EDITORIAL

Primary central nervous system lymphoma

Patients with non-Hodgkin's lymphoma often have neurological complications. These include not only metastases, but also infectious, toxic-metabolic, cerebrovascular, paraneoplastic, and treatment related complications. Infections of the CNS related to disease induced immunosuppression occur with increased frequency; toxoplasmosis, fungal meningitis, herpes zoster, and papova virus infection leading to progressive multifocal leukoencephalopathy are among the most common. Metabolic encephalopathy from organ failure, sepsis, and drug induced encephalopathy commonly produce confusion, lethargy, seizures, and occasionally coma. Strokes from non-bacterial thrombotic endocarditis, disseminated intravascular coagulation, and venous sinus occlusion can produce lateralising or global CNS symptoms. Paraneoplastic syndromes seen in non-Hodgkin's lymphoma include motor neuronopathy and necrotising myelopathy. Treatment induced neurotoxicities include vincristine neuropathy, ifosfamide or cytarabine encephalopathy, radiation myelopathy, or radiation related cognitive impairment. A comprehensive discussion of these many entities is beyond the scope of this *editorial*, but can be found in several recent monographs.^{1,2} The CNS may also be directly involved by lymphoma, either metastatic or primary. Lymphoma of the CNS is often a major diagnostic challenge for the neurologist and will be the focus of this discussion.

Non-Hodgkin's lymphoma is a collection of diseases involving malignant transformation of usually B lymphocytes. Typically, the disease presents with adenopathy involving the major lymph node chains throughout the body. Other organs can become involved in later stages of the disease, usually due to haematogenous metastases which arise from nodal sites or bone marrow involvement. Occasionally, the disease can arise in a non-lymphoid organ such as skin or the gastrointestinal tract, but lymphocytes are an important component of the normal structure of these organs. The CNS contains no lymph nodes or lymphatics. Metastatic lymphoma spreads to the CNS usually as a consequence of haematogenous dissemination from widespread systemic disease. Given the absence of a lymphatic system in the CNS, it would not be anticipated that lymphomas could arise there as a primary site. Normally, T cells traffic in and out of the CNS, as manifest by the few lymphocytes which can be found in normal CSF, but B cells are not normally found in the CNS. Despite this paradox, B cell non-Hodgkin's lymphomas do develop in the CNS as the primary and sole site of disease. There are several hypotheses to explain the origin of B cell primary CNS lymphoma but no definitive data which explain their pathophysiology. B Cells may trans-

form outside the CNS and then "home" into the CNS where they grow in a relatively immunoprivileged environment. This mechanism would suggest that these tumour cells have unique surface markers which would induce migration into the CNS; however, primary CNS lymphoma cells have the same cell surface receptors as standard systemic non-Hodgkin's lymphoma cells and no unique markers have been identified to date.³ Alternatively, a B cell passing through the CNS, even intravascularly, becomes transformed during this passage and then remains in the brain, developing into primary CNS lymphoma.

When non-Hodgkin's lymphoma involves the CNS, metastasis is the most frequent cause. Metastatic lymphoma usually involves the leptomeninges without parenchymal invasion. This complication develops in 4% to 11% of patients with systemic lymphoma and can occur in as many as 40% of patients with lymphoma proximate to the CNS, such as orbital or paranasal sinus disease.⁴⁻⁶ Leptomeningeal metastasis is characterised by multifocal involvement along the neuraxis. Patients may develop cranial neuropathies; radiculopathy or radicular pain, especially in the lumbosacral region; raised intracranial pressure with or without hydrocephalus; seizures; or cognitive impairment. The diagnosis is established by identification of malignant cells in the CSF or occasionally by finding a mass lesion or diffuse enhancement of cranial or spinal nerves on postgadolinium MRI. However, because lymphoma cells are not as cohesive as carcinoma cells and thus do not tend to form nodules, MRI is more often normal in patients with known leptomeningeal disease from non-Hodgkin's lymphoma than in patients with leptomeningeal metastases from carcinoma.⁷ Metastatic involvement of the brain parenchyma by systemic non-Hodgkin's lymphoma occurs in about 1% of patients with the disease.⁴ This unusual complication of systemic lymphoma tends to occur in patients with widespread active systemic disease. Epidural metastases occur in 0.1%-6.5% of patients with non-Hodgkin's lymphoma.^{8,9} Although epidural non-Hodgkin's lymphoma does not directly involve the CNS, patients present with back pain and symptoms and signs of myelopathy. Treatment of these metastatic complications of systemic lymphoma often depend in part on the patient's systemic disease and what prior treatment they have received, but may involve chemotherapy, radiotherapy, and, rarely, surgery.

Unlike metastatic lymphoma, primary CNS lymphoma usually presents as a brain tumour. The disease can involve the leptomeninges, the eyes, and spinal cord parenchyma, sometimes as the primary site of symptoms, but more commonly in conjunction with parenchymal brain

lesions.¹⁰ Typically, the lesions are periventricular, produce symptoms within days to weeks, and on MRI have a characteristic diffuse and prominent enhancement pattern. Multifocal disease is seen in about 40% of patients. Primary CNS lymphoma is a highly aggressive brain tumour which requires rapid diagnosis and treatment.

Diagnosis should be established pathologically. Tissue is best obtained by stereotactic biopsy as the lesions are often deep and involve critical structures. Unlike malignant gliomas, gross total resection does not improve disease control or survival and, consequently, offers no therapeutic advantage. Moreover, attempts at resection can produce severe neurological deficits because of the location of most primary CNS lymphoma lesions.¹¹ Stereotactic biopsy is safe, efficient, and usually provides diagnostic tissue. However, the diagnosis can be obscured by presurgical administration of corticosteroids. The identification of mass lesions on a cranial image usually results in the immediate institution of corticosteroids to reduce oedema and improve neurological function. Ordinarily, this is the proper approach regardless of the cause of the intracranial mass. However, like systemic non-Hodgkin's lymphoma, corticosteroids can be cytotoxic for primary CNS lymphoma, resulting in marked shrinkage or even disappearance of tumour.¹² This can occur even after a few days of the standard dose of corticosteroids. If this happens, biopsy is impossible if the lesion has vanished or may yield non-diagnostic tissue if marked shrinkage has occurred. Although occasionally clinicians find themselves in this situation unintentionally, corticosteroids should not be used as a diagnostic test for primary CNS lymphoma. Other processes such as sarcoidosis or multiple sclerosis can occasionally mimic primary CNS lymphoma and respond to corticosteroids. Therefore, it is critical that primary CNS lymphoma be considered among the diagnostic possibilities when reviewing a cranial image. If primary CNS lymphoma is among the diagnostic considerations, then corticosteroids should be avoided until biopsy has been performed. Patients with rapid and serious neurological deterioration may not be able to defer corticosteroids; however, this is highly unusual in primary CNS lymphoma, in which the lesions on MRI typically look much worse than the patient's clinical condition.

Once the diagnosis has been confirmed, treatment should be instituted rapidly. Because primary CNS lymphoma remains a relatively rare tumour, even with the reported increase in incidence among immunocompetent patients, large randomised phase III trials have not been feasible to do a rigorous comparison of different therapeutic approaches for this disease. However, all of the evidence to date indicates that the addition of appropriate chemotherapy to cranial irradiation markedly improves disease control and survival. Both historical data and the prospective study completed by the Radiation Therapy Oncology Group (RTOG) show that cranial irradiation alone achieves a median survival of only 12 to 18 months with a 5 year survival of 3–4% in patients with primary CNS lymphoma.^{12, 13}

The addition of high-dose methotrexate based chemotherapy has increased median survival to about 40 months with a 22% 5 year survival rate.¹⁴ No other single chemotherapeutic agent has proved more effective in the treatment of this disease than methotrexate.¹⁵ The drug is administered at high doses to penetrate areas with an intact blood-brain barrier that often hides microscopic disease. Occasional patients have diffuse microscopic infiltration of brain by primary CNS lymphoma without focal masses and without MRI enhancement.¹⁶ Moreover, all patients with primary CNS lymphoma have areas of microscopic tumour infiltration residing behind an intact blood-brain

barrier even though the barrier is markedly disrupted in areas of bulky disease. This phenomenon likely explains some of the poor results seen with standard systemic non-Hodgkin's lymphoma chemotherapy regimens such as cyclophosphamide, doxorubicin, vincristine, and prednisone or dexamethasone (CHOP or CHOD). The RTOG studied preradiation CHOP followed by whole brain radiotherapy. Although the lesions may initially respond, patients often progressed between the second and third cycle and median survival was only 16 months, no better than radiotherapy alone.¹⁷ A second multi-institutional trial studied preradiation CHOD. Their patients had significant chemotherapy toxicity and only half of the patients progressed to cranial irradiation; the median survival was only 9.5 months, clearly not an advantage over radiotherapy alone.¹⁸ A primary reason for failure is that none of the drugs, except steroids, can penetrate an intact blood-brain barrier and thus reach areas of microscopic disease. Studies of other standard systemic non-Hodgkin's lymphoma chemotherapeutic regimens have similar results and none have demonstrated improved survival over whole-brain radiotherapy alone. Consequently, these regimens should be abandoned in the treatment of primary CNS lymphoma.

Another approach has been developed to deliver effective chemotherapeutic agents behind the intact blood-brain barrier. Disruption of the blood-brain barrier with intra-arterial mannitol, followed by intra-arterial methotrexate in combination with systemic cyclophosphamide, procarbazine, and dexamethasone has been used to treat primary CNS lymphoma. Dahlborg *et al* reported on 39 patients treated at initial diagnosis with this approach.¹⁹ The drugs are delivered into two of the three cerebral arterial circulations every month over the course of a year so that each territory is treated eight times. The goal of this therapy is to treat patients with chemotherapy alone and to avoid cranial irradiation, thus reducing the potential for neurotoxicity. This regimen is effective in the treatment of primary CNS lymphoma and they reported a median survival of 40 months, which is substantially better than cranial irradiation alone. However, 31% of their initial patients required whole-brain radiotherapy, either because of disease progression or non-response to treatment; disease-free survival was not reported. Moreover, the authors reported no late neurotoxicity except in those patients who received cranial radiotherapy. However, the chemotherapy regimen can cause significant acute toxicity, such as seizures and cerebral oedema. In addition, methotrexate alone is a known neurotoxin and can be particularly neurotoxic when delivered in this intra-arterial fashion. The regimen is difficult and cumbersome to administer, causes acute toxicity, and continues to have the potential for delayed toxicity; therefore, it has not been widely adopted and has not been verified by other investigators.

Delivery of methotrexate by intra-arterial methods is not necessary to achieve adequate concentrations behind the blood-brain barrier.²⁰ Methotrexate given in high doses can penetrate an intact blood-brain barrier and high-dose methotrexate gives responses in about 85% of patients even before cranial irradiation is administered. Primary CNS lymphoma usually responds rapidly to high-dose methotrexate and durable responses are often seen. This is in contradistinction to systemic lymphomas in which single agent methotrexate does not produce durable remissions. The improved survival seen when high-dose methotrexate is added to cranial irradiation has made patients vulnerable to late toxicity as a consequence of combined modality treatment. In patients we have now followed up for many years, it has become evident that patients over the age of 60

at diagnosis and treatment are extremely vulnerable to leukoencephalopathy from methotrexate plus cranial irradiation.²¹ This devastating complication, which can produce severe progressive dementia, ataxia, and urinary incontinence, is seen in at least 50% of older patients and can be seen in as many as 100% as they are followed up for years after successful treatment of their primary CNS lymphoma. Younger patients have a much lower risk of developing leukoencephalopathy; however, they are not exempt as about 30% of patients under the age of 60 will develop this severe complication if followed up for 6–8 years after diagnosis. This high incidence of toxicity was seen even though methotrexate was administered before cranial irradiation, a sequence which reduces the synergistic toxic effects of these two modalities and experimentally has been reported to protect against neurotoxicity.

In an effort to reduce this complication, we and others are currently exploring the use of chemotherapy as the sole modality of treatment for primary CNS lymphoma.^{22–23} Preliminary evidence suggests that it is effective in older patients, but it is unclear if disease control is equivalent to that achieved when cranial irradiation follows chemotherapy. A separate issue is whether the use of combination chemotherapy can enhance the rate and duration of remissions in cerebral lymphoma.^{15–23} In systemic non-Hodgkin's lymphoma, combination chemotherapy is substantially more effective than single agent therapy. It is unclear whether a combination employing those agents which can penetrate the blood-brain barrier will afford better disease control in primary CNS lymphoma.

In an effort to clarify these issues, we are currently investigating the use of high-dose chemotherapy with autologous stem cell rescue after successful induction with high-dose methotrexate and cytarabine. Patients would not receive radiotherapy as part of this treatment. Others are exploring the use of long term maintenance therapy with monthly high-dose methotrexate after initial remission has been achieved. Again, elimination of cranial radiotherapy is a goal of this therapeutic approach. The optimal treatment of primary CNS lymphoma has yet to be defined, but these studies should enable us to deliver effective but less neurotoxic treatment to the growing number of patients who develop this disease.

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