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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.