ADVANCES IN LLM

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

Section Editor: Susan O'Brien, MD

Prophylaxis of Central Nervous System Relapse in Patients With Lymphoma

Avyakta Kallam, MD
Assistant Professor, Internal Medicine
Division of Oncology & Hematology
University of Nebraska Medical Center
Omaha, Nebraska

H&O How common is central nervous system relapse in lymphoma?

AK The incidence of central nervous system (CNS) relapse in lymphoma depends on the type of disease. In more-aggressive, high-grade lymphomas, such as Burkitt lymphoma and lymphoblastic lymphoma, the rate of CNS relapse can reach 30% to 50%. In diffuse large B-cell lymphoma, CNS involvement occurs in approximately 2% to 5% of patients.

H&O What are the risk factors?

AK The validated Central Nervous System–International Prognostic Index (CNS-IPI) scoring system is used to identify patients who are at high risk for CNS relapse. The scoring system takes into account 6 characteristics: age older than 60 years, elevated serum levels of lactate dehydrogenase, performance status higher than 1, stage III or IV disease, more than 1 extranodal site, and kidney or adrenal gland involvement.

A point is assigned for each factor present. Based on this scoring system, patients with 0 points or 1 point are considered at low risk for CNS relapse (estimated CNS disease <1%). Patients with 2 to 3 points are at intermediate risk (estimated CNS disease 2%-10%). Patients who score 4 to 6 points are at high risk (estimated CNS disease >10%).

H&O What are the symptoms and diagnostic criteria?

AK Patients can be asymptomatic at the time of diagnosis. When symptoms do occur, they can be subtle, and include nonspecific headaches, blurred vision, and mild confusion. Overt symptoms include cranial nerve palsies and focal neurologic deficits, such as weakness and imbalance.

Imaging studies, such as magnetic resonance imaging of the brain, can help detect the presence of CNS involvement. The diagnostic test of choice, however, is lumbar puncture with flow cytometry of the cerebral spinal fluid.

H&O Does CNS relapse impact prognosis?

AK CNS relapse confers a poor prognosis in patients with lymphoma, particularly diffuse large B-cell lymphoma. The median overall survival in a patient who develops CNS relapse is approximately 3 to 4 months.

H&O What are the components of the algorithm used at your institution?

AK The first step in our algorithm is to identify patients who are at high risk for CNS relapse (Figure). Doing so helps determine which patients need CNS prophylaxis. At the University of Nebraska Medical Center, we use a risk stratification tool that incorporates the CNS-IPI scoring system. High-risk criteria include a CNS-IPI score of 4 or higher; testicular, renal, adrenal, and epidural involvement, irrespective of the CNS-IPI score; and double-hit, triple-hit, or other high-risk lymphomas, such as those related to HIV. Patients who meet any of these criteria are

Characteristics Indicating High Risk

- CNS-IPI score ≥4 (1 point each for age >60 years, ECOG >2, stage III/IV, elevated LDH, ≥2 extranodal sites, renal/adrenal gland involvement)
- Testicular, adrenal, renal, or epidural involvement, irrespective of the CNS-IPI score
- Double-hit lymphoma/triple-hit lymphoma
- HIV-related lymphoma

Proposed Treatment Algorithm

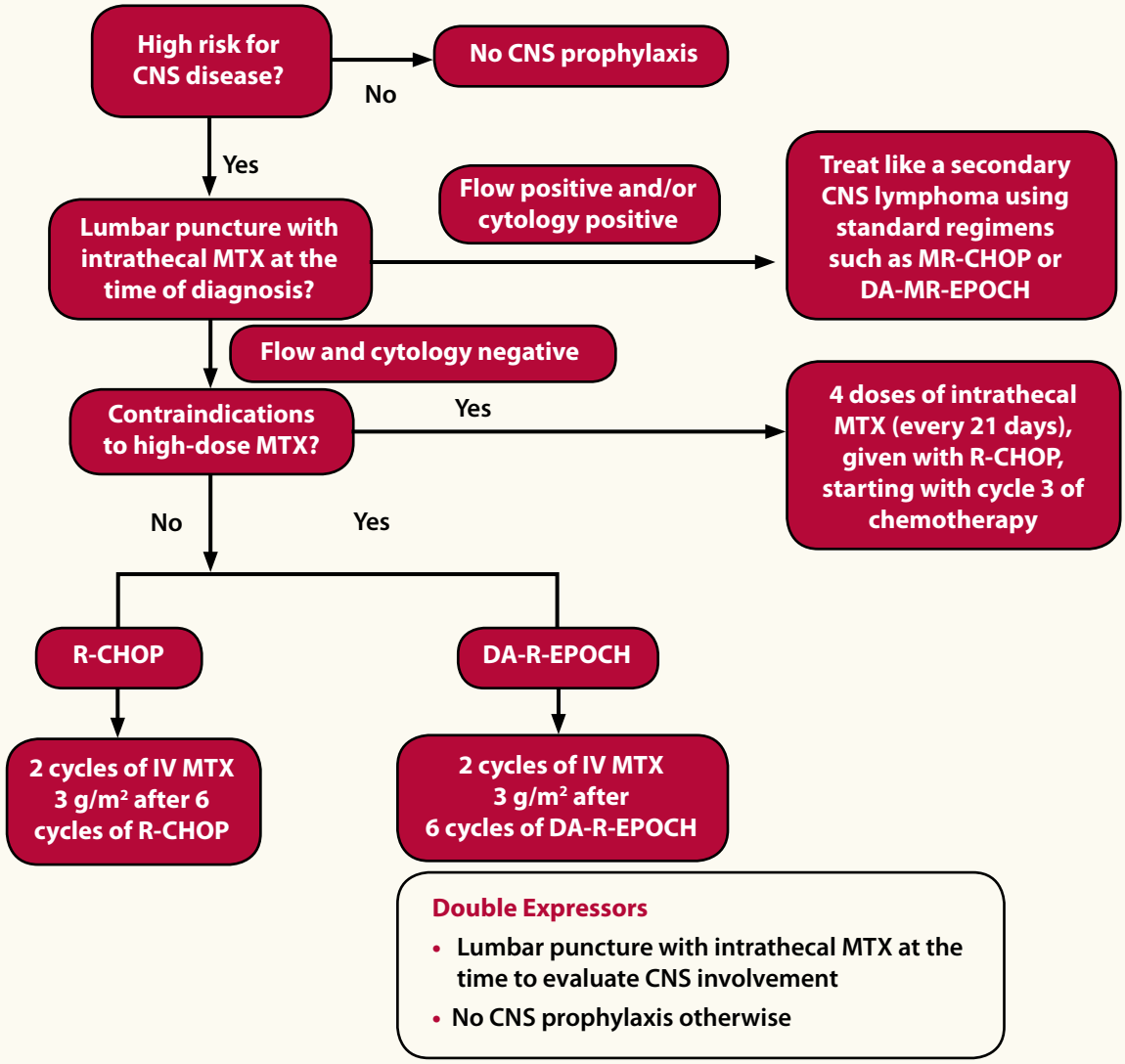

Figure. Prophylaxis of CNS relapse in patients with DLBCL. CNS, central nervous system; CNS-IPI, central nervous system–International Prognostic Index; DA-MR-EPOCH, dose-adjusted methotrexate and rituximab plus etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; DA-R-EPOCH, dose-adjusted rituximab plus etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; LDH, lactate dehydrogenase; MR-CHOP, methotrexate and rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; MTX, methotrexate; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

considered to be at high risk for CNS disease. We consider CNS prophylaxis for these patients. We perform a lumbar puncture and flow cytometry to detect CNS involvement. At the time of the lumbar puncture, we administer a dose of intrathecal methotrexate.

> For prophylaxis, it appears that high-dose methotrexate works better than intrathecal methotrexate.

Patients with CNS involvement receive treatment. If the lumbar puncture with flow cytometry is negative for CNS involvement, then we determine if the patient needs intrathecal chemotherapy or high-dose chemotherapy. High-dose methotrexate is generally our preferred regimen because it prevents CNS relapse more effectively than intrathecal chemotherapy. However, high-dose methotrexate can be difficult for patients to tolerate. When determining whether a patient is an appropriate candidate for high-dose methotrexate, we consider factors such as age, comorbid conditions, renal function, and performance status.

If we determine that the patient can tolerate high-dose methotrexate, this treatment is administered after completion of treatment for lymphoma. Patients who are not good candidates for high-dose methotrexate receive 4 doses of intrathecal methotrexate. These doses are administered concurrently with their treatment for lymphoma starting with cycle 3 of chemotherapy.

H&O Are there any promising areas of research into the prophylaxis or treatment of CNS relapse?

AK There are 2 main areas of research in this field. It is necessary to accurately identify high-risk patients. Although we do have the CNS-IPI scoring system, better tools are needed to ensure that we capture all patients who are at high risk for CNS relapse. At the same time, we do not want to administer unnecessary treatment to patients who are not at high risk, but who might be categorized as so by the CNS-IPI scoring system. We are always concerned about overtreatment or undertreatment. Studies are evaluating whether next-generation sequencing of circulating tumor DNA can identify high-risk patients.

The second area of research concerns administration of high-dose methotrexate—in particular, when to give it and the best way to do so. At our institution, we are leaning toward administering high-dose methotrexate after 6 cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or rituximab plus etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (R-EPOCH). Some studies have suggested that giving high-dose methotrexate earlier in the treatment course might be beneficial. More studies are needed to determine the timing of administration of these drugs.

H&O Do you have any other recommendations for the prophylaxis or treatment of CNS relapse?

AK For prophylaxis, it appears that high-dose methotrexate works better than intrathecal methotrexate. Intrathecal methotrexate does not penetrate the brain parenchyma as efficiently as high-dose methotrexate. Guidelines and clinical practice are moving toward the use of high-dose methotrexate vs other regimens. My main recommendation is to give high-dose methotrexate when possible and feasible.

Another area of interest concerns the subpopulation of patients with diffuse large B-cell lymphoma who are double expressers. In these patients, immunohistochemical staining shows expression of BCL2, MYC, or BCL6. Some initial studies suggest that these patients might be at increased risk for CNS relapse. More data and follow-up are needed to determine whether these patients would benefit from CNS prophylaxis.

Disclosure

Dr Kallam has no real or apparent conflicts of interest to report.

Suggested Readings

Cabannes-Hamy A, Peyrade F, Jardin F, et al; LYSA; Lymphoma Study Association. Central nervous system relapse in patients over 80 years with diffuse large B-cell lymphoma: an analysis of two LYSA studies. *Cancer Med*. 2018;7(3):539-548.

Gleeson M, Counsell N, Cunningham D, et al. Central nervous system relapse of diffuse large B-cell lymphoma in the rituximab era: results of the UK NCRI R-CHOP-14 versus 21 trial. *Ann Oncol*. 2017;28(10):2511-2516.

Hall KH, Panjic EH, Valla K, Flowers CR, Cohen JB. How to decide which DLBCL patients should receive CNS prophylaxis. *Oncology (Williston Park)*. 2018;32(6):303-309.

Schmitz N, Zeynalova S, Nickelsen M, et al. CNS International Prognostic Index: a risk model for CNS relapse in patients with diffuse large B-cell lymphoma treated with R-CHOP. *J Clin Oncol*. 2016;34(26):3150-3156.

Thanarajasingam G, Maurer MJ, Farooq U, et al. Event-free survival at 24 months captures central nervous system relapse of systemic diffuse large B-cell lymphoma in the immunochemotherapy era. *Br J Haematol*. 2018;183(1):149-152.