure in only about 10% of patients. In about 90%, primary CNS lymphoma relapses occur in the brain, often at sites remote from the original tumor location. Some brain recurrences may be attributed to progression from ocular or meningeal sites, but uncontrolled brain lymphoma is the most likely source for the majority of relapses. Relapse within the irradiated field is common after focal radiotherapy for primary CNS lymphoma, unlike stage IE systemic lymphoma, indicating that primary CNS lymphoma is a more biologically aggressive disease than comparably staged systemic non-Hodgkin’s lymphoma [16]. No molecular features responsible for this biologic aggression have been identified.

Issues In AIDS-Related Disease

The problem of nervous system dissemination is also applicable to AIDS-related primary CNS lymphoma. Most non-Hodgkin’s lymphomas in AIDS patients arise in extranodal sites; the brain is the single most common location [17,18]. Central nervous system metastases, usually leptomeningeal, are especially common in AIDS patients with systemic non-Hodgkin’s lymphoma. Although no AIDS
patient has been reported with systemic lymphoma presenting as an intracranial mass lesion, this remains at least a theoretical possibility. At present, it is prudent to do a systemic staging evaluation with body CT scans and bone marrow biopsy on all AIDS patients with primary CNS lymphoma (Table 2).

Dissemination of primary CNS lymphoma throughout the nervous system is particularly striking in AIDS patients. Multifocal primary CNS lymphoma occurs in virtually 100% of AIDS patients at autopsy, and leptomeningeal spread is often pronounced [19,20]. Ocular disease can occur in AIDS-related primary CNS lymphoma, but its incidence is unknown, since few patients have been studied prospectively. Cerebrospinal fluid involvement is common, and CSF cytology establishes the diagnosis in 30% of our patients [21].

A lumbar puncture should be performed in every patient with a mass lesion, to identify this significant minority of patients whose primary CNS lymphoma can be diagnosed immediately and appropriate therapy instituted. Lumbar puncture is safe in almost all patients with primary CNS lymphoma, AIDS and non-AIDS; we avoid lumbar puncture for fear of cerebral herniation only in patients with large posterior fossa lesions. This is particularly important in AIDS patients, because most who have an intracranial mass lesion identified on CT/MR scan are placed on empiric anti-toxoplasmosis therapy for 2 to 3 weeks to treat the most common cause of cerebral lesions in this population. However, primary CNS lymphoma is the second most common cause, and patients with primary CNS lymphoma usually deteriorate neurologically while on antibiotics. This deterioration may not be recovered once the correct diagnosis is made on brain biopsy, and poor neurologic condition frequently contributes to the patient's early demise. Two circumstances warrant consideration of an early brain biopsy:

1. The patient with negative toxoplasmosis titers.
2. The patient who has clear clinical deterioration within the first week of anti-toxoplasmosis treatment.

Primary CNS lymphoma in the AIDS population presents other unique issues. In the non-AIDS patient, mortality is determined by the successful treatment of the tumor; however, in AIDS patients, mortality is affected not only by the tumor but also by systemic and neurologic infections [21,22]. Depending on the series, 25% to 100% of autopsied AIDS patients with primary CNS lymphoma have coexistent CNS infections, including HIV encephalitis, toxoplasmosis, cryptococcal meningitis, CMV encephalitis, and others [19,20]. Often, multiple infections are present. Many of these infections are not easily diagnosed prior to autopsy or do not have effective therapies. They confound the clinical assessment of primary CNS lymphoma treatment and often lead to the patient's death even when the primary CNS lymphoma has been eradicated. Likewise, systemic opportunistic infections frequently result in death during or after successful treatment. These factors explain the much poorer outcome of primary CNS lymphoma in AIDS patients compared with identical treatment in the non-AIDS population.

### Treatment Of Immunocompetent Patients

#### Chemotherapy

The development of new therapies for primary CNS lymphoma in immunocompetent patients has, to some extent, paralleled recent therapeutic developments for bulky stage I and II systemic non-Hodgkin's lymphomas. Patients with geographically limited but large-volume systemic lymphoma are at risk for relapse after treatment with focal irradiation because of microscopic disease that had spread beyond the radiotherapy port but was not detected by standard staging strategies. Medical oncologists began treating these patients more aggressively, using combination chemotherapy regimens successful in the treatment of more advanced lymphomas. The addition of chemotherapy to focal radiotherapy has significantly prolonged disease-free survival and increased the cure rate for patients with intermediate- or high-grade lymphomas [23,24].

In primary CNS lymphoma, systemic chemotherapy was initially used in the treatment of individual patients who relapsed after cranial irradiation. Patients received single-agent therapy, using drugs that penetrated into the CNS when delivered in high doses, such as methotrexate and cytarabine [25-27]. Complete or substantial partial remissions of primary CNS lymphoma or metastatic brain lymphoma were seen in the few patients reported, but remission duration was only a few months. Nevertheless, this preliminary work established the chemosensitivity of primary CNS lymphoma and pointed to some potentially useful drugs.

In the early 1980s, there were reports of combining chemotherapy with radiation as initial treatment. Most of the regimens used methotrexate or a nitrosourea-based regimen because of the lipophilic
nature of these drugs and their ability to penetrate into the nervous system [28,29]. Individual patients often received different regimens, and patients were not treated in a uniform manner, but there was suggestive evidence that combined modality therapy was superior to cranial irradiation alone.

Memorial Sloan-Kettering Study—Subsequently, there have been several reports documenting improved survival when chemotherapy is added to radiotherapy (Table 3). At Memorial Sloan-Kettering Cancer Center, we treated 31 patients with preradiation systemic and intra-Ommaya methotrexate, followed by radiotherapy and high-dose cytarabine [30]. Our latest follow-up, as of April, 1994, confirmed a disease-free median survival of 41 months, and our longest survivor is now 9 years without recurrence. We have recently found that age is an important prognostic factor; patients younger than 50 have significantly better response and longer survival than those older than 50. Furthermore, late neurologic toxicity in the form of dementia and ataxia does not occur in younger patients, but has a 27% incidence among older patients who achieve a complete response.

Other Studies—Using a combination of procarbazine, CCNU, and vincristine (PCV) with radiotherapy, Chamberlain and Levin [31] achieved a median survival of 30 months. Gabbai et al [32] have used single-agent high-dose methotrexate with cranial irradiation with good results; 3 of 13 patients were alive at 29 months or longer. Pollack et al [33] reported on 9 patients, Socie et al [34] on 13 patients, and Watne et al [35] on 9 patients who received a variety of chemotherapeutic agents; all noted an increase in survival over patients treated with radiotherapy alone. All of these studies strongly support the addition of chemotherapy to cranial irradiation as initial treatment of primary CNS lymphoma, but all are phase II trials. No randomized controlled study has been performed, nor is it likely to be done because of the relative rarity of this tumor and the seeming consistency of the results.

The Rationale Behind Chemotherapy Followed By Radiation—All of these studies have utilized chemotherapy prior to radiation for several reasons:

First, it permits an assessment of response to treatment. Almost all patients have a complete, albeit short-lived, response after radiotherapy alone, and therefore no measurable disease is present during postradiation chemotherapy administration. This is particularly important in primary CNS lymphoma because we are still learning about the efficacy of individual agents, as it has become apparent that one cannot simply adopt regimens that are effective for the treatment of comparable systemic non-Hodgkin's lymphomas (see below).

Second, the administration of drugs prior to radiation may reduce the risk of late neurotoxicity, particularly with methotrexate. Data from children with acute lymphocytic leukemia treated with CNS prophylaxis indicate that late neurologic sequelae are less common and less severe when methotrexate precedes cranial irradiation, compared with simultaneous or postradiotherapy administration [36]. Experimental evidence suggests that methotrexate prior to cranial radiotherapy may even be protective against late neurologic toxicity in laboratory animals [37]. Although this issue has been studied only for methotrexate, the toxicity concerns may apply to other agents as well. Opening of the blood-brain barrier by cranial irradiation can persist for weeks to months after completion of radiotherapy [38]. This persistent breakdown of the blood-brain barrier is the postulated mechanism to explain the enhanced neurotoxic potential seen when methotrexate follows radiotherapy, since greater concentrations of drug can accumulate in normal brain tissue. Clearly, any water-soluble agent would have greater access to normal brain tissue if delivered after whole brain radiotherapy.

Non-conventional Delivery Systems—Most regimens have employed agents delivered in a conventional manner, but alternative approaches have also been used successfully. Neuwelt et al [39] have pioneered the technique of blood-brain barrier disruption with intra-arterial mannitol followed by intra-arterial methotrexate in combination with systemic cyclophosphamide (Cytoxan, Neosar), procarbazine, and dexamethasone. This regimen is designed to treat the entire CNS by delivering therapy to all three cerebral circulations in a rotating fashion over the course of 1 year. The intent of this program is to treat primary CNS lymphoma with chemotherapy alone, thus avoiding cranial irradiation and its attendant neurotoxicity.

Neuwelt et al have reported on 17 patients treated with this regimen at diagnosis. Sixteen patients were evaluable, and they had a median survival of 44.5 months. However, nine of these patients required radiotherapy, and the time to relapse was not reported. The regimen was reported to be nontoxic, although this may be a direct reflection of the considerable experience and skill these investigators have developed using this technique over the years and may not be applicable at less experienced centers.

CHOP and CHOD—Several investigators have used or adopted chemotherapeutic regimens
successful in the treatment of systemic non-Hodgkin's lymphoma for primary CNS lymphoma. One would expect the disease to be sensitive to the same drugs and hopefully to achieve the same remission and cure rates; however, these regimens have proved uniformly ineffective. Stewart et al [40] first utilized cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) with radiotherapy, but reported that after an initial response to chemotherapy, patients went on to develop florid leptomeningeal tumor, which progressed and led to death. At Memorial Sloan-Kettering, we treated five patients with CHOD (dexamethasone replacing prednisone) at recurrence. Only one patient achieved a complete response, and the other four had progressive disease (two) or developed refractory leptomeningeal lymphoma (two) [11]. Lachance et al [41] used CHOP followed by neuraxis radiotherapy at diagnosis. All patients had an initial response to CHOP, but developed multifocal recurrence in sites remote from the original areas of disease before chemotherapy could be completed.

The RTOG and Other Studies—CHOD received its most extensive assessment in a recently completed study conducted by the Radiation Therapy Oncology Group (RTOG) [42]. The study called for three cycles of chemotherapy followed by definitive radiation. Preliminary results show a median survival of only 12.8 months for the 51 patients treated. Furthermore, it appears that when effective, CHOP may be associated with a high incidence of delayed neurologic toxicity. Liang et al [43] reported enhanced efficacy with CHOP and intrathecal methotrexate and cranial irradiation, seeing a median survival of 30 months in nine patients so treated. However, eight of their nine patients received all or at least half of their chemotherapy after radiation, and they had a very high incidence of leukoencephalopathy (seven of nine patients) with cognitive decline in five of the seven. Brada et al [44] combined the MACOP-B regimen with cranial radiotherapy, but had a median survival of only 14 months, no better than radiation alone.

Those regimens that failed to prolong survival over that seen with radiotherapy alone are based upon cyclophosphamide and doxorubicin, unquestionably the best agents for the treatment of non-Hodgkin's lymphomas. However, neither of these drugs penetrates an intact blood-brain barrier. Reasonable concentrations are likely achieved in areas of bulky disease clearly seen on contrast-enhanced cranial scans, which account for the initial response to these regimens with reduction of tumor masses. However, the rapid appearance of progressive tumor in areas that had a relatively intact blood-brain barrier (the leptomeninges and regions remote from the original disease) further supports the concept of disseminated nervous system disease at diagnosis and highlights the importance of using agents that can reach these areas. This is supported by some experimental work done by Ott et al on a patient treated with the MACOP-B regimen [45]. Blood-brain barrier integrity was studied by positron emission tomography (PET) prior to, during, and after chemotherapy. As expected, the blood-brain barrier was markedly abnormal in regions of disease seen on cranial MR/CT scan, but the barrier was reconstituted and normal permeability was restored halfway through the chemotherapeutic regimen. Consequently, no effective agents could reach tumor throughout half of the therapeutic program, even in areas where the blood-brain barrier was initially impaired. These data strongly argue for the use of drugs that penetrate an intact blood-brain barrier to reach all areas of tumor. Furthermore, the history of treatment for systemic non-Hodgkin's lymphomas documents the superiority of combination chemotherapy over single agents, and this may be particularly important in the treatment of primary CNS lymphoma, since some of the best antilymphoma agents are not useful in this setting. Consequently, new protocols are being used that attempt to combine these two requirements (using multiple drugs that penetrate the blood-brain barrier).

At Memorial Sloan-Kettering Cancer Center, we are currently studying preradiation high-dose methotrexate (2.5 g/m2), procarbazine, and vincristine delivered over a 10-week period followed by whole brain radiotherapy and high-dose cytarabine (3 g/m2) for two cycles. This regimen will be implemented in an intergroup trial through RTOG and the Southwest Oncology Group (SWOG) later this year, and therefore will be available to many physicians.

Chemotherapy Following Radiation

Most of the chemotherapy studies have focused on the use of preradiation chemotherapy. What about the patient who is first referred after cranial irradiation has already been administered? Is there a role for adjuvant chemotherapy? This question has not been adequately studied, and we do not know if adjuvant chemotherapy is equivalent to preradiation drug. However, some preliminary evidence suggests that it is superior to radiotherapy alone. Chamberlain and Levin gave their PCV regimen after cranial radiotherapy [31]. Unlike methotrexate, these drugs do not potentiate the
delayed toxic effects of radiotherapy, and no enhanced neurotoxicity was reported. We have chosen to
give four to six cycles of PCV after completion of cranial radiotherapy to those patients who
received no prior chemotherapy. These patients usually have had a complete response to
radiotherapy, and there is no measurable disease to follow, making an assessment of the regimen's
efficacy impossible during its administration. We have avoided methotrexate and even high-dose
cytarabine as adjuvant drugs in this setting because of the toxicity issues, despite their known
activity against primary CNS lymphoma.

**Radiotherapy**

The addition of chemotherapy is the most important recent advance in the treatment of primary CNS
lymphoma; however, some radiotherapeutic issues have also been clarified. A dose-response study
has never been done for this tumor, but retrospective data suggest that 4,000 to 5,000 cGy
improves survival over lower doses [46]. The RTOG completed a prospective study of non-AIDS
patients with primary CNS lymphoma treated with 4,000 cGy whole brain radiotherapy plus a 2,000
cGy boost to the involved area, to assess whether dose intensification improved outcome [47]. The
median survival for the group as a whole was only 12.2 months, and most recurrences were in the
boosted field. In this study, young age (less than 60 years) and better performance status were
identified as important prognostic factors.

In our study of patients receiving preradiation methotrexate and high-dose cytarabine after
radiation, patients received 4,000 cGy whole brain radiotherapy plus 1,440 cGy boost to the tumor
bed [30]. In patients who recurred, relapse occurred within the boosted region as frequently as
outside the boosted area, suggesting that the added radiotherapy did little to improve local control.
This is in keeping with data obtained from systemic non-Hodgkin's disease, for which a dose of 4,200
cGy is optimal to treat stage I and II disease [46]. Furthermore, the risk of late neurologic sequelae
increases with increasing radiation dose. Consequently, we have eliminated the boost and now use
4,500 cGy whole brain irradiation in our current therapeutic protocol. This should provide maximal
efficacy and reduced toxicity.

**Ocular Lymphoma**

Ocular lymphoma deserves special consideration. Ocular involvement is almost always a bilateral
process, although it may be asymmetric. Radiotherapy is the most important therapeutic modality to
treat ocular lymphoma, and both eyes should be irradiated to a total dose of approximately 3,600
cGy [12,48]. When ocular lymphoma is present at diagnosis of cerebral lymphoma, the ocular
radiotherapy must be administered concurrently with the whole brain irradiation to eliminate the
problem of overlapping ports in the region of the optic nerve and posterior retina. If a patient who
has had prior cranial irradiation develops an ocular recurrence, ocular radiotherapy can still be
administered, but must be done with great care to avoid overlap and the subsequent complications
of radiation-induced optic atrophy or retinal degeneration. Ocular irradiation is usually effective in
reducing or eliminating cells in the vitreous or retina, and in improving vision. Remissions may be
durable for many years, or local recurrence can develop within months.

Treatment of patients with isolated ocular lymphoma is controversial. Previously, these patients all
received focal ocular radiotherapy alone. However, because of their high incidence of subsequent
cerebral lymphoma, several investigators have advocated treating such patients with ocular and
whole brain radiotherapy [13]. To date, there are no data to suggest that this approach reduces the
incidence of brain lymphoma. Because CNS radiotherapy is potentially toxic, and the latency
between ocular lymphoma and eventual brain disease can be many years, we administer only ocular
radiotherapy to patients with isolated ocular lymphoma. Further investigation may clarify this issue
in the future.

Chemotherapy has limited efficacy in the treatment of ocular lymphoma because penetration of
most chemotherapeutic agents into the vitreous is so poor. The best agent is high-dose cytarabine (3
g/m²), which can clear the vitreous of malignant cells, often for prolonged periods of time [12,49].
Cytarabine may be used for recurrent ocular disease, but the role of adjuvant chemotherapy is not
clear in the treatment of ocular lymphoma at diagnosis. Other drugs have been reported to be of use
in isolated instances, but there is much less experience with these agents.

**Recurrent Disease**

In spite of the best treatment, many patients develop recurrent primary CNS lymphoma involving
brain, eyes, leptomeninges, or some combination. Most patients will have already received cranial irradiation, but may be eligible to receive ocular or focal spinal radiotherapy for recurrent disease in these areas. However, chemotherapy is the mainstay of treatment for recurrent disease. The choice of drug is determined by the patient's previous chemotherapy exposure and the location of the recurrence (eg, high-dose cytarabine for relapsed ocular lymphoma). The best agents are those described above for the initial treatment of primary CNS lymphoma. Although the chemotherapeutic options are more limited for primary CNS lymphoma than for systemic lymphoma, durable second remissions of a few years may be obtained in some patients.

Treatment of Immunosuppressed Patients

The treatment modalities for primary CNS lymphoma in immunocompetent patients are also used to treat AIDS-related primary CNS lymphoma, although in general they are less effective and more toxic in immunodeficient patients. Cranial irradiation alone gives a median survival of only 2 to 5 months in AIDS-related primary CNS lymphoma, compared with 12 to 18 months in the non-AIDS patient [22,50-52]. For most patients, radiotherapy achieves an excellent partial or complete response, but patients do not always experience a commensurate improvement in their neurologic condition, due to coexistent CNS infections. Although systemic and neurologic infections are a major cause of death in AIDS patients with primary CNS lymphoma, many die of uncontrolled cerebral lymphoma.

Chemotherapy

Chemotherapy has been added to radiotherapy in a small number of patients in an effort to improve response duration. Gill et al [51] reported two patients who survived 28+ and 16 months after systemic chemotherapy (type unknown) and radiotherapy, and Formenti et al [52] reported one patient who survived 16 months. Chamberlain [53] gave whole brain radiotherapy followed by three cycles of PCV to four patients with AIDS-related primary CNS lymphoma and saw survivals of 11 to 16 months, with a median of 13.5 months.

At Memorial Sloan-Kettering Cancer Center, we have treated 10 patients with chemotherapy, nine at diagnosis and one at relapse after radiotherapy alone [21]. Two patients died of treatment-related complications. Seven of the other eight had a response to treatment (88%). The median survival for all 10 patients was only 3.5 months, and was 7 months for the eight patients who completed therapy. Although these median survivals are not different from treatment with whole brain irradiation alone, two patients survived for 1 year or longer, and one is still alive at 54 months after diagnosis. Toxicity was primarily due to myelosuppression and the development of intercurrent infections, but no toxic deaths occurred after colony stimulating factors became clinically available. Concurrent cytotoxic drugs such as zidovudine (Retrovir) or ganciclovir (Cytovene) should be discontinued during chemotherapy until there has been full recovery from any myelotoxicity. These data suggest that some AIDS patients may benefit from a more vigorous therapeutic approach. The best candidates are those with CD4 counts greater than 200/mm³, a good performance status, and no active comorbid conditions [53]. Other patients who are in poor clinical condition, have CD4 counts less than 50/mm³, and are not expected to survive more than 2 months are best treated with palliative radiotherapy. In some patients, a rapid fractionation schedule, such as 3,000 cGy in 10 fractions, may be most appropriate.

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