Treatment of Primary CNS Lymphoma With Methotrexate and Deferred Radiotherapy: A Report of NABTT 96-07

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Purpose: A multicenter, phase II study of single-agent, intravenous methotrexate in newly diagnosed non-AIDS-related primary CNS lymphoma was conducted in the New Approaches to Brain Tumor Therapy (NABTT) CNS Consortium.

Methods: Methotrexate (8 g/m^2) was initially administered every 2 weeks. The primary end point was radiographic CR or PR, as defined by standard radiographic criteria, and secondary end points were survival and drug-related toxicity.

Results: Twenty-five patients were enrolled with a mean age of 60 years and median Karnofsky Performance Score of 80. Three of 14 patients who underwent lumbar puncture had malignant cells on CSF cytopathology, and five of 25 patients had ocular involvement. Two patients could not be evaluated for the primary end point because of the absence of measurable disease in one and death before radiologic imaging in another. All patients have completed the treatment program or progressed. Among 23 patients, there were 12 CR (52%), five PR (22%), one (4%) with stable disease, and five progressions (22%) while on therapy. Seven patients died of tumor progression, and two died of other causes. Median progression-free survival was 12.8 months. Median overall survival for the entire group had not been reached at 22.8+ months. The toxicity of this regimen was modest, with no grade 3 or 4 toxicity in 13 of 25 patients, grade 3 toxicity in eight of 25 patients, and grade 4 toxicity in four of 25 patients after 287 cycles of chemotherapy.

Conclusion: These results indicate that high-dose methotrexate is associated with modest toxicity and a radiographic response proportion (74%) comparable to more toxic regimens.

J Clin Oncol 21:1044-1049. © *2003 by American Society of Clinical Oncology.*

P RIMARY CNS lymphoma (PCNSL) is a rare non-Hodgkin's lymphoma (NHL) confined to the nervous system, with an incidence of 0.38 per 100,000 person-years.[1] There are approximately 1,000 incident cases of PCNSL in the United States each year, accounting for 3% of all primary brain tumors and 2% of all cases of NHL.[1] However, the incidence of PCNSL has increased almost three-fold over the last three decades in parallel with an increase in systemic NHL.[2] The increasing incidence has been most dramatic in the elderly population and can only be partially attributed to the human immunodeficiency virus (HIV) epidemic. Using the Working Formulation and Revised European-American Lymphoma (REAL) classification systems, most cases of PCNSL are high-grade, diffuse, large B-cell lymphomas.[3] The management of PCNSL is different than the usual treatment of either primary brain tumors or systemic NHL. First-generation chemotherapy regimens used successfully in systemic NHL are ineffective in PCNSL, in part because of the existence of the blood-brain barrier (BBB).[4,5] Whole-brain radiation therapy (WBRT) results in high response rates but rapid relapse. Moreover, this treatment is associated with delayed neurotoxicity, especially in elderly patients with PCNSL.[6,7] The addition of methotrexate-based chemotherapy has improved survival for this patient population. Studies of high-dose methotrexate in combination with other chemotherapy drugs or as single-agent therapy have demonstrated response rates higher than 50% in patients with newly diagnosed PCNSL. Combination regimens seem to be associated with more toxicity than methotrexate monotherapy.[8-19] The optimal chemotherapy regimen for PCNSL has yet to be defined. On the basis of pilot data from a single institution, we conducted a multicenter, phase II study of high-dose methotrexate in patients with newly diagnosed PCNSL.

PATIENTS AND METHODS

Patients

The methotrexate protocol described in this study was reviewed and approved by the National Cancer Institute and the institutional review boards at each participating center. Patients with newly diagnosed PCNSL were eligible for enrollment into this study if a pathologic diagnosis had been established and all the following criteria were met: age more than 18 years, Karnofsky Performance Score (KPS) $\geq$ 60, negative HIV serology, creatinine clearance $\geq$ 60, and no evidence of lymphoma elsewhere in the body after computerized tomography scans of chest, abdomen, and pelvis. After accrual began, the protocol was amended to include the criterion of more than 1 cm of measurable contrast-enhancing disease present on neuroimaging. Voluntary, informed, written consent was obtained from all patients who participated in this study.

Methods

Baseline prechemotherapy studies included neurological and physical examinations, Mini-Mental State Examination (MMSE), contrast-enhanced cranial magnetic resonance imaging (MRI), ophthalmologic examination including slit-lamp evaluation, and CSF cytopathology if lumbar puncture could be performed safely. A 24-hour urine collection was obtained at baseline and before each chemotherapy cycle to calculate creatinine clear-

ance. Patients were treated with methotrexate in induction, maintenance, and consolidation phases. In the induction phase, patients received methotrexate 8 g/m² every 14 days until a complete response (CR) was achieved or a maximum of eight cycles was administered. In patients who achieved a CR to induction chemotherapy, two consolidation cycles of methotrexate 8 g/m² were administered every 14 days and 11 maintenance cycles of methotrexate 8 g/m² were administered every 28 days.

Each treatment cycle was standardized and required admission to the hospital. Before infusion of methotrexate, each patient received intravenous (IV) hydration and oral or IV sodium bicarbonate for urine alkalization. Once a urine output of more than 100 (mL/h) and a urine pH of 7 had been maintained for at least 4 consecutive hours, antiemetic medication was administered and methotrexate, 8 g/m², was infused over 4 hours. The total dose was adjusted based on the prechemotherapy creatinine clearance. The dose was reduced by the percentage reduction of the creatinine clearance below 100. For example, a creatinine clearance of 75 mandated a 25% reduction in the dose of methotrexate. During and after infusion of methotrexate, IV hydration and urine alkalization were continued to maintain urine output more than 100 mL/h and urine pH more than 7. Daily laboratory tests included blood urea nitrogen, creatinine, WBC count, hemoglobin, platelet count, and methotrexate level. Calcium leucovorin rescue was started 24 hours after the methotrexate infusion and was continued until the methotrexate level was less than 0.10 μM, at which point the patient was discharged from the hospital.

Follow-up studies included physical and neurological examinations, MMSE, 24-hour urine collection for creatinine clearance with each cycle of chemotherapy, complete blood counts with differentials, cranial MRI after every two cycles of chemotherapy, ophthalmologic examination, and CSF cytopathology if it was originally positive. Standardized response criteria were used to grade each MRI scan.[20] All data were reported to the NABTT Central Operations Office at the Johns Hopkins Oncology Center.

Statistical Methods

The primary end point of this phase II study was radiographic response (CR or partial response [PR]). This study used a two-stage design to assess whether the response rate for methotrexate alone was equivalent to the approximately 80% response rate reported for conventional treatment (multiple agents and radiation therapy). In the first stage, 15 patients were to be placed on the study. If fewer than six patients responded, the 90% confidence limits would exclude 0.80 and the study would terminate. Otherwise, the study would accrue a total of 25 patients, providing an estimate of the response rate with a precision of ± 20%. Therefore, if the point estimate of the response rate was ≥ 0.6, the hypothesis that the study treatment was equivalent to combined modalities would not be rejected.

Secondary end points included survival and progression-free survival. Event time was calculated from the time treatment began until death (for overall survival), progression or death (for progression-free survival), or date of last follow-up for patients without an event. Survival distributions were estimated by the product-limit method,[21] and 95% confidence intervals were calculated using Greenwood's formula.[22]

Exploratory analysis of predictors of response and survival were conducted using exact logistic regression and proportional hazards regression models.[23] Factors examined included age, sex, KPS, CSF cytopathology results, ocular involvement, MMSE scores, and median peak methotrexate levels.

Descriptive statistics were calculated for baseline demographic and clinical characteristics, as well as toxicity. MMSE scores by patients over time were plotted to assess neurotoxicity. Analyses were performed using SAS (Version 8.2, SAS Institute, Cary, NC).[24] All P values reported are two sided.

RESULTS

Fifteen patients were accrued to the first stage of the study between June 1998 and August 1999. There were sufficient responses (seven CR and three PR) to continue to the second stage, and an additional 10 patients were accrued through December 1999. Baseline features of the 25 patients are summarized in Table 1. Twenty-four patients had the diagnosis of PCNSL established by tumor biopsy (n = 22) or resection (n =

Table 1. Baseline Demographic and Clinical Characteristics

| Characteristic	Mean (SD) or No.* (%)
Age, years	59.8 (12.2)
KPS	78.4 (13.1)
KPS ≥ 80	14 (56.0%)
Mini-Mental State Examination	24.6 (5.9)
Males	17 (68%)
Females	8 (32%)
Multiple brain lesions	14 of 24 (58.3%)
Leptomeningeal lymphoma	3 of 14 (21.4%)
Ocular involvement	5 (20.0%)
Pathology	
Diffuse, Large B Cell	22 (88.0%)
B-CLL/SLL	3 (12.0%)
Median peak MTX level	11.7 (22.0)

Abbreviations: KPS, Karnofsky Performance Score; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; MTX, methotrexate.

*N = 25, unless stated otherwise.

2), whereas one patient had the diagnosis made by CSF cytopathology. Using the REAL classification system, pathologic diagnosis was diffuse, large B-cell lymphoma in 22 of 25 patients and B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma in three of 25 patients. At the discretion of the attending physician, 14 of 25 patients had a dural puncture for CSF and three of these 14 patients had malignant cells identified. All 25 patients had ophthalmologic evaluation and five of 25 had signs of ocular lymphoma.

Twenty-three patients could be evaluated for the primary end point, radiographic response. There were 12 (52%) of 23 CR (Fig 1) and five (22%) of 23 PRs (total response = 74%), whereas five (22%) patients progressed during methotrexate treatment, and one patient had stable disease at the time of death from cardiac arrest after two cycles of methotrexate. Two patients could not be evaluated for the primary end point: one was an early accrual and had gross total resection of the tumor, and the other died before follow-up MRI and, therefore, could not be evaluated for progression. In the 12 patients who achieved a CR to methotrexate, the median number of cycles to CR was six. In the five patients with concurrent ocular lymphoma, four achieved CR and one achieved PR in the brain, and four had resolution of ocular signs with methotrexate alone. In the three patients with positive CSF cytopathology at baseline, two had their intracranial lesions progress during induction methotrexate. Overall, 13 patients have progressed, five during induction methotrexate, two after initial PR, and six after initial CR. Among the 12 patients who achieved an initial CR, four have relapsed in the brain, one in the peripheral nervous system, and one in the testicle. Nine patients have died, seven as a result of progressive disease and two because of other causes. The median follow-up time for all 25 patients in this study was 22.8 months (range, 1.4 to 37.3 months) and for surviving patients, median follow-up time was 25.3 months (range, 19.8 to 37.3 months). Median progression-free survival for all patients was 12.8 months, and median overall survival had not been reached at 22.8+ months of follow-up. The Kaplan-Meier survival estimates and 95% confidence intervals are shown in Fig 2A and 2B.
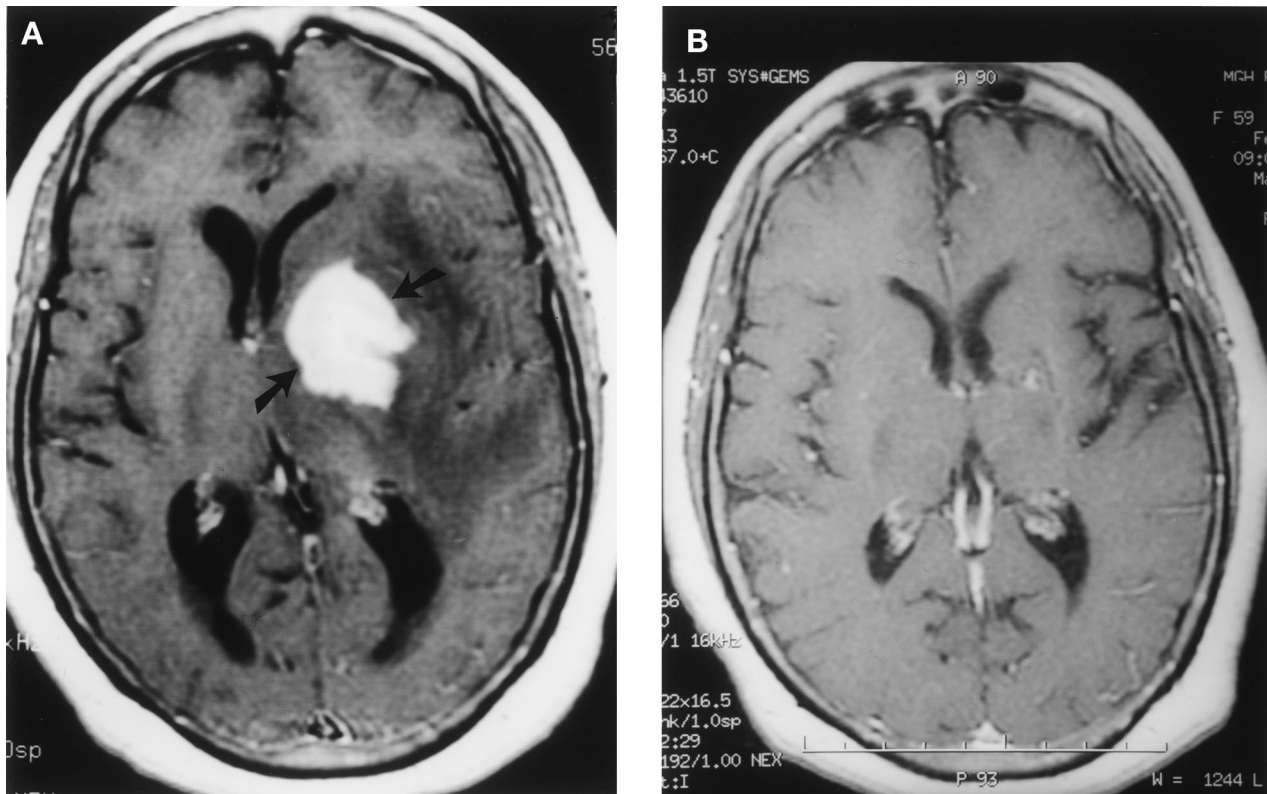
Fig 1. (A) Premethotrexate gadolinium-enhanced cranial magnetic resonance imaging (MRI) of a patient with a homogeneously enhancing, single periventricular diffuse B-cell lymphoma. (B) MRI of same patient after four cycles (2 months) of methotrexate.

Five patients who achieved CR with methotrexate remain in remission with 23 to 38 months of follow-up. One patient who had no measurable disease at the start of treatment and received only methotrexate remains in remission 40 months after diagnosis.

Exploratory analysis of a number of clinical variables did not reveal a strong association with response to chemotherapy or survival. Descriptive statistics by response are presented in Table 2. In this study, only KPS was associated with survival ($P < .1$). However, the small number of subjects in this study limits the power to detect such prognostic variables.

After 287 cycles of hospital-based, high-dose methotrexate, toxicity has been modest. Thirteen patients have experienced no grade 3 or 4 toxicity, whereas 12 patients have experienced 18 episodes of grade 3 or 4 toxicity. Four of these 18 episodes were felt to be unlikely to be related to methotrexate.

MMSE scores by patient over time are shown in Fig 3. Though the data could be biased if the patients with neurotoxicity did not return for MMSE testing, of the 19 patients that had at least one follow-up MMSE score, only one declined from baseline (from 29 to 27).

DISCUSSION

In this multicenter, phase II study, we have demonstrated the feasibility of administering high-dose methotrexate to patients with PCNSL, and our results indicate that more than half of these patients achieve CR and that a quarter of these responses are durable. Moreover, the toxicity of this regimen was modest, with no dose-limiting toxicities in more than half the patients enrolled.

The initial treatment approaches for PCNSL grew out of the experience in treating systemic NHL. CHOP (cyclophospha-

mide, doxorubicin, vincristine, and prednisone) is an effective treatment for patients with systemic NHL and was expected to be effective therapy for PCNSL.[25] However, in clinical trials of CHOP in patients with PCNSL, radiographic response rates are 32% to 67%, local recurrence is common, patients die of progressive disease, and median survival is not significantly greater than with radiation therapy alone.[4,5] Thus, a standard, effective regimen for systemic NHL—CHOP—shows little efficacy in the treatment of PCNSL, probably because these drugs poorly penetrate an intact BBB.

Methotrexate is an antimetabolite that can penetrate the BBB when given in high doses by the intravenous route. Numerous studies of methotrexate or methotrexate-based chemotherapy in combination with WBRT have been conducted in patients with PCNSL.[8-16] These studies demonstrate that the addition of methotrexate alone or that of methotrexate-based chemotherapy to WBRT results in extension of progression-free survival when compared with historical series treated with WBRT alone. Moreover, these studies also demonstrate that preirradiation, methotrexate-based therapy results in a high proportion of radiographic responses.

On the basis of clinical experience in systemic NHL, it has been predicted that combination chemotherapy will be essential for the successful treatment of PCNSL. In a recent multicenter, phase II trial of preirradiation combination chemotherapy, 98 patients were treated with five cycles of IV methotrexate (2.5 g/m²), IV vincristine, and oral procarbazine before 45 Gy of WBRT and IV cytarabine (3 g/m²) after radiation. The overall response rate to chemotherapy was 94% (57% CR and 37% PR). The median survival had not been reached at the time of

A Overall Survival
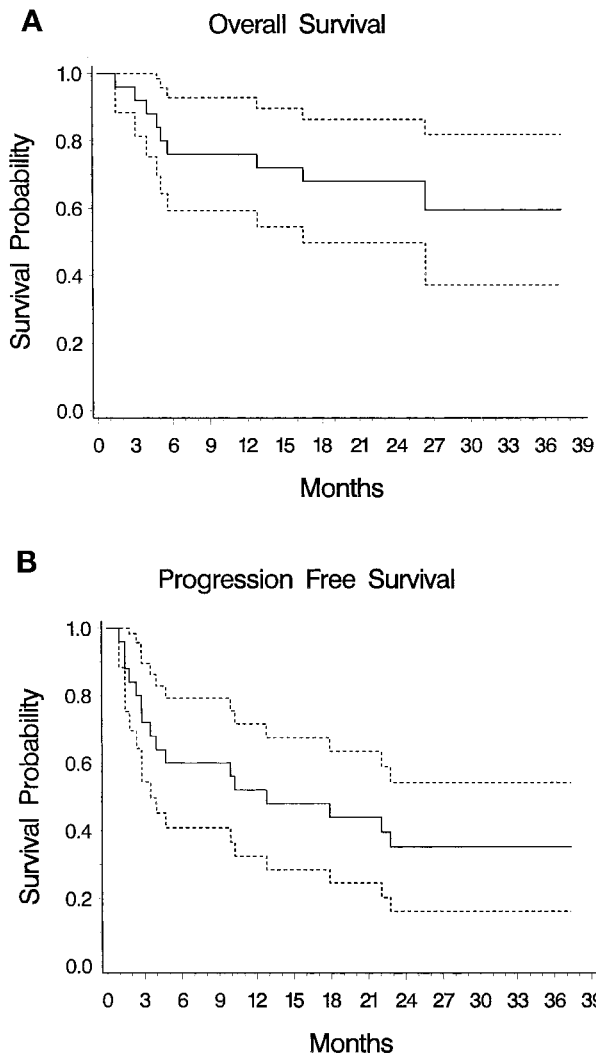

B Progression Free Survival

Fig 2. (A) Overall survival and 95% confidence intervals (Kaplan-Meier curves). (B) Progression-free survival and 95% confidence intervals (Kaplan-Meier curves).

Fig 3. Mini-Mental State Examination (MMSE) scores over time. Same patient scores are connected.

publication, and over 50% of enrollees were alive at 30 months. In this study, grades 3 or 4 toxicity occurred in 30 (58%) of 52 patients, and two patients died from treatment-related leukoencephalopathy.[26]

An important complication of combined-modality therapy is delayed neurotoxicity. This condition is usually characterized by

Table 2. Mean (SD) or No. (%) of Baseline Clinical Characteristics by Radiographic Response

Characteristic	No Response	Partial or Compete Response
No.	6	17
Age, years	65.8 (8.2)	58.2 (13.2)
KPS	70.0 (11.0)	80.0 (12.7)
KPS ≥ 80	1 (16.7%)	11 (64.7%)
Mini-Mental State Examination	24.7 (4.8)	24.5 (6.5)
Females	3 (50.0%)	5 (29.4%)
Multiple brain lesions	2 (33.3%)	11 (64.7%)
Leptomeningeal lymphoma	2 of 3 (67%)	0 (0.0%)
Ocular involvement	0 (0.0%)	5 (29.4%)
Median peak MTX level	22.4 (37.5)	8.4 (16.7)

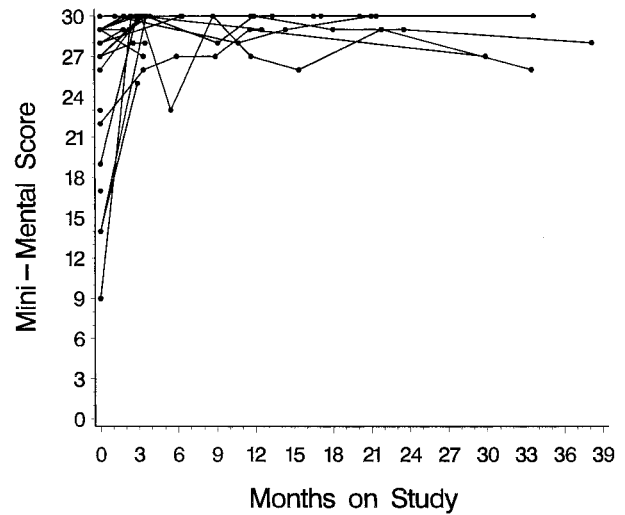Abbreviations: KPS, Karnofsky Performance Score; MTX, methotrexate.

a combination of memory impairment, gait failure, and incontinence. In one study of 117 patients treated with combined-modality therapy (radiation plus chemotherapy), 37 (32%) developed late neurotoxicity. Median time to onset of symptoms was 9 months. Symptoms were associated with a decline in median KPS from 80 to 50. Significant risk factors for neurotoxicity included age greater than 60 years and history of WBRT.[7] There is debate whether WBRT should be administered to all patients with newly diagnosed PCNSL. The use of WBRT in the elderly population is especially controversial. In one retrospective study that included 34 patients older than age 60 years, there was no difference in survival between those patients who received WBRT as part of the treatment regimen and those who did not receive WBRT. However, in those elderly patients who received WBRT, 83% developed delayed neurotoxicity.[27] Thus, the utility and safety of WBRT in the elderly patient population with PCNSL is questionable.

The recognition that neurotoxicity occurs in a significant proportion of PCNSL patients receiving WBRT has led to efforts to defer or eliminate WBRT in this patient population. These approaches involve the use of chemotherapeutic drugs with demonstrated antilymphoma activity and physicochemical properties compatible with BBB penetration.

One method developed for improving drug delivery across the BBB is BBB disruption (BBBD) followed by intraarterial or IV chemotherapy. In a summary of 74 patients with PCNSL treated with this modality over 15 years, 48 patients (65%) achieved a CR, 14 patients (19%) had a PR, and 12 patients (16%) had stable or progressive disease.[17] The estimated 5-year survival rate was 42%, and the estimated median survival was 40.7 months. However, BBBD was associated with significant procedure-related, acute toxicities. Of 74 patients, four (5.4%) died within 30 days of the procedure, five experienced stroke (6.8%), and one (1.4%) experienced status epilepticus. In contrast to the high proportion of acute toxicities, late neurotoxicity in this cohort of patients treated without WBRT was minimal. Comprehensive neuropsychological testing was performed in 36 patients who achieved a CR lasting longer than 1 year. There were no

cases of dementia detected, and significant improvements were noted in several cognitive domains.[17] Although this study demonstrated the efficacy and lack of delayed neurotoxicity of chemotherapy alone in patients with PCNSL, the technical complexities of BBBD and the associated acute toxicities limit wide application of this method in the treatment of PCNSL.

Approximately 10 years ago, several investigators started to treat patients with newly diagnosed PCNSL with methotrexate alone and deferred WBRT. One study reported 31 patients with newly diagnosed PCNSL treated with methotrexate alone.[19] Induction methotrexate was delivered at 8 g/m^2 and was followed by indefinite maintenance therapy at 3.5 g/m^2 at 3-month intervals. The overall response rate was 100%, with 20 CRs (65%) and 11 PRs (35%). The median progression-free survival was 16.7 months, and the median overall survival was 30.4 months. After 375 cycles of methotrexate, toxicity was minimal, as leukopenia without fever was documented in only four cycles and reversible renal insufficiency was seen in only three patients.[19] On the basis of these promising results from a single institution, 25 patients were treated with high-dose methotrexate monotherapy in this study.

This study indicates that methotrexate monotherapy results in radiographic response proportions comparable to potentially more toxic combination regimens. Although further follow-up is necessary, it seems that some CR are durable. Moreover, these results with high-dose methotrexate alone are better than historical series treated with WBRT alone.[6] Despite these encouraging results, the median progression-free survival achieved in this study (12.8 months) is inferior to that achieved with other, albeit more toxic, combination chemotherapy plus radiation regimens. To enhance the initial response rate and improve progression-free survival it will be necessary to add additional agents to high-dose methotrexate.

The observation that four of five patients with presumed ocular lymphoma initially responded to methotrexate is worthy of follow-up. Other investigators have noted that when IV methotrexate is administered at a dose of 8 g/m^2, potentially cytotoxic, micromolar concentrations of the drug are achieved in the aqueous and vitreous humor.[28]

In contrast to treatment regimens for PCNSL that contain WBRT or multiple chemotherapy agents, toxicity from this regimen was modest, with only 12 of 25 patients experiencing grade 3 or 4 toxicity after 287 cycles of hospital-based, high-dose IV methotrexate. In addition, no episodes of clinical leukoencephalopathy have been reported in patients receiving high-dose methotrexate as part of this study. However, the regimen requires hospitalization, close medical and nursing management, and daily measurements of blood methotrexate to achieve the level of safety observed.

Despite deferral of radiation in patients with newly diagnosed PCNSL, treatment with WBRT at the time of progression or relapse may still be effective. In a series of 16 patients treated with the same methotrexate regimen as in this study, WBRT resulted in a 76% radiographic response rate at the time of relapse after initial CR.[29] Thus, WBRT may still be effective in patients who progress or relapse during treatment with methotrexate. However, the optimal treatment for refractory or relapsed PCNSL has yet to be defined. In the subset of PCNSL patients who relapse after initial CR to methotrexate, reinduction with methotrexate may be successful. In a series of 11 such patients, nine (82%) achieved a subsequent CR after reinduction with methotrexate.[30] Moreover, survival of these nine patients was 21+ months, indicating that durable second remissions are possible with this strategy. Further studies are required to validate these observations.

The optimal chemotherapy regimen for PCNSL that maximizes response and survival while minimizing toxicity has not been defined. Although methotrexate monotherapy does not result in remission in a significant fraction of patients and is associated with eventual relapse, the response proportions observed in this and other studies are comparable to more toxic combination regimens currently in use. Furthermore, the deferral of WBRT is associated with less neurotoxicity in this elderly patient population. In another study using the same dose of IV methotrexate, CRs were reported in only 29.7% of patients.[31] However, in this study, patients could receive a maximum of six cycles of methotrexate. It is noteworthy that in our study, the median number of cycles until CR was achieved was six. Therefore, it is likely that the CR proportion would have been higher in this earlier study if further cycles had been administered. Moreover, the proportion of CR in our study is consistent with two other published reports using the same regimen.[8,32] Further improvements in the proportion of PCNSL patients who achieve a CR as well as in survival will likely require the addition of chemotherapeutic agents with demonstrated antilymphoma activity and physicochemical properties predictive of BBB penetration. Ongoing, cooperative group, phase II studies aim to identify an optimal, methotrexate-based treatment regimen. A major challenge for future studies of patients with PCNSL will be the development of biologic assays that will allow better prognostic stratification and risk-adjusted therapy.

REFERENCES

1. Statistical Report: Primary Brain Tumors in the United States, 1992-1997. Chicago, IL, Central Brain Tumor Registry of the United States, 2002

2. Eby NL, Grufferman S, Flannelly CM, et al: Increasing incidence of primary brain lymphoma in the US. Cancer 62:2461-2465, 1988

3. Paulus W, Jellinger K, Morgello S: Malignant lymphomas, in Kleihues P, Cavenee WK (eds): Pathology and Genetics. Tumours of the Nervous System. Lyon, France, IARC Press, 1997

4. O'Neill BP, O'Fallon JR, Earle JD, et al: Primary central nervous system non-Hodgkin's lymphoma: Survival advantages with combined initial therapy? Int J Radiat Oncol Biol Phys 33:663-673, 1995

5. Schultz C, Scott C, Sherman W, et al: Preirradiation chemotherapy with cyclophosphamide, doxorubicin, vincristine, and dexamethasone for primary CNS lymphomas: Initial report of radiation therapy oncology group protocol 88-06. J Clin Oncol 14:556-564, 1996

6. Nelson DF, Martz KL, Bonner H, et al: Non-Hodgkin's lymphoma of the brain: Can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG): RTOG 8315. Int J Radiat Oncol Biol Phys 23:9-17, 1992

7. Abrey LE, Yahalom J, DeAngelis LM: Relapse and late neurotoxicity in primary central nervous system lymphoma (PCNSL). Neurology 48:A18, 1997

8. Loeffler JS, Ervin TJ, Mauch P, et al: Primary lymphomas of the central nervous system: Patterns of failure and factors that influence survival. J Clin Oncol 3:490-494, 1985

9. Gabbai AA, Hochberg FH, Linggood RM, et al: High-dose methotrexate for non-AIDS primary central nervous system lymphoma. Report of 13 cases. J Neurosurg 70:190-194, 1989

10. Glass J, Gruber ML, Cher L, et al: Preirradiation methotrexate chemotherapy of primary central nervous system lymphoma: Long-term outcome. J Neurosurg 81:188-195, 1994

11. O'Brien P, Roos D, Pratt G, et al: Phase II multicenter study of brief single-agent methotrexate followed by irradiation in primary CNS lymphoma. J Clin Oncol 18:519-526, 2000

12. Glass J, Shustik C, Hochberg FH, et al: Therapy of primary central nervous system lymphoma with pre-irradiation methotrexate, cyclophosphamide, doxorubicin, vincristine, and dexamethasone (MCHOD). J Neurooncol 30:257-265, 1996

13. Brada M, Dearnaley D, Horwich A, et al: Management of primary cerebral lymphoma with initial chemotherapy: Preliminary results and comparison with patients treated with radiotherapy alone. Int J Radiat Oncol Biol Phys 18:787-792, 1990

14. Boiardi A, Silvani A, Valentini S, et al: Chemotherapy as first treatment for primary malignant non-Hodgkin's lymphoma of the central nervous system preliminary data. J Neurol 241:96-100, 1993

15. Boiardi A, Silvani A, Pozzi A, et al: Chemotherapy is effective as early treatment for primary central nervous system lymphoma. J Neurol 246:31-37, 1999

16. Brada M, Hjiyiannakis D, Hines F, et al: Short intensive primary chemotherapy and radiotherapy in sporadic primary CNS lymphoma (PCL). Int J Radiat Oncol Biol Phys 40:1157-1162, 1998

17. McAllister LD, Doolittle ND, Guastadisegni PE, et al: Cognitive outcomes and long-term follow-up results after enhanced chemotherapy delivery for primary central nervous system lymphoma. Neurosurgery 46:51-60, 2000

18. Cher L, Glass J, Harsh GR, et al: Therapy of primary CNS lymphoma with methotrexate-based chemotherapy and deferred radiotherapy: Preliminary results. Neurology 46:1757-1759, 1996

19. Guha-Thakurta N, Damek D, Pollack C, et al: Intravenous methotrexate as initial treatment for primary central nervous system lymphoma: Response to therapy and quality of life of patients. J Neurooncol 43:259-268, 1999

20. Macdonald DR, Cascino TL, Schold CS Jr, et al: Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 8:1277-1280, 1990

21. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958

22. Kalbfleisch JD, Prentice RL: The Statistical Analysis of Failure Time Data. New York, Wiley, 1980, pp 14

23. Cox DR: Regression models and life tables (with discussion). J R Stat Soc B 34:187-220, 1972

24. SAS Institute Inc.: SAS Proprietary Software Release 8.2 (TS2MO), Cary, NC, SAS Institute Inc., 1999-2001

25. Fisher RI, Gaynor ER, Dahlberg S, et al: Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 328:1002-1006, 1993

26. Schultz C, Scott C, DeAngelis L, et al: Radiation therapy (RT) alone vs. pre-RT chemotherapy (CTX) for the treatment of primary CNS lymphoma (PCNSL): Age matched survival analysis of RTOG 83-15 and RTOG 93-10. Proc Am Soc Clin Oncol 19:159a. 2000 (abstr 617)

27. Abrey LE, Yahalom J, DeAngelis LM: Treatment for primary CNS lymphoma: The next step. J Clin Oncol 18:3144-3150, 2000

28. Henson JW, Yang J, Batchelor T: Vitreous methotrexate concentration after high-dose intravenous therapy for primary central nervous system lymphoma. J Clin Oncol 17: 1329, 1999 (letter)

29. Sharis CM, Hochberg FH, Thornton AF, et al: Is there a role for cranial radiotherapy after primary high dose intravenous methotrexate in primary central nervous system lymphoma? Int J Radiat Oncol Biol Phys 45:327, 1999

30. Cho B, Hochberg F, Loeffler J, et al: Methotrexate reinduction in patients with relapsed primary central nervous system lymphoma. Neuro-Oncology 3:356, 2001

31. Herrlinger U, Schabet M, Brugger W, et al: German Cancer Society Neuro-Oncology Working Group NOA-03 multicenter trial of single-agent high-dose methotrexate for primary central nervous system lymphoma. Ann Neurol 51:247-252, 2002

32. Ng S, Rosenthal MA, Ashley D, et al: High-dose methotrexate for primary CNS lymphomas in the elderly. Neuro-Oncology 2:40-44, 2000