Combination Chemotherapy and Radiotherapy for Primary Central Nervous System Lymphoma: Radiation Therapy Oncology Group Study 93-10

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Purpose: **Primary CNS lymphoma (PCNSL) is an aggressive primary brain tumor. Cranial irradiation alone rarely results in long-term disease control or prolonged survival. We prospectively studied the use of combination chemotherapy plus cranial irradiation in newly diagnosed patients with PCNSL.**

Patients and Methods: **We enrolled 102 newly diagnosed, immunocompetent patients with PCNSL; 98 were assessable. Patients first received five cycles of methotrexate 2.5 g/m^2, vincristine, procarbazine, and intraventricular methotrexate (12 mg). Whole-brain radiotherapy (RT) was administered to a total dose of 45 Gy and all patients received high-dose cytarabine after RT.**

Results: **Fifty-eight percent of patients with measurable disease had a complete response to preirradiation chemotherapy and 36% had a partial (> 50%) response, for a 94% response rate. Median progression-free survival was 24.0 months and overall survival was 36.9 months. Age was an important prognostic factor; median survival was 50.4 months in patients younger than 60 and only 21.8 months in those aged 60 or older ($P < .001$). Fifty-three percent of patients had grade 3 or 4 toxicity during induction chemotherapy, half of which was hematologic. However, 12 patients (15%) experienced severe delayed neurologic toxicity, eight of whom died.**

Conclusion: **This is the first multicenter trial demonstrating improved survival with the combination of chemotherapy plus RT compared with previous reports of RT alone. A high-dose methotrexate-based regimen produced a high response rate before RT was administered. High-dose methotrexate combined with cranial irradiation is an effective therapeutic approach to PCNSL, but neurotoxicity is a delayed risk of this approach.**

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PRIMARY CNS LYMPHOMA (PCNSL) is a highly aggressive malignant brain tumor that often involves the leptomeninges, the eye, and rarely the spinal cord.[1] In older series of primary brain tumors, it accounted for 1% of all intracranial malignancies. However, its incidence has been increasing steadily, and the most recent analysis from the Central Brain Tumor Registry reveals that it now represents 4% of all brain tumors.[2]

Historically, treatment for this rare malignancy consisted of whole-brain radiotherapy (RT), which frequently produced a complete tumor response and ameliorated symptoms in most patients but resulted in a median survival of only 12 to 18 months and a 5-year survival rate of less than 5%. This was established definitively by the Radiation Therapy Oncology Group (RTOG) in the only prospective trial of cranial irradiation alone.[3] That trial, along with the experience of other institutions, also established that RT dose escalation by incorporating a boost to areas of bulky disease did not achieve improved disease control or survival.[3,4]

As increasing numbers of patients developed PCNSL, chemotherapy was incorporated into the therapeutic plan. The combination chemotherapy regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) is the best treatment for comparable systemic non-Hodgkin's lymphoma (NHL). However, three large, independent, multicenter trials combining CHOP with cranial irradiation for PCNSL have been conducted, and none demonstrated improved survival over RT alone.[5-7] Furthermore, chemotherapy toxicity was substantial, particularly in the North Central Cancer Treatment Group trial.[5]

On the basis of several reports of single-institution experiences using high-dose methotrexate-based regimens, the RTOG and the Southwest Oncology Group (SWOG) initiated, in 1993, a phase II trial of newly diagnosed patients with PCNSL using preradiotherapy methotrexate-based chemotherapy.[4,8] In addition to methotrexate, procarbazine and vincristine were added to the preradiotherapy regimen because combination chemotherapy is superior to single-agent treatment of systemic NHL. This regimen was derived from then-pilot data from the Memorial Sloan-Kettering Cancer Center that have since been published; the median survival of 60 months from that experience is the longest reported in patients with PCNSL.[9] For this RTOG-SWOG study, the dose of methotrexate was reduced from 3.5 g/m^2 to 2.5 g/m^2 because of the participating investigators' concern for possible acute methotrexate toxicity. Procarbazine was chosen because it has activity against NHL and can penetrate the blood-brain barrier as a result of its lipophilic structure. Vincristine does not permeate the intact blood-brain barrier but may reach areas of bulky disease where the integrity of the barrier is disrupted by tumor.[10] It is a highly active agent against NHL and has a different toxicity profile from the other drugs, making it attractive in a combination regimen. Postradio-

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Table 1. Treatment Flow Chart

	Weeks																		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Methotrexate IV 2.5 g/m^2	X		X		X		X		X										
Vincristine IV 1.4 mg/m^2	X		X		X		X		X										
Procarbazine PO 100 mg/m^2/d for 7 days	X				X				X										
Methotrexate Intra-Ommaya 12 mg		X		X		X		X		X									
Leucovorin 20 mg PO every 6 hours for 12 doses	X		X		X		X		X										
Leucovorin 10 mg PO bid for 8 doses		X		X		X		X		X									
Decadron, mg/d for 7 days	16	12	8	6	4	2													
Whole-brain RT											X	X	X	X	X				
Cytarabine 3 mg/m^2/d for 2 days																X			X

Abbreviations: IV, intravenously; PO, orally.

therapy high-dose cytarabine was part of an original effective combined-modality regimen used for PCNSL[4]; it has known efficacy against CNS NHL and therefore was incorporated into this protocol.[11] This report presents mature results from the first multicenter, prospective chemoradiotherapy trial of PCNSL that shows a significant improvement in survival and outcome over cranial irradiation alone.

PATIENTS AND METHODS

Newly diagnosed immunocompetent patients with PCNSL were evaluated for participation. All patients had intracranial mass lesions, and histologic documentation of PCNSL was required either by brain biopsy or resection, CSF analysis demonstrating lymphoma cells, or vitrectomy documenting concomitant ocular lymphoma. To exclude evidence of systemic lymphoma, patients had to have a negative staging evaluation, including chest, abdomen, and pelvic computed tomography scan and bone marrow biopsy. Negative human immunodeficiency virus serology and normal blood counts, electrolytes, and hepatic and renal function were required; the creatinine clearance had to be at least 50 mL/min/1.73 m^2 to ensure adequate renal function to handle the chemotherapy regimen.

All patients underwent cranial neuroimaging at diagnosis, preferably with magnetic resonance scan. Lumbar puncture and complete ophthalmologic evaluation, including slit-lamp examination, were required in all patients unless a large posterior fossa mass precluded a safe lumbar puncture. Repeat neuroimaging was required at completion of (1) preirradiation chemotherapy, (2) RT, and (3) all treatment; and then every 2 months for the first year, every 4 months for the second year, and every 6 months thereafter. A comprehensive central review of chemotherapy records was performed to assess adherence to the protocol. Central radiology review was performed to assess response after preradiotherapy chemotherapy. Neurotoxicity was evaluated using Mini-Mental State Examination (MMSE) score, Karnofsky performance status, and the National Cancer Institute common toxicity criteria. The protocol was approved by all local institutional review boards and all patients signed an informed consent.

Treatment

Chemotherapy was administered for five cycles over a 10-week period (Table 1). Each cycle consisted of methotrexate at 2.5 g/m^2 infused over 2 to 3 hours and vincristine 1.4 mg/m^2 with a cap at 2.8 mg (2 m^2). Methotrexate was followed by vigorous hydration at a rate of 1,500 to 1,800 mL/m^2 for the first 24 hours, followed by a rate of 2,000 mL/m^2 for the subsequent 48 hours. Urine alkalinization was accomplished with intravenous bicarbonate, and leucovorin rescue was initiated 24 hours after methotrexate administration at a dose of 20 mg orally every 6 hours for 12 doses. In addition to methotrexate and vincristine, procarbazine 100 mg/m^2/d for 7 days was administered on cycles 1, 3, and 5. All patients underwent placement of an Ommaya reservoir, and 12 mg of methotrexate was given for five cycles the week after each dose of intravenous methotrexate. Intra-Ommaya methotrexate was followed by oral leucovorin 10 mg every 6 hours for eight doses beginning the evening after drug administration. Dexamethasone was administered on a standard schedule of 16 mg/d for the first week, 12 mg/d for week 2, 8 mg/d for week 3, 6 mg/d for week 4, 4 mg/d for week 5, and 2 mg/d for week 6 and was then discontinued; however, the dose of dexamethasone could be adjusted according to the patient's neurologic condition. All patients received trimethoprim/sulfamethoxazole prophylaxis and clotrimazole troches.

Whole-brain RT was planned for a total dose of 45 Gy in 1.80-Gy fractions. If ocular lymphoma was present, both eyes were included in the RT field to a total dose of 36 Gy in 20 fractions. Approximately halfway through the study there was growing evidence from single-institution experience that long-term survivors of combined methotrexate-based chemotherapy and cranial irradiation were developing permanent, severe neurotoxicity.[9] This was a particularly significant issue for older patients. The study was then modified so that those patients who achieved a complete response at the end of 10 weeks of chemotherapy would receive a hyperfractionated whole-brain radiation course for a total dose of 36 Gy given in 1.20-Gy fractions twice daily for 15 days; the twice-daily RT doses were separated by a minimum of 6 hours.

At completion of cranial irradiation, all patients received two courses of high-dose cytarabine. Each course consisted of two doses separated by 24 hours of cytarabine 3 g/m^2/d infused over 3 hours.

Statistical Analysis

The primary end point of this study was estimation of 2-year overall survival. Secondary end points were tumor response before the start of RT and the frequency and severity of treatment morbidity. Survival was measured from the date of study entry to the date of death or last follow-up. For the purposes of this analysis, progression was defined as growth of the original disease, either locally or distantly within the CNS, or the development of "lymphoma outside the CNS." Estimates of the survival and progression-free survival were derived by the Kaplan-Meier method.[12] Log-rank tests were used to compare survival, progression-free survival, and

Table 2. Clinical Characteristics of 98 Patients With PCNSL

	No.	%
Age		
Median	56.5	
< 60 years	57	58
≥ 60 years	41	42
Sex		
Male	53	54
Female	45	46
KPS score		
Median	80	
40-60	28	29
70-100	70	71
MMSE score (n = 94)		
Median	26.5	
10-24	32	34
25-30	62	66
CSF (n = 98)		
Negative	60	74
Positive	17	21
None done	17	21
Equivocal	4	5

Abbreviation: KPS, Karnofsky performance status.

time to decrease of MMSE score below 24 between groups.[13] A *t* test was used to compare change in MMSE at 8 months.

RESULTS

One hundred two patients were enrolled onto the trial: 67 from the RTOG and 35 from the SWOG. Four patients were excluded from analysis; no pretreatment information was provided for one patient, and three patients did not receive protocol treatment because one refused therapy and two had a sudden decline in health status.

Of the 98 patients, 53 (54%) were men, and the median age was 56.5 years (Table 2). The median Karnofsky performance status score was 80 and the median MMSE score at baseline was 26.5 of a maximum of 30. The systemic extent of disease work-up was negative in all patients. Malignant cells were seen in the CSF in 21% of tested patients (17 of 81); ocular involvement was documented in only one patient. Gross total excision was performed in 26 patients and biopsy or subtotal resection in 69.

Response

Induction chemotherapy was delivered according to protocol or with minor variations in 70 of the 77 patients, with full documentation of the drugs administered; the other seven had otherwise acceptable variations. Thus, no reviewed patient had a major deviation from the prescribed chemotherapeutic regimen. Detailed chemotherapy logs were not available at the time of review for the remaining 21 patients. Thus, all 98 patients were analyzed for relapse and survival. There was central review of response to preirradiation chemotherapy in 70 patients, 50 of whom did not have complete tumor resection: 58% (29 of 50) had a complete response (CR), 36% (18 of 50) had a partial response, 4% (two of 50) had stable disease, and 2% (one of 50) had progressive disease.

RT records were available for 82 patients; 14 patients stopped protocol treatment before starting RT and no treatment data were available for two patients. A total dose of 45 Gy was delivered to 63 patients. One patient received 55 Gy, one patient's treatment was terminated early at 31 Gy because of tumor progression, and another stopped radiotherapy after 38 Gy because of toxicity. The hyperfractionation schedule was administered to 16 patients, all of whom completed the prescribed course of 36 Gy. A CR after induction chemotherapy was confirmed on central imaging review in 13 patients treated with the hyperfractionated schedule as required by the protocol.

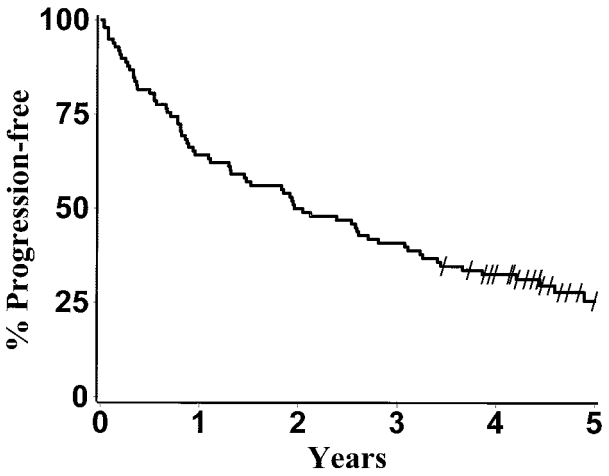

Fig 1. Progression-free survival for all patients.

Relapse

Relapse was observed in 33 patients (34%), 28 (29%) of whom had a CNS relapse. Disease recurred at the original site (n = 9), at a new site in the brain (n = 9), at the original and a new site (n = 2), in the CSF (n = 2), in the spinal cord parenchyma (n = 1), and in the eyes (n = 5). Five patients (5%) developed extra-CNS disease in the breast (n = 1), orbit (n = 1), lymph node (n = 1), and muscle/subcutaneous tissue (n = 2).

Survival

The median duration of follow-up for patients alive at the time of analysis was 55.9 months. The median progression-free survival was 24.0 months (Fig 1). In 50% of patients, disease had not progressed at 2 years; 41% remained progression-free at 3 years; and 25% remained progression-free at 5 years (Table 3). The median overall survival was 36.9 months, with 64% of patients alive at 2 years, 52% at 3 years, and 32% at 5 years (Fig 2). There was no difference in survival on the basis of whether or not patients had achieved a CR to the induction chemotherapy (median, 41.3 *v* 39.1 months; $P = .97$).

Older age was associated with a worse outcome. The median progression-free survival was 38.8 months in patients younger

Table 3. Survival of All Patients

	Progression-Free Survival*		Overall Survival†	
Years	Progression Free (%)	No. At Risk	Alive (%)	No. At Risk
0	100	98	100	98
1	64	63	79	77
2	50	49	64	62
3	41	40	52	50
4	33	27	39	32
5	25	11	32	13

*Median, 24.0 months (failed/total, 70/98).
†Median, 36.9 months (dead/total, 63/98).

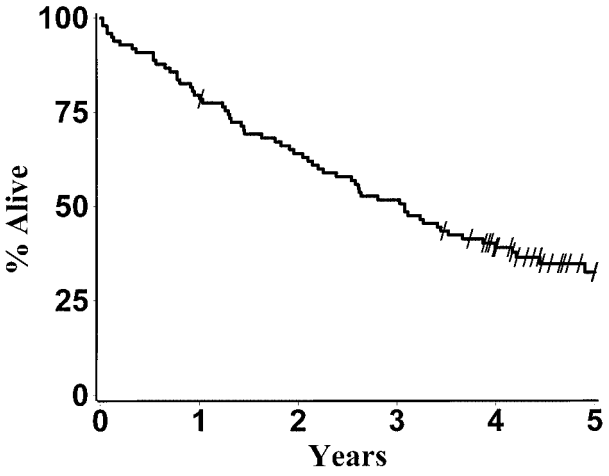

Fig 2. Overall survival for all patients.

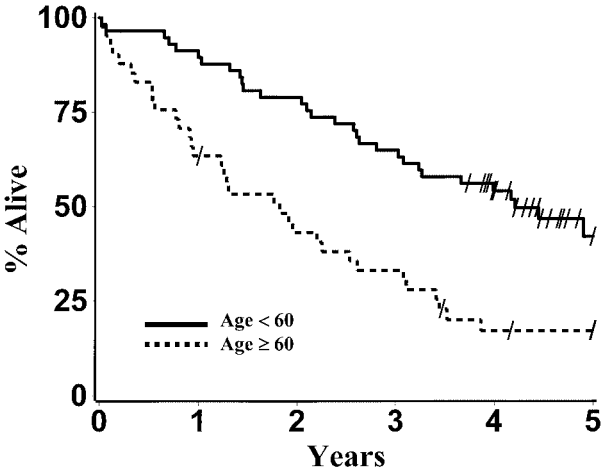

Fig 4. Overall survival according to patient age ($P < .001$).

than 60 years of age but only 11.1 months in those 60 and older ($P < .001$) (Fig 3). Overall survival was similarly affected. The median survival was 50.4 months in those younger than 60 and 21.8 months in those aged 60 or older ($P < .001$) (Fig 4).

For patients achieving a CR to induction chemotherapy, there was no difference in progression-free survival between those (n = 27) who received 45 Gy standard whole-brain RT and those (n = 13) who received 36 Gy hyperfractionated RT (median, 24.5 *v* 23.3 months; $P = .81$). Overall survival was also similar, with a median of 37.0 months for those receiving 45 Gy and 47.9 months for those who received the 36-Gy hyperfractionated regimen ($P = .65$).

Toxicity

Fifty-two patients (53%) had a maximum grade 3 or 4 toxicity during induction chemotherapy, 52% of which was attributable to myelosuppression. Grade 3 and 4 toxicities occurred in 46% of patients younger than age 60 and in 63% of patients aged 60 and older. There were three grade 3/4 renal toxicities, with one patient experiencing acute renal failure attributed to high-dose methotrexate; they all recovered. Nine patients experienced acute grade 3/4 CNS symptoms during induction chemotherapy. The most common abnormalities were confusion, somnolence, and headache. Although some of these symptoms may have been related to the underlying disease, they may also have been related to the therapy, particularly the high-dose methotrexate, and were recorded as such.

Eighty-two patients received radiotherapy, 60 (73%) of whom experienced grade 3, 4, or 5 toxicities. Sixty-three percent of these toxicities were related to myelosuppression, which could have also been a consequence of the final cycle of chemotherapy. However, 12 patients (12 of 82 [15%]) experienced severe delayed neurologic toxicities characterized primarily as leukoencephalopathy; onset began a median time of 504 days (range, 80 to 1540 days) after the start of cranial irradiation. Leukoencephalopathy was seen as frequently in patients younger than 60 (seven of 50 [14%]) as in those 60 or older (six of 32 [19%]). Eight of these toxicities were fatal (10%); five of them occurred in patients 60 years of age or older (five of 32 [16%]) compared with three in the younger age group (three of 50 [6%]).

Of the 27 patients who achieved a CR after chemotherapy and received standard RT, one (3.7%) developed grade 3 neurotoxicity. Three patients (23%) from the hyperfractionated group (n = 13) developed grade 4 (one patient) or grade 5 (two patients) neurotoxicity. There was no significant difference in MMSE scores at 8 months or time to decrease of MMSE score below 24, used as a measure of dementia, between these two groups (data not shown).

DISCUSSION

This is the first multicenter therapeutic trial for PCNSL that demonstrated a marked survival benefit from chemotherapy combined with RT with respect to previously reported studies using RT alone.[1,3] The use of a preirradiation high-dose methotrexate-based regimen achieved a 58% CR rate before RT and a median overall survival of 36.9 months, supporting the improved survival reported by single institutions using a comparable approach.[4,8] Furthermore, more than half of the patients are alive at 3 years. These data demonstrate the efficacy of this regimen for PCNSL.

The drugs chosen for this combination chemotherapy protocol are unusual agents for the treatment of NHLs. The failure of standard regimens such as CHOP may be partly explained by the fact that none of the agents used in that regimen, except prednisone, can adequately penetrate an intact blood-brain barrier. Areas of bulky disease have a disrupted blood-brain barrier,

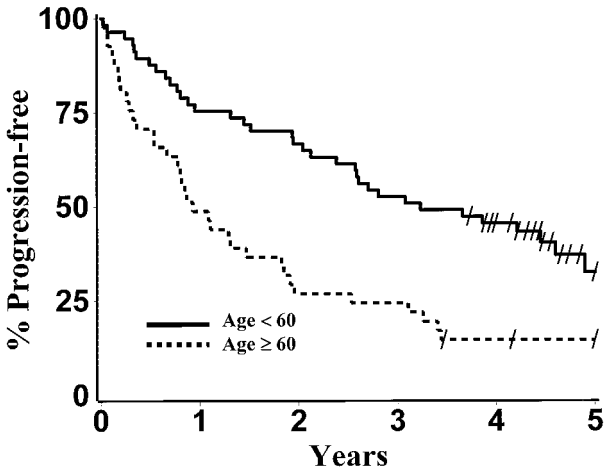

Fig 3. Progression-free survival according to patient age ($P < .001$).

as evidenced by enhancement on neuroimaging studies. Water-soluble drugs can reach these areas of tumor and be effective locally, but the drug cannot reach areas of infiltrative disease that reside behind a relatively intact blood-brain barrier. This is reflected in the rapid regression of contrast-enhancing tumor after the initial cycles of CHOP only for tumor to progress either in the spinal fluid or other areas of brain.[5,6] This strongly suggests that although neither cyclophosphamide, nor doxorubicin, nor vincristine can penetrate an intact blood-brain barrier, they reach disease where the barrier is disrupted and therefore permeable, which allows these otherwise active agents to reach tumor. The regimen used in this study was chosen on the basis of pilot data from a single institution using a comparable combination. Lymphoma is sensitive to these agents, and high-dose methotrexate and procarbazine both penetrate the normal blood-brain barrier. Vincristine does not penetrate the blood-brain barrier but may reach areas of bulky disease as described for CHOP.

High-dose methotrexate is widely recognized as the single most effective chemotherapeutic agent for PCNSL.[1,4,8,9,14-17] The methotrexate dose of 2.5 mg/m^2 used in this study is relatively modest, but there are data to show that it can achieve therapeutic concentrations in the CSF of most patients, particularly when given as a rapid infusion as performed in this study.[18,19] Supplementary intra-Ommaya methotrexate was also used to facilitate sustained exposure of the leptomeninges to therapeutic drug concentrations. This would treat the microscopic subarachnoid disease seen in many PCNSL patients at autopsy even though only 21% (17 of 81) of tested patients had tumor cells on CSF cytologic examination.[20] Subsequent experience suggests that intrathecal methotrexate may not be necessary to treat the subarachnoid space in PCNSL patients when adequate intravenous doses are administered.[21,22]

Relapses occurred primarily within the brain, but only 33% of these were at the original site of disease. The incidence of leptomeningeal relapse was low, and only one patient had recurrence of disease in the spinal cord. However, five patients each had a systemic recurrence and an ocular relapse. Recurrences in these sites each account for 15% of all recurrences, but they each affected only 5% of all patients. The overall incidence of systemic relapse is similar to the 7% to 8% frequency of systemic lymphoma found at autopsy.[1] The relatively high incidence of ocular relapse suggests that the eye remains a potential sanctuary for PCNSL. Therapeutic methotrexate levels have been documented in the vitreous of a single patient treated with 8 g/m^2, and adequate ocular concentrations of cytarabine have been documented after 3 g/m^2.[23,24] However, whether this dose of methotrexate is required or whether methotrexate penetration is reliable in all patients and sufficient to eradicate disease is unknown. Furthermore, detection of ocular lymphoma is difficult and may have been missed in some patients at presentation so that full therapy with ocular RT (given to only one patient) may not have been administered to all patients with ocular involvement.

Myelosuppression was the primary acute toxicity from this therapeutic regimen along with other toxicities that were readily reversible. Delayed neurotoxicity was the most significant long-term sequela of this regimen. Detailed prospective neuropsychologic testing was not performed in this population, and leukoencephalopathy was diagnosed clinically by each investigator. Therefore, our 15% incidence of neurotoxicity is a minimum and we likely detected only the most severely affected patients. Patients treated with other high-dose methotrexate regimens had a 25% to 32% overall incidence of late toxicity after prolonged follow-up.[9,14] However, in those reports, the risk of neurotoxicity was a function of older age and prolonged follow-up. With follow-up of 4 years or more, almost all patients over the age of 60 developed dementia.[14] Despite a median follow-up of 55.9 months in this study, the incidence of neurotoxicity was relatively low in our population, even among older patients. There is no reason to expect this regimen to be less neurotoxic than previously reported similar regimens, suggesting that clinical manifestations of neurotoxicity were underappreciated in this multicenter trial. This highlights another difference in outcome identified between the single-institutional and multi-institutional experience treating these patients.

Hyperfractionation schedules of RT allow normal tissues to repair sublethal radiation damage and, therefore, should minimize deleterious effects on normal brain structures. Theoretically, this should reduce the risk of leukoencephalopathy; however, severe neurotoxicity was observed in 23% of patients treated with hyperfractionated RT compared with only 3.7% of those treated with the standard regimen. These data suggest that the hyperfractionated schedule used in this study did not eliminate neurotoxicity; however, this cohort is small. Importantly, the reduced total dose of RT used in these patients did not compromise disease control.

Severe neurotoxicity is an unacceptable consequence of otherwise successful treatment of PCNSL. Therefore, more effective and safer regimens must be developed for patients with this disease, particularly for older patients who are at greatest risk for the late consequences of treatment.[9,14] Toxicity is likely attributable to the potent combination of high doses of intravenous methotrexate, a known neurotoxin, intrathecal methotrexate, and cranial irradiation, a combination known to produce leukoencephalopathy and cerebral toxicity. There are conflicting data that chemotherapy alone for PCNSL is an effective alternative for many patients; some authors report prolonged disease control, but others note frequent tumor progression.[9,16,17,25] The use of blood-brain barrier disruption and intra-arterial chemotherapy has been reported effective in PCNSL, and no neurotoxicity has been identified in patients studied with neuropsychologic testing.[26] However, these data must be interpreted cautiously in view of the fact that methotrexate alone in high doses can produce significant cognitive problems and cerebral damage.

Our study demonstrates that a high-dose methotrexate combination regimen is an effective treatment for PCNSL. Drugs that penetrate the intact blood-brain barrier are essential. The optimal dose and schedule of cranial RT remain to be defined, and further efforts must be directed at reducing the neurologic sequelae of such treatment in these patients. Prolonged follow-up for patients who have been treated with a reduced dose of hyperfractionated RT may help point toward the direction of effective but less toxic therapy.

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