

ADVANCES IN LLM

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

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Managing Primary Central Nervous System Lymphoma



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H&O Could you briefly describe primary central nervous system (CNS) lymphoma in immunocompetent patients?

TB Most cases are a form of extranodal non-Hodgkin lymphoma. Primary CNS lymphoma implies that the lymphoma is confined to the nervous system, meaning the brain, cerebrospinal fluid, spinal cord, and eye. The lymphoma could be present in any or all of those compartments, but the distinguishing feature is that it is confined to the CNS and not present elsewhere in the body. Primary CNS lymphomas are less common than secondary CNS lymphomas, which occur when an established systemic body lymphoma disseminates into the nervous system.

Approximately 1000 to 1500 new cases of primary CNS lymphoma are diagnosed each year in the United States, making it one of the rarest lymphomas and one of the rarest subtypes of brain tumor. More than 90% are diffuse large B-cell lymphomas (DLBCLs), and more than 90% of those are the activated B cell (ABC) subtype.

H&O How is primary CNS lymphoma diagnosed?

TB Most commonly, patients will present with an alteration of mental status or cognitive function. Typically, a computed tomography (CT) scan and a magnetic resonance imaging (MRI) scan are performed using contrast material in order to visualize the tumor. Tumors are single lesions approximately two-thirds of the time, and they tend to have a uniform pattern of contrast enhancement that is distinct from other types of malignant brain tumors.

The next step is a biopsy, typically a stereotactic needle biopsy, performed by a neurosurgeon. There is no clear evidence that resection benefits these patients, so a biopsy should be performed instead. The pathologic diagnosis is usually made by a neuropathologist or a hematopathologist based on hematoxylin and eosin staining and immunophenotyping.

Once the diagnosis is made, the extent of disease must be established. We advise that all patients have an eye examination by an ophthalmologist, because as many as 20% of patients will have concurrent involvement of the eye. We also advise patients to have a lumbar puncture if possible, because as many as 20% of patients will have concurrent involvement of the cerebrospinal fluid.

In order to establish the diagnosis of primary CNS lymphoma, a body CT or positron emission tomography (PET) scan must be performed to ensure that there are no other sites of disease. Also, we still recommend a bone marrow biopsy for these patients to establish the diagnosis of primary CNS lymphoma.

H&O What is the typical prognosis for these patients?

TB There are several prognostic factors of importance. The 2 key factors are age and performance status. Two different prognostic scales are commonly used; one was developed by the International Extranodal Lymphoma Study Group (IELSG), and the other was developed by a group at Memorial Sloan Kettering Cancer Center in collaboration with the Radiation Therapy Oncology Group

(RTOG). Prognosis varies according to these systems. During clinical trials, we usually use one of those 2 systems in order to appropriately balance prognostic factors between the patients enrolled.

Prognosis is variable, but survival usually is approximately 2 to 5 years. The outcomes of primary CNS lymphoma are better than those of other malignant brain tumors, but worse than those of systemic DLBCL.

H&O What is the typical first-line treatment?

TB We treat patients with an induction strategy followed by a consolidation strategy, as with systemic lymphoma. The induction treatment is typically a chemotherapy regimen based on methotrexate. High-dose methotrexate, typically defined as 3 g/m² or higher, generally is needed to effectively treat these patients and can be very successful.

The optimal consolidation treatment has not been established. One possible option is to use different chemotherapy regimens, some including cytarabine. Other options include using whole-brain radiation therapy or high-dose chemotherapy with autologous stem cell transplantation in eligible patients. Various ongoing trials are examining which of these may emerge as the optimal consolidation treatment for primary CNS lymphoma.

H&O How effective is this treatment?

TB Most patients have some radiographic response. Depending on the study, the majority of patients can achieve a complete remission with induction therapy. The outcomes of consolidation therapy are somewhat different across the groups, and we do not have any clear-cut evidence that one is better than another. However, these tumors generally respond to chemotherapy, and a significant proportion of these patients can achieve a durable remission with the consolidation treatments that are currently available.

H&O How well are the treatments tolerated?

TB The treatments are generally well tolerated. We do not use the same induction chemotherapy that is used for systemic non-Hodgkin lymphomas because drugs in this regimen (ie, cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]) are not ideal for tumors that occur in the CNS beyond the blood-brain barrier. Therefore, drugs are chosen based on their blood-brain barrier permeability and their anti-lymphoma properties. The induction regimens are different than in systemic disease, but they are generally well tolerated.

The consolidation treatments also have potential toxicities, including the well-known toxicities of high-dose chemotherapy treatment and stem cell transplantation.

There is also an additional risk with whole-brain radiation therapy. Neurotoxicity can occur and is especially notable for patients older than 60 years, who can develop cognitive impairment after standard doses of whole-brain radiation. It may be possible to lower the dose of whole-brain radiation in order to mitigate the risk of neurotoxicity, but this is still a risk for most patients.

H&O What is used to treat recurrence or relapse?

TB The literature is sparse regarding the treatment of refractory or relapsed primary CNS lymphoma. Most of the studies are single-institution studies, or small studies done at several institutions. There is no standard of care for refractory or relapsed primary CNS lymphoma; however, a number of strategies have been employed. A few small phase 2 trials suggest that whole-brain radiation can be effective in the relapsed or refractory setting if the patients had not received that therapy previously. A study from France suggests that stem cell transplantation also can be an effective salvage strategy. A number of chemotherapeutic approaches have been employed at the time of relapse, including combinations such as ifosfamide, carboplatin, and etoposide (ICE) or procarbazine, lomustine, and vincristine (PCV). There is intriguing, but very limited, research on novel agents in relapsed and refractory primary CNS lymphoma. An abstract presented by our colleagues at the National Cancer Institute (NCI) during the 2014 American Society of Hematology (ASH) annual meeting suggested that a combination of drugs tailored to the ABC subtype of lymphoma and including ibrutinib (Imbruvica, Pharmacyclics/Janssen Biotech) can result in responses in these patients, though the follow-up is still early. Overall, the studies have been small and limited, but there is interest in defining the enrollment criteria and performing more clinical trials for patients with refractory or relapsed disease.

H&O Are the treatment regimens the same for all patients?

TB No; each decision depends on whether we think the patient can tolerate the treatment, typically based on the patient's age and performance status. Because the median age of diagnosis is 60 years, this becomes an important consideration for a number of patients. For elderly patients, we often are unable to offer high-dose chemotherapy, stem cell transplantation, or whole-brain radiation therapy because of the treatment toxicity.

For many diseases, treatment regimens are altered for unfit patients. However, primary CNS lymphoma is one of the few brain diseases in which a patient can be quite compromised neurologically and still have a good

outcome after treatment with chemotherapy. Our entry criteria for performance status in clinical trials tend to be lower because if the patients respond, their neurological deficits often will improve.

Immunocompromised patients also can develop primary CNS lymphoma, but this disease is different from that of the immunocompetent patients I have discussed. Treatment options have not been well studied in this group of patients. Methotrexate-based treatments are commonly used in immunocompromised patients along with rituximab (Rituxan, Genentech/Biogen Idec), especially in patients who have posttransplant lymphoproliferative disease of the nervous system. Depending on the patient population, physicians might use different strategies, but they are largely the same as the regimens used in immunocompetent patients.

H&O Are any clinical trials investigating new therapies or regimens for primary CNS lymphoma?

TB It is exciting that now, unlike 10 years ago, we have a significant number of ongoing prospective clinical trials, including a number of randomized trials. Some of the promising trials are examining high-dose chemotherapy and stem cell transplantation (NCT01511562), a lower dose of whole-brain radiation (NCT01399372), and the addition of rituximab (NCT01011920). Several other randomized trials are still in the planning stages. This would not be possible in this rare tumor without significant collaboration among institutions, as well as cooperative groups. For example, we formed a group called the International Primary CNS Lymphoma Collaborative Group (IPCG). This group has brought together different cooperative groups and different institutions to develop these multi-institutional trials, which are absolutely essential for the successful accrual and execution of clinical trials in a rare disease.

H&O Could you describe the IPCG?

TB The IPCG, formed more than 10 years ago, meets each year at the ASH annual meeting. We have developed a number of tools that have been employed in clinical trials, such as a neurocognitive assessment battery. We also published response and evaluation criteria for primary CNS lymphoma patients treated in trials. For the 2015 meeting, we are developing entry criteria and response and evaluation criteria for patients who have refractory or relapsed primary CNS lymphoma, hoping to expand the number of clinical trials for that group of patients. More information is available in a brief letter published in the *Journal of Clinical Oncology* by Ferreri and colleagues.

H&O What are the challenges of treating this disease?

TB I think the rarity is a big challenge; accruing enough patients for randomized trials can be difficult. Historically, treating the disease has been a challenge because it involves multiple disciplines, such as hematology, medical oncology, and neuro-oncology. However, we have largely overcome that challenge with our IPCG collaborative group.

H&O What is the future for treatment of primary CNS lymphoma?

TB I am hopeful that we will have a higher proportion of patients cured as we develop these new treatment regimens. This is a tumor where a cure is possible, but is not likely for most patients today. We are trying to develop and optimize our chemotherapy and consolidation regimens in order to increase the proportion of patients that we are curing. Another promising area is the use of targeted approaches, such as the regimens that include novel agents and agents that target the nervous system. Overall, I am optimistic about future treatments in primary CNS lymphoma.

Suggested Reading

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