Intensive Methotrexate and Cytarabine Followed by High-Dose Chemotherapy With Autologous Stem-Cell Rescue in Patients With Newly Diagnosed Primary CNS Lymphoma: An Intent-to-Treat Analysis

By Lauren E. Abrey, Craig H. Moskowitz, Warren P. Mason, Michael Crump, Douglas Stewart, Peter Forsyth, Nina Paleologos, Denise D. Correa, Nicole D. Anderson, Dawn Caron, Andrew Zelenetz, Stephen D. Nimer, and Lisa M. DeAngelis

Purpose: **To assess the safety and efficacy of intensive methotrexate-based chemotherapy followed by high-dose chemotherapy (HDT) with autologous stem-cell rescue in patients with newly diagnosed primary CNS lymphoma (PCNSL).**

Patients and Methods: **Twenty-eight patients received induction chemotherapy using high-dose systemic methotrexate (3.5 g/m^2) and cytarabine (3 g/m^2 daily for 2 days). Fourteen patients with chemosensitive disease evident on neuroimaging then received high-dose therapy using carmustine, etoposide, cytarabine, and melphalan with autologous stem-cell rescue.**

Results: **The objective response rate to the induction-phase chemotherapy was 57%, and median overall survival is not yet assessable, with a median follow-up time of 28 months. The overall median event-free survival time is 5.6 months for all patients and 9.3 months for 14 patients who underwent transplantation. Six of these 14 patients (43%) remained disease-free at last follow-up. Treatment was well tolerated; there was one transplantation-related death. Prospective neuropsychologic evaluations have revealed no evidence of treatment-related neurotoxicity.**

Conclusion: **This treatment approach is feasible in patients with newly diagnosed PCNSL without evidence of significant related neurotoxicity. Although the transplantation results are similar to those achieved in patients with aggressive or poor-prognosis systemic lymphoma, the low response rate to induction chemotherapy and the significant number of patients who experienced relapse soon after HDT suggest that more aggressive induction chemotherapy may be warranted.**

J Clin Oncol 21:4151-4156.

PRIMARY CNS lymphoma (PCNSL) is an aggressive non-Hodgkin's lymphoma (NHL) confined to the brain, eyes, and CSF. Histologically, these tumors are most often classified as diffuse large B-cell lymphoma (DLBCL). Event-free survival (EFS) and overall survival (OS) are similar in aggressively treated PCNSL and systemic DLBCL patients.[1-3]

The best available therapy for PCNSL is a combination of methotrexate-based chemotherapy and cranial radiation; with this approach, median survival time ranges from 30 to 60 months.[4-7] Unfortunately, recurrent or progressive disease is common, and significant neurotoxicity is seen in long-term survivors. Patients older than 60 years who attain remission after receiving combined-modality therapy have at least a 70% risk of developing significant dementia.[7,8] Younger patients have a lower risk of treatment-related neurotoxicity, but this risk continues to increase with longer survival. For these reasons, efforts to improve the treatment of PCNSL have increasingly focused on ways to enhance the efficacy of chemotherapy and to eliminate or defer the need for cranial irradiation.

High-dose chemotherapy (HDT) with autologous stem-cell transplantation (ASCT) is an effective salvage treatment for relapsed or primary refractory NHL. In patients with chemosensitive disease, the long-term progression-free survival rate approaches 50%.[9] Similar results have been reported in one trial using HDT for relapsed or primary refractory PCNSL.[10] Because several studies have suggested an improved outcome when HDT with ASCT is used as part of the initial treatment of patients with high-risk NHL,[11,12] we applied this treatment strategy to patients with newly diagnosed PCNSL.

In this article, we report the results of a multicenter phase II trial using induction therapy with high-dose methotrexate and cytarabine followed by consolidative HDT and ASCT using the carmustine, etoposide, cytarabine, and melphalan (BEAM) regimen for patients with newly diagnosed PCNSL. Methotrexate and cytarabine were selected for the induction regimen on the basis of their ability to penetrate the blood-brain barrier when given systemically. Both drugs are currently used in the treatment of PCNSL, and methotrexate has been identified in many studies as the single most effective drug.[4,5,13] In addition, experimental studies have demonstrated synergistic

From the Departments of Neurology and Medicine and the Office of Clinical Research, Memorial Sloan-Kettering Cancer Center, New York, NY; Princess Margaret Hospital, University of Toronto, Toronto; Tom Baker Cancer Center, University of Calgary, Calgary, Canada; and the Department of Neurology, Evanston Hospital, Northwestern University, Chicago, IL.

Submitted May 2, 2003; accepted August 20, 2003.

Presented in part at the 37th American Society of Clinical Oncology Annual Meeting, San Francisco, CA, May 12-15, 2001.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Lauren Abrey, MD, Memorial Sloan-Kettering Cancer Center, Department of Neurology, 1275 York Ave, New York, NY 10021; e-mail: abreyl@mskcc.org.

0732-183X/03/2122-4151/$20.00

DOI: 10.1200/JCO.2003.05.024

cytotoxicity of methotrexate and cytarabine when administered in sequence.[14,15]

BEAM was selected as the ASCT conditioning regimen for several reasons: This regimen can be safely administered to older patients. (The median age of PCNSL patients is 60 years.) BEAM is the most common HDT regimen used for systemic DLBCL. Moreover, each of the agents included in this regimen has the ability to cross the blood-brain barrier and treat areas of microscopic disease.

PATIENTS AND METHODS

Patients

Immunocompetent, HIV-1–negative patients with newly diagnosed PCNSL were eligible for enrollment. All patients were required to have a histologic diagnosis of NHL by brain biopsy. Pretreatment evaluation to exclude systemic NHL included a bone marrow aspirate and biopsy, chest x-ray, and a computed tomography scan of the chest, abdomen, and pelvis. Patients were required to have adequate bone marrow function (peripheral leukocyte count $\geq$ 4,000 cells/μL and platelet count $\geq$ 150,000 cells/μL), liver function (bilirubin $\leq$ 2.0 mg/100 mL and AST $\leq 2 \times$ upper limit of normal) and renal function (creatinine clearance $\geq$ 50 mL/min/1.73 m^2). Patients with a history of prior cranial irradiation, other active primary malignancy, pre-existing immunodeficiency, or prior treatment for PCNSL were excluded. Patients with isolated CNS relapse of systemic NHL were eligible to participate if all other inclusion criteria were satisfied. All patients were required to have pretreatment lumbar puncture for CSF cytology and a complete ophthalmologic evaluation, including slit-lamp examination. The institutional review boards at all participating centers reviewed and approved this protocol. All patients provided written informed consent. The treatment protocol is summarized in Table 1.

Treatment

Methotrexate 3.5 g/m^2 was administered intravenously during 2 hours on weeks 1, 3, 5, 7, and 9. The dose was capped at a body-surface area of 2 m^2 or not to exceed 7 g total dose. Leucovorin rescue (25 mg orally every 6 hours) began 24 hours after treatment with methotrexate and continued for a total of 12 doses or until the daily serum methotrexate level was $\leq 1 \times 10^{-7}$ M. After four cycles of methotrexate, patients were assessed for response; a complete response (CR) or partial response (PR) was required to continue on protocol.

Table 1. Treatment Summary

Induction chemotherapy	
Methotrexate 3.5 g/m^2	
Administered every other week for 5 cycles	
Initial assessment of response performed after cycle 4	
Cytarabine 3 g/m^2 daily for 2 days	
Administered monthly for 2 days	
First dose given 72-96 hours after cycle 5 of methotrexate	
PBPC harvested after cycle 1	
High-dose chemotherapy, BEAM	
Day 7	Carmustine 300 mg/m^2
Day 6	
Day 5	Etoposide 100 mg/m^2 every 12 hours for 8 doses
Day 4	Cytarabine 200 mg/m^2 every 12 hours for 8 doses
Day 3	
Day 2	Melphalan 140 mg/m^2
Day 1	
Day 0	PBPC reinfusion

Abbreviations: PBPC, peripheral-blood progenitor cell; BEAM, carmustine, etoposide, cytarabine, and melphalan.

Two courses of cytarabine separated by 1 month were administered. Each course consisted of cytarabine 3 g/m^2/d for 2 days. The first dose of cytarabine was administered approximately 72 hours after the fifth dose of methotrexate or when the methotrexate level was $\leq 1 \times 10^{-7}$ M. Filgrastim 10 μg/kg/d was started 48 hours after the first course of cytarabine and continued until stem-cell leukapheresis was complete. Filgrastim 5 μg /kg/d was given after the second course of cytarabine and continued for 2 weeks or until the absolute neutrophil count was more than 3,000/μL.

Peripheral-blood progenitor cells were collected after the first course of cytarabine. Leukapheresis was started when the WBC count was more than 3000/μL or the number of CD34$^+$ cells as determined by flow cytometry was $\geq$ 50/μL. The target for cell collection was $\geq 2.5 \times 10^6$ CD34$^+$ cells/kg. A maximum of five leukaphereses were allowed. If fewer than 2.5×10^6 CD34$^+$ cells/kg were collected, bone marrow collection was permitted.

BEAM chemotherapy was administered in a dedicated in-patient stem-cell transplant service to all patients who had a CR or PR to induction-phase chemotherapy. Before HDT, all patients were evaluated with pulmonary function studies (including diffusing capacity for carbon monoxide), a dental consultation, and an echocardiogram or multiple-gated acquisition scan. Carmustine 300 mg/m^2 was given on day -7. On days -6 to -3, patients received etoposide 100 mg/m^2 every 12 hours (total dose, 800 mg/m^2) and cytarabine 200 mg/m^2 every 12 hours (total dose, 1,600 mg/m^2). Melphalan 140 mg/m^2 was given on day -2. There was a minimum period of 24 hours between the last dose of chemotherapy and the peripheral-blood progenitor cell infusion on day 0. Granulocyte colony-stimulating factor was administered at 5 μg/kg every 12 hours beginning on day $+1$ and continued until the absolute neutrophil count was more than 1,000/μL for 3 days or more than 10,000/μL for 1 day. Standard supportive measures as described by institutional guidelines were followed for all patients throughout their hospitalization.

Response to treatment was assessed in all patients after four cycles of methotrexate, immediately before BEAM chemotherapy, 3 months after transplantation, and approximately every 3 months thereafter. Magnetic resonance imaging (MRI) of the brain with gadolinium was used to assess radiographic response; baseline MRI was obtained in all patients within 2 weeks before initiating therapy. In patients with positive CSF cytology at diagnosis, repeat lumbar puncture was required to assess response; patients with ocular lymphoma required repeat slit-lamp examination. CR was defined as the disappearance of all enhancing tumor. In addition, patients must have discontinued corticosteroid therapy and be neurologically stable or improved. Repeat CSF cytology must be negative for malignant cells and repeat ophthalmologic examination was required to be negative for persistent tumor. PR was defined as a $\geq$ 50% decrease in tumor size in comparison with the baseline MRI scan. Patients must be neurologically improved or stable while receiving a decreasing or stable dose of corticosteroids. Progressive disease was defined as a more than 25% increase in enhancing tumor or the appearance of any new lesion in the brain, CSF, or eyes. Stable disease included all other situations.

Prospective neuropsychologic evaluations were performed at baseline, immediately before HDT, 6 months after ASCT, and every 6 months thereafter. A battery of neuropsychologic tests was administered to assess multiple cognitive domains, including attention and executive function, learning and memory, psychomotor, language, and visual-construction abilities; mood and quality of life measures were also included (Table 2). Patients were allowed to refuse neuropsychologic testing and still participate in the therapeutic portion of this trial.

Statistics

The primary end point of this study was to assess the feasibility of this treatment regimen in patients with PCNSL. Toxicity was graded using the National Cancer Institute common toxicity criteria, version 2.0. An early stopping rule was included to protect against excess mortality related to HDT and ASCT.

EFS and OS were assessed from the first day of induction-phase methotrexate. An event was defined as a treatment failure (a treatment-related toxicity precluding HDT and ASCT or a failure to achieve a PR or better

during the induction phase), relapse or progression after ASCT, or death as a result of any cause. If relapse or treatment failure occurred before a patient's death, the former date was used for the calculation of EFS. Survival curves were generated using the Kaplan-Meier product limit method[16] and were compared using the log-rank test. Analysis of discrete variables was performed using the χ^2 method, with Yates correction for expected values less than 5. All patients who began this treatment regimen were included in the analysis in an intent-to-treat fashion. Follow-up extended through December 31, 2002.

RESULTS

Patients

Twenty eight patients—10 women and 18 men—were enrolled onto the study. Median age was 53 years (range, 25 to 71 years), and median Karnofsky performance score (KPS) was 70 (range, 30 to 100). All patients had parenchymal brain disease; three also had positive CSF cytology, and three others had concomitant ocular lymphoma. No patient had evidence of disease in all three compartments. One patient with systemic lymphoma diagnosed and treated 10 years prior was enrolled with isolated CNS lymphoma. No patient had evidence of systemic lymphoma at the time of enrollment.

Overall median survival time for all patients (n = 28) enrolled onto this trial has not been assessed (Fig 1); median EFS time is 5.6 months. Eighteen patients remain alive with an intent-to-treat EFS and OS of 20% and 55%, respectively, at 28 months median follow-up (range, 1 to 49). There was no significant difference in either EFS or OS as a result of age (< 50 *v* ≥ 50 years) or KPS (< 70 *v* ≥ 70 years).

Toxicity

There was one death attributed to toxicity during treatment; this patient died as a result of liver failure 2 months after ASCT. An autopsy found only steatosis with no evidence of recurrent tumor. A total of 13 serious adverse events were reported; 11 occurred during the induction phase and two during HDT. One patient developed both grade 4 infection without neutropenia and grade 3 melena while hospitalized for HDT. This required intensive care unit management and resulted in a prolonged hospital stay of 36 days. The nine serious adverse events attributed to the induction-phase chemotherapy were grade 4 neutropenia, grade 3 neutropenia, grade 4 hemorrhage, grade 3 bone pain, grade 3 fatigue, grade 3 ALT or AST elevation, grade 4 pneumonitis, and two deep venous thromboses. The remaining two adverse events occurring during induction chemotherapy and most likely unrelated to treatment included one seizure and one grade 3 dyspnea that could not be explained despite extensive workup.

Response to Induction Chemotherapy

Twenty-five patients were assessed for radiographic response after four cycles of methotrexate; 16 patients (57%; 95% CI, 39% to 75%) had a PR or better and proceeded to high-dose cytarabine. Nine patients had no improvement and were removed from protocol, three patients had stable disease, and six experienced disease progression during initial treatment with methotrexate. Three additional patients were removed from the protocol during induction methotrexate and were not assessed for response. One patient developed a breast mass that proved to be DLBCL on biopsy; this mass was not present on initial systemic evaluation. One patient developed grade 2 renal insufficiency that precluded additional treatment with methotrexate, and another patient was removed at the request of the family as a result of poor neurologic condition. These three patients were not considered assessable.

Fourteen patients had either a PR (six patients) or CR (eight patients) after completing two cycles of high-dose cytarabine and proceeded to HDT. One patient experienced disease progression during high-dose cytarabine and was removed from the study. Another patient had a gastrointestinal hemorrhage into a pancreatic pseudocyst while receiving anticoagulation for a deep venous thrombosis; this occurred during his first cycle of cytarabine and necessitated transfer to the intensive care unit. This complication precluded additional treatment on protocol.

HDT With ASCT

Fourteen patients (50% by intention-to-treat analysis) completed HDT and ASCT (Table 2). The median number of $CD34^+$

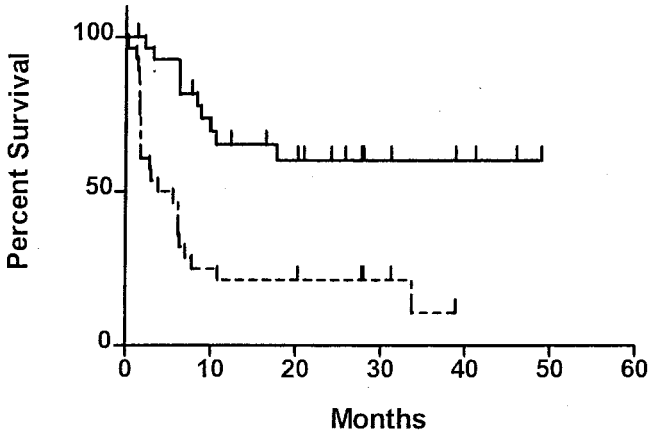

Fig 1. Kaplan-Meier plot: event-free survival (···) and overall survival (——) of all patients (n = 28).

Table 2. Neuropsychologic Test Battery

Attention and execution
Digit span subtest of the Wechsler Adult Intelligence Scale—III
Trail making test (parts A and B)
Brief test of attention
Stroop color-word test
Phonemic verbal fluency test
Learning and memory
Hopkins Verbal Learning Test, revised
Psychomotor skills
Grooved pegboard test
Language and visual-construction ability
Boston Naming Test
Category fluency test
Clock drawing test
Mood and quality of life
Beck Depression Inventory
Functional Assessment of Cancer Therapy—Brain (FACT-Br)

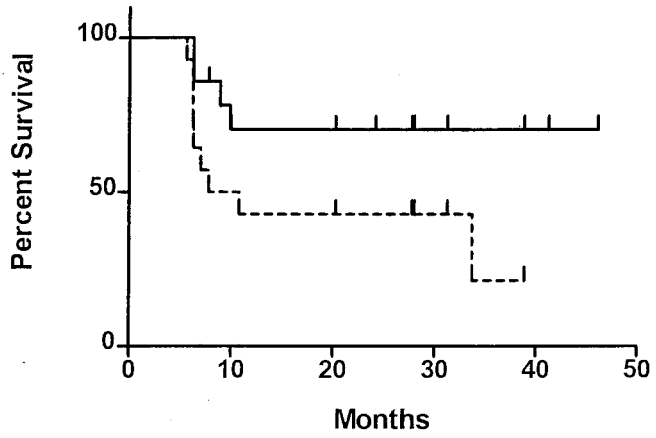

Fig 2. Kaplan-Meier plot: event-free survival (···) and overall survival (——) of the 14 patients who completed high-dose chemotherapy.

cells collected by leukapheresis was 25.8×10^6 cells/kg (range, 8.56 to 254×10^6cells/kg); no patient required a bone marrow collection. In general, treatment was well tolerated. Median hospital stay was 14 days after ASCT (range, 11 to 36 days). All patients had pancytopenia, and marrow engraftment occurred in all cases. Median time to absolute neutrophil count $\geq 500/\mu L$ was 8 days, and median time to platelet count $\geq 2{,}000/\mu L$ was 9 days after ASCT. No unexpected side effects, neurotoxicity, or seizures were seen. Only one patient experienced any serious adverse event that resulted in a prolonged hospitalization. There was one death before day 100 after ASCT that was considered a transplantation-related mortality.

Median OS of patients who completed HDT with ASCT is not yet assessable (Fig 2); the median follow-up of these surviving patients is 28 months (range, 10 to 46 months). Median EFS is 9.3 months. EFS and OS rates for patients undergoing transplantation are 43% and 60%, respectively.

Patterns of Failure After HDT

Eight patients developed progressive disease a median of 2.3 months after transplantation (range, 1.3 to 29.6 months); all but one patient experienced relapse within 7 months of transplantation. Four patients experienced relapse in the brain alone, and one patient each experienced relapse systemically, in the CSF, in the brain and CSF, and in the brain and systemically. Neither response to induction phase (PR *v* CR; $P = .9$) nor extent of disease (absence *v* presence of ocular or CSF lymphoma; $P = .79$) predicted risk of subsequent relapse. The one patient with isolated systemic relapse is the only patient enrolled on protocol with a history of systemic NHL and isolated brain disease at enrollment. The two patients with leptomeningeal relapse had positive CSF cytology at diagnosis, but both had a negative CSF cytology before HDT.

Seven of the eight patients received additional treatment for progressive disease; four were treated with additional chemotherapy and have not received cranial irradiation, two received whole-brain radiotherapy, and one received whole-brain radiotherapy and additional chemotherapy (Table 3). Four patients remain alive more than 1 year after relapse (13+, 15+, 31+, and 35+ months, respectively), three of whom were treated with chemotherapy alone.

Neuropsychologic Assessment

In total, 14 patients completed a cognitive evaluation at diagnosis. Seven patients were assessed after induction-phase chemotherapy and had serial examinations for comparison; all demonstrated improvement in all cognitive domains concomitant

Table 3. Patients Undergoing Transplantation

Age	Sex	KPS	EOD	Pre-ASCT	Post-ASCT	TTP (months)	Site of Relapse	Treatment for Relapse	Time Survival (months)	Status
32	Female	100	Brain and eye	CR	PD	1.7	Brain	WBRT	37.4	AWD
60	Male	70	Brain	PR	CR				23.2	NED
41	Female	50	Brain	CR	CR	5.1	Systemic	Rituximab, CHOP	20.1	NED
59	Male	90	Brain and CSF	PR	PD	1.3	CSF	IO Ara-C	4	DOD
52	Male	70	Brain	CR	CR	2.3	Brain	None	2.4	DOD
58	Male	90	Brain	CR	CR				27.1	NED
49	Male	50	Brain	PR	CR	29.6	Brain and systemic	MPV, proMACE-cytaBOM, rituximab	42	AWD
35	Female	100	Brain	CR	CR				23.7	NED
56	Male	60	Brain	PR	PR	2.7	Brain	WBRT	5.6	DOD
41	Male	70	Brain	PR	PR	6.8	Brain	Busulfan, thiotepa, CTX with ASCT	37.9	NED
55	Female	70	Brain	CR	NA				2.5	DOC
25	Male	50	Brain and CSF	CR	PD	2	Brain and CSF	WBRT	5.6	DOD
59	Female	60	Brain and eye	CR	CR				36.8	NED
60	Male	90	Brain	PR	CR				34	NED

Abbreviations: KPS, Karnofsky performance status; EOD, initial extent of disease at diagnosis; Pre-ASCT, radiographic response prior to high-dose chemotherapy; Post-ASCT, best radiographic response following high-dose chemotherapy and autologous stem-cell transplantation; TTP, time to progression from day of stem-cell reinfusion; CR, complete response; PD, progressive disease; PR, partial response; NA, not assessable; WBRT, whole-brain radiotherapy; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; IO Ara-C, intra-Ommaya cytarabine; MPV, methotrexate, procarbazine, and vincristine; proMACE-cytaBOM, prednisone, methotrexate-levcovorin, Adriamycin, cyclophosphamide, etoposide + cytarabine, bleomycin, oncovin, and methotrexate; CTX, cyclophosphamide; ASCT, autologous stem cell transplantation; AWD, alive with disease; NED, no evidence of disease; DOD, dead of disease; DOC, dead of complications.

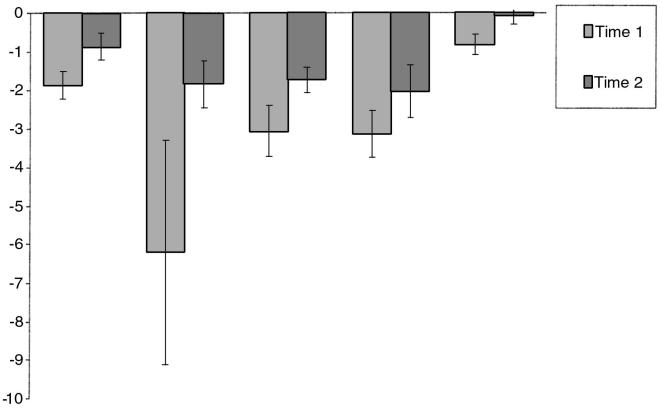

Fig 3. Neurocognitive test results showing mean *z* scores at baseline (Time 1) and after induction chemotherapy (Time 2); error bars = 1 SE.

with a response of their disease to treatment (Fig 3). Patients who were removed from the study for any reason were not reexamined. Four patients with continued follow-up after ASCT displayed average to low average performance with no evidence of significant delayed treatment-related neurocognitive decline. Three patients returned to their usual work after ASCT; one 60-year-old man retired but reportedly returned to his normal level of function.

DISCUSSION

Our experience with this treatment regimen clearly indicates that this is a feasible approach for patients with newly diagnosed PCNSL. Patients tolerated both the induction phase and the HDT plus ASCT with acceptable toxicity. Some patients have had prolonged disease control using chemotherapy alone. Significantly, no patient has developed cognitive impairment as a consequence of treatment, including patients older than 50 years at the time of diagnosis. Although the average age and KPS of patients enrolled onto this trial may be somewhat better than that of the so-called usual PCNSL patient, neither age nor KPS correlated with EFS or OS. In fact, the patients who derived the greatest benefit from this trial tended to be older patients.

The primary rationale to explore this treatment strategy in newly diagnosed PCNSL patients was to deliver an intensive and exclusively chemotherapy-based treatment. Although our small sample size, in particular the number of patients who completed HDT, limits the interpretation of our results, studies of newly diagnosed high-risk systemic lymphoma patients treated with HDT have reported similar findings. The 3-year OS probability of our 28 patients (60%) is similar to other HDT protocols for systemic NHL patients[12,17,18] and compares favorably with other recent trials reported for PCNSL.[19,20] In assessing the feasibility of this approach for patients with PCNSL, the 50% of our patients who completed HDT is comparable to other reported studies of HDT with ASCT in NHL, in which 40% or more of patients experience disease progression during induction-phase chemotherapy.[17,21]

The radiographic response rate to the induction-phase chemotherapy was lower than expected; 50% of patients had an inadequate response to single-agent methotrexate at this dose. Other studies using single-agent methotrexate regimens in PCNSL have also reported low response rates ranging from 30% to 50%.[19,22] Although this may suggest that some patients have inherently chemoresistant tumor, it may also indicate that a more aggressive multiagent induction strategy is necessary to cytoreduce these tumors. In contrast, we have previously reported a combination regimen of high-dose methotrexate (3.5 g/m^2) with procarbazine and vincristine that resulted in an objective response rate (CR + PR) of 90%,[4] and similar results were obtained by the Radiation Therapy Oncology Group using the same combination regimen with a lower dose of methotrexate (2.5 g/m^2).[20] For the current protocol, a simplified regimen of single-agent methotrexate was used to ensure that patients would not have significant myelosuppression during the induction phase that might compromise the stem-cell collection. Given the excellent results of our stem-cell collection, a more aggressive induction regimen may be feasible; alternatively, stem cells could be collected earlier. The need to use a more aggressive induction regimen is also supported by several studies in systemic NHL, in which abbreviated induction regimens followed by HDT have had inferior outcomes to those studies using HDT after conventional induction regimens.[12,17,18]

The choice of the optimal HDT regimen to use for PCNSL is difficult. Perhaps the most important rationale for using BEAM is that this regimen is generally well tolerated in older patients, and half of the patient population with PCNSL is older than 60 years. However, although our patients tolerated the regimen well, nearly 50% experienced disease relapse within a few months of ASCT. Although each of the agents in BEAM can cross the blood-brain barrier, the levels achieved in the CNS may be suboptimal. Furthermore, our patients had been exposed previously to higher doses of cytarabine during the induction phase. In contrast, Soussain et al[10] published their experience using an HDT regimen of busulfan, thiotepa, and cyclophosphamide for patients with recurrent or refractory PCNSL or ocular lymphoma. In their series, only four of 20 patients experienced disease progression after HDT with ASCT, suggesting that these agents may be more effective in the treatment of CNS disease. In particular, busulfan and thiotepa have excellent CNS penetration, with CSF levels in excess of 80% serum levels.[23] However, high-dose busulfan-containing regimens may be significantly more toxic and therefore more difficult to administer safely to older patients. Soussain et al[10] noted increased toxicity in their PCNSL patients older than 60 years. A recent series of seven newly diagnosed or recurrent PCNSL patients with a poor prognosis treated by Cheng et al[24] suggests that a transplant regimen including busulfan and thiotepa may be both tolerable and efficacious in the patient population, although in this series, two of three patients older than 60 years had significant complications.

Interestingly, half of our patients with recurrent lymphoma after HDT were able to attain a second durable remission in excess of 1 year, frequently with additional chemotherapy alone. One patient was given salvage therapy with a second HDT and ASCT treatment (using thiotepa and busulfan), and he remains

alive with no evidence of disease nearly 3 years after his relapse. Furthermore, it is noteworthy that four of five patients who remain disease-free after HDT are older than 55 years. Therefore, older patients, who constitute approximately half of the patients with PCNSL, can benefit from this intensive chemotherapy approach.

Finally, one of the most compelling reasons to pursue this aggressive chemotherapy-only treatment strategy in newly diagnosed PCNSL patients was to eliminate the need for radiotherapy and thereby eliminate or diminish the risk of treatment-related neurocognitive toxicity. Thus, a crucial finding of this study is the lack of any significant treatment-related neurocognitive decline. This is particularly important because neurocognitive dysfunction has been reported as a complication of high-dose chemotherapy with stem-cell rescue in the breast cancer population. Furthermore, several trials have been published using high-dose chemotherapy with stem-cell rescue for patients with recurrent or refractory primary brain tumors. In each of these series, there has been a significant incidence of treatment-related neurotoxicity, suggesting that an HDT with ASCT strategy may not be feasible in patients who have received prior cranial radiation.[10,25]

In conclusion, the development of new strategies to treat PCNSL using intensive chemotherapy alone or in combination with reduced doses of radiotherapy is critical to improve disease control while maintaining cognitive function. The use of HDT and ASCT is clearly feasible in this patient population and, given the success of this strategy in systemic NHL, additional study using a more intensive, conventional induction regimen and possibly a different HDT conditioning regimen, including agents such as busulfan and thiotepa, is warranted.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

REFERENCES

1. Deangelis LM: Current management of primary central nervous system lymphoma. Oncology 9:63-76, 1995
2. Fisher R, 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
3. Coltman AC Jr, Dahlberg S, Jones ES, et al: CHOP is curative in thirty percent of patients with large cell lymphoma: A twelve year Southwest Oncology Group follow up. Skarin AT (ed): Update on Treatment for Diffuse Large Cell Lymphoma. New York, NY, Park Row, 1986, pp 71-77
4. Abrey LE, Yahalom J, DeAngelis LM: Treatment for primary central nervous system lymphoma (PCNSL): The next step. J Clin Oncol 18:3144-3150, 2000
5. DeAngelis LM, Seiferheld W, Schold SC, et al: Combination chemotherapy and radiotherapy for primary central nervous system lymphoma: Radiation Therapy Oncology Group Study 93-10. J Clin Oncol 20:4643-4648, 2002
6. 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
7. Abrey LE, Yahalom J, DeAngelis LM: Long term survival in primary central nervous system lymphoma (PCNSL). J Clin Oncol 16:859-863, 1998
8. Abrey LE, Yahalom J, DeAngelis LM: Relapse and late neurotoxicity in primary central nervous system lymphoma. Neurology 48:A18, 1997 (abstr 18)
9. Philip T, Guglielmi C, Hagenbeek A, et al: Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med 333:1540-1545, 1995
10. Soussain C, Suzan F, Hoang-Xuan K, et al: Results of intensive chemotherapy followed by hematopoietic stem-cell rescue in 22 patients with refractory or recurrent primary CNS lymphoma or intraocular lymphoma. J Clin Oncol 19:742-749, 2001
11. Kewalramani T, Moskowitz CH: Upfront transplantation for poor-risk aggressive non-Hodgkin lymphoma and Hodgkin's disease: Who benefits? Curr Oncol Rep 3:271-278, 2001
12. Haioun C, Lepage E, Gisselbrecht C, et al: Survival benefit of high dose therapy in poor-risk non-Hodgkin's lymphoma: Final analysis of the prospective LNH87-2 protocol—A Groupe d'Etude des Lymphomes de l'Adulte study. J Clin Oncol 18:3025-3030, 2000
13. Doolittle ND, Miner ME, Hall WA, et al: Safety and efficacy of a multicenter study using intraarterial chemotherapy in conjunction with osmotic opening of the blood-brain barrier for the treatment of patients with malignant brain tumors. Cancer 88:637-647, 2000
14. Edelstein M, Vietti T, Valeriote F: The enhanced cytotoxicity of combinations of 1-beta-D-arabinofuranosylcytosine and methotrexate. Cancer Res 35:1555-1558, 1975
15. Cadman E, Eiferman F: Mechanisms of synergistic cell killing when methotrexate precedes cytosine arabinoside. J Clin Invest 64:788-797, 1979
16. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958
17. Martelli M, Gherlinzoni F, De Renzo A, et al: Early autologous stem-cell transplantation versus conventional chemotherapy as front-line therapy in high-risk, aggressive non-Hodgkin's lymphoma: An Italian multicenter randomized trial. J Clin Oncol 21:1255-1262, 2003
18. Santini G, Coser P, Congiu AM, et al: VACOP-B, high-dose cyclophosphamide and high-dose therapy with peripheral blood progenitor cell rescue for aggressive non-Hodgkin's lymphoma with bone marrow involvement: A study by the non-Hodgkin's Lymphoma Co-operative Study Group. Haematologica 85:160-166, 2000
19. Batchelor T, Carson K, O'Neill A, et al: Treatment of primary CNS lymphoma with methotrexate and deferred radiotherapy: A report of NABTT 96-07. J Clin Oncol 21:1044-1049, 2003
20. DeAngelis LM, Seiferheld W, Schold SC, et al: Combination chemotherapy and radiotherapy for primary central nervous system lymphoma: Radiation Therapy Oncology Group Study 93-10. J Clin Oncol 20:4615-4617, 2002
21. Kluin-Nelemans HC, Zagonel V, Anastasopoulou A, et al: Standard chemotherapy with or without high-dose chemotherapy for aggressive non-Hodgkin's lymphoma: Randomized phase III EORTC study. J Natl Cancer Inst 93:4-5, 2001
22. 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
23. Wiebe VJ, Smith BR, DeGregorio MW, et al: Pharmacology of agents used in bone marrow transplant conditioning regimens. Crit Rev Oncol Hematol 13:241-270, 1992
24. Cheng T, Forsyth P, Chaudhry A, et al: Lymphoma: High-dose thiotepa, busulfan, cyclophosphamide and ASCT without whole-brain radiotherapy for poor prognosis primary CNS lymphoma. Bone Marrow Transplant 31:679-685, 2003
25. Cairncross JG, Swinnen L, Bayer R, et al: Myeloablative chemotherapy for recurrent aggressive oligodendroglioma. J Neurooncol 2:114-119, 2000