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High-Dose Therapy and Blood or Marrow Transplantation for Non-Hodgkin Lymphoma with Central Nervous System Involvement

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ABSTRACT

The role of autologous or allogeneic blood or marrow transplantation (BMT) remains undefined in patients with central nervous system (CNS) involvement by lymphoma. The records of all adult and pediatric non-Hodgkin lymphoma patients receiving BMT at Johns Hopkins from 1980 to 2003 were reviewed, and 37 patients were identified who had CNS involvement that was treated into remission by the time of BMT. The chief histologies were diffuse large B-cell lymphoma and T-cell lymphoblastic lymphoma/leukemia. Twenty-four percent received intrathecal chemotherapy alone, and 70% received intrathecal chemotherapy and CNS irradiation before BMT. The main preparative regimens were cyclophosphamide/total body irradiation and busulfan/cyclophosphamide. Forty-one percent received an allogeneic transplant. Lymphoma relapsed after BMT in 14 patients (38%), and at least 5 had documented or suspected CNS relapse. In multivariate models, age ≥18 years at diagnosis, resistant systemic disease, busulfan/cyclophosphamide conditioning, and lack of intrathecal consolidation after BMT were statistically significant predictors of inferior survival. The 5-year actuarial event-free survival was 36%, and overall survival was 39%. After BMT, long-term survival is thus achievable in a subset of patients with a history of treated CNS involvement by non-Hodgkin lymphoma. The survival rates are not dissimilar to those typically seen in other high-risk lymphoma patients undergoing BMT. These data suggest that patients with lymphomatous involvement of the CNS who achieve CNS remission should be offered BMT if it is otherwise indicated.

KEY WORDS

Blood or marrow transplantation • Non-Hodgkin lymphoma • Central nervous system lymphoma

INTRODUCTION

Central nervous system (CNS) involvement by non-Hodgkin lymphoma (NHL) has historically carried a dismal prognosis. In prior series, survival has typically been measured in months [1-7]. Currently, there is no consensus regarding the optimal treatment for these patients. There are multiple potential barriers to the achievement of long-term remission in patients with NHL involving the CNS, including advanced systemic disease, therapeutic toxicities, and the difficulty inherent to treating lymphoma in a sanctuary site. Conventional doses of most chemotherapeutic agents have poor penetration into the CNS [8,9]. Intraventricular or intrathecal administration of chemotherapy can in part circumvent this problem; however, toxicities are often dose limiting, and CNS penetration by chemotherapeutic agents can be uneven. Portions of the CNS may therefore remain untreated, leading to disease persistence and the potential for systemic reseeding. Cranial or spinal irradiation can be effective in this regard, but at the potential cost of increased neurotoxicity, including late effects [10].

High doses of chemotherapy with or without total

body irradiation (TBI) given in the setting of blood or marrow transplantation (BMT) may both reach disease sanctuaries and eradicate systemic disease, thus improving overall survival [11-14]. However, available data do not permit conclusive recommendations on the role of BMT in patients with CNS involvement by lymphoma, and there has been a relatively high rate of neurotoxicity [13]. To evaluate the role of high-dose therapy combined with BMT in such patients, we describe the outcomes of 37 patients with prior lymphomatous involvement of the CNS who underwent BMT at our institution. We report prognostic models for event-free and overall survival and discuss treatment considerations in patients with this presentation.

MATERIALS AND METHODS

Study Population

We screened the medical records of all individuals who received an autologous or allogeneic BMT for NHL at the Johns Hopkins Oncology Center between 1980 and 2003. Permission to perform this study was granted by the institutional review board. Patients who had leptomeningeal or intraparenchymal CNS involvement by lymphoma and who had reached CNS remission before BMT were selected for this analysis.

Patients with primary CNS lymphoma or B-lineage acute lymphoblastic leukemia were excluded. All original diagnostic specimens were reviewed by the pathology department at Johns Hopkins. Allogeneic BMT was prioritized in patients <50 years of age who had an HLA-identical sibling. The transplantation was performed in accordance with institutional policies or approved protocols in effect at the time. Intrathecal consolidation after BMT was routinely recommended for patients with prior CNS disease or for those with other high-risk features, such as bone marrow involvement by aggressive lymphoma.

Patients with CNS disease present at initial diagnosis, during first-line therapy, or upon systemic or isolated CNS relapse were included. Lymphomatous involvement of the CNS was diagnosed on the basis of cytopathologic examination of the cerebrospinal fluid (CSF) or tissue biopsy samples, with or without characteristic radiographic and neurologic findings. In cases of suggestive but not definitive cytopathology, increased CSF protein or characteristic radiographic signs were required. Radiographic signs were considered characteristic of leptomeningeal or intraparenchymal disease if there was no evidence supporting any other reasonable or likely cause of the findings, such as infection, a vascular event, or therapeutic toxicity [2]. CNS remission was defined as the clearance of lymphoma cells from the CSF with improvement or stabilization of neurologic symptoms and radiographic abnormalities.

Follow-up Procedures

After discharge from the inpatient transplant unit, patients were observed closely by the transplantation team until transfusion independence and resolution of active issues. Subsequently, patients were asked to return to the Johns Hopkins outpatient clinic periodically for a minimum of 5 years. Patients afterward either continued to return to Johns Hopkins for annual evaluation or saw their referring oncologists for all care. Remission status and vital status were monitored by the data management office at least annually. Methods of ascertaining remission and survival status included contacting family members or the referring physician's office, scanning obituaries, searching the Social Security Death Index, and obtaining death certificates through vital records agencies.

Study variables included basic demographic data, histology, type of CNS treatment, systemic remission status at the time of BMT, presence of residual neurologic signs or symptoms, preparative regimen, type of graft, administration of intrathecal consolidation therapy, and occurrence of neurologic complications after BMT. Neurotoxicities were graded according to the National Cancer Institute common toxicity criteria, version 2.0.

Statistical Analysis

A primary aim was to determine prognostic factors for BMT recipients with a history of CNS involvement by lymphoma. The primary statistical end points were relapse, diagnosis of a second malignancy, and all-cause mortality after BMT. Event-free survival and overall survival rates were estimated by using the product-limit method [15], with calculation of the 95% confidence interval (CI). Event-free survival was defined as the interval between the date of BMT and the date of relapse, diagnosis of a second malignancy, death from any cause, or the date last known to be alive and disease free. Overall survival was defined as the interval between the date of BMT and the date of death or last contact. Survival outcomes according to grouped variables were compared by using the log-rank statistic [16].

Several potential prognostic factors were analyzed to determine their effect on the recurrence of systemic or CNS disease and overall survival. Hazard ratios for event-free and overall survival were estimated by using the proportional hazards model [17]. A hazard ratio >1 indicated an increased risk of treatment failure associated with having the variable relative to its reference level. To account for the simultaneous effects of more than 1 prognostic factor, a multivariate proportional hazards model was used. Candidate predictors were selected from the factors that seemed to be significant or almost significant in univariate analysis. All such prognostic factors were included in the proportional hazards model.

Nonsignificant variables were sequentially removed, and hazard ratios and significance levels were re-estimated after each step. We also investigated possible differences in the early event rates in the allogeneic and autologous BMT subsets. To do this, survival times were truncated at 12 months, and patients who had events after this cutoff were censored at 12 months. Analyses were performed with SAS software for Windows, version 8.02 (SAS Institute, Cary, NC). All *P* values reported are 2 sided.

RESULTS

Patient Characteristics

From a group of more than 750 NHL patients undergoing BMT, 37 were identified who had prior CNS involvement and who were determined to be in a CNS remission by the time of BMT (Table 1). Four additional patients with CNS involvement were excluded from analysis because there was persistent CNS disease at the time of BMT or because the CNS remission status at the time of BMT was uncertain; these 4 patients died of either relapse or transplant-related complications. The median age at diagnosis was 23 years, and 12 patients (32%) were <18 years of age when diagnosed with systemic lymphoma. The chief histologic subtypes were diffuse large B-cell lymphoma (43%) and T-cell lymphoblastic lymphoma/leukemia (41%). In more than half, the diagnosis of CNS lymphoma was first made in the setting of relapsed disease. Before high-dose therapy, all patients received intrathecal chemotherapy, and the majority received localized, whole-brain, and/or spinal irradiation. Pretransplantation lumbar puncture results were available for rereview in all cases but 1. Rare patients had persistent CSF pleocytosis that was assumed to be secondary to meningeal inflammation from the CNS therapy.

Fifteen patients (41%) received allografts. Only 3 patients had systemic disease that was unresponsive to the last regimen given before BMT; 2 of these received allogeneic transplants. All patients received either cyclophosphamide with TBI or the combination of busulfan and cyclophosphamide (Table 1). A minority received additional agents as part of these preparative regimens. More than half received consolidation with intrathecal chemotherapy after BMT; most others were not able to receive it (eg, because of a transplant-related complication or early relapse).

Table 1. *Patient Characteristics (n = 37)*

Variable	Value
Age at diagnosis, y, median (range)	23 (2-65)
Age at diagnosis ≥18 y	25 (68%)
Age at BMT, y, median (range)	24 (2-71)
Male sex	28
Stage	
I	3
II	6
III	2
IV	26
Histology	
High grade	18 (49%)
T-cell lymphoblastic lymphoma/leukemia	15
Burkitt or Burkitt-like lymphoma/leukemia	3
Diffuse large B cell	16 (43%)
Anaplastic large cell	2
Chronic lymphocytic leukemia/small lymphocytic lymphoma	1
CNS lymphoma: presentation	
Initial (before or during first-line chemotherapy)	15
Relapse (systemic or isolated CNS)	22 (59%)
Intraparenchymal CNS involvement	4
CNS lymphoma: diagnosis	
CSF: malignant cells ± radiographic findings	32
CSF: suspicious cells + increased protein	1
CSF: suspicious cells + increased protein + radiographic findings	1
CNS biopsy ± malignant cells in CSF	3
CNS lymphoma: treatment	
Intrathecal therapy	9
Intrathecal therapy + radiation	25
Intrathecal therapy + radiation after resection	1
Intrathecal therapy + high-dose methotrexate	2
Residual neurologic signs or symptoms before BMT	
Present	15
Unknown	1
Systemic disease status before BMT	
Sensitive	33 (89%)
Resistant	3
Unmeasurable disease	1
Preparative regimen	
Cyclophosphamide, TBI	17
Doxorubicin, cyclophosphamide, TBI	2
Busulfan, cyclophosphamide	13
Busulfan, cyclophosphamide, etoposide	5
Type of BMT	
Autologous	22 (59%)
Allogeneic	15
Intrathecal consolidation after BMT	22 (59%)

CNS indicates central nervous system; CSF, cerebrospinal fluid; TBI, total body irradiation; BMT, blood or marrow transplantation.

Relapse and Survival after BMT

As of last follow-up, 13 patients (35%) were alive at a median of 10.2 years after transplantation (range, 0.8 to 21.7 years). The median event-free survival of the entire cohort was 5 months from the time of BMT (range, 0.2 months to 21.7 years), and the median overall survival was 10 months (range, 0.2 months to 21.7 years). The actuarial event-free survival was 40% at 3 years (95% CI, 24%-56%) and 37% at 5 years (95% CI, 21%-53%; Figure 1). The actuarial overall survival was 39% at both 3 and 5 years (95% CI, 24%-55%; Figure 2).

Ten of 15 allogeneic transplant recipients and 14 of 22 autologous transplant recipients died. Fourteen patients (38%) died from relapsed lymphoma, and no patients were alive with relapsed disease as of last follow-up. It is interesting to note that all relapses occurred

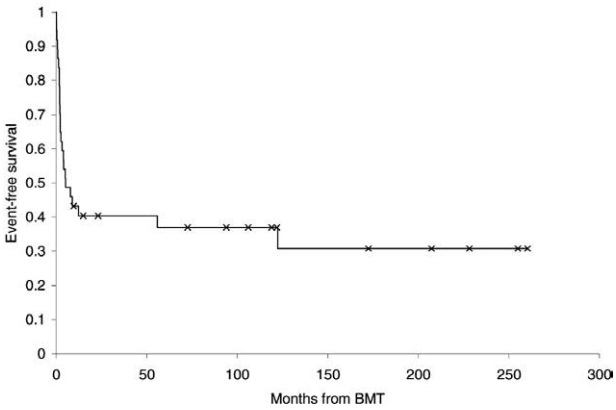

Figure 1. Kaplan-Meier estimates of event-free survival after BMT in patients with prior central nervous system involvement by lymphoma.

within 13 months and that most (79%) occurred within 6 months of transplantation. In at least 5 patients there was evidence of CNS relapse. In 1 patient who died of disease progression, the site of relapse was unknown. In another patient, the disease status at the time of death was unknown, but he was believed to be in remission shortly beforehand. The causes of death in the allogeneic transplant recipients were relapse (n = 4), sepsis (n = 1), respiratory failure (n = 2), heart and renal failure (n = 1), hepatic failure (n = 1), and a second lymphoma that was transmitted from the donor, as previously described [18]. Deaths in the autologous subgroup were due to relapse (n = 10), aspergillosis (n = 1), respiratory failure (n = 1), cardiac arrest from suspected cyclophosphamide-induced cardiotoxicity (n = 1), and complications from leukoencephalopathy (n = 1).

Predictors of Survival

On univariate analysis (Table 2), the administration of consolidative intrathecal therapy after BMT was associated with a 70% improvement in event-free and overall survival (P = .005 and P = .004, respectively). Resistant systemic disease before BMT, residual neurologic signs or symptoms before BMT, and busulfan/cyclophosphamide conditioning were associated with a statistically significantly inferior event-free survival and overall-survival: having resistant disease was associated with a >7-fold increased risk of death (P = .004), having residual neurologic findings with a >2-fold increased risk (P = .04), and receiving busulfan/cyclophosphamide with a >3-fold risk (P = .008) compared with receiving cyclophosphamide/TBI. There was also a trend toward worse event-free and overall survival as a function of older age: patients older than 18 years at the time of diagnosis were 2.5 times as likely to die as younger patients (P = .07; Figure 3), and when age at BMT was grouped by decade, a cumulative 22% relative increase in risk of death per decade was observed (P = .06).

There was no statistically significant association between exposure to CNS irradiation and survival after BMT. There was also no significant difference in outcome according to the year in which BMT was performed. There were other factors that predicted inferior outcomes, but the strength of the associations did not reach statistical significance. These included histology other than Burkitt or T-cell lymphoblastic lymphoma/leukemia, diagnosis of CNS disease in the relapsed setting, intraparenchymal CNS involvement, and allogeneic BMT. The early (12-month) event rates and death rates in the allogeneic and autologous subgroups are compared in Table 3.

Prognostic models were also explored through multivariate regression analysis. The final results of the step-down procedures are shown in Table 4. In the first and perhaps most robust multivariate model, resistant systemic disease and busulfan/cyclophosphamide conditioning were significantly associated with an inferior outcome. A nearly significant (P = .06) inferior outcome was also associated with the presence of residual neurologic symptoms at BMT. In contrast to the univariate analysis, the effect of intrathecal consolidation was not statistically significant (ie, it was redundant with other effects retained in the model).

However, in a separate and nonoverlapping model that differed only by the exclusion of residual neurologic symptoms from the initial conditions, the previously described factors were no longer statistically significant (Table 4). Instead, the administration of intrathecal consolidation emerged as a strong independent prognostic factor for both event-free and overall survival, with a >3-fold reduction in risk. Age group at diagnosis (adult versus pediatric) also emerged as an independent predictor of overall survival: older age adversely affected outcome. It is interesting to note that the estimated 5-year overall survival was 58% (95% CI, 30%-86%) for pediatric patients and 29% (95% CI, 10%-48%) for adult patients (P = .07; Figure 3).

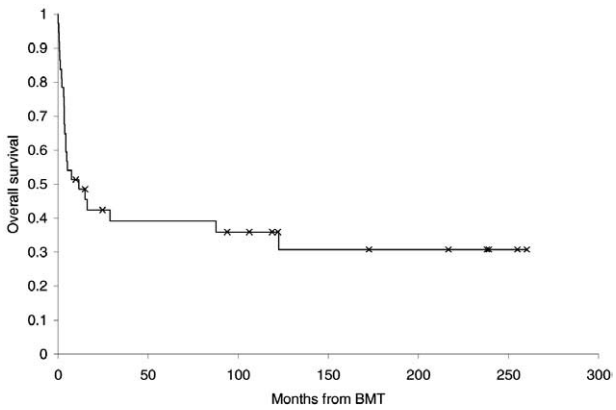

Figure 2. Kaplan-Meier estimates of overall survival after BMT.

Table 2. *Univariate Predictors of Survival after BMT*

Variable	Event-Free Survival			Overall Survival		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age ≥18 y at diagnosis	2.27	0.84-6.17	.11	2.49	0.91-6.76	.07
Older age at BMT by decade	1.20	0.98-1.47	.09	1.22	1.00-1.49	.06
High-grade histology*	0.61	0.26-1.44	.26	0.57	0.24-1.35	.20
CNS disease at relapse†	1.71	0.73-4.02	.22	1.65	0.71-3.88	.25
Intraparenchymal disease‡	1.89	0.56-6.44	.31	1.68	0.50-5.70	.40
CNS irradiation before BMT	0.95	0.39-2.29	.90	0.89	0.37-2.15	.79
Neurologic symptoms at BMT	2.32	1.01-5.33	.05	2.43	1.06-5.57	.04
Year of BMT§	1.02	0.96-1.08	.60	1.03	0.96-1.09	.43
Resistant systemic disease‡	5.22	1.45-18.73	.01	7.67	1.93-30.45	.004
Bu-Cy-based regimen‖	3.17	1.33-7.51	.009	3.21	1.35-7.64	.008
Allograft	1.21	0.54-2.75	.65	1.37	0.60-3.12	.45
GVHD	0.93	0.39-2.25	.87	1.08	0.45-2.61	.87
Intrathecal consolidation	0.31	0.14-0.70	.005	0.31	0.14-0.69	.004

Bu indicates busulfan; CI, confidence interval; CNS, central nervous system; Cy, cyclophosphamide; GVHD, graft versus host disease; HR, hazard ratio; BMT, blood or marrow transplantation.

*Burkitt, Burkitt-like, or T-cell lymphoblastic lymphoma/leukemia, compared with diffuse large B-cell lymphoma.

†Compared with CNS disease diagnosed before or during first-line therapy.

‡Based on <5 patients.

§The reference year is 1980.

‖Compared with Cy/total body irradiation (TBI)-based regimens. Bu/Cy/etoposide was included in the Bu/Cy group, and doxorubicin/Cy/TBI was included in the Cy/TBI group.

Neurologic Complications

Neurotoxicities, either transplant-related or possibly transplant-related, occurred in a number of cases and had variable clinical consequences. Although we do not have the results of formal neuropsychiatric testing for most patients, global functional status seemed to be preserved on the last available assessment of the 13 surviving patients.

Grade 1 toxicities manifested as possible mild cognitive decline were described in 4 patients. The first patient, who underwent BMT in early childhood and is a long-term survivor, had mild neurocognitive delay but is functioning in school. The second patient, also pediatric, has survived for >2 years and is likewise functioning in school with an average to low-average intelligence quotient. The other patients, both adults, reported some difficulty with short-term memory or cognition; in 1 of these, a Mini-Mental State Examination was normal. Grade 2 toxicities included chemical arachnoiditis (n = 2), transient visual changes (n = 1), and sensory neuropathy in a patient who died of relapse. There was also a case of self-limited seizures that occurred more than 12 years after BMT and was associated with a nontraumatic punctate intracranial bleed without other neurologic sequelae.

Grade 3 toxicities consisted of chronic worsening of preexisting neuropathic pain and weakness (n = 1); chronic lower extremity motor weakness (n = 1); chronic sensorineural hearing loss attributed to aminoglycosides (n = 1); and leukoencephalopathy manifested as confusion, headache, and hearing loss, with diffuse white matter changes, in a patient who died of other transplant-related complications (n = 1). There was another case of leukoencephalopathy with progressive severe dementia that contributed to the patient's death more than 10 years after BMT and was therefore regarded as grade 5.

Additionally, there were 3 cases of life-threatening cerebral infarction or coma that occurred during the early posttransplantation period; all of these patients died. We view these cases as complications of BMT but not frank neurotoxicities, because they occurred in the setting of severe infection, multisystem organ failure, or both.

DISCUSSION

Many patients with a history of lymphomatous involvement of the CNS have traditionally been ex-

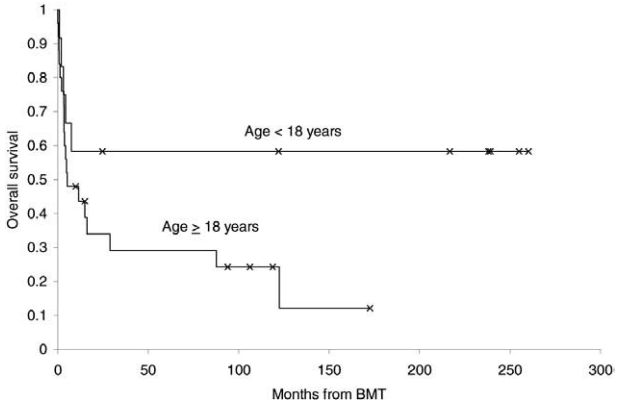

Figure 3. Kaplan-Meier estimates of overall survival after BMT according to age at diagnosis of lymphoma (*P* = .07).

Table 3. *Early Failure Rates According to Type of Transplant*

Variable	Type of BMT	No. Failures	Exposure (mo)*	Failure Rate (patient mos)	HR	95% CI
Event	Autologous	12	155	0.078	1.00	—
	Allogeneic	9	94	0.096	1.24	0.81-1.89
Death	Autologous	10	174	0.057	1.00	—
	Allogeneic	9	103	0.087	1.52	0.97-2.38

CI indicates confidence interval; HR, hazard ratio; BMT, blood or marrow transplantation.
*All follow-up times are censored as of 12 months after BMT.

cluded from high-dose systemic therapy, either because of concerns of increased toxicity or the perception of futility with this approach. Our long-term data suggest that a history of lymphomatous involvement of the CNS is not necessarily a poor prognostic feature in patients undergoing high-dose therapy and BMT. In this series, high-dose therapy produced durable remissions and long-term survival in a considerable subset of patients with treated leptomeningeal or intraparenchymal lymphoma.

High-dose therapy in the setting of BMT affords several potential advantages in the treatment of CNS lymphoma. The use of high-dose therapy may overcome the inability of many chemotherapeutic agents to cross the blood-brain barrier and the inconsistent distribution of intrathecal or intraventricular chemotherapy. Busulfan is one of the few agents that can cross the blood-brain barrier and attain therapeutic concentrations in the brain parenchyma [19,20]. Additionally, CNS involvement with lymphoma is associated with a poor prognosis in part because it often occurs in the setting of aggressive disease or a high systemic tumor burden [14]. In a series of patients with small non–cleaved-cell lymphoma treated with standard-dose regimens, the event-free survival was similar in the presence or absence of CNS disease after controlling for bone marrow involvement or high serum lactate dehydrogenase levels [14]. Patients with a history of CNS involvement by lymphoma who are treated with conventional therapy alone frequently die of systemic progression [21]. BMT has been shown to be superior to conventional-dose therapy for patients with relapsed, chemosensitive, aggressive lymphomas [22]. High-dose therapeutic strategies aimed at more effectively eradicating systemic lymphoma in conjunction with CNS-directed therapy would conceivably yield a greater chance for prolonged survival than conventional-dose therapy alone [23].

Another important consideration is that patients in this series did not have evidence of persistent CNS lymphoma at the time of BMT. Patients with active CNS disease who receive high-dose therapy and BMT have distinctly poorer prognoses than those without active CNS disease [12]. In a study of adult and pediatric patients with NHL, the European Bone Marrow Transplant Lymphoma Registry reported a progression-free survival of only 9% if the CNS disease was active at the time of autologous BMT, compared with 42% if the CNS was cleared [12]. In fact, the outcomes of patients achieving CNS remission before BMT were not significantly different from those of matched patients without a history of CNS involvement [12].

In this review, we identified a number of potentially independent prognostic factors for survival after BMT in patients with prior CNS involvement by lymphoma. Age at diagnosis (adult versus pediatric), disease chemosensitivity before BMT, the type of preparative regimen, and the receipt of intrathecal consolidation were statistically significantly associated with outcome in multivariate models. Whether intrathecal consolidation confers a true survival advantage, or whether it is simply a marker for those who survive

Table 4. *Multivariate Regression Models for BMT Outcomes*

Variable	Event-Free Survival			Overall Survival		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Resistant systemic disease	5.09	1.20-21.65	.03	7.19	1.58-32.68	.01
Bu-Cy-based regimen	2.67	1.02-6.95	.05	2.76	1.06-7.18	.04
Neurologic symptoms at BMT	2.40	0.96-6.02	.06	2.34	0.98-5.59	.06
Resistant systemic disease	3.24	0.86-12.20	.08	5.45	1.28-23.16	.02
Bu-Cy–based regimen	3.21	1.25-8.26	.02	3.21	1.25-8.29	.02
Age ≥18 y at diagnosis	2.46	0.91-6.67	.08	2.85	1.05-7.75	.04
Intrathecal consolidation	0.29	0.13-0.66	.003	0.28	0.12-0.63	.002

Bu indicates busulfan; CI, confidence interval; Cy, cyclophosphamide; HR, hazard ratio; BMT, blood or marrow transplantation.
Each panel is a separate multivariate model.

the immediate posttransplantation period and are able to receive consolidation, remains to be determined.

Neurologic complications after BMT may be increased in those with a history of CNS disease and have been seen with variable frequency [11,13]. We did not observe the relatively high rate of seizures reported by one group [13], perhaps because of differences in patient characteristics, methods of CNS treatment, or preparative regimens. Although there were a few cases of severe neurotoxicities, including 1 case of progressive, fatal leukoencephalopathy, most of the neurotoxicities were mild and did not seem to affect long-term outcome or functional status. Because of the relatively few severe neurotoxicities observed in this series, we could not assess the influence of factors such as age, prior CNS irradiation, or preparative regimen on the rate of development of these complications. Patients may have heightened susceptibility to neurologic complications because of their previous exposure to CNS irradiation or intrathecal chemotherapy and possibly because of preexisting neurologic signs and symptoms. Intrathecal chemotherapy and CNS irradiation may result in a spectrum of neurotoxicities, including spinal cord damage and cognitive decline. The choice of preparative regimen may also be important in this regard; systemic administration of high doses of cyclophosphamide in combination with high doses of busulfan or TBI can increase the risk of neurologic complications [24,25].

Given the limitations inherent to a retrospective study and the generally low frequency of prior CNS lymphoma in transplant recipients, several central questions remain. Because of the variability in patient characteristics and transplantation procedures, one cannot draw definite conclusions about the influence of histologic subtype, type of CNS treatment, preparative regimen, type of graft, or intrathecal consolidation on ultimate outcome. From this analysis, we are also unable to address what proportion of patients with a history of CNS lymphoma actually receive BMT. Nevertheless, our results are consistent with those of other groups, who have also found that a subset of patients with CNS involvement can achieve long-term survival with high-dose therapy and BMT [11,13]. For instance, in 20 adults with prior CNS involvement by a variety of hematologic malignancies, including NHL, van Besien et al. [13] reported a 2-year disease-free survival of 23%. In 15 adults with NHL undergoing autologous BMT, most of whom did not have active CNS disease, Alvarnas et al. [11] found a 5-year actuarial event-free and overall survival of >40%.

Long-term survival can be achieved through high-dose therapy and BMT in patients with secondary CNS involvement by NHL who are treated in an aggressive manner to induce a CNS remission. Thus, if otherwise indicated, patients with prior, controlled CNS involvement by NHL should be offered BMT with curative intent. This approach can translate into long-term disease-free survival rates that are comparable to those of other high-risk patients who do not have CNS disease.

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