Update on the Management of Primary CNS Lymphoma

By Brian P. O’Neill, MD and Thomas E. Witzig, MD

Primary central nervous system (CNS) lymphoma is a non-Hodgkin’s lymphoma restricted to the nervous system. The incidence of this lymphoma is rising in the immunocompetent population but may be decreasing in

In their well-written update on the management of primary central nervous system (CNS) lymphoma, Drs. Nasir and DeAngelis of Memorial Sloan-Kettering Cancer Center (MSKCC) combine extensive personal experience with a timely, critical review of the pertinent literature to provide readers with a well-balanced view of the current management of the patient with primary CNS lymphoma. The initial diagnosis and evaluation of a patient with primary CNS lymphoma is truly a multidisciplinary effort involving the neurosurgeon, hematopathologist, neurologist, ophthalmologist, hematologist, and radiation therapist. This team must act quickly and smoothly to initiate therapy as soon as possible, before the onset of additional neurologic disability.

Drs. Nasir and DeAngelis provide helpful, practical suggestions for the diagnosis and staging of patients with this disease; these suggestions are succinctly summarized in the tables that accompany the article. The authors appropriately offer a cautionary note regarding corticosteroid use prior to biopsy that will be useful to clinicians outside of major centers when they encounter this uncommon tumor.

In the section on treatment, the authors review the major studies of radiation therapy alone, combined chemotherapy and radiotherapy, and chemotherapy alone. They conclude that the conventional chemotherapy programs used for systemic large-cell non-Hodgkin’s lymphoma (NHL) eg, cyclophosphamide, doxorubicin HCl, Oncovin, and prednisone (CHOP) are not effective for primary CNS lymphoma. The authors suggest that a chemotherapy program that includes high-dose methotrexate and/or cytarabine produces optimal survival.

Avoiding Neurocognitive Defects
The authors are appropriately circumspect regarding the neurocognitive impact of previous and current therapies. The ability of a regimen to achieve a complete tumor response and long-term survival must be balanced against the toxicity of the regimen, especially its long-term neurocognitive defects. Careful analyses of the experiences of the Oregon group[1] as well as our own[2] suggest that, given sufficient follow-up, these regimens may be shifting the time to disease progression, and perhaps altering the patterns of progression, without increasing the number of cured patients, or certainly the number of cured patients with preserved functionality.

Treating Patients With Non-AIDS Primary CNS Lymphoma
Is the experience with primary CNS lymphoma at MSKCC typical of the patient with non-acquired immunodeficiency syndrome (AIDS) primary CNS lymphoma who is seen in the community? There are some suggestions that it may not be, as indicated by the following two examples.

First, the incidence of cerebrospinal fluid (CSF) involvement among MSKCC patients has always been greater than that recorded at other institutions, including our own. The paper by Balmaceda and colleagues[3] cited by Drs. Nasir and DeAngelis provides convincing data that confirm the MSKCC experience. However, is the difference between these data and those from other institutions due to better cytologic preparation and analysis, a longer time from symptom onset to diagnosis and CSF sampling, or a biologically different group of patients?

Certainly, these latter two possibilities might also convey a statistical advantage to any administered therapy, independent of its antineoplastic effect.[4] In fact, the authors quote reviews by Corry et al[5] and Blay et al[6] suggesting that CSF involvement may impart a survival advantage.

Second, the survival and time to progression in the MSKCC experience are similar to those in other single-institution studies,[7] but differ from the experiences of our group and others.

The Radiation Therapy Oncology Group (RTOG) is testing the MSKCC regimen in a phase II setting. These results should provide data for comparison with the North American and European studies that the authors cite in their article.
Primary CNS Lymphoma in AIDS Patients
The authors also provide a useful section on primary CNS lymphoma patients infected with the AIDS virus. Their experience at an institution with a high number of AIDS patients is useful for those of us who practice in areas with low numbers of such patients.

What Is the Preferred Treatment for Newly Diagnosed Primary CNS Lymphoma?
Although the authors provide a useful summary of each treatment modality, they do not provide their recommendations about the current preferred treatment approach for a patient with newly diagnosed primary CNS lymphoma. Should readers administer the MSKCC regimen to newly diagnosed non-AIDS primary CNS lymphoma patients?

According to the authors: "To date, there is no reason to believe that the biology of primary CNS lymphoma differs markedly from comparable systemic lymphoma. Therefore, a combination chemotherapy approach is most likely to succeed by using non-cross-resistant agents to avoid drug resistance. However, the authors also provide convincing data that single-agent, high-dose, intravenous methotrexate with expectant follow-up, without whole-brain radiation therapy (as advocated by Cher et al[8]) may be appropriate, even preferable, management. The authors do not mention the role of high-dose therapy with stem-cell rescue in these patients, although there are European reports of its use."[9]

Primary CNS Lymphoma in Older Individuals
What about newly diagnosed non-AIDS primary CNS lymphoma in older individuals? The authors refer to the work of Freilich et al, which describes the use of chemotherapy alone to manage primary CNS lymphoma in the older adult patient.[10] However, the median survival of biopsy-proven patients in that series is no different than the survival observed with conventional management. The authors clearly state that lesions that have features suggestive of primary CNS lymphoma should be confirmed in all patients before making a treatment recommendation. Yet, the authors do not clearly state their treatment recommendation for such individuals. Our current North Central Cancer Treatment Group study (NCCTG 96 73 51) proposes to treat eligible, older patients with whole-brain radiation therapy, followed by monthly methylprednisolone maintenance.

Conclusions
So where do we stand with regard to the treatment of primary CNS lymphoma? The answer is: in roughly the same place. The dilemma of this potentially curable tumor is that the patients most in need of curative treatment are those who are most vulnerable to the toxicity of such treatments because of age and attendant comorbidity. Safe, effective therapies that cure the lymphoma without unacceptable toxicity must be found.

References:
7. Ferrari AJ, Reni M, Villa F: Primary central nervous system lymphoma in immunocompetent


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