Primary CNS lymphoma (PCNSL) is an infiltrative, primarily large B-cell lymphoma confined to the CNS or eyes at the time of diagnosis, with an incidence of 5 per million. Because of its rarity, phase III trials to determine the best treatment regimen have been difficult to perform and no single standard of care exists. Current guidelines suggest initial high-dose methotrexate-based (HDMTX) chemotherapy is the most active regimen. In general, 3 first-line chemotherapy treatment approaches are currently used by most PCNSL investigators: (1) HDMTX-based chemotherapy with or without subsequent whole-brain radiotherapy (WBRT); (2) induction HDMTX-based chemotherapy followed by high-dose chemotherapy consolidation with or without autologous stem cell transplantation; and (3) standard dose HDMTX-based chemotherapy with mechanisms to increase delivery to the CNS such as blood–brain barrier disruption (BBBD).²

As the largest and only published phase III trial to date in PCNSL, the article by Korfel et al.³ in this issue of Neurology® represents a landmark effort. This trial, originally designed in 1999, randomized 551 patients with non-AIDS PCNSL to HDMTX-based chemotherapy ± WBRT; patients randomized to no WBRT who had residual tumor post-HDMTX received high-dose cytarabine.⁴ The results, initially reported in 2010 with shorter follow-up, provide Class II evidence that adding WBRT does not increase survival compared to HDMTX alone.⁴

The execution of the clinical trial was not ideal. As the authors acknowledge, initial single agent HDMTX was recognized as suboptimal, and hence ifosfamide was added to the chemotherapy regimen midway through the trial. There was a strikingly high mortality rate (13%) with HDMTX-based chemotherapy, which exceeds currently published data. While this mortality rate may be partly attributable to a high percentage of patients over age 70 or poor performance status, it substantially exceeds what is currently seen in centers with HDMTX experience. Although designed as a noninferiority trial, the study failed to meet the prespecified criteria for noninferiority and had reduced power due to withholding early WBRT, protocol violations, and the refusal of some complete responders to chemotherapy to proceed with WBRT. Finally, the study lacked the neurocognitive and quality of life assessments necessary to exclude an important survival benefit or harm from WBRT. Increased survival in combination with preservation of cognitive abilities is a critical benchmark for determining the optimum therapy for this disease.⁵ Delayed WBRT-related neurotoxicity has emerged as an important disabling complication of combined HDMTX plus WBRT especially in patients older than 60 years. Phase II studies have demonstrated that there are effective HDMTX-based chemotherapy regimens that may be combined with substantially reduced-dose WBRT, or delivered through osmotic BBBD without incorporation of WBRT, with much less associated neurotoxicity.⁵ ⁶

Despite high initial response rates following first-line HDMTX-based regimens, at least 50% of patients relapse within 2 years of diagnosis. Korfel et al. make the important suggestion that alternative non-neurotoxic strategies should be explored for complete response (CR) consolidation to maintain disease control and thus extend remission. One potential relatively nontoxic means to accomplish this may be through the use of immunotherapy targeting malignant B cells. Many investigators have added the anti-CD20 monoclonal antibody (mAb) rituximab to chemotherapy for the treatment of CD20⁺ B-cell PCNSL, and nonrandomized studies indicate that very high initial response rates are attainable, although the optimal timing and treatment regimen remain to be determined. For example, the addition of rituximab to first-line BBBD chemotherapy provides a CR rate of 74% (n = 24 patients) and median survival of 61 months. A similar retrospective single-institution study demonstrated CR rates of 73% (n = 81) with addition of rituximab to IV HDMTX, although median overall survival has not yet been reached in this cohort at publication.⁷

Maintenance immunotherapy may provide an alternative strategy for disease control in PCNSL.
Rituximab has been investigated as maintenance in follicular and mantle cell lymphoma, in both the first-line and relapsed settings, using a variety of induction regimens. Several studies have demonstrated improvement in progression-free survival in patients receiving maintenance compared to those observed, unlike patients with diffuse large B-cell non-Hodgkin lymphoma. In PCNSL, Ney and Abrey\(^8\) hypothesized that maintenance immunotherapy may be effective in patients at high risk for relapse after achieving CR. Although their series was small, maintenance was defined as the delivery of regularly scheduled rituximab following CR after treatment for CNS lymphoma. At the time of their report, most patients were alive with a median follow-up of 33.9 months (range 24.7–58.9+ months).

Recurrence in brain may be due to seeding from distant subclinical systemic malignant lymphocytes. Support for this mechanism includes different sites of brain recurrence compared to the original mass, suggesting that recurrence may not be merely a regrowth of residual disease, although occult systemic disease may not be detectable by routine staging procedures.\(^9\) In this case, systemic exposure to an anti-CD20 mAb may be more protective than CNS exposure. A second possible mechanism of disease recurrence in brain is that microscopic PCNSL cells remain dormant behind a minimally leaky blood–brain barrier in the sanctuary of the CNS. If so, long-term leakage and accumulation of mAb in the brain may be the mechanism to maintain CR, as shown in preclinical studies.\(^{10}\)

Obinutuzumab (GA101) is a second-generation anti-CD20 mAb that appears to have improved targeting and efficacy compared to rituximab. We are initiating a randomized clinical trial of maintenance obinutuzumab in PCNSL, compared with observation. The hypothesis is that maintenance obinutuzumab will improve the duration of CR and overall survival in patients with PCNSL who achieve CR with first-line HD MTX-based chemotherapy, without substantial toxicity or decline in cognitive function. Favorable results may not only provide a new therapeutic option, but may also shed some light into the mechanism of disease recurrence and etiology of PCNSL.

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**DISCLOSURE**

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**REFERENCES**