

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Susan O'Brien, MD

Insights Into the Management of Patients With Primary Central Nervous System Lymphoma



Christopher P. Fox, MBChB(Hons), PhD, FRCP FRCPath
Consultant Hematologist, Nottingham University Hospitals NHS Trust
Professor of Haematology, School of Medicine, University of Nottingham
Nottingham, United Kingdom

H&O What is the definition of primary central nervous system (CNS) lymphoma?

CF Primary CNS lymphoma is referred to as primary diffuse large B-cell lymphoma of the CNS within the World Health Organization classification, as this histopathologic subtype accounts for at least 95% of the lymphomas that primarily affect the CNS. Among patients with primary CNS lymphoma, the disease is found in one or more CNS compartments, including the brain parenchyma, the leptomeninges, the vitreoretinal compartment of the eye and, rarely, the spinal cord. A diagnosis of primary CNS lymphoma requires evidence that systemic disease is absent, which is usually confirmed by whole-body positron emission tomography (PET)/computed tomography (CT).

The best imaging modality for primary CNS lymphoma is contrast-enhanced (usually with gadolinium) magnetic resonance imaging (MRI). Contrast-enhanced MRIs are used to help diagnose CNS lymphoma, as well as for follow-up imaging to assess response to treatment and for subsequent monitoring.

H&O How common is primary CNS lymphoma, and what are the risk factors?

CF Primary CNS lymphoma is rare, for both brain tumors and lymphomas. Estimates from population-based data in North America, Europe, and other regions suggest that the annual incidence is approximately 4 to 5 new diagnoses per million people per year. The incidence has been rising throughout the past 2 or 3 decades, for unclear

reasons. The increase may result from better diagnostic techniques, or it may reflect the aging population. The median age at diagnosis is usually the late 60s or early 70s. Clinicians may now be more willing to biopsy patients who present with tumors in the brain. These patients may be more fit compared with previous older generations.

There are no specific risk factors associated with the development of primary CNS lymphoma. There are no clear links with any type of environmental, lifestyle, or genetic factors.

H&O What are the symptoms of primary CNS lymphoma?

CF Patients typically present with a range of central neurologic symptoms. Commonly, the history of these symptoms spans weeks to months. The initial symptoms can be subtle. Family or friends might notice a change in behavior or personality, particularly when the disease affects the frontal lobes. Disturbances in speech, memory, or other higher cognitive functions are also common. Symptoms can be similar to a stroke, and include motor weakness, for example, in an arm or a leg. Visual disturbances can be caused by direct infiltration into the visual cortex in the occipital lobe or may result from direct infiltration into the vitreoretinal compartment.

Less commonly, an acute presentation can include symptoms of raised intracranial pressure, headache, and a reduced level of consciousness. Patients may first seek care in an emergency department. Occasionally, deep-brain disease can affect areas such as the brainstem or thalamus,

which often results in a disturbance in the level of consciousness. A proportion of patients are quite unwell, with a poor performance status at first presentation. There is a spectrum of clinical presentation, which is quite heterogeneous, but always includes a central neurologic deficit of some kind.

H&O How is CNS lymphoma diagnosed?

CF In most cases, patients with primary CNS lymphoma initially develop central neurologic symptoms and present to a neurologist or a neurosurgeon, who will undertake a brain scan with contrast-enhanced MRI. Findings on contrast-enhanced MRI that raise suspicion of primary CNS lymphoma include a single mass or multifocal lesions that avidly enhance with contrast (usually gadolinium). Moderate edema is seen around the enhancing tumor. Imaging sequences have shown that these tumors are very cellular. Diffusion restriction, as seen on specific MRI sequences, is characteristic of CNS lymphoma. The movement of water through the cellular lesion is restricted, which produces a particular type of image on this MRI sequence. A good-quality MRI scan with expert neuroradiology review can provide a high degree of confidence in diagnosing primary CNS lymphoma. However, even the best imaging and neuroradiology review are not sufficient for a definitive diagnosis. Patients always need a biopsy. The standard of care is a stereotactic core biopsy of a lesion performed by a neurosurgical team, typically under a general anesthetic, using CT imaging to guide the needle. In many neurosurgical centers, an intraoperative frozen section or intraoperative cellular smear is obtained to immediately determine whether the amount of tissue taken is sufficient and if there is high suspicion of CNS lymphoma. In this situation, no further surgery is performed. An important point is that a biopsy is needed to confirm the diagnosis, but there is no established role for surgery in the treatment of primary CNS lymphoma.

H&O What are the current treatment options?

CF The widely accepted approach to the treatment of primary CNS lymphoma involves 2 phases. In the first phase, the patient receives intravenous chemotherapy. There are several different protocols, but all include high-dose methotrexate according to international consensus. Methotrexate is an antimetabolite, antifolate agent that is given intravenously. Administration typically requires inpatient admission. The usual dose of high-dose methotrexate is at least 3 g/m² administered as a rapid infusion to deliver a sufficient amount of the drug into the CNS. Some groups use higher doses of up to 8 g/m². In most protocols, the high-dose methotrexate is combined with

the anti-CD20 monoclonal antibody rituximab, and a number of different cytotoxic chemotherapies can be partnered with methotrexate and rituximab. In the United Kingdom, Europe, and some parts of North America, clinicians use the MATRix regimen, which is a combination of high-dose methotrexate; high-dose cytarabine; thiotepa, which is an alkylating agent that very effectively penetrates the blood-brain barrier; and rituximab. These drugs are administered intravenously over several days in the hospital. The treatment results in high response rates. Similar protocols are typically repeated every 2 to 3 weeks to induce a partial response or, ideally, a complete response as measured by MRI imaging. This initial phase of treatment is known as remission induction.

In the future, it may be possible to avoid biopsies in some patients if sufficient information can be obtained from ctDNA sequencing.

Among patients who respond to high-dose methotrexate-based chemotherapy, most clinicians would then move to phase 2 of treatment, which is often referred to as the consolidation phase. There are 2 common strategies for consolidation. The traditional approach was to use whole-brain radiotherapy, which is an effective way of prolonging response and survival as consolidation in this disease. However, whole-brain radiotherapy carries a significant risk of long-term neurocognitive dysfunction. In many cases, whole-brain radiotherapy leads to long-term, often disabling problems with memory and other higher cognitive functions. Personality changes and issues with mobility may arise. Therefore, in recent years, members of the CNS community have moved away from whole-brain radiotherapy as the preferred consolidation treatment. In the modern era, the preferred consolidation option for fit patients is high-dose chemotherapy with autologous stem cell transplant. The chemotherapy conditioning protocols all incorporate thiotepa, with other CNS-penetrant chemotherapy agents, such as carmustine or busulfan. This strategy is potentially toxic and carries more risks in the short-term for patients, and patients require several months to recover from treatment. However, the long-term outcomes are encouraging. Fit patients are typically

those who are younger than 70 years. However, we judge patients on their physiologic fitness, rather than their chronologic age. This consolidation strategy appears to be at least as effective as whole-brain radiotherapy. In some cases, it appears to be superior. Importantly, this treatment avoids the long-term neurocognitive dysfunction seen with whole-brain radiotherapy.

H&O What are the challenges in treating primary CNS lymphoma?

CF The disease and the treatment present unique challenges. Patients have neurologic and neurocognitive disability at the time they present with lymphoma. Their performance status is often impaired. They may be bed-bound or have limited mobility. Some patients may lack the capacity to consent to treatment, or to understand and retain information about treatment. From the outset, these patients present with impaired physical strength, performance status, and neurocognitive function, thus presenting challenges to the oncologist when he or she is explaining the diagnosis, discussing the treatment, obtaining consent, and delivering the treatment. Protocols that include high-dose methotrexate confer risks of early toxicities. In the early weeks of treatment, these toxicities can include infectious complications, serious infections, neutropenic sepsis, and acute nephrotoxicity. These early toxicities are more likely when the patient's performance status is impaired. Importantly, these patients often receive high doses of corticosteroids, typically dexamethasone, which are initiated immediately after the biopsy to help reduce edema and control of the tumor. Corticosteroids can also carry a high risk of infection and other complications.

Another challenge is that first-line treatment with high-dose methotrexate-containing protocols may not be successful. In approximately one-third of patients, the lymphoma will not respond to treatment or will progress afterward. Typically, an insufficient response to treatment becomes apparent in the early months. In studies of primary CNS lymphoma, Kaplan-Meier curves for progression-free survival show that the main attrition in terms of disease progression occurs during the first 6 to 12 months of treatment. This observation applies to intensive protocols, such as the MATRix multiagent chemotherapy regimen followed by autologous stem cell transplant. Among patients who achieve a remission following stem cell transplant, approximately 1 in 5 will develop early relapse or early progression, typically in the first year after treatment. It is extremely challenging to treat patients with relapsed or refractory primary CNS lymphoma, for whom survival outcomes remain poor. After second-line treatment, progression-free survival typically ranges from

4 to 6 months. This is a major area of unmet need.

Elderly patients with primary CNS lymphoma may be too frail or unfit to undergo intensive chemotherapy, such as the MATRix protocol. Elderly patients typically have a poorer performance status at the outset and are unable to tolerate intensive therapies. They have a higher rate of relapsed/refractory disease.

Another challenge in the treatment of primary CNS lymphoma is that the surrounding brain tissue—the normal brain—is particularly vulnerable to treatment toxicities. As an example, whole-brain radiotherapy can be detrimental to normal brain tissue and function. When thinking about current or future therapies for primary CNS lymphoma, it is necessary to be mindful that the normal brain tissue is vulnerable to treatment toxicities. Preservation of neurocognitive function in the context of patients who respond well to treatment should be a priority.

H&O Are there any recent insights into the pathology of primary CNS lymphoma?

CF The understanding of the pathobiology of CNS lymphoma is limited and has lagged behind that of systemic lymphoma. In CNS lymphoma, the tumor is hard to access, which has impacted the ability to perform research. We perform stereotactic biopsy for diagnosis, and the amount of tumor tissue obtained is very small, often only millimeters.

In recent years, however, we have learned more about the biology of diffuse large B-cell lymphoma of the CNS. This type of diffuse large B-cell lymphoma is most similar to the so-called “activated B-cell” subset. For example, there are certain mutations that are very common in primary CNS lymphoma, such as the MYD88 mutation (seen in up to three-quarters of patients) and mutations in parts of the B-cell receptors, such as CD79B. These mutations may be important to the development of new targeted agents. For example, it may be possible to develop agents that interfere with downstream signaling of the B-cell receptor. Inhibitors of Bruton tyrosine kinase (BTK) have been successful in systemic lymphoma. In early studies of patients with primary CNS lymphoma, treatment with BTK inhibitors has led to high response rates, albeit with limited duration of response when used as monotherapy.

Scientific techniques such as next-generation genome sequencing and RNA sequencing are enabling researchers to obtain more information from smaller pieces of tissue. I expect that our understanding of primary CNS lymphoma will rapidly improve in the coming years. Recent data show that the vast majority of patients with primary CNS lymphoma have detectable circulating tumor (ct) DNA in their cerebral spinal fluid. A proportion of patients also

have ctDNA in the plasma. These findings are a big step forward for diagnosis. In the future, it may be possible to avoid biopsies in some patients if sufficient information can be obtained from ctDNA sequencing. Analysis of ctDNA might also help clarify the disease pathobiology and assess response to treatment. ctDNA is an important area of research in primary CNS lymphoma.

H&O Is the treatment approach to CNS lymphoma evolving?

CF In recent years, significant advances in the first-line treatment of primary CNS lymphoma have occurred. Chemotherapy regimens have been intensified. CD20 monoclonal antibodies, such as rituximab, have improved clinical outcomes. There is increasing application of high-dose, thiotepa-based chemotherapy and autologous stem cell transplant as consolidation. These changes to treatment have improved rates of response, progression-free survival, and overall survival, particularly in younger, fitter patients. This intensive treatment, including autologous stem cell transplant, can typically be offered to patients ages 70 years and younger, as well as very fit patients in their early 70s. In most cases, whole-brain radiotherapy is reserved for patients with refractory or relapsed disease, in order to avoid or reduce the risks of long-term neurocognitive dysfunction associated with this treatment.

Despite these improved treatment approaches, a significant proportion of patients still develop relapsed or refractory disease. Research is focusing on these patients. Ongoing clinical trials are evaluating novel targeted agents. These trials are informed by the improved understanding of the biology of primary CNS lymphoma. As an example, studies are evaluating BTK inhibitors, which interfere with signaling of the B-cell receptor. A note of caution is that recent results from clinical trials of novel targeted agents, such as BTK inhibitors and immunomodulatory imide drugs, have shown a high rate of response, but the duration is limited. There is much excitement regarding the potential for these targeted agents, but it is necessary to be cautious about what they can deliver. Future clinical trials will evaluate combination regimens to further improve the duration of response.

H&O Are there any recent clinical trials of treatments for CNS lymphoma?

CF It is challenging to conduct trials in primary CNS lymphoma. This disease is rare. Patients often need urgent treatment. Patients sometimes lack the ability and capacity to consent to enrollment in a complex clinical trial. Nevertheless, a few clinical trials have been performed in recent years. The randomized IELSG32 trial showed the

superiority of the MATRix regimen over more conventional remission induction therapies, and also showed efficacy for high-dose thiotepa and carmustine-conditioned autologous stem cell transplant. This regimen resulted in similar survival outcomes compared with whole-brain radiotherapy, but with less neurocognitive dysfunction. The PRECIS study explored a similar question in consolidation therapy, and randomly assigned patients to treatment with thiotepa-based autologous stem cell transplant vs whole-brain radiotherapy. In this study, high-dose thiotepa-based autologous stem cell transplant appeared to be superior in terms of efficacy and survival, while causing less neurocognitive dysfunction.

H&O Do long-term survivors of primary CNS lymphoma have any particular needs?

CF This important question has not received enough attention over the years. A decade ago, there were few long-term survivors of primary CNS lymphoma. Recent data now show that treatment with intensive protocols, such as the MATRix regimen and autologous stem cell transplant, can lead to a 7-year survival rate of 70%. The main needs of such patients are twofold. First, some patients are left with neurologic deficits as a result of the original disease. The primary CNS lymphoma, although in remission, has resulted in neurologic damage. Some patients may be left with long-term memory deficits or motor problems that hamper mobility. The neurologic recovery is not always as good as we would like it to be. The rehabilitation of such patients might be improved earlier by working with physiotherapists and neuropsychologists, when needed.

Another need for survivors is to address long-term toxicities from treatment. For example, patients treated with whole-brain radiotherapy commonly have significant neurocognitive dysfunction, which can impact their ability to work. These patients may require help with personal care, as well as social support. Most patients who are treated with chemotherapy alone do not develop significant neurocognitive dysfunction, and most toxicities arise in the early months of treatment. Thankfully, many patients will have a good recovery. Increasingly, patients are able to return to work. Some are able to regain their driver's license after a couple of years.

H&O Do you have any other observations regarding the management of patients with primary CNS lymphoma?

CF I would like to emphasize the importance of early diagnosis and early initiation of treatment. Because patients present with symptoms and signs of a brain tumor,

often the diagnosis of CNS lymphoma is not immediately considered. Prognosis is better for patients with primary CNS lymphoma vs other types of brain tumors. My own experience and published data suggest that a rapid route to diagnosis quickly followed by initiation of treatment is very important in terms of survival outcomes. Neurologists and neurosurgeons should always consider the possible diagnosis of primary CNS lymphoma. Corticosteroids should not be administered before a biopsy is obtained because they can interfere with the diagnosis. Once a diagnosis of primary CNS lymphoma is confirmed, the patient should be rapidly transferred to the treating clinicians—typically hematologists, oncologists, or neuro-oncologists—for initiation of treatment. Compressing the diagnostic pathway from clinical presentation to diagnosis and treatment will help to preserve the patient's performance status, decrease neurocognitive disability, and increase the chances of long-term survival.

Disclosure

Dr Fox declares remunerated consultancy and educational activities for AbbVie, AstraZeneca, Atara Bio, Celgene/BMS, Genmab, Gilead/Kite, Incyte, Janssen, MorphoSys, Ono, Roche, and Takeda. He has received research funding from BeiGene and Adienne.

Suggested Readings

Ambady P, Doolittle ND, Fox CP. Relapsed and refractory primary CNS lymphoma: treatment approaches in routine practice. *Ann Lymphoma*. 2021;5:23.

Ferreri AJM, Cwynarski K, Pulczynski E, et al; International Extranodal Lymphoma Study Group (IELSG). Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial. *Lancet Haematol*. 2016;3(5):e217-e227.

Fox CP, Ali AS, McIlroy G, et al. A phase 1/2 study of thiotepa-based immunochemotherapy in relapsed/refractory primary CNS lymphoma: the TIER trial. *Blood Adv*. 2021;5(20):4073-4082.

Fox CP, Phillips EH, Smith J, et al; British Society for Haematology. Guidelines for the diagnosis and management of primary central nervous system diffuse large B-cell lymphoma. *Br J Haematol*. 2019;184(3):348-363.

Houillier C, Taillandier L, Dureau S, et al; Intergroupe GOELAMS-ANOCEF and the LOC Network for CNS Lymphoma. Radiotherapy or autologous stem-cell transplantation for primary CNS lymphoma in patients 60 years of age and younger: results of the intergroup ANOCEF-GOELAMS randomized phase II PRECIS study. *J Clin Oncol*. 2019;37(10):823-833.

Kaji FA, Martinez-Calle N, Bishton MJ, et al. Improved survival outcomes despite older age at diagnosis: an era-by-era analysis of patients with primary central nervous system lymphoma treated at a single referral centre in the United Kingdom. *Br J Haematol*. 2021;195(4):561-570.

Martinez-Calle N, Isbell LK, Cwynarski K, Schorb E. Advances in treatment of elderly primary central nervous system lymphoma. *Br J Haematol*. 2022;196(3):473-487.