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## **EDITORIAL**

### **Primary Central Nervous System Lymphoma: A Curable Brain Tumor**

**O**NCE A rare tumor and the subject of individual case reports, primary CNS lymphoma (PCNSL) now afflicts approximately 1,000 people in the United States each year. Although less common than gliomas, PCNSL has captured the attention of neuro-oncologists for several reasons. First, it arises from a cell type not normally present in CNS. Second, it can completely regress with either corticosteroids or cranial irradiation, only to recur, and like glioblastoma multiforme, it kills most patients within a year or two. Third, the blood-brain barrier (BBB) is critically important because much of the tumor resides behind an intact BBB and often cannot be visualized radiographically.<sup>1</sup> Fourth, unlike malignant gliomas, appropriate treatment of PCNSL can result in prolonged survival and even cure. Such good results are achieved only when chemotherapy is incorporated into treatment.<sup>2-5</sup> The dramatic benefits of chemotherapy have been observed in a series of phase II trials that demonstrated the superiority of high-dose methotrexate as part of the initial therapeutic regimen, compared with radiotherapy alone. These phase II experiences have never been validated in a randomized prospective phase III trial, and at this point, such a trial probably would not and should not be conducted, primarily because of the small number of patients. Investigators in the United Kingdom attempted such a randomized phase III study, but terminated it after 7 years because of insufficient enrollment.<sup>6</sup> In addition, most physicians who treat PCNSL would be unwilling to randomize patients to a study with cranial irradiation alone as the control arm, and a chemotherapy-based treatment as the “experimental” arm. Consequently, chemotherapy has become standard practice; while this is based on imperfect evidence, the superiority of chemotherapy-based regimens to radiation alone nonetheless seems solid and consistent among the many studies reported to date.

In this issue of the *Journal of Clinical Oncology*, two additional studies provide validation of the value of chemotherapy for PCNSL, with both reporting improved outcomes over historical treatment with radiotherapy alone. In this issue of the *Journal of Clinical Oncology*, Poortmans et al<sup>7</sup> report on a European Organization for Research and Treatment of Cancer study incorporating high-dose

methotrexate, teniposide, carmustine, and intrathecal therapy preceding 40 Gy of whole-brain radiotherapy. The overall response rate at the end of treatment was 81%, and median survival was 46 months. However, these excellent results were associated with significant acute chemotherapy-related toxicity and a 10% toxic death rate. In the European Organization for Research and Treatment of Cancer study, this high toxicity rate was observed even though patients older than 65 years were excluded from the protocol. Since the median age of PCNSL patients is approximately 60 years, almost half of all potential PCNSL patients were therefore excluded from this study. Most trials reported to date have noted the critical effect of age on outcome; regardless of treatment older patients do significantly worse than younger patients. Consequently, the excellent results reported by Poortmans et al cannot be generalized to these older PCNSL patients. Furthermore, one would also anticipate the toxicity to be substantially higher in older patients treated with this approach.

Pels et al<sup>8</sup> report on the expanded experience of a German group who used chemotherapy as sole treatment for PCNSL. Using a complicated three-cycle regimen that included high-dose methotrexate and high-dose cytarabine, vincristine, ifosfamide, cyclophosphamide, vindesine, dexamethasone, and triple intrathecal therapy, the authors achieved a 71% response rate and a median overall survival of 50 months. They enrolled all patients into the study regardless of age or performance status, and confirmed previous observations that patients older than 60 years did substantially worse, with a 5-year survival rate of 19%, compared with 75% for younger patients. Severe myelosuppression was significant, and 9% died from treatment-related toxicity. Given the degree of myelosuppression and the biology of PCNSL, one should question the incorporation of cyclophosphamide and ifosfamide into this treatment program since neither penetrates the BBB well and cyclophosphamide in the cyclophosphamide, doxorubicin, vincristine, and prednisone regimen is ineffective for PCNSL.<sup>9,10</sup> Consequently, these agents may have contributed little more than toxicity to this regimen.

These studies again confirm the importance of chemotherapy for PCNSL, and the question is not whether chemotherapy should be administered, but what is the best regimen? High-dose methotrexate is the single most active agent in PCNSL, but what is the optimal dose and can it be given as a single agent or is combination therapy necessary? A recent report on a National Cancer Institute–sponsored New Approaches to Brain Tumor Therapy consortium study of single-agent high-dose methotrexate as sole treatment demonstrated a 74% response rate, but patients relapsed a median of 12.8 months from diagnosis, which means that at least half of patients relapsed while they were still receiving induction or maintenance therapy.<sup>5</sup> These results were interpreted as positive, but a similarly designed study reported by Herrlinger et al was terminated early because of a low response rate (29.7% complete response) and high incidence of progressive disease during treatment (37.8%); they reported a comparable median relapse-free survival of 13.7 months.<sup>11</sup> These two studies combined would suggest that single-agent high-dose methotrexate even when given at 8 g/M<sup>2</sup> is insufficient treatment for PCNSL. This is not surprising given the ease of inducing methotrexate resistance in leukemia cells and the role of combination therapy in eradicating lymphoma in any other organ site.<sup>12</sup> In addition, single-agent high-dose methotrexate induces different genomic cellular responses than methotrexate-based combination therapy, which may provide insight into drug response.<sup>13</sup> If multiple agents are to be used, which other drugs have clear efficacy against PCNSL? Alkylating agents are a critical component of every regimen designed to treat comparable systemic non-Hodgkin's lymphomas, but most are unable to penetrate the intact BBB. Agents such as procarbazine, thiopeta, temozolomide, and the nitrosoureas are likely to be the most successful and have demonstrated some efficacy.<sup>3,14-16</sup> However, the optimal combination is yet to be defined. Lastly, initial trials of high-dose chemotherapy with autologous stem cell rescue have produced some potentially exciting results.<sup>17,18</sup> This approach may prove to be the best use of chemotherapy in the treatment of PCNSL and allow radiation to be deferred, but this requires further study.

Radiotherapy is commonly eliminated or deferred in the treatment of older patients because the risk of permanent neurotoxicity is unacceptably high; however, it is an active

treatment against PCNSL, and its role, particularly in younger patients, is unclear. A single report suggests that a reduction from 40 to 30 Gy of whole-brain radiotherapy combined with a cyclophosphamide, doxorubicin, vincristine, and prednisone–based chemotherapy regimen compromises disease control.<sup>19</sup> However, patients who achieve a complete response after methotrexate-based chemotherapy may benefit from a dose of radiotherapy that could contribute to disease control without incurring significant neurocognitive damage, particularly in younger patients.<sup>4</sup>

No study, to date, has incorporated investigation of the biology of PCNSL into the treatment protocol. Efforts in this area have largely been thwarted by the fact that because most patients are diagnosed by stereotactic biopsy, little tissue is obtained and frequently not frozen as part of a tumor bank. Nevertheless, efforts in this area may ultimately facilitate our choice of treatment for an individual patient and enable us to understand how a lymphoma arises within an organ that has no lymphatic system or lymph nodes. Reported clinical trials, including the two in this issue of the *Journal of Clinical Oncology*, demonstrate one of the most exciting aspects of effective treatment for PCNSL: these patients can recover from a malignant brain tumor. The brain is an unforgiving organ, and there has been a longstanding concern that even if effective therapy were to become available for malignant primary brain tumors, eradication of the tumor may not necessarily translate into improved neurologic outcome for patients. However, PCNSL serves as a shining example that this is not the case. If treatment is effective and does not damage the brain, patients make a remarkable recovery and can lead highly productive and useful lives. This example has implications that extend far beyond the specific situation of PCNSL, and reverberates throughout the field of neuro-oncology. Yes, brain tumor patients can be restored, and it is incumbent on us to identify the treatments that will accomplish that restoration.

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#### AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author indicated no potential conflicts of interest.

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