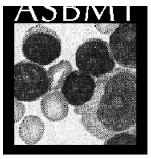

High-Dose Therapy With Hematopoietic Cell Transplantation for Patients With Central Nervous System Involvement by Non-Hodgkin's Lymphoma

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ABSTRACT

Central nervous system (CNS) involvement by non-Hodgkin's lymphoma (NHL) carries a poor patient prognosis whether it occurs as a primary site of disease or secondarily in patients with systemic disease. In a group of 481 patients undergoing high-dose therapy with hematopoietic cell transplantation (HCT) for NHL, 15 patients (3.1%) were identified with CNS involvement. Two patients had primary CNS lymphoma, and 13 had secondary disease. All patients received intrathecal chemotherapy, and 13 received CNS radiotherapy before transplantation. Fourteen patients received systemic chemotherapy. At the time of transplantation, both patients with primary CNS lymphoma and 8 patients with secondary disease had achieved a complete response, 3 patients had achieved a partial response, 1 had failed induction therapy, and 1 had progression of CNS disease before high-dose therapy. Fourteen patients received carmustine, etoposide, and cyclophosphamide as the preparative regimen, and 1 patient received fractionated total body irradiation instead of carmustine. The 2 patients with primary CNS lymphoma were alive and free of disease, 1 at 1085 days after HCT and 1 at 3704 days after HCT. The actuarial 5-year event-free survival (EFS) was 46% ± 26%, and overall survival (OS) was 41% ± 28%. The median EFS and OS were 2.2 and 1.5 years, respectively. Three patients experienced symptomatic memory loss or intellectual decline after therapy, 1 patient developed paraplegia, and 1 patient had a thrombotic stroke 20 months after HCT. Despite treatment-related toxicities, 7 patients responding to quality-of-life questions at approximately 1 year after HCT gave their overall quality of life a median rating of 9 out of a possible 10 (range, 6-10). High-dose therapy with autologous HCT can produce extended EFS in patients with secondary CNS lymphoma and possibly in those with primary CNS NHL.

KEY WORDS

CNS lymphoma • Autologous transplantation • Non-Hodgkin's lymphoma

INTRODUCTION

Central nervous system (CNS) involvement by non-Hodgkin's lymphoma (NHL) carries a poor patient prognosis [1-6]. CNS involvement occurs as a secondary site of disease in 5% to 19% of patients with advanced systemic NHL [2,3]. A review of 2 Southwest Oncology Group studies demonstrated a median survival of 2 months after the diagnosis of secondary CNS disease [1]. A 1982 Stanford University study showed comparably poor results, with a median survival of only 9 weeks [7]. Mortality in these patients is often the result of progressive systemic NHL rather than refractory CNS disease.

Primary CNS involvement occurs as a distinct clinical entity that accounts for 1% to 2% of cases of NHL [5,8]. Despite the use of intensive therapies, including CNS radiation [3-5], combination chemotherapy with or without radiotherapy [8-12], and systemic chemotherapy with osmotic disruption of the blood-brain barrier, median survival remains poor. In addition, these therapies have often resulted in

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significant late neurotoxicity. At this time the optimal management of patients with CNS disease remains unclear.

High-dose therapy with autologous hematopoietic cell transplantation (HCT) is superior to standard-dose therapy and can be curative for patients with recurrent intermediate- and high-grade NHL [13]. There are sparse data concerning the use of autologous HCT in patients with secondary CNS lymphoma [14,15]. European Bone Marrow Transplant (EBMT) Lymphoma Registry data demonstrate that patients with responsive NHL and CNS disease may achieve durable remissions with HCT [14]. Not surprisingly, patients with persisting CNS lymphoma at the time of high-dose therapy respond poorly to HCT. To date, there are no published reports of autologous HCT for patients with primary CNS lymphoma (PCNSL).

To evaluate the role of high-dose therapy in patients with CNS lymphoma, we reviewed the records of patients who underwent autologous HCT for NHL at Stanford University Medical Center. In this group of 481 patients were 15 patients (3.1%) with CNS involvement by NHL, including 2 patients with primary CNS lymphoma. This report reviews the course and outcome of these patients.

PATIENTS AND METHODS

Patients

Between September 1988 and December 1998, 481 patients with NHL underwent high-dose therapy with autologous HCT at Stanford University Medical Center. A database review identified 15 patients with CNS involvement by NHL. Patient characteristics are detailed in the Table. All treatment protocols were reviewed and approved by the Human Subjects Committee of the Stanford University Medical Center.

High-Dose Therapy

The high-dose preparative regimen consisted of either carmustine (15 mg/kg, to a maximum dose of 550 mg/m^2) or 12 Gy of fractionated total body irradiation (fTBI), followed by etoposide (60 mg/kg) and cyclophosphamide (100 mg/kg of ideal body weight). This regimen was administered as previously described [16,17].

Patients who underwent transplantation after August 1993 received chemotherapy and granulocyte colony-stimulating factor (G-CSF)–mobilized and purged peripheral blood progenitor cells (PBPCs) rather than bone marrow grafts [18]. Patients who underwent transplantation before then received purged bone marrow grafts. Some of the bone marrow and all of the PBPC grafts were purged with a panel of monoclonal antibodies (mAbs) directed against either B-cell (CD9, CD10, CD19, or CD20) or T-cell (CD2, CD3, CD4, CD5, CD6, or CD8) antigens and rabbit complement [16,19]. The methods for bone marrow and PBPC collection have been previously described [18,19].

Posttransplantation supportive care included hospitalization in private, air-filtered rooms, antimicrobial therapy, and blood product transfusion support as previously described [16]. Patients who were treated after April 1991 received G-CSF 5 μg/kg daily commencing on day 1 after stem cell transplantation and continuing through the period of neutrophil recovery [16,20].

Quality-of-Life Assessment

Commencing at day 90 and continuing through 1 year after HCT, surviving patients were asked to respond to a telephone survey reviewing selected quality-of-life parameters. The 1-year time point was chosen for review to evaluate patients' overall quality of life after completion of posttransplantation therapy and recovery from acute treatment-related toxicities. The questionnaires were developed internally to address issues unique to the transplantation process but were modeled on other measures that assessed overall health, employment, marital, sexual, and functional status. Patients were asked to assign an overall numeric score to their quality of life on a scale of 1 to 10 (with 1 being a "low point" in life, and 10 the "best ever"). The questionnaires were administered by a nursing specialist and scored as previously described [21].

Statistical Analysis

Event-free survival (EFS) and overall survival (OS) were determined from the time of transplantation to the date of documented recurrence, death, or most recent follow-up. OS and EFS curves were derived using the methods of Kaplan and Meier [22].

RESULTS

Therapy Before Transplantation

CNS involvement was documented by cytology in 7 patients (patient numbers [SPN] 50, 126, 135, 940, 999, 1405, and 1409), cytology and imaging studies in 2 patients (SPN 1303 and 1502), biopsy in 3 patients (SPN 387, 842, and 1515), and imaging studies alone in 3 patients (SPN 138, 295, and 1330). Two patients had primary CNS lymphoma (1 with leptomeningeal disease and 1 with cauda equina disease, a positive cerebrospinal fluid cytology result, and brain parenchymal abnormalities on a magnetic resonance imaging [MRI] scan). Thirteen patients had secondary CNS involvement. CNS disease was present in 5 of these patients at the time of diagnosis and was diagnosed in 8 patients at the time of progression during therapy or relapse. Fourteen of 15 patients received doxorubicin-based combination chemotherapy before PBPC mobilization. One patient (SPN 50) with primary CNS lymphoma was treated with intrathecal (IT) therapy and cranial-spinal radiotherapy alone before high-dose therapy. All patients received IT therapy with methotrexate, cytarabine, or both before transplantation. Thirteen of 15 patients received CNS radiotherapy before HCT (pretransplantation CNS radiotherapy is detailed in the Table).

Before HCT, both of the patients with PCNSL achieved a complete response (CR). Of the 5 patients with secondary CNS disease identified at the time of diagnosis, 2 (SPN 940 and 1405) achieved a CR before HCT, 3 (SPN 138, 295, and 1330) had residual imaging study abnormalities in the CNS, and 1 (SPN 138) had residual bulky adenopathy. Of the 8 patients who had CNS disease identified at relapse or progression, 6 (SPN 126, 135, 387, 842, 999, and 1409) achieved a CR; 1 (SPN 1515) had a residual MRI parenchymal abnormality, and another (SPN 1502) developed new MRI evidence of lumbar spine nerve root abnormalities after mobilization.

*Patient Characteristics, Therapy, and Outcome**

	SPN	Age	Sex	Sites of Disease	Pretransplantation Histology	Pretransplantation Response	Pretransplantation Systemic Regimen	CNS Therapy	Outcome
Primary CNS lymphoma	50	40	M	Meningeal	DLCL	CR	None	IT	CCR (3704 d)
	1303	42	M	Parenchymal	SNCCL	CR	CEPP, CHOP	IT	CCR (1085 d)
Secondary CNS lymphoma at diagnosis	138	39	M	Parenchymal	DLCL	IF	MACOP-B	Radiotherapy	CCR (3530 d)
	295	24	F	Parenchymal	DLCL, DM	PR	M-BACOD, CHOP	None	Hepatic veno-occlusive disease, death (21 d)
	940	28	F	Meningeal	High-grade (immunoblastic)	CR	CHOP, high-dose methotrexate	None	Relapse (33 d), death (35 d)
	1330	54	F	Parenchymal	DLCL	PR	CHOP	IT	CCR (800 d)
	1405	24	M	Meningeal	DLCL	CR	CHOP	Radiotherapy	CCR (761 d)
Secondary CNS lymphoma at relapse/progression	126	31	M	Meningeal	DM	CR	M-BACOD	None	Relapse (75 d), death (109 d)
	135	53	M	Meningeal	DLCL, DM	CR	CHOP, MACOP-B, COP-BLAM	None	Relapse (72 d), death (84 d)
	387	51	F	Parenchymal	LL	CR	CHOP	None	CCR (2826 d)
	842	33	F	Parenchymal	DLCL	CR	CAP, MACOP-B	IT	Relapse (579 d), death (1033 d)
	999	47	M	Meningeal	FSCCL, DLCL	CR	CHOP, ESHAP, cytarabine	None	Relapse (532 d), death (799 d)
	1409	24	M	Meningeal	LL	CR	Nebraska lymphoblastic lymphoma regimen	None	Relapse (76 d), death (112 d)
	1502	25	M	Meningeal	DLCL (T cell)	PD	CHOP, DHAP	None	Relapse (41 d), death (43 d)
	1515	28	F	Parenchymal	DLCL	PR	CHOP	None	CCR (539 d)

*CAP indicates cyclophosphamide, doxorubicin, cisplatin; CCR, continuing complete response; CEPP indicates cyclophosphamide, etoposide, procarbazine, prednisone; CHOP indicates cyclophosphamide, doxorubicin, vincristine, prednisone; COP-BLAM indicates cyclophosphamide, vincristine, prednisone, bleomycin, doxorubicin, procarbazine; CR, complete response; DHAP indicates dexamethasone, cisplatin, cytarabine; DLCL, diffuse large cell lymphoma; DM, diffuse mixed; ESHAP indicates etoposide, methylprednisolone, cisplatin, cytarabine; FSCCL, follicular small cleaved cell lymphoma; IF, induction failure; LL, lymphoblastic lymphoma; MACOP-B indicates methotrexate, leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; M-BACOD indicates methotrexate, leucovorin, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone; PD, progressive disease; PR, partial response; SNCCL, small, non-cleaved cell lymphoma (non-Burkitt's); SPN, patient number.

High-Dose Therapy and Transplantation

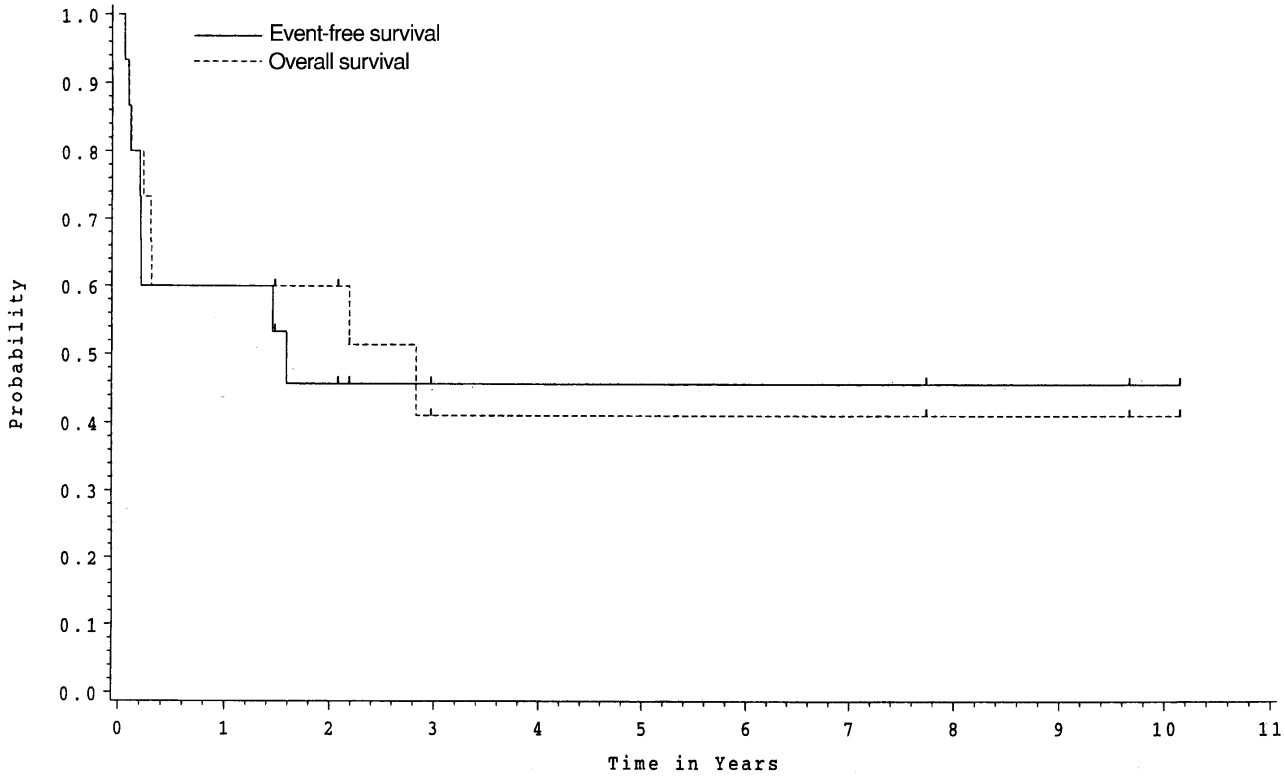
Fourteen patients received carmustine, etoposide, and cyclophosphamide as their preparative regimen. One patient who did not receive pretransplantation radiotherapy received fTBI instead of carmustine. Hematopoietic cell support consisted of bone marrow grafts in 6 patients, 3 of whom also received a boost of peripheral blood mononuclear cells. Four of the bone marrow grafts were purged with mAbs and complement before cryopreservation; 1 was purged with 4-hydroxycyclophosphamide. All of the remaining patients received chemotherapy (cyclophosphamide 4 gm/m^2 [1 patient] or etoposide 2 gm/m^2 [8 patients]) and G-CSF–mobilized, mAb-purged PBPC grafts.

The patients who received bone marrow grafts achieved an absolute neutrophil count (ANC) ≥500/mm^3 in a median of 16.5 days (range, 9-19 days). Two patients did not achieve platelet engraftment; 1 patient (SPN 135) experienced a rapid bone marrow recurrence of NHL, and another (SPN 295) died of hepatic veno-occlusive disease before platelet engraftment. The remaining 4 patients achieved a platelet count ≥20,000/mm^3 in a median of 16 days (range, 15-21 days). Patients who received PBPC grafts achieved an ANC ≥500/mm^3 and a platelet count ≥20,000/mm^3 in a median of 8 days (range, 8-9 days) and 14 days (range, 11-23), respectively. These recovery times are comparable to those previously published [16].

Posttransplantation Therapy

Six patients received posttransplantation therapy with either radiotherapy or IT chemotherapy after adequate hematologic recovery from high-dose therapy. Posttransplantation therapy was performed at the discretion of the investigator. None of the patients received both CNS radiotherapy and IT chemotherapy after transplantation.

One patient (SPN 1405) received radiotherapy to the paranasal sinuses after recovery from HCT. Five patients received additional CNS therapy after transplantation. Both of the patients with PCNSL received additional IT chemotherapy (1 received 1 dose and 1 received 3 doses), 2 of the patients with secondary CNS lymphoma received additional IT therapy (1 received 5 doses and 1 received 11 doses), and 1 patient with secondary CNS lymphoma who had not undergone radiotherapy before transplantation received a radiation dose of 35.3 Gy to the parasellar region of the brain.



Event-free and overall survival for all 15 patients with central nervous system lymphoma who underwent high-dose therapy and hematopoietic cell transplantation.

Outcome

Seven patients remained alive and free of disease after a median follow-up of 1085 days after HCT (range, 539-3704 days). The 2 patients with PCNSL were alive and disease free, 1 at 1085 days and 1 at 3704 days after transplantation. Five of 13 patients with secondary CNS involvement were alive and well. For all 15 patients, the rate of OS and EFS was 47% (7 of 15 patients). The 5-year actuarial OS was 41% ± 28% (95% confidence interval), and the 5-year actuarial EFS was 46% ± 26% (95% confidence interval). The median EFS and OS were 1.5 and 2.2 years, respectively (Figure). One patient (SPN 1303) with primary CNS lymphoma and spinal cord disease who was paraplegic at the time of HCT gradually recovered significant motor function within 6 months after HCT and is able to walk without assistance.

Seven patients experienced a recurrence of disease at a median of 75 days (range, 33-582 days) after HCT. There were no documented CNS relapses. Six patients died after experiencing a relapse of NHL. One patient (SPN 295) died of veno-occlusive disease of the liver on day 21 after transplantation. No unusual treatment-related toxicities occurred. One patient (SPN 842) who experienced relapse died from secondary acute myelogenous leukemia (AML) 1033 days after transplantation. The patient with progressive CNS disease before the time of transplantation (SPN 1502) died from recurrent lymphoma.

CNS Toxicity

Neuropsychiatric testing was not performed prospectively. One patient (SPN 50) with primary CNS lymphoma experienced a decline in neurocognitive function that led to discontinuation of posttransplantation IT therapy. This patient was unable to remain employed as a trial lawyer because of these deficits. One patient (SPN 1303) reported short-term memory loss, and another patient (SPN 1515) developed short- and long-term memory deficits. Two patients with secondary CNS disease had computed tomography (SPN 387) or MRI (SPN 842) evidence of therapy-related white matter changes. One patient (SPN 1405) developed paraplegia, thought to be caused by radiation-induced transverse myelitis, 2 years after HCT. Another patient (SPN 1330) experienced a right-sided thrombotic stroke, believed to be unrelated to transplantation, approximately 20 months after high-dose therapy.

Quality-of-Life Assessment

Patients surviving transplantation underwent periodic telephone surveys assessing their quality of life. At approximately 1 year after transplantation (range, 94 to 411 days), 7 of 9 surviving patients responded to the survey. Five of 7 patients were employed either full or part time. Two patients reported difficulties with sleep. One patient described his or her appearance as "poor," whereas 6 described it as either "good" or "better than expected." One patient (SPN 50) noted persisting fatigue, multiple gastrointestinal complaints, and difficulties with gait. Another patient (SPN 1303) complained of impairment in memory. The remaining patients assessed their overall level of energy as 80% to 90% of their premorbid level. The responding group of patients gave their overall quality of life a median rating of 9 out of a possible 10 (range, 6-10).

DISCUSSION

The treatment of patients with CNS involvement by NHL is difficult. Patients with secondary CNS disease usually have been treated with a variety of regimens, including systemic high-dose methotrexate with leucovorin rescue [23], systemic high-dose cytarabine [24-26], radiotherapy, and IT chemotherapy [7]. Despite cytologic and imaging studies indicating clearing of the CNS, patients often die from progressive systemic disease [27,28]. Among 16 patients with the concomitant diagnoses of systemic NHL and CNS NHL, median survival was only 22 weeks, and only 3 patients survived for 1 year [7]. Patients diagnosed with CNS disease at the time of recurrence or progression have a comparably dismal prognosis, with a median survival of only 2 months in one series [27]. In multiple published series, the overall median survival for patients with secondary CNS involvement treated with conventional-dose therapy ranged from only 9 weeks to 10 months [1,2,7,29,30].

High-dose chemotherapy with autologous HCT may produce long-term complete remissions in patients with relapsed primarily refractory or high-risk NHL [13,16, 31,32]. EBMT Lymphoma Registry data support a possible role for this treatment modality for patients with CNS involvement by NHL. The EBMT Lymphoma Registry study retrospectively identified 62 patients with secondary CNS NHL who underwent HCT at participating European centers using a variety of total body irradiation (TBI)- and non-TBI–based preparative regimens. The 5-year actuarial progression-free survival (PFS) was 42% for the 45 patients who demonstrated CNS clearing before HCT and 9% for the 17 patients with residual or refractory CNS disease. Patients who received both radiotherapy and IT chemotherapy before HCT had a better outcome than those who received either modality alone. Age, tumor histology, graft purging, and the preparative regimen did not appear to significantly alter patient outcome [14].

An M.D. Anderson Cancer Center (MDCC) study reported on 24 patients with CNS leukemia or NHL who underwent either autologous or allogeneic HCT. Nine patients in this series had secondary CNS NHL. Five of the 20 patients who demonstrated clearing of CNS leukemia or lymphoma before transplantation were alive at the time of the report; 4 were disease free. None of the 4 patients (including 1 patient with NHL) who had active CNS disease at the time of HCT survived [15]. The variability in patient diagnosis and type of transplantation, however, makes it difficult to derive any clear conclusions regarding the use of autologous HCT for patients with secondary CNS lymphoma.

The patient group reported here includes 13 patients with secondary CNS NHL. Unlike patients in the EBMT Lymphoma Registry, these patients were treated using a consistent preparative regimen at a single institution. All of the patients were treated with the intention of clearing the CNS before HCT. Five patients (38%) are alive and free of disease after HCT. There have been no documented CNS recurrences. Similar to the group with the best outcome in the EBMT Lymphoma Registry report [14], all of the surviving patients in this study received IT therapy and CNS radiotherapy as part of their treatment regimen.

This report also includes what we believe to be the first report of the treatment of primary CNS lymphoma with high-dose therapy and autologous HCT. PCNSL is a distinct clinical entity in which there is involvement of the brain, leptomeninges, or spinal cord with or without ocular disease, and the absence of other systemic disease [4,8]. In addition, local progression, rather than systemic dissemination, accounts for the majority of treatment failures [3-5]. Surgical resection provides no improvement in survival, and CNS radiotherapy alone produces a median survival of only 12 to 16 months [4,6]. Combinations of radiotherapy with systemic high-dose methotrexate have improved the response rate and median survival [12]. Recently the Memorial Sloan-Kettering Cancer Center group has published a protocol that utilizes systemic and intraventricular doses of methotrexate, high-dose cytarabine, and CNS radiotherapy. This regimen produced complete responses in 27 of 31 patients and a median survival of 41 months [8]. This approach, however, has been associated with significant late neurotoxicity.

The Oregon Health Sciences University group has used osmotic disruption of the blood-brain barrier before systemic chemotherapy with methotrexate, cyclophosphamide, procarbazine, and dexamethasone [33]. This regimen produced complete responses in 29 of 34 evaluable patients not previously treated with radiotherapy, with a median survival of 41 months and no evidence of significant late neurotoxicity on prospective neuropsychiatric tests [33]. Osmotic disruption, however, remains a cumbersome process, and administration of this regimen may be complicated by seizures, strokes, and sepsis.

One of the 2 patients with primary CNS lymphoma in this report had brain parenchymal abnormalities and leptomeningeal and cauda equina disease, whereas the other had leptomeningeal disease alone. Both of these patients remain in remission at 1085 and 3704 days after transplantation, respectively. Although the findings from our treatment group raise the prospect that high-dose therapy with HCT may hold promise for some patients with primary CNS lymphoma, we cannot draw any definite conclusions regarding the potential efficacy of HCT in this patient population. Of note, these 2 patients were younger than those included in many PCNSL series, and age is an important determinant of prognosis in patients with this disease [9,34]. HCT, however, may provide a mechanism for the use of intensified systemic therapy and may avoid some of the significant complications of dose-escalated therapy without stem cell support.

Late neurotoxicity, however, remains a concern for patients receiving intensive CNS therapy [11,35]. Intellectual impairment, seizures, dementia, and spinal cord myelopathy have been reported in survivors of childhood acute lymphoblastic leukemia and CNS lymphoma [10, 11,35-37]. The MDCC report documented grade III or IV treatment-related neurotoxicity in 8 of 20 patients whose CNS was cleared of disease before HCT. Of the 15 patients in this group, 3 developed symptomatic neurotoxicity, including impaired cognition/memory deficits in 3 patients and spinal cord myelopathy resulting in paraplegia in 1 patient. Two other asymptomatic patients had evidence of leuko-encephalopathic changes on imaging studies. The limited size of our treatment group and the lack of prospective neuropsychiatric testing preclude an exact characteriza-

tion of any subclinical neurologic changes or a comparison between the neurotoxicity of this regimen and that of other therapeutic regimens.

Despite the potential for late neurologic toxicity associated with this treatment regimen, patients who responded to the 1-year quality-of-life survey appeared overall to have a positive assessment. Although the small number of surviving patients limits the power of this tool to assess a global outcome for this patient population, it is encouraging that the majority of responding patients had resumed employment and reported a good to excellent self-assessment.

The three chemotherapeutic drugs used in this preparative regimen all have the capacity to achieve some degree of CNS penetration. Carmustine is a highly lipid-soluble drug that readily penetrates the CNS and achieves cerebrospinal fluid concentrations that are greater than 50% of those in plasma. Although the CNS penetration of etoposide and cyclophosphamide is more limited, there may be factors that enhance the penetration of these drugs in patients with CNS disease [38-42]. Within brain parenchymal tumors, etoposide may achieve concentrations that are 3.5% to 74.6% of those in serum as a result of local disruption of the blood-brain barrier. Similarly, cyclophosphamide may poorly penetrate an intact blood-brain barrier but achieve higher concentrations within intracerebral tumors [41,43]. A number of alternative chemotherapeutic agents, including nitrogen mustard, methotrexate, thiotepa, cytarabine, melphalan, and lomustine, have good CNS penetration and could conceivably be used in the development of novel high-dose treatment protocols [4,42]. In protocols recently developed for the treatment of patients with primary CNS lymphoma, investigators are attempting to use agents such as these without radiotherapy in the hope of reducing the risk of late neurotoxicity [44].

This study demonstrates that high-dose therapy and autologous HCT can produce extended disease-free survival in patients with secondary CNS involvement by NHL. Available data indicate that if HCT is to be successful, it is essential that clinicians attempt to clear the CNS of disease before transplantation. This report also raises the question of whether high-dose therapy with autologous HCT may have the potential to play a role in the management of patients with primary CNS lymphoma. Despite the ability of high-dose therapy to produce durable remissions in affected patients, this report illustrates that this treatment approach may be accompanied by a significant degree of neurotoxicity. Further study must be directed toward the development of alternative high-dose preparative regimens that limit or omit radiotherapy in the hope of decreasing late neurotoxicity.

Authors' Note: As this paper was going to press, one of the patients (SPN 50) developed a right cerebellar mass that was a biopsy-proven recurrence of non-Hodgkin's lymphoma at 4000 days posttransplantation. At the time of last follow-up, the patient was alive after 4 cycles of high-dose methotrexate.

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