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Allogeneic Hematopoietic Cell Transplantation in Children with Relapsed Acute Lymphoblastic Leukemia Isolated to the Central Nervous System

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ABSTRACT

Allogeneic hematopoietic cell transplantation (HCT) is the standard of care for pediatric patients with early medullary relapse of acute lymphoblastic leukemia (ALL). Most patients with isolated central nervous system (CNS) relapse have good outcomes when treated with intrathecal and systemic chemotherapy followed by irradiation to the neuroaxis. However, the role of HCT remains unclear for those patients with early isolated CNS relapse (<18 months) or who had high risk disease at diagnosis. We therefore compared the HCT outcomes of 116 children treated at the University of Minnesota from 1991 to 2006 with relapsed ALL involving the CNS alone (CNS, n = 14), the bone marrow alone (BM, n = 85), or both bone marrow and CNS (BM + CNS, n = 17). There were no significant differences among groups in age at diagnosis or transplant, length of first complete remission (CR1), remission status (CR2 versus ≥CR3), graft source, or preparative regimen. The incidence of acute GVHD was similar between groups. Patients with isolated CNS relapse had the lowest cumulative incidence of mortality following transplant (CNS: 0%, BM: 19%, BM + CNS: 29%, $P = .03$) and relapse (CNS: 0% BM: 30%, BM + CNS: 12%, at 2 years, $P = .01$) and highest leukemia-free survival (CNS: 91%, BM: 35%, BM + CNS: 46%, $P < .01$) at 5 years. Risk factors for poor survival were: T cell leukemia or BCR-ABL gene rearrangement, history of marrow relapse, and receipt of HLA-mismatched marrow. These data support the use of allogeneic HCT in the treatment of children with poor prognosis isolated CNS relapse.

KEY WORDS

Bone marrow • Graft-versus-host disease • Stem cell • Umbilical cord blood • Acute lymphocytic leukemia • CNS relapse

INTRODUCTION

Current therapies incorporating intensive systemic and central nervous system (CNS)-directed therapy have reduced the incidence of CNS relapse to <5% in pediatric patients with acute lymphoblastic leukemia (ALL) [1,2]. Nonetheless, when relapse does occur, the CNS is involved in 22% to 40% of cases [1-5]. Using current protocols, pediatric patients with standard-risk ALL with late CNS relapse (≥18 months following the first complete remission [CR1]) have an expected leukemia-free survival (LFS) of approximately 70% when treated with intensive chemotherapy and CNS irradiation [6,7]. In contrast, survival is poorer in patients with very early CNS relapse (CR1 <18 months), or CNS relapse and high-risk factors at diagnosis (ie, age <1 or >10 years or white blood cell count >50,000 at diagnosis) [7]. Induction and consolidative therapy followed by allogeneic hematopoietic cell transplantation (HCT) is considered by many to be the standard of care for pediatric patients

with ALL and medullary relapse <36 months from diagnosis. The risks and potential benefits of HCT, however, in this subgroup of children with isolated CNS relapse has remained unclear. Therefore, we evaluated the transplant outcomes in patients with relapsed ALL with and without CNS involvement.

PATIENTS AND METHODS

Patient and Transplant Characteristics

One hundred sixteen pediatric patients with relapsed ALL involving either the CNS, bone marrow, or both were treated at the University of Minnesota between 1991 and 2006 (Table 1). All transplant protocols were approved by the University of Minnesota institutional review board, and written, informed consent was provided by either the patient or their legal guardian(s). Methods of HLA matching, donor selection, marrow, and UCB processing and infusion, testing for chimerism, infection disease prophylaxis and cytomegalovirus monitoring, and treatment of graft-versus-host disease (GVHD) have been described previously [8-16].

All patients were in CR at the time of HCT, and patients were grouped according to the site of relapse in the CR immediately prior to transplantation; isolated CNS relapse (CNS, n = 14), relapse involving both the CNS and bone marrow (BM + CNS, n = 17), or bone marrow alone (BM, n = 85). As shown in Table 1, among the groups, there were no significant differences in the proportion of patients who were male or Caucasian, the median age at diagnosis of ALL or at transplant, length of CR1, or proportion in CR2. Forty-eight patients underwent HCT from 1991 to 1995, 39 from 1996 to 2000, and 29 from 2001 to 2006. All patients were conditioned with cyclophosphamide (120 mg/kg) and total-body irradiation (TBI) (1320-1375 cGy) alone (n = 69) or with the addition of etoposide in 38 or fludarabine in 8. Five patients with isolated CNS relapse (patients 1, 3, 5, 7, and 12) had no CNS irradiation prior to HCT. These patients were treated with additional irradiation to the brain immediately prior to the HCT conditioning chemotherapy. Thus, patients with isolated CNS relapse received a total cumulative dose of 2800 ± 230 cGy to the brain and 2260 ± 230 cGy to the spinal cord. Following HCT, no patients received intrathecal chemotherapy. There were no significant differences among groups in year of HCT, preparative regimen, or graft source.

The indication to proceed with HCT for the majority of patients in our study was medullary leukemic relapse. All of the 14 patients referred for HCT for isolated CNS relapse had features associated with poor outcomes. Of the 7 who underwent HCT in CR2, 5 had high WBC at diagnosis (>50,000 cells/μL, range:

Table 1. *Patient and Transplant Characteristics*

Factor			Site of Relapse Prior to Transplantation			
			CNS	BM + CNS	BM	P
Male			7/14 (50%)	11/17 (65%)	55/85 (65%)	.58
Caucasian			12/14 (86%)	16/17 (94%)	74/85 (87%)	.80
Median age at diagnosis (years, range)			3.7 (1.2-7.7)	3.7 (1.4-17.0)	4.5 (1.0-16.0)	.23
Median age at transplant (years, range)			8.0 (3.2-17.3)	7.8 (3.1-17.9)	8.3 (3.5-17.9)	.40
Length of CR1 (months, range)			22.8 (8.6-58.4)	34.2 (3.3-74.1)	26.9 (0.8-74.3)	.80
Remission status at transplant						
CR2 (n, %)			7 (50%)	14 (82%)	66 (78%)	.09
CR3+ (n, %)*			7 (50%)	3 (18%)	19 (22%)	
Year of HCT						
1991-1995			6 (43%)	6 (35%)	36 (42%)	.08
1996-2000			1 (7%)	8 (47%)	30 (35%)	
2001-2006			7 (50%)	3 (18%)	19 (22%)	
Conditioning						
CY/TBI			10 (71%)	10 (59%)	49 (58%)	.76
CY/TBI/FLU			4 (29%)	7 (41%)	35 (41%)	
Other			0	0	1 (1%)	
Transplant						
HCT	Donor	HLA Match				
BM	Related	6/6	3 (21%)	8 (47%)	27 (32%)	.20
BM	Related	5/6	2 (14%)	0	4 (5%)	
BM	Unrelated	6/6	0	1 (6%)	20 (24%)	
BM	Unrelated	5/6	3 (21%)	3 (18%)	15 (18%)	
Cord	Unrelated	6/6	1 (7%)	0	3 (4%)	
Cord	Unrelated	5/6	3 (21%)	4 (24%)	7 (8%)	
Cord	Unrelated	4/6	2 (14%)	1 (6%)	9 (11%)	

BM indicates bone marrow; TBI, total-body irridiation; HCT, hematopoietic cell transplant; CY, cyclophosphamide; CR, complete remission.
*One patient in the CNS group underwent HCT in CR5.

59-282,000), 4 had early relapse (CR1 of <18 months), and 1 had T cell disease, a risk factor for CNS relapse [1] (Table 2). In addition, patients 6 and 7 had CNS involvement at diagnosis. Patient #6 developed seizures as a complication of intrathecal chemotherapy, and Patient #7 had suffered a CNS relapse while receiving intrathecal triple therapy with hydrocortisone, methotrexate, and cytarabine. The remaining 7 patients with isolated CNS relapse underwent HCT in CR3 (n = 6) or CR5 (n = 1), and were considered poor prognosis because of history of multiple relapses of ALL.

Analysis

To compare the baseline demographics and transplantation-related characteristics among the 3 groups (CNS, BM + CNS, and BM), the Fisher's exact test was used for categoric variables including gender, race, remission status at transplant, year of HCT, HCT donor source, and HLA-matching. The *F* test was used for continuous variables including age at diagnosis, age at transplant, and length of CR1. Cumulative incidence was used to estimate transplant-related mortality (TRM), relapse, and incidence of GVHD [17], and the comparison of cumulative incidence was conducted by using the log-rank test [18]. The Kaplan-Meier method was used to estimate 5-year LFS and overall survival (OS), and the log-rank test was used to compare survival among the 3 groups. Factors associated with adverse outcomes were analyzed using Cox multiple regression models on the OS [19].

RESULTS

TRM and GVHD

TRM for pediatric patients undergoing HCT for relapsed ALL is shown in Figure 1A. In our series, no TRM has been observed in patients with isolated CNS relapse. Day 100 TRM was 19% (confidence interval [CI]: 11%-27%) for patients with bone marrow relapse and 29% (CI: 8%-51%) for patients with combined marrow and CNS relapse ($P = .10$ at day 100). The cumulative incidence of mortality 2 years following HCT was lowest for patients transplanted for isolated CNS relapse (0%), compared with 34% (CI: 23%-44%) for patients with bone marrow relapse and 35% (CI: 13%-58%) for patients with combined marrow and CNS relapse. These data were statistically significant ($P = .03$).

Notably, the incidence of grade II-IV acute GVHD (aGVHD) at day 100 after transplantation was similar between groups (CNS only, 51% [CI: 24-78], BM only, 36% [CI: 26-47], or CNS + BM, 18% [CI: 0-35]) (Figure 1B). Similarly, there was no significant difference in the cumulative incidence of severe, grade III-IV aGVHD.

Relapse, LFS, and OS

At 2 years, patients undergoing HCT for isolated CNS relapse had the lowest incidence of relapse after transplant (0%, $P = .01$) compared to patients with combined bone marrow and CNS relapse (12%; CI: 0-27) and patients with marrow involvement only (30%; CI: 20-41) (Figure 2A). One patient who underwent transplant for isolated CNS relapse developed

Table 2. *Characteristics of Patients with Isolated CNS Relapse*

	At Diagnosis											
Patient	Age (Years)	WBC	ALL*	CNS+	CR1 Duration(Months)	Relapse #1 (Site)	CR2 Duration(Months)	Relapse #2 (Site)	CR at HCT	HCT Graft Source	Patient Status	Survival (Years)
1	8	282	T	No	14	CNS			2	UCB	Alive	0.2
2	2	5.6	B	No	14	CNS			2	UCB	Alive	2.4
3	4	135	B	No	16	CNS			2	UCB	Alive	2.1
4	2	N/A	B	No	22	CNS			2	MRD	Alive	11.3
5	2	104	B	Yes	9	CNS			2	UCB	Alive	1.5
6	7	60	B	Yes	28	CNS			2	URD	Alive	10.3
7	3	59	B	Yes	31	CNS			2	MRD	Alive	3.0
8	5	N/A	NOS	No	19	CNS	15	CNS	3	UCB	Alive	7.0
9	4	N/A	B	No	17	CNS	6	CNS	3	URD	Alive	13.1
10	2	114	B	No	26	CNS	41	CNS	3	URD	Alive	3.1
11	1	101	B	No	23	CNS	15	CNS	3	UCB	Alive	2.4
12	4	1.2	B	No	52	Marrow	22	CNS	3	URD	Dead	4.8
13	6	81	B	Yes	35	Marrow	14	CNS	3	URD	Alive	12.4
14	5	5.6	B	No	58	Marrow	42	**	5	MRD	Alive	10.2

CNS indicates central nervous system; WBC, white blood cells; CR, complete remission; HCT, hematopoietic cell transplants; MRD, matched, related donor bone marrow transplantation; URD, unrelated donor bone marrow transplantation; UCB, umbilical cord blood transplantation; N/A, not available.

*B lineage or T lineage leukemia.

**Patient 14 had 4 relapses, involving marrow, testes, CNS, and CNS, respectively.

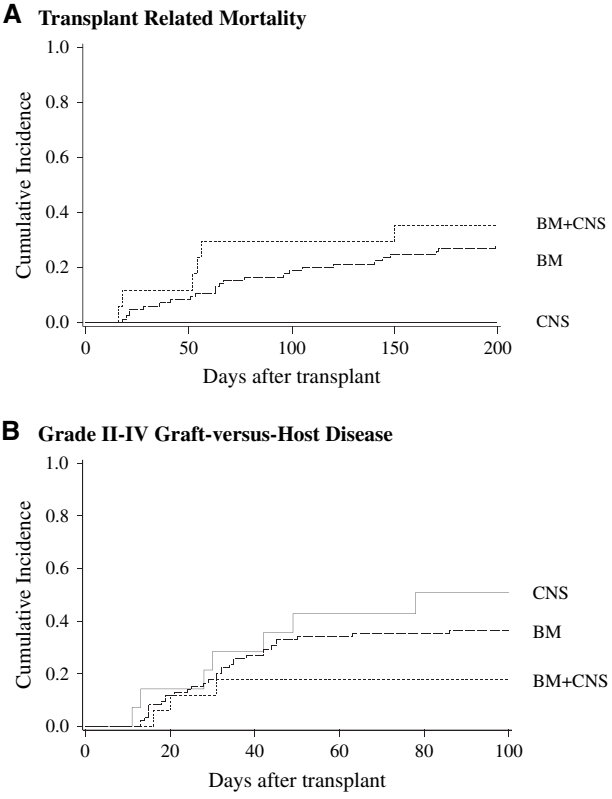

Figure 1. Complications following HCT. (A) TRM. The cumulative incidence of TRM for pediatric patients undergoing HCT for ALL was lowest for patients with isolated CNS relapse (CNS: 0; $P = .03$), versus patients with bone marrow relapse (BM: 19%; CI: 11%-27%) or combined marrow and CNS relapse (BM + CNS: 29%; CI: 8%-51%). (B) Acute GVHD. The cumulative incidence of stage II-IV aGVHD was not significantly different between patients with isolated CNS relapse (CNS: 51% CI: 24%-78%), bone marrow relapse (BM: 36%; CI: 26%-47%), or combined marrow and CNS relapse (BM + CNS: 18% CI: 0%-35%).

a late CNS relapse 2.3 years following HCT. The probability of LFS at 5 years (Figure 2B) was highest for patients with isolated CNS relapse (91%, CI: 51-99, $P < .01$), with no difference in LFS in patients with marrow involvement alone or in combination with CNS involvement (BM: 35%, CI: 25-45; BM + CNS: 46%, CI: 22-68). Similarly, the probability of OS (Figure 2C) was higher for the CNS group (86% CI: 33-98%; $P < .01$) than the groups with medullary disease (BM: 38%, CI 27-49; BM + CNS: 53%, CI 28-73).

Prognostic Factors Impacting Survival

In this series, 14 of 15 patients with isolated CNS relapse survived beyond 5 years. Because of the high rate of survival of patients transplanted for isolated CNS relapse, independent risk factors for relapse or mortality could not be established within this group. We therefore combined the 3 relapse groups and calculated hazard ratios using Cox multiple regression analysis to determine risk factors associated with

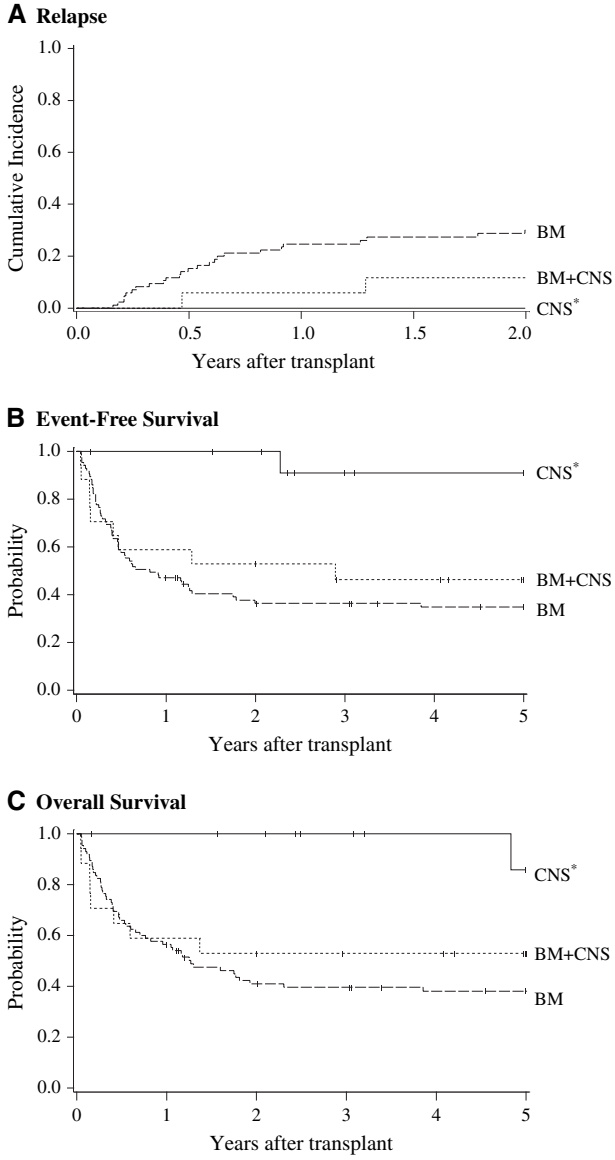

Figure 2. Outcomes following HCT. (A) Relapse. The cumulative incidence of 2 year posttransplant relapse for pediatric patients undergoing HCT for relapsed ALL was lowest for patients with isolated CNS relapse (CNS: 0%; $P = .01$) when compared with patients with bone marrow relapse (BM: 30%; CI: 20%-41%) or combined marrow and CNS relapse (BM + CNS: 12%; CI: 0%-27%). (B) EFS. Kaplan-Meier estimates of the probability of 5-year EFS of pediatric patients undergoing HCT for ALL were highest for patients with isolated CNS relapse (CNS: 91% CI: 51%-99%; $*P < .01$), compared with patients with bone marrow relapse (BM: 35%; CI: 25%-45%), or combined marrow and CNS relapse (BM + CNS: 46%, CI: 22%-68%). (C) OS. Kaplan-Meier estimates of the probability of 5-year OS of pediatric patients undergoing HCT for ALL with isolated CNS relapse (CNS: 86% CI: 33%-98%), bone marrow relapse (BM: 38%; CI: 27%-49%) or combined marrow and CNS relapse (BM + CNS: 53%, CI: 28%-73%) ($*P < .01$).

poorer survival (Table 3). Neither length of CR1 (calculated as a contiguous or dichotomous variable) nor age >10 years at diagnosis (versus age 1-9.99) was associated with decreased survival in this study. Patients

Table 3. *Prognostic Factors for Decreased Overall Survival Using Multivariate Cox Proportional Hazards Models*

Prognostic Factor	Hazard Ratio	(95% CI)	P
Length of CR1 (months)	1.00	(0.98-1.02)	.88
Age ≥10 at Diagnosis (versus age 1-9.99)	1.25	(0.66-2.39)	.48
Ph+ or T lineage ALL (versus B lineage)	1.96	(1.06-3.62)	.03
Any Marrow Involvement (versus isolated CNS relapse)	20.52	(2.60-162.7)	<.01
Unrelated mismatched marrow (versus cord or matched marrow)	4.29	(2.20-8.38)	<.01

CI indicates confidence interval; ALL, acute lymphoblastic leukemia; CNS, central nervous system; CR, complete remission.

with T lineage disease or the presence of the Philadelphia chromosome had decreased survival (hazard ratio [HR] 1.96; CI: 1.06-3.62, $P = .03$). Although all patients were in remission at the time of HCT, patients who had any marrow involvement during the relapse immediately prior to HCT had worse outcomes compared with patients with isolated CNS relapse (HR 20.52; CI: 2.60-162.7; $P < .01$). In addition, whereas the graft source (marrow versus UCB) did not impact survival, patients receiving an HLA mismatched, related, or unrelated BM graft (N = 27) had poorer survival compared with patients receiving either UCB or an HLA matched BM graft (N = 89) (HR 4.29; 2.20-8.38; $P < .01$). Although death because of relapse was not statistically different in the mismatched group (3 of 27; 11%) versus the cord blood/matched marrow group (24 of 89; 27%: $P = .09$), death related to GVHD was different in these groups (10 of 27; 37% and 8/89; 9%, respectively: $P < .01$). The death rate in regard to infection was not statistically different (5 of 27; 19% versus 7/89; 8%: $P = .11$).

DISCUSSION

Induction and consolidative therapy followed by allogeneic HCT may be considered the standard of care for pediatric patients with ALL suffering an early bone marrow relapse. In contrast, the routine use of allogeneic HCT in children with isolated CNS relapse is controversial. The purpose of this single institution study was to evaluate outcomes of HCT for pediatric patients with relapsed ALL with and without CNS involvement. Patients with isolated CNS relapse had the lowest TRM and the lowest incidence of relapse following transplant when compared with patients with marrow involvement of their leukemic relapse (regardless of CNS status). Similarly, of the 3 treatment groups, patients with isolated CNS relapse had the highest 5-year LFS (91%, CI: 51%-99%) and OS (86%, CI: 33%-98%). Importantly, all of the patients with isolated CNS relapse had features associated with very poor outcomes using standard therapies. Half of the patients in this group were either high risk by National Cancer Institute (NCI) criteria (age >10 years or WBC >50,000 at diagnosis) or suffered a very early CNS relapse (duration of CR1 <18 months), whereas the remainder had experienced multiple relapses of their leukemia prior to transplantation (transplant performed in CR3: n = 6; or CR5: n = 1). Despite these risk factors, the very favorable outcomes observed suggest HCT should be considered a reasonable treatment option for pediatric patients with poor prognosis isolated CNS relapse.

Systemic chemotherapy followed by irradiation to the brain and spinal cord has been the mainstay of therapy for isolated CNS relapse of ALL. Using this approach, Pediatric Oncology Group (POG) protocols for pediatric patients with isolated CNS relapse of ALL include POG 9061 (accrual 1990-1993, n = 83) and POG 9412 (accrual 1996-2000, n = 71) and have yielded LFS of approximately 70% when all patient data are pooled [6,7]. Subgroup analysis of POG 9412 revealed that patients with NCI standard risk ALL had 4-year EFS of 80 ± 6%, and patients treated for late CNS relapse had 4-year EFS of 78 ± 6% [7]. In contrast, patients with high-risk ALL according to NCI criteria or patients with very early relapse did significantly worse, with an estimated 5-year LFS of 51% ± 11% and 52% ± 11%, respectively [7]. In addition, the prognosis for patients with multiple relapses of ALL is extremely poor. Data from the Medical Research Council acute lymphoblastic leukemia trials (UKALL X and XI) included 47 pediatric patients whose second leukemic relapse of ALL was limited to the CNS [20]. Therapies for these patients were heterogeneous, and only 10 (21%) survived with a median follow-up of 22 months (range: 1-154). Similarly, survival in pediatric patients with bone marrow involvement at second relapse (with or without disease) is also poor, ranging from 20% to 48% despite HCT [21-24]. Thus, patients with early isolated CNS relapse, CNS relapse of high-risk ALL, or isolated CNS involvement of multiply relapsed ALL appear to have poor outcomes with standard therapies, and may be best served with novel or more aggressive approaches. Although the number of patients in the present study is small, our outcomes for these poor prognosis patients compare favorably with reports of outcomes in patients with similar risk features.

No randomized controlled clinical trials have compared HCT to chemotherapy and irradiation for CNS relapse of ALL. However, since 1990, nearly 20 publications have contributed data to this topic (reviewed in [7,25]). Studies were predominantly case series and

retrospective reviews, and therapeutic approaches ranged from chemotherapy and craniospinal irradiation to autologous and allogeneic HCT. The reported survival in individual studies varied widely, and was likely was reflective of small numbers of patients, and may also reflect changes in approaches to care over this time period. These limitations are relevant to our study as well. Nonetheless, one of the largest studies to address this topic reported outcomes of HCT for 31 pediatric patients with isolated CNS relapse using a conditioning regimen of TBI, cytarabine, and melphalan [23]. Median age at HCT was 6.5 years (range: 3-17 years) and 16 of 31 patients had an initial CR1 of <18 months. In this study, TRM was 13% and second relapse of leukemia was 10% ± 11%, resulting in LFS of 77% ± 15%. Although at least half of the patients could be considered poor prognosis based on age at diagnosis or time to relapse (as discussed above), the overall survival in this study was comparable to more recent protocols using chemotherapy and irradiation. Importantly, the authors did not note any survival difference in patients with CR1 <18 months or age ≥10 years. Yoshihara et al. [25] recently reported the results of allogeneic HCT for 7 pediatric patients with isolated CNS relapse of ALL and 1 with T cell non-Hodgkin's lymphoma. Six of the leukemia patients were characterized as having a poor prognosis because of NCI high-risk disease or early relapse, and all were alive at time of publication, with only 1 patient experiencing an additional isolated CNS relapse.

Presymptomatic CNS therapy has reduced the rate of relapse involving the CNS from approximately 50% of patients to <10%. Although effective in treating CNS leukemia, initial therapies incorporating 2400 cGy to the brain induced significant long-term neurocognitive deficits, and have largely been replaced by protocols incorporating more intensive systemic and intrathecal chemotherapy. The patients in our series underwent HCT over 15 years. Modifications in CNS irradiation as presymptomatic CNS therapy may over this time period may have resulted in inadequate control of CNS leukemia and been responsible for relapses in some patients. Conversely, patients who had not received CNS irradiation prior to relapse (patients 1, 3, 5, 7, and 12; Table 2), might be expected to have better response to the HCT conditioning regimens that incorporated TBI and cranial boosts to the conditioning chemotherapy. Although the high survival and small sample size of our study makes it impossible to quantify the relative contributions of presymptomatic CNS-directed therapy, CNS irradiation, and conditioning chemotherapy, it is likely that CNS irradiation delivered in addition to the TBI in the transplant regimen contributed to the favorable survival outcomes. Patients with isolated CNS relapse could have received CNS irradiation as part of initial therapy, at relapse, and at transplant (TBI with or without cranial boosts), and the cumulative doses of irradiation averaged 2800 ± 230 cGy to the brain and 2260 ± 230 cGy to the spinal cord. These high doses contrast with trends in POG and Children's Oncology Group (COG) protocols for the treatment of isolated CNS relapse of ALL, which, over the last 2 decades, have increased the intensity and duration of systemic and intrathecal chemotherapy and reduced cranial and spinal irradiation [6,7]. For example, in POG 9061, all patients received 6 months of systemic and intrathecal chemotherapy followed by 2400 cGy to the brain and 1500 cGy to the spinal cord. In POG 9412, duration of chemotherapy was increased to 12 months, but irradiation was reduced to 1800 cGy and limited to the brain only for patients with late relapse (CR1 ≥18 months). Finally, the COG study AALL02P2 (which enrolled patients with isolated CNS relapse in CR2 and initial CR1<18 months) further reduced CNS irradiation to 1200 cGy to the whole brain. Known side effects of irradiation to the brain and spinal cord include neurocognitive deficits, second neoplasms, decreased growth, and impaired cardiopulmonary, renal, and endocrine function (reviewed in [26-29]). Thus, although our survival data appear very encouraging when compared with survival outcomes from standard therapies, the patients in our study have increased risks of developing significant long-term, radiation-induced complications.

The remainder of the patients in our study had bone marrow involvement at leukemic relapse. A recently published COG and Center for International Blood and Marrow Transplant Research (CIBMTR) study of HLA-matched sibling HCT for pediatric patients with BM relapse of pre-B ALL in CR2 reported 8-year LFS of 41% (CI: 31%-52%) for patients with relapse occurring <36 months from diagnosis to first relapse and 60% (CI: 46%-71%) for patients with relapse occurring >36 months after diagnosis [30]. In our series, LFS for patients with medullary relapse was comparable at 35% (CI: 25%-45%); however, the median duration of CR1 in our population was only 26.9 weeks and 22% of patients were transplanted in CR3, reflecting inclusion of higher risk patients. Survival in our patients with BM and CNS relapse was 45% (CI: 22%-68%). Previous studies have suggested superior outcomes associated with longer time to relapse for patients with relapsed ALL involving both the marrow and CNS compared with BM relapse alone [31,32]. In our patients, there was no statistically significant difference in length of CR1 (in months) between these 2 groups, and similarly, we did not detect a survival advantage in patients with combined CNS and BM relapse.

In conclusion we have observed favorable survival in children with relapsed ALL with isolated CNS involvement despite poor prognostic features. Risk of TRM and relapse was low, although this study could not address long-term toxicity of transplantation and

make comparisons to what is observed with standard chemotherapy. In these investigations, the presence of CNS disease did not impact survival in those with concomitant marrow disease. Risk factors for decreased survival included T cell leukemia or BCR-ABL gene rearrangement, any marrow relapse, and receipt of HLA mismatched unrelated marrow. These data support HCT as a viable option for pediatric patients with isolated CNS relapse of ALL, including those associated with poor prognostic features.

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