Primary CNS lymphoma (PCNSL) is an uncommon type of extranodal non-Hodgkin lymphoma confined to the brain, leptomeninges, or eyes. Although more than 90% of PCNSL tumors are classified histologically as diffuse large B-cell lymphoma, the survival of patients with PCNSL remains inferior to that observed in patients with diffuse large B-cell lymphoma occurring in other body sites. This may result from the unique biologic properties of PCNSL, the role of the blood brain barrier in limiting drug delivery to the tumor, and/or the lack of effective therapeutics. Consensus is lacking regarding the optimal induction and consolidative treatments for PCNSL. Although methotrexate is widely accepted as the foundation of induction chemotherapy for PCNSL, the optimal dose and schedule for this drug have not been defined. At the dose of 8 g/m², cytotoxic concentrations of methotrexate are achieved in CSF, obviating the need for intrathecal chemotherapy.1

Whole-brain radiation therapy (WBRT), although effective in achieving complete responses in the brain in most patients with PCNSL, might not improve survival over chemotherapy alone, does not adequately treat the entire craniospinal axis, and is associated with delayed neurotoxicity in most patients.2,4 The latter complication of WBRT may adversely impact cognition, functional status, and quality of life in patients otherwise successfully treated for PCNSL. Although reduced doses of WBRT might be associated with a lower incidence and severity of neurotoxicity in humans, this remains unproven and experimental studies have demonstrated that even single fractions of WBRT result in ablation of hippocampal neurogenesis and consequent neurotoxicity.4,5 The latter observation raises the question as to whether any dose of WBRT is safe, an important issue for a disease with survival measured in years. Despite these limitations, WBRT has been viewed historically as an integral component of either induction or consolidative therapy for PCNSL.

This view has been challenged in recent years given that studies of chemotherapy alone suggest a diminished risk of neurotoxicity and promising efficacy in patients with PCNSL. In a long-term follow-up study of patients with PCNSL treated with chemotherapy alone and monitored with serial neuropsychological tests, cognitive function and quality of life were maintained.6 In the article that accompanies this editorial, Rubenstein et al2 report results from a cooperative group, multicenter, phase II clinical trial (CALGB 50202) of chemotherapy without WBRT in 44 patients with newly diagnosed PCNSL. Consensus guidelines were used to establish extent of disease and for response assessment and there were no eligibility restrictions with respect to age or sites of disease involvement (brain, leptomeninges, eyes).8 A sound scientific rationale was employed for the selection of the drugs in the induction and consolidation regimens employed in CALGB 50202. Each of the drugs selected for the methotrexate, temozolomide, and rituximab (MT-R) induction regimen had demonstrated safety and efficacy as a single agent in prior clinical studies in patients with either newly diagnosed or relapsed PCNSL.9-11 Etoposide and cytarabine (EA) had previously been combined as effective salvage therapy in a study of patients with relapsed PCNSL.12

Rubenstein et al7 demonstrated that this induction (MT-R) and consolidation (EA) regimen is feasible and safe in the multicenter setting with expected, reversible myelotoxicity associated primarily with consolidative EA therapy. There was one treatment-related death resulting from sepsis in a patient managed as an outpatient during EA consolidation prompting the authors to wisely advise that both the induction and consolidative components of this chemotherapy regimen should be administered on an inpatient basis with appropriate supportive care. Two thirds (66%) of the patients with PCNSL enrolled onto this trial achieved a complete response (CR) to induction MT-R, the primary end point of the study. This CR proportion is comparable or superior to that reported in other prospective, multicenter trials of induction chemotherapy for PCNSL.13,14 However, additional optimization of induction chemotherapy for PCNSL is a high priority, given that one-third of patients did not achieve CR, and these patients were excluded from proceeding to consolidative EA therapy. Moreover, it is worth considering whether patients who achieved a partial response after induction chemotherapy might have benefitted from EA. In a trial of myeloablative consolidative chemotherapy in patients with PCNSL, it was observed that patients who achieved a partial response after induction chemotherapy had similar, favorable outcomes after consolidative high-dose chemotherapy and autologous stem-cell transplantation compared with those who achieved a CR after induction chemotherapy.15 The 44 patients enrolled onto CALGB 50202 had a median progression-free survival of 4 years, and 59% of these patients were progression-free at 2 years. These are impressive achievements, comparable with or superior to results obtained in other prospective, multicenter trials with regimens that included WBRT as consolidative therapy.13,14 Median overall survival (OS) for the CALGB 50202 study had not been reached at the time of publication with a 4-year OS probability estimated at 65%. On the basis of these outcomes, it appears that omission of WBRT from the
initial treatment plan for PCNSL did not compromise progression-free survival or OS in the patients enrolled onto this clinical trial. The authors’ report that there were no cases of severe neurotoxicity in the patients enrolled onto CALGB 50202. However, there was no prospective, serial assessment of neurocognitive function in this study, a limitation common to many other PCNSL clinical trials. Although other studies strongly suggest that treatment regimens for PCNSL that include WBRT are associated with a higher incidence of symptomatic neurotoxicity than regimens that do not include WBRT, it is equally important to prospectively assess whether and to what extent chemotherapy might adversely impact neurocognitive function in this population. A battery and schedule for such assessment has been developed and is incorporated into several ongoing, prospective, multicenter clinical trials for patients with PCNSL.16 An important observation of CALGB 50202 by the authors was that a delay in starting induction chemotherapy had a detrimental impact on tumor response and outcomes in patients enrolled onto this study. More than half of the patients with a more than 30-day delay in treatment initiation died from their lymphoma compared with less than 30% of patients who started treatment within 30 days. This observation highlights the importance of early diagnosis and prompt initiation of chemotherapy in patients diagnosed with PCNSL.

The diagnosis of PCNSL is typically achieved after stereotactic brain biopsy, with sparse tumor tissue remaining for biologic studies. This has compromised our understanding of this unique subtype of non-Hodgkin lymphoma. There are no established imaging or biomarkers that can identify treatment-resistant versus sensitive PCNSL subpopulations at the time of diagnosis. It is encouraging that 26 (59%) of 44 patients enrolled onto the multicenter CALGB 50202 trial had sufficient tissue collected and provided for centralized immunohistochemical analysis. On the basis of preliminary data generated from single institutions or retrospective studies, the authors examined the prognostic utility of two biomarkers, BCL6 and MYC, in a correlative biospecimen study as part of CALGB 50202. In these studies, MYC expression did not correlate with outcome. However, BCL6 expression in more than 60% of tumor cell nuclei was associated with inferior progression-free survival, event-free survival, and OS. Although this suggests that BCL6 expression might be a marker of a more resistant subtype of PCNSL, these results should be interpreted with caution as they are based on tumor specimens from 26 patients, and previous reports of BCL6 expression in PCNSL have yielded conflicting results with respect to outcomes.17,18 Nevertheless, the authors demonstrated the feasibility and potential importance of incorporating biospecimen studies into prospective clinical trials in PCNSL.

The results of CALGB 50202 reported by Rubenstein et al7 demonstrate the feasibility, safety, and efficacy of the MT-R induction and EA consolidation regimens in patients with newly diagnosed PCNSL. Omission of consolidative WBRT did not compromise PFS and eliminated the risk of radiation-induced neurotoxicity. Although additional study is required before these results can be generalized to the entire PCNSL population, especially elderly patients, the authors are to be commended for their effort, which has raised new questions and set the stage for subsequent clinical trials to build on the success of CALGB 50202. Given that less than one fifth of the grade 4 cytopenias observed in this study occurred after MT-R an important question is whether this induction regimen can be intensified to increase the proportion of patients experiencing CR before consolidation. Another question is whether the results achieved with EA consolidation could be improved by substitution of high-dose chemotherapy followed by autologous stem-cell transplantation, a consolidative strategy that has achieved encouraging results in a prospective, multicenter phase II study.15 The latter question will be assessed in CALGB 51101 (NCT01511562), an ongoing, intergroup, randomized trial in which all patients with PCNSL are treated with induction MT-R followed by consolidative EA versus high-dose chemotherapy and autologous stem-cell transplantation. Following in the footsteps of Rubenstein et al,7 CALGB 51101 includes correlative biospecimen, imaging, neurocognitive, and quality of life studies in an effort to better understand patient outcomes, including the short-term and long-term consequences of these treatments on the growing proportion of long-term survivors with PCNSL.

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