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Outcomes after Second Hematopoietic Cell Transplantation in Children and Young Adults with Relapsed Acute Leukemia

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A B S T R A C T

Children with acute leukemia who relapse after hematopoietic cell transplantation (HCT) have few therapeutic options. We studied 251 children and young adults with acute myelogenous or lymphoblastic leukemia who underwent a second HCT for relapse after their first HCT. The median age at second HCT was 11 years, and the median interval between first and second HCT was 17 months. Most of the patients (n = 187; 75%) were in remission, received a myeloablative conditioning regimen (n = 157; 63%), and underwent unrelated donor HCT (n = 230; 92%). The 2-year probability of leukemia-free survival (LFS) was 33% after transplantation in patients in remission, compared with 19% after transplantation in patients not in remission ($P = .02$). The corresponding 8-year probabilities were 24% and 10% ($P = .003$). A higher rate of relapse contributed to the difference in LFS. The 2-year probability of relapse after transplantation was 42% in patients in remission and 56% in those in relapse ($P = .05$). The corresponding 8-year probabilities were 49% and 64% ($P = .04$). These data extend the findings of others showing that patients with a low disease burden are more likely to benefit from a second transplantation. Late relapse led to a 10% decrement in LFS beyond the second year after second HCT. This differs from first HCT, in which most relapses occur within 2 years after HCT.

INTRODUCTION

Treatment options are limited for children with acute myelogenous leukemia (AML) or acute lymphoblastic leukemia

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(ALL) who relapse after their first allogeneic hematopoietic cell transplantation (HCT). Although a second HCT is an option, its outcome is dependent on morbidities experienced from initial and salvage chemotherapies, as well as the first HCT, performance status, interval between first HCT and relapse, and disease status at second HCT [1-8]. Previous reports have largely focused on adults with acute and chronic leukemia, with only modest inclusion of children [2,7,9]. The largest study of 2632 second HCT recipients included 569 (21%) children and adolescents [2]. That study concluded that survival after second HCT was better with a diagnosis of chronic myeloid leukemia, longer duration of remission after first HCT, longer interval between first and second HCT, low disease burden at second HCT, younger age, no previous acute or chronic graft-versus-host disease (GVHD), and more recent transplantation period. The study also concluded there was no benefit to changing the donor for the second HCT [2]. The 3 earlier studies that included children also concluded that age at second HCT is an important determinant of survival, along with low disease burden, duration of remission after first HCT, and interval between first and second HCT [7-9].

It is important to recognize that in the reports that included children and adolescents, the predominant donor type was an HLA-matched sibling [2,7-9]. Donor choice has evolved over time, and today 60% of allogeneic HCTs performed for pediatric AML and ALL use grafts from unrelated donors [10]. Therefore, to better understand prognostic factors associated with relapse and leukemia-free survival (LFS) after second HCT in children, adolescents, and young adults who had undergone HLA-matched sibling donor or unrelated donor first HCT, we studied 251 patients reported to the Center for International Blood and Marrow Transplant Research (CIBMTR). Our primary objectives were to identify subset(s) within a cohort of relatively young patients (age <25 years) who are most likely to benefit from second HCT and to provide objective data that can be used to counsel patients and families regarding treatment for relapse after a first allogeneic HCT.

METHODS

Patients

The CIBMTR is a voluntary group of more than 400 transplantation centers that report data prospectively on consecutive transplantations. Patients are followed longitudinally until death or loss to follow-up. Included in the current analyses are patients age <25 years with AML (n = 141) or ALL (n = 110) who underwent a second HCT for relapse (morphologic, cytogenetic, or molecular) after their first allogeneic HCT. Recipients of myeloablative (total body irradiation [TBI] dose ≥1000 cGy, busulfan ≥10 mg/kg, melphalan >140 mg/m^2) and reduced-intensity conditioning regimens were included. All second HCTs were performed between 2001 and 2014. Parents or patients age 18 years or older provided written informed consent for research. The Institutional Review Board of the National Marrow Donor Program approved this study.

Endpoints

The primary endpoint was LFS, defined as the likelihood of being in remission and alive. Relapse or as death from any cause were considered events (treatment failure). Overall survival (OS) was defined as the likelihood of being alive. Death from any cause was considered an event, and surviving patients were censored at last follow-up. Neutrophil recovery was defined as achieving an absolute neutrophil count $\geq .5 \times 10^9$/L for 3 consecutive days and a platelet count $\geq 20 \times 10^9$/L, for 7 days unsupported by transfusion. Grade II-IV acute GVHD and chronic GVHD were based on reports from each transplantation center using standard criteria [11,12]. Relapse was defined as morphologic, cytogenetic, or molecular recurrence of leukemia. Nonrelapse mortality was defined as death in remission.

Statistical Methods

The probabilities of OS and LFS were calculated using the Kaplan-Meier estimator [13]. The cumulative incidences of neutrophil and platelet recovery, acute and chronic GVHD, nonrelapse mortality, and relapse were calculated using the cumulative incidence estimator to accommodate competing risks [14]. Cox regression models were built to identify patient-, disease-, and transplantation-related characteristics on OS, LFS, nonrelapse mortality, and relapse [15]. The variables tested are shown in Table 1. Only variables that attained $P \leq .05$ were held in the final multivariate model. The potential effect of transplantation center was tested using the frailty model [16]. All P values are 2-sided, and all analyses were done using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient-, Disease-, and Transplantation-Related Characteristics

The characteristics of the study population are shown in Table 1. The median age at second HCT was 11 years, and 21% of the study population were young adults (18 to 24 years). Seventy-two percent of patients had performance scores of 90 or 100, and 75% were in hematologic remission at transplantation. The median time between first and second HCT was 17 months, with one-third of the patients undergoing their second HCT less than 1 year after their first HCT. Most (92%) of the patients received their graft from an unrelated donor, but the same donor was used for both transplants in only 14% of the patients. Of the 36 patients who received grafts from the same donor for both transplants, 12 donors were HLA-matched siblings, 13 were HLA-matched unrelated donors, and 11 were HLA-mismatched unrelated donors. Myeloablative conditioning regimens were used more frequently than reduced-intensity regimens (66% versus 34%). In contrast, 93% of conditioning regimens for the first HCT were myeloablative. Approximately 25% of the patients developed grade II-IV acute GVHD and 25% developed chronic GVHD after their first HCT. The proportion of patients who developed grade II-IV acute GVHD and chronic GVHD did not differ between those who received grafts from the same donor and those who received grafts from different donors for their first and second HCTs. The median duration of follow-up of surviving patients was 72 months (range, 11 to 170 months).

Hematopoietic Recovery

The median time to neutrophil recovery was 16 days, and that for platelet recovery was 27 days. The day 28 incidence of neutrophil recovery was 82% (95% confidence interval [CI], 77% to 87%), and the day 100 incidence of platelet recovery was 72% (95% CI, 66% to 78%).

GVHD

The day 100 incidence of grade II-IV acute GVHD was 36% (95% CI, 32% to 44%). Among the 96 patients with acute GVHD, almost one-half (n = 45; 47%) were grade II. The 2- and 8-year incidences of chronic GVHD were 31% (95% CI, 25% to 37%) and 32% (95% CI, 26% to 38%), respectively. The severity of chronic GVHD was reported as mild in 34 patients (41%), moderate in 25 (31%), and severe in 23 (28%).

LFS and OS

LFS was higher for patients who underwent HCT while in remission, when the interval between relapse and second HCT was 5 months or less, in patients with a history of chronic GVHD after first HCT, and when the same donor was used for both the first and second HCTs (Table 2). The 1-, 2-, 5-, and 8-year probabilities of LFS are shown in Table 3 and Figure 1. OS was also higher for patients who underwent HCT while in remission, but was not associated with timing of second HCT, history of chronic GVHD, or use of the same donor for both transplants (Table 2). OS after transplantation of unrelated cord blood grafts was lower than that after transplantation of grafts from HLA-matched and HLA-mismatched unrelated donors. It was also lower than OS after transplantation of grafts from HLA-matched

Table 1
Patient, Disease, and Transplantation Characteristics

Characteristic	Value
Patients, n (%)	251
Disease, n (%)	
AML	141 (56)
ALL	110 (44)
Age, n (%)	
1-9 yr	111 (44)
10-24 yr	140 (56)
Sex, n (%)	
Male	160 (64)
Female	91 (36)
Performance score, n (%)	
90–100	181 (72)
<90	53 (21)
Not reported	17 (7)
Disease status, n (%)	
Complete remission	187 (75)
Relapse	64 (25)
Conditioning regimen intensity, n (%)	
Myeloablative	
TBI + cyclophosphamide ± other	55 (22)
TBI + other	17 (7)
Busulfan + cyclophosphamide	37 (15)
Busulfan + melphalan ± other	27 (11)
Busulfan + fludarabine	19 (8)
Melphalan + fludarabine	8 (3)
Reduced intensity	
TBI + cyclophosphamide + fludarabine	9 (3)
TBI + other	24 (10)
Busulfan + fludarabine	15 (6)
Melphalan + fludarabine	36 (14)
Cyclophosphamide + fludarabine	4 (1)
Donor, n (%)	
HLA-matched sibling	21 (8)
Unrelated donor	230 (92)
Same donor for both transplants	
Yes	36 (14)
No	215 (86)
Graft, n (%)	
Bone marrow	72 (29)
Peripheral blood	96 (38)
Cord blood	83 (33)
Duration of remission after first HCT, n (%)	
<6 mo	53 (21)
6-12 mo	53 (21)
12-24 mo	56 (22)
>24 mo	39 (16)
Unknown	50 (20)
Interval between relapse and second HCT, n (%)	
≤5 mo	64 (25)
>5 mo	137 (55)
Unknown	50 (20)
Interval between first and second HCTs, n (%)	
<12 mo	74 (29)
12-23 mo	105 (42)
≥24 mo	72 (28)
GVHD prophylaxis, n (%)	
Cyclosporine-containing	119 (47)
Tacrolimus-containing	110 (44)
Other agents	22 (9)
Previous grade II-IV acute GVHD, n (%)	
No	185 (74)
Yes	66 (26)
Previous chronic GVHD, n (%)	
No	185 (74)
Yes	66 (26)
Transplantation period, n (%)	
2001-2005	59 (24)
2006-2010	126 (50)
2011-2014	66 (26)
Follow-up of survivors, mo, median (range)	72 (11-170)

Table 2
Risk Factors for Treatment Failure, Overall Mortality, Relapse, and Nonrelapse Mortality

Risk Factor	Hazard Ratio (95% CI)	*P* Value
Treatment failure (inverse of LFS)		
Disease status at HCT		
Complete remission	1.00	
Not in remission	1.79 (1.30-2.47)	.0003
Interval from relapse to second HCT		
>5 mo	1.00	
≤5 mo	.63 (.45-.88)	.017
Same donor for both transplants		
No	1.00	
Yes	.56 (.36-.87)	.009
History of chronic GVHD		
No	1.00	
Yes	.65 (.47-.91)	.012
Overall mortality		
Disease status at HCT		
Complete remission	1.00	
Not in remission	1.63 (1.17–2.27)	.004
Donor type		
Unrelated cord blood	1.00	
HLA-matched sibling	.59 (.32-1.07)	.082
HLA-matched unrelated	.63 (.44-.89)	.011
HLA-mismatched unrelated	.67 (.45-1.00)	.053
Relapse		
Disease status at HCT		
Complete remission	1.00	
Not in remission	2.02 (1.37-2.98)	.0004
Same donor for both transplants		
Yes	1.00	
No	2.09 (1.18-3.69)	.011
Nonrelapse mortality		
Age		
1-9 yr	1.00	
≥10 yr	2.13 (1.24-3.66)	.006
Performance score		
90-100	1.00	
<90	1.89 (1.10-3.27)	.039
Conditioning regimen intensity		
Myeloablative, TBI-containing	1.00	
Myeloablative, non-TBI-containing	.54 (.31-.93)	.027
Reduced-intensity TBI-containing	.16 (.06-.48)	.001
Reduced-intensity non-TBI-containing	.34 (.16-.72)	.005
Donor type		
Unrelated cord blood	1.00	
HLA-matched sibling	.29 (.10-.85)	.023
HLA-matched unrelated	.54 (.30-.97)	.038
HLA-mismatched unrelated	.52 (.26-1.03)	.062

siblings, but the difference did not reach the level of significance set for this study. The 1-, 2-, 5-, and 8-year probabilities of OS are presented in Table 3. There were 180 deaths, with recurrent leukemia the most common cause (n = 95; 53%). Other causes of death were infection (n = 23; 13%), multiorgan failure (n = 27; 15%), GVHD (n = 12; 7%), interstitial pneumonitis/acute respiratory distress syndrome (n = 13; 7%), and not reported (n = 10; 5%).

Relapse and Transplantation-Related Mortality

The risk of relapse was higher for transplantations in relapse and with different donors for first and second HCT (Table 3). The 1, 2, 5 and 8-year probabilities of relapse are shown in Table 3 and Figure 2. Transplantation-related mortality was higher in older patients (age ≥10 years), patients with a performance score ≤80, and after transplantation of unrelated cord blood grafts (Table 3). Transplantation-related mortality was lower after non-TBI-containing myeloablative and reduced-intensity conditioning regimens compared with

Table 3
Probabilities of LFS, OS, Relapse, and Nonrelapse Mortality by Disease Status at HCT

Parameter	Probability, % (95% CI)			
	1 Year	2 Years	5 Years	8 Years
LFS				
Complete remission	47 (40-54)	32 (26-39)	27 (20-33)	24 (18-31)
Not in remission	24 (14-34)	19 (10-28)	10 (3-17)	10 (3-17)
OS				
Complete remission	56 (49-63)	43 (36-50)	31 (24-38)	28 (21-36)
Not in remission	38 (26-49)	26 (16-37)	15 (6-23)	15 (6-23)
Relapse				
Complete remission	29 (23-35)	42 (35-49)	46 (39-53)	49 (41-56)
Not in remission	51 (39-63)	56 (43-68)	64 (52-76)	64 (52-76)
Nonrelapse mortality				
Complete remission	25 (19-31)	27 (21-33)	29 (23-35)	29 (23-35)
Not in remission	20 (11-30)	20 (11-30)	22 (12-31)	24 (14-34)

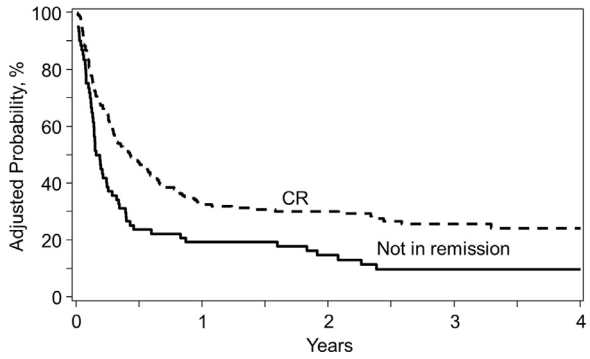

Figure 1. LFS by disease status at second HCT.

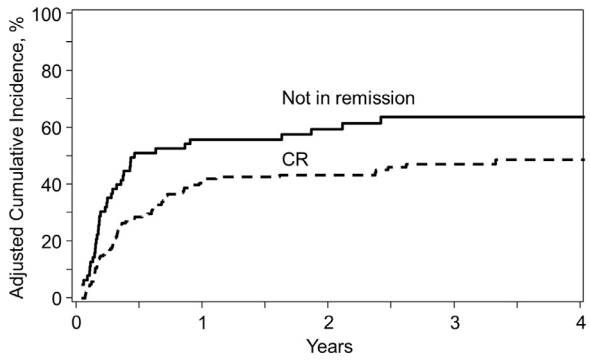

Figure 2. Relapse by disease status at second HCT.

TBI-containing myeloablative regimens. The 1-, 2-, 5-, and 8-year probabilities of nonrelapse mortality are presented in Table 3.

DISCUSSION

There are several published reports on outcomes after second HCT with a primary focus on adults. Factors that have been consistently identified as prognostic for survival include age, interval between first HCT and relapse, and disease status before transplantation [1-8,17]. Therefore, our study population with its median age of 11 years reports outcomes after second HCT in a relatively young cohort of patients with AML or ALL who relapsed after their first HCT. Consistent with all other reports, including a recent European paper [18], disease status at second HCT was associated with relapse, LFS, and OS, implying that careful selection of patients for second HCT can extend LFS and OS. Nonrelapse mortality was high in the first year after HCT, ranging from 20% to 25%. Thereafter, relatively few events occurred with a 5% absolute increment from between year 1 and year 8 after HCT. Recurrent leukemia was the predominant cause of failure of second HCT; however, the pattern of recurrence differed by disease burden. For patients who underwent HCT in relapse, most events occurred within the first year after HCT. Relapse occurred over a longer period for patients who underwent HCT in remission, resulting in a 10% decrement in LFS beyond the second year after HCT.

These data are informative and challenging. First, careful selection of patients for second HCT is key, given that disease burden is critical for a successful outcome. The transplantations in this study were performed over a 15-year period, and the indications for proceeding to transplantation have evolved during that period. With the body of literature supporting the adverse effect of minimal residual disease (MRD) on relapse and survival for ALL, it is compelling to suggest that second HCT should be offered for those in whom MRD cannot be detected [19-21]. There is also growing evidence that detection of subclinical levels of leukemia using molecular-based or multiparameter flow cytometry in AML is also independently prognostic before HCT [22,23] Second, with the increasing availability of novel agents for the treatment of ALL and AML, our observations provide a compelling argument for planned therapy to achieve MRD negativity to lower the risk of relapse after second HCT, underscoring the need for careful selection of patients who can tolerate continued treatment post-HCT [24-27].

Others have reported on the importance of duration of remission after first HCT as a prognostic factor for survival [2,7,8]. Instead, we observed that the interval between relapse and second HCT was associated with improved LFS. The observed advantage regarding LFS in the timing of second HCT (ie, $<$5 months after relapse) in our study is a surrogate for the duration of remission after first HCT. The duration of remission between first HCT and relapse post-HCT was $>$12 months for one-half of patients undergoing second HCT $<$6 months after relapse. In contrast, the duration of remission between first HCT and subsequent relapse was $<$12 months for 56% of patients undergoing second HCT $\geq$6 months after relapse.

Although others have reported no advantage to using a different donor for the second HCT, we observed a significantly lower rate of relapse and higher LFS with the same donor for both transplantations [2,5,8,28]. Consequently, we conclude that our findings do not support the need to change the donor for the second HCT or to use an unrelated donor instead of a sibling donor. We observed similar mortality risks after HCT with HLA-matched and -mismatched unrelated donor transplants compared with HLA-matched sibling transplants, but acknowledge that a modest sample of 251 donor-recipient pairs is not adequately powered to detect differences in HLA disparity.

There are likely several reasons for the higher nonrelapse and overall mortality risks with cord blood transplants in this population. The majority of cord blood units were mismatched at 1 or 2 HLA loci considering lower-resolution HLA matching at HLA-A and -B, and we did not consider matching at HLA-C. Consequently, the majority of cord blood units would have been mismatched to their recipients at 2, 3, or more HLA loci when considering allele-level HLA matching at HLA-A, -B, -C, and -DRB1 [29]. HLA mismatch leads to slower hematopoietic recovery and increases the risk for acute GVHD and severe

infections in heavily pretreated patients, which in turn increases mortality risk. Therefore, our findings lend support to selecting HLA-matched sibling or HLA-matched unrelated donors when available and if umbilical cord blood is the sole option to prioritize HLA matching (allele-level) after ensuring that potential units have the minimum prefreeze total nucleated cell dose of 3×10^7/kg [29]. Selecting units with a total nucleated cell dose exceeding the required minimum does not overcome the mortality risk associated with HLA disparity [29]. The use of bone marrow or peripheral blood had no significant predictive value for nonrelapse mortality, relapse, or survival, consistent with a previous report [30].

Consistent with other studies, we also observed significant associations of age and performance score with HCT outcomes. Those studies concluded that patients age <20 years fare better. In our population that was predominantly children, we found that patients age <10 years fared better. Similarly, a performance score of ≤80 at HCT was associated with higher nonrelapse mortality. Arguably, the HCT Comorbidity Index is a better predictor for mortality, but this was not available for all patients, because approximately one-half of the transplantations were performed before the introduction and validation of the HCT Comorbidity Index [31]. The intensity of conditioning regimen was not associated with relapse or OS, consistent with the recent European paper [18]. An earlier European study that included children and adults showed a difference in outcomes by conditioning intensity, which was most likely explained by the inclusion of adults [2]. However, nonrelapse mortality was lower with non-TBI-containing myeloablative and reduced-intensity conditioning regimens compared with TBI-containing myeloablative regimens [28].

The spectrum of conditioning regimens used in the present analysis is wide, and in the absence of an association with relapse or survival, we conclude that the transplantation conditioning regimen for second HCT should be tailored for the individual patient considering his or her HCT Comorbidity Index, overall fitness for second HCT, and perhaps their response to reinduction chemotherapy (ie, remission and MRD status) before transplantation. We observed higher LFS in patients with a history of chronic GVHD after first HCT, consistent with other reports [18]; however, in another study from our group that focused on predictors for late mortality, chronic GVHD was a significant predictor of death [32].

Our study has limitations in terms of its retrospective nature, the factors that led to the decision to offer second HCT, and an inability to evaluate ALL and AML separately and to control for unknown or unmeasured factors. Nevertheless, the study was limited to children and young adults, and we were able to identify disease- and transplantation-related prognostic factors as well as patterns in treatment failure that may prove insightful in the planning of prospective trials to lower relapse risks after second HCT. Our findings confirm that using a different donor for the second HCT does not improve outcomes and that umbilical cord blood transplants should be avoided whenever possible.

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