Commentary (Hochberg/Cher): Current Management of Primary Central Nervous System Lymphoma

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Dr. DeAngelis provides a succinct analysis of primary central nervous system lymphoma and its management. This malignancy remains a puzzle because of its unusual behavior, being widely disseminated within the CNS, and yet rarely involving the systemic compartment. Patients who develop primary central nervous system lymphoma need to be divided into two groups: Those who are immunocompetent and those who are immunocompromised, including patients with HIV infection and transplantation recipients.

It is clear that the majority of primary central nervous system lymphoma occurring in the latter group is associated with persistent Epstein-Barr virus infection within the lymphoma cell population [1]. In those whose immune system compromise is due to treatment, modification of the regimen to reduce the degree of immunosuppression may allow the immune system to function sufficiently to regulate the growth of the clonal lymphocytes driven by Epstein-Barr virus infection. The origin of the lymphoma cells and the reasons for their restriction to the CNS remain unclear. Pathologically, primary central nervous system lymphoma appears to arise from blood vessels and spread into the brain [2,3], thus suggesting that the cells arise systemically but can only develop into tumors within the central nervous system. It is possible that as yet unidentified B-cell lymphocyte homing markers are key to the selective localization of the malignant clone. Some preliminary data support this view [4].

Diagnosis in immunocompetent patients may be difficult. The use of corticosteroids in the interval between diagnosis of an intracerebral lesion and biopsy reduces the yield of a diagnostic result. Glucocorticoids are lymphocytotoxic, and may lead to a rapid melting of the tumor and the disappearance of malignant lymphoma cells. Therefore, when primary central nervous system lymphoma is suspected on clinical and radiological grounds (eg, periventricular lesion(s), which are hyperdense on noncontrast T1-weighted imaging and diffusely enhance) an expedient biopsy is the prudent option rather than the automatic response of administering high-dose corticosteroids. Immunoperoxidase studies (and, when appropriate, flow cytometry) of cerebral biopsies, CSF, and vitreal fluid may also increase the diagnostic yield. The identification of clonal B-cells (population of either kappa or lambda positive cells etc.) can be helpful. Unfortunately, the presence of reactive cells (often T-cells) can mask the malignant clone. PCR techniques to identify clonal lymphocyte populations by immunoglobulin gene rearrangements may prove more sensitive, but are not yet routine nor widely available. They may be helpful in patients who have chronic uveitis with suspected lymphomatous involvement, but whose diagnosis has not been pathologically confirmed.

The Importance of Chemotherapy

Chemotherapy has provided a significant improvement in the treatment of this disease. As detailed by Dr. DeAngelis, the median survival in patients who receive radiation therapy alone is equivalent to that of patients with glioblastoma multiforme. With the use of chemotherapy that can "negotiate" the blood brain barrier, the median survival is 3 to 4 times greater. However, results using chemotherapy that does not cross the blood brain barrier are uniformly dismal. There remains no consensus as to the best regimen for use in this disease, and at present many centers have different protocols. In non-AIDS patients, our group has used methotrexate as the foundation of therapy for this tumor. We recently published our updated experience with
methotrexate as preirradiation chemotherapy (3.5 g/m²). A complete or partial response was achieved in 88% of patients prior to radiation therapy, and median duration of response was 32 months [5]. The addition of CHOD (cyclophosphamide, doxorubicin, Oncovin, dexamethasone) to methotrexate as preirradiation therapy did not improve the response rate nor the median duration of response, and was associated with significant increases in toxicity [6].

Based on the response to methotrexate-based protocols, we now use high-dose methotrexate (8 g/m² induction; 3.5 g/m² maintenance) alone without radiation therapy. High-dose systemic methotrexate achieves therapeutic levels in both the cerebrospinal fluid and brain parenchyma without the need for intrathecal therapy. The toxicity of methotrexate is ameliorated by leucovorin rescue. Our initial experience has been promising [7]. In patients treated with methotrexate-based chemotherapy, an 80% complete response was achieved, with a median duration of response of 13+ months.

HIV Patients Present a Challenge

HIV patients represent a different challenge, and whole brain radiation therapy in patients with pathologically proven primary central nervous system lymphoma remains the standard. Whether a subgroup of such patients will benefit from chemotherapy remains uncertain. Any benefit from chemotherapy needs to be weighed against the exaggerated toxicity seen in these patients, as well as the fact that primary central nervous system lymphoma often occurs late in the course of AIDS, together with multiple other processes, reducing the therapeutic window.

In summary, it is likely that primary central nervous system lymphoma will become an increasing problem. It remains fascinating because of its protean manifestations, unusual behavior, and because of its strange predilection for the CNS. Important advances in therapy have been made, but we have a long way to go. These patients can be rewarding to treat, however, because of their responsiveness to chemotherapy, a relatively unusual feature of neuro-oncologic practice.

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