ADVANCES IN LLM

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

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Central Nervous System Prophylaxis in Non-Hodgkin Lymphoma

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H&O Please provide an overview of central nervous system (CNS) metastases in non-Hodgkin lymphoma (NHL).

MC Leptomeningeal metastasis (LM) is the most common nervous system complication of NHL, occurring in approximately 2–4% of patients with aggressive NHL. Conversely, patients with NHL represent one quarter of all patients with LM. LM is more common in patients who have primary CNS lymphoma—a subset of NHL—and in that population, lymphomatous meningitis is seen in 30–40% of all patients. Table 1 highlights some key issues concerning CNS prophylaxis in NHL.

H&O Which patients are believed to be at risk for developing CNS metastasis?

MC Previously and before highly active retroviral therapy (HART), patients with AIDS made up a large population of patients with NHL in whom CNS metastasis was relatively common (approximately 25% overall). Today, with the use of HART, the incidence of LM in AIDS patients has decreased to nearly the same incidence seen in NHL patients who are not immunocompromised. In patients with B-cell NHL, indolent disease, or follicular lymphoma and related subtypes, there is a relatively low incidence of LM. The risk of LM increases in patients with aggressive lymphomas, including patients with diffuse large B-cell lymphoma and mantle cell lymphoma. Those who are at very high risk of CNS metastasis and lymphomatous meningitis include patients with very aggressive lymphomas, such as Burkitt's lymphoma, plasma cell leukemia, and precursor B-lymphoblastic lymphoma.

Table 1. Central Nervous System Prophylaxis in Non-Hodgkin Lymphoma

Key Issues
Consensus that central nervous system (CNS) disease is relevant • 55% of diffuse large B-cell lymphoma (DLBCL) patients relapse systematically • 2–4% of DLBCL patients relapse in the CNS, half with concurrent systemic disease
Consensus regarding identification of high-risk patients at diagnosis
Recognition of "occult" CNS disease at diagnosis • Cytometry versus conventional cytology
Evidence that CNS prophylaxis is of benefit
Availability of active therapy for CNS prophylaxis

H&O What are some areas of discrepancy within the literature?

MC The literature is challenging with regard to what is meant by CNS metastasis in NHL. Series from Europe and the United States are somewhat different. European series indicate that, for at least half of all patients who have systemic lymphoma and who develop CNS metastasis, the CNS disease is in fact parenchymal and not within the leptomeningeal or cerebrospinal fluid (CSF) compartments. However, American series state almost the opposite, wherein the majority of patients who have systemic lymphoma and develop CNS metastasis develop LM and not parenchymal metastasis. I

think it is reasonable to conclude that in all patients with CNS metastasis, there is a significant fraction of patients with CNS metastasis from systemic lymphoma who develop parenchymal metastasis and not leptomeningeal or lymphomatous meningitis.

H&O What are some limitations and considerations for clinical trials that involve CNS prophylaxis?

MC Unfortunately, there have been disappointing clinical trials in NHL that have attempted to provide CNS prophylaxis at the time of systemic lymphoma diagnosis so as to decrease the risk of CNS metastasis. Risk assessment for CNS metastasis has used a model not unlike that used in childhood acute lymphoblastic leukemia (ALL). However, when children with ALL develop CNS metastasis, it is almost exclusively leukemic meningitis, so providing preventative CNS treatment (ie, intra-CSF chemotherapy at the time of ALL diagnosis) has markedly reduced the risk of leukemic meningitis. The challenge with adults and CNS metastasis from systemic lymphoma is in part related to the fact that a large fraction of patients—Europeans would say the majority—develop parenchymal metastasis. Intra-CSF–based chemotherapy, which is the commonly employed technique for CNS prevention, has limited intra-parenchymal penetration. Consequently, a number of CNS prevention studies have had disappointing outcomes with respect to having an impact on the later development of CNS metastasis by way of intra-CSF–based chemotherapy or the application of whole-brain radiation therapy.

Where there has been encouraging signs, albeit by no means definitive, is with the use of rituximab (Rituxan, Genentech/Biogen Idec) in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), as is now commonly employed for NHL. R-CHOP appears to decrease the incidence of LM, as well as improve overall outcome in patients with systemic lymphoma.

H&O Are there any risk models for identifying high-risk patients with aggressive NHL?

MC There have been several attempts to develop risk models to determine which patients with NHL would be best treated with preventative CNS-directed therapy and who are at high risk for developing LM. The most commonly quoted study is the trial from the Nordic Lymphoma Group by Hollender and associates. They found that 2 or more sites of extranodal disease, a relatively young age (<60 years), a depressed serum albumin, elevated lactate dehydrogenase, and bulky retroperitoneal lymphadenopathy were risk factors for the development of CNS metastasis. This model, which is nearly a decade old, suggests that patients with 4 or more of these risk factors appear to be at substantial increased risk for developing lymphomatous meningitis. Treatment with intra-CSF–based chemotherapy as a preventative measure to decrease the incidence of lymphomatous meningitis in this patient population was recommended. Although there are neither prognostic models established in randomized clinical trials nor an established CNS metatases preventative strategy, there remains considerable interest in clinical practice in administering CNS prophylaxis in select patients with NHL.

H&O What are the biggest remaining challenges?

MC There remains no consensus as to what constitutes effective prophylactic treatment for this CNS metastasis, or what group of NHL patients should be treated with CNS preventative therapy. When looking at CNS prophylaxis strategies, systemic rituximab appears to decrease the incidence of LM, and is now widely accepted. It has been suggested that the addition of high-dose methotrexate to systemic rituximab may decrease the incidence of CNS disease. This has not been well tested, but it is an option that warrants further investigation.

Studies of intra-CSF–based chemotherapy have shown disappointing results, such as those observed in the large SWOG 8516 study reported in the *Journal of Clinical Oncology* by Bernstein and colleagues in 2009. Similarly, whole-brain radiation therapy was disappointing in that same trial. There has been limited prospective investigation of the use of CNS-penetrating chemotherapy regimens, such as etoposide plus CHOP (CHOEP), as a potential strategy for the prevention of LM.

We know that there is a unique subset of patients who at diagnosis of NHL manifest CNS metastasis (and who may either be neurologically symptomatic or asymptomatic), and this group of patients differs from patients who develop lymphomatous meningitis or parenchymal metastasis during the course of therapy. The majority of patients who develop LM as a CNS metastatic complication of NHL typically develop it, on average, 5–6 months after diagnosis. In fact, the majority of these patients are just completing their systemic chemotherapy with R-CHOP or a similar regimen.

H&O Where should we focus our efforts for the future?

MC When using CSF analysis to evaluate patients who have neurologic symptoms that suggest CNS metastasis, such analysis should always and primarily include the use of CSF flow cytometry. It is now recognized that flow

cytometry is far more accurate and sensitive than CSF cytology and should therefore be the laboratory test of first choice in evaluating patients with this disease complication. Nonetheless, this laboratory assessment has not been universally agreed upon nor universally employed, primarily because flow cytometry laboratories remain rather few and far between. As an example, there are challenges in Europe with cooperative groups being able to utilize a central reference laboratory. Nevertheless, efforts to standardize the procedure and data interpretation will be crucial in order to permit broader clinical applications. Another strategy mentioned above would be to agree upon patients with newly diagnosed LM that are at high risk for CNS metastasis and assess these patients (using CSF flow cytometry) at the time of diagnosis. Identifying patients at risk would permit a rational application of CNS preventative therapy. Lastly, defining an effective CNS preventative therapy, such as the use of high-dose methotrexate as is employed in part B of the cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) regimen in combination with R-CHOP or CHOEP, in a prospective randomized trial would provide much needed guidance in the management of NHL patients at risk for CNS relapse.

Suggested Readings

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