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Clinical Research

Outcome of Transplantation for Acute Myelogenous Leukemia in Children with Down Syndrome

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A B S T R A C T

Data on outcomes of allogeneic transplantation in children with Down syndrome and acute myelogenous leukemia (DS-AML) are scarce and conflicting. Early reports stress treatment-related mortality as the main barrier; a recent case series points to posttransplantation relapse. We reviewed outcome data for 28 patients with DS-AML reported to the Center for International Blood and Marrow Transplant Research between 2000 and 2009 and performed a first matched-pair analysis of 21 patients with DS-AML and 80 non-DS AML controls. The median age at transplantation for DS-AML was 3 years, and almost half of the cohort was in second remission. The 3-year probability of overall survival was only 19%. In multivariate analysis, adjusting for interval from diagnosis to transplantation, risks of relapse (hazard ratio [HR], 2.84; $P < .001$; 62% versus 37%) and transplant-related mortality (HR, 2.52; $P = .04$; 24% versus 15%) were significantly higher for DS-AML compared to non-DS AML. Overall mortality risk (HR, 2.86; $P < .001$; 21% versus 52%) was significantly higher for DS-AML. Both transplant-related mortality and relapse contribute to higher mortality. Excess mortality in DS-AML patients can only effectively be addressed through an international multicenter effort to pilot strategies aimed at lowering both transplant-related mortality and relapse risks.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is an integral part of treatment for high-risk acute myelogenous leukemia (AML) in children and adolescents. Disease-free survival (DFS) for pediatric AML after HCT ranges between 40% and 60%, and varies depending on donor and graft source [1-3]. For patients with Down syndrome (DS) and acute leukemia, the role of HCT remains unclear. Children with DS (OMIM, #190685) have a 10- to 20-fold increased risk for acute leukemia compared to the general pediatric population [4]. AML in DS (DS-AML) is characterized by young age of onset, somatic mutations of the hematopoietic transcription factor *GATA1*, and excellent outcomes with chemotherapy (DFS of 80%) [5-7] because of the increased drug sensitivity of DS-AML blasts, especially in the younger patients, most of whom have M7 disease [8]. Consequently, HCT is not typically considered for DS-AML in first remission. For patients beyond first remission, allogeneic transplantation may be offered; however, data are scarce and the pattern of treatment failure is unclear. An earlier report of 27 patients with DS and AML or acute lymphoblastic leukemia suggested treatment-related mortality (TRM) was the predominant cause of treatment failure [9], although a later report of 11 patients suggested relapse as the primary cause of treatment failure [10]. To our

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knowledge, there are no reports that have directly compared transplant outcomes for AML in patients with or without DS. Therefore, to better define patterns of posttransplantation treatment failure we conducted a matched-pair analysis of patients with DS-AML and non-DS AML.

PATIENTS AND METHODS

Data Source

Data were obtained from the Center for International Blood and Marrow Transplant Research, which is a working group of more than 400 transplant centers worldwide that provide detailed patient, disease, and transplant characteristics and outcomes on consecutive transplantations to the statistical center at the Medical College of Wisconsin or the data-coordinating center of the National Marrow Donor Program. Participating centers report data on consecutive transplantations; all patients are followed longitudinally until death or lost to follow-up. Guardians provided written informed consent for data submission and research participation. The Institutional Review Boards of the Medical College of Wisconsin and the National Marrow Donor Program approved this study.

Inclusion Criteria

Patients with DS-AML who received grafts from human leukocyte antigen (HLA)-matched siblings, and matched or mismatched unrelated adult donors or umbilical cord blood were eligible. A similar population of non-DS AML patients served as controls. All transplantations occurred between 2000 and 2009. Transplantations before 2000 were excluded because of substantial changes in front-line chemotherapeutic regimens and supportive care after transplantation.

Risk Classification

Risk classification was assigned based on cytogenetic and molecular markers. Patients were classified into 3 risk groups: the favorable risk group included the t(8;21), t(15;17) and inv(16) karyotypes; high risk was defined by the presence of -7, -5, del (5q), abnormalities of the long arm of chromosome 3 or complex karyotype that was defined as more than 4 abnormalities; all other AML karyotypes were classified as intermediate risk [11]. Blast phenotype was not used for risk stratification or matching of cases and controls (see below). This approach is consistent with the exclusion of blast phenotype from contemporary prognostication and treatment stratification of AML in children with [5,7,12] and without DS [2,11,13]. FLT3 mutations were not considered, as this information was not systematically collected in the early 2000s.

Outcomes

Neutrophil recovery was defined by an absolute neutrophil count (ANC) $\geq$500/μl for 3 consecutive measurements; platelet recovery as a platelet count >20,000/μL for 7 days without transfusion. Grades 2 to 4 acute graft-versus-host disease (GVHD) and chronic GVHD were defined using standard criteria [14,15]. TRM was defined as death occurring in remission. Relapse was defined as morphological recurrence of leukemia at any site. DFS (inverse of treatment failure; relapse, or death) was defined as survival in continuous complete remission. Surviving patients were censored at last contact.

Statistical Analyses

The probabilities of neutrophil and platelet recovery, acute and chronic GVHD, TRM, and relapse were calculated using the cumulative incidence function estimator [16]. For neutrophil and platelet recovery and GVHD, death without the event was the competing risk. For TRM, relapse was the competing event, and for relapse, TRM was the competing event. The probabilities of DFS and overall survival were calculated using the Kaplan-Meier estimator [16]. The 95% confidence intervals were calculated using log transformation. For overall survival, death from any cause was considered an event, and for DFS, relapse or death were considered events.

Patients with DS-AML (cases) were matched to patients with non-DS AML (controls). Cases and controls were matched on disease status, risk group, donor and graft source, and donor-recipient HLA match. Additionally, matched pairs with the smallest age difference between the case and controls were selected. Among the 28 patients with DS-AML, 7 patients were excluded from the matched analysis: age >18 years (n = 1), reduced-intensity conditioning regimen (n = 1), absence of cytogenetic data (n = 4), or control case not available (n = 1). Twenty-one cases were matched to 80 controls from a population of 746 controls: 18 pairs matched 1:4, 2 pairs matched 1:3, and 1 pair matched 1:2. All patients included in the matched pair analysis received myeloablative transplant conditioning regimen. Cox regression models [16] were built to examine the risk of relapse, TRM, treatment failure, and overall mortality for patients with DS-AML and non-DS AML. As cases and controls were matched on known prognostic factors, the only additional variable considered was interval from diagnosis to transplantation ($\leq$12 months versus >12 months) to adjust for the prognostic impact of early relapse. All *P* values are 2-sided and value $\leq$.05 was considered significant. All analyses were performed using SAS version 9.1 (Cary, NC).

Table 1
Patient, Disease and Transplant Characteristics

Number of patients	28
Number of transplant centers	24
Age, median (range), yr	3 (2-24)
Age, $\leq$5 yr	25
Age, 6 to 18 yr	2
Age, >18 yr	1
Lansky performance score	
<90	1
90 to 100	25
Not reported	2
Disease status	
First complete remission	5
Second complete remission*	12
Relapse	9
Primary induction failure	2
Blast phenotype (FAB)	
M0	2
M1	1
M2	3
M3	0
M4	1
M5	0
M6	0
M7	16
Not specified	5
Risk group	
Intermediate risk	16
High risk	6
Not reported	6
Time from diagnosis to transplantation	
$\leq$12 mo	18
13 to 36 mo	10
Conditioning regimen	
Total body irradiation + cyclophosphamide	7
Total body irradiation + other agents	2
Busulfan + cyclophosphamide	13
Busulfan + fludarabine	2
Busulfan + melphalan	4
In vivo T cell depletion (ATG or alemtuzumab)	
None	18
Yes	10
Graft-versus-host disease prophylaxis	
Cyclosporine-containing	22
Tacrolimus-containing	5
Not reported	1
Donor type	
HLA-matched sibling (BM 1, PBSC 3, CB 0)	4
HLA-matched unrelated donor (BM 5, PBSC 2, CB 2)	9
HLA-mismatched unrelated donor (BM 2, PBSC 1, CB 12)	15
Graft type	
Bone marrow	8
Peripheral blood progenitor cells	6
Umbilical cord blood	14
Transplant period	
2000 to 2005	17
2005 to 2009	11
Median follow-up, (range), mo	47 (7-60)

ATG indicates anti-thymocyte globulin; HLA, human leukocyte antigen; BM, bone marrow; PBSC, peripheral blood stem cells; CB, cord blood.
Data are presented as n unless otherwise indicated.
* Duration 4.8 to 22.0 months.

RESULTS

Patient, disease, and transplant characteristics for all patients with DS-AML are shown in Table 1. The median age at transplantation was 3 years; all patients were aged less

Table 2
Univariate Analysis

Outcomes	Number Events of Evaluable	Probability (95% CI)
Neutrophil recovery	24 of 28	
At 28 d		75 (58-89)
Platelet recovery	15 of 25	
At 100 d		52 (31-69)
Grades 2 to 4 acute graft-versus-host disease	8 of 28	
At 100 d		29 (14-46)
Chronic graft-versus-host disease	6 of 28	
At 3 yr		23 (9-40)
Transplant-related mortality	7 of 28	
At 100 d		14 (4-29)
At 3 yr		25 (11-42)
Relapse	17 of 28	
At 3 yr		61 (42-78)
Disease-free survival	24 of 28	
At 3 yr		14 (4-29)
Overall survival	23 of 28	
At 3 yr		19 (7-36)

than 18 years, except for one patient who was age 24 years. Forty-three percent of transplantations occurred in second remission and 39% in relapse or after primary induction failure. Most patients were transplanted for early treatment failure, as 64% of patients were transplanted within a year from diagnosis. All but one patient received myeloablative transplant-conditioning regimens. Grafts from mismatched unrelated donors or umbilical cord blood units each accounted for 40% of all transplantations and HLA-mismatching was almost entirely confined to the cord blood grafts. All patients received cyclosporine or tacrolimus containing GVHD prophylaxis and approximately 30% received methotrexate or mycophenolate mofetil with the calcineurin inhibitor.

The probabilities of hematopoietic recovery, GVHD, TRM, relapse, DFS, and OS are shown in Table 2. The TRM rate was high, but the relapse rate was substantially higher for DS-AML than non-DS AML patients. One patient with DS-AML age 24 years was included in the unmatched analysis and should not have significantly influenced the aforementioned poor outcomes. An additional univariate analysis restricted to patients age 18 years or younger at transplantation confirmed that no differences emerged when this young adult was excluded (data not shown). Only 4 of 28 patients are alive and disease-free. Of the 23 patients who are dead, 16 (70%) died of recurrent disease. Other causes of death include organ failure (n = 4), hemorrhage (n = 1), infection (n = 1) and cause of death not reported (n = 1). One patient who relapsed is alive at last follow-up.

The characteristics of cases (DS-AML; n = 21) and controls (non-DS AML; n = 80) are shown in Table 3. Figure 1A through 1D show the probabilities of relapse, TRM, DFS, and overall survival of cases (DS-AML) and controls (non-DS AML). Consistent with the results of univariate analysis, in multivariate analysis, after adjusting for interval from diagnosis to transplantation, risks of TRM, relapse, treatment failure (inverse of DFS), and overall mortality are significantly higher in DS-AML patients compared with non-DS AML (Table 4).

Table 3
Characteristics of DS-AML and Non DS-AML Patients Matched for Age, Cytogenetic Risk, Disease Status, Donor and Graft Source, and Donor-Recipient HLA-Match

	Non DS-AML n (%)	DS-AML n (%)
Number of patients	80	21
Number of centers	47	19
Age		
≤5 yr	60 (75)	19 (90)
6 to 10 yr	14 (18)	1 (5)
11 to 18 yr	6 (8)	1 (5)
Sex		
Male	54 (68)	13 (62)
Female	26 (33)	8 (38)
Lansky performance score		
<90	16 (20)	1 (5)
≥90	60 (75)	18 (86)
Unknown	4 (5)	2 (10)
Time from diagnosis to transplant, mo		
≤12 mo	46 (58)	13 (62)
13 to 36 mo	34 (43)	8 (38)
Disease status prior to transplantation		
First remission	16 (20)	4 (19)
Second remission	36 (45)	9 (43)
Relapse	16 (20)	7 (33)
Primary induction failure	12 (15)	1 (5)
Blast phenotype (FAB)		
M0	3 (4)	2 (10)
M1	5 (6)	1 (5)
M2	15 (19)	1 (5)
M3	1 (1)	0
M4	5 (6)	1 (5)
M5	25 (31)	0
M6	3 (4)	0
M7	10 (13)	12 (57)
Not specified	13 (16)	4 (19)
Risk groups		
Intermediate risk	67 (84)	17 (81)
High risk	13 (16)	4 (19)
Conditioning regimen		
Total body irradiation + cyclophosphamide	38 (48)	6 (29)
Total body irradiation + other agents	4 (5)	2 (10)
Busulfan + cyclophosphamide	25 (31)	10 (48)
Busulfan + fludarabine	4 (5)	0
Busulfan + melphalan	9 (11)	3 (14)
Graft-versus-host disease prophylaxis		
Cyclosporine-containing	64 (80)	15 (71)
Tacrolimus-containing	11 (14)	5 (24)
Methotrexate	3 (3)	0
Not reported	3 (3)	1 (5)
Donor type		
HLA-matched sibling	4 (5)	1 (5)
BM	0	0
PBSC	4	1
CB	0	0
Matched unrelated	33 (41)	9 (43)
BM	20	5
PBSC	5	2
CB	8	2
Mismatched unrelated	43 (54)	11 (52)
BM	4	1
PBSC	4	1
CB	35	9
Graft type		
Bone marrow	24 (30)	6 (29)
Peripheral blood progenitor cells	13 (16)	4 (19)
Umbilical cord blood	43 (54)	11 (52)
Median (range) follow-up, mo	37 (3-120)	47 (7-60)

BM indicates bone marrow; PBSC, peripheral blood stem cells; CB, cord blood.

DISCUSSION

Although chemotherapy approaches are now well defined for DS-AML [5,7,8,17-20], the role of allogeneic transplantation has been limited to case reports and small series [21] that are more pertinent to previous treatment eras [22], and the results are conflicting [9,10,22]. Our current analysis sought to delineate the relative contributions of TRM and relapse to treatment failure after allogeneic

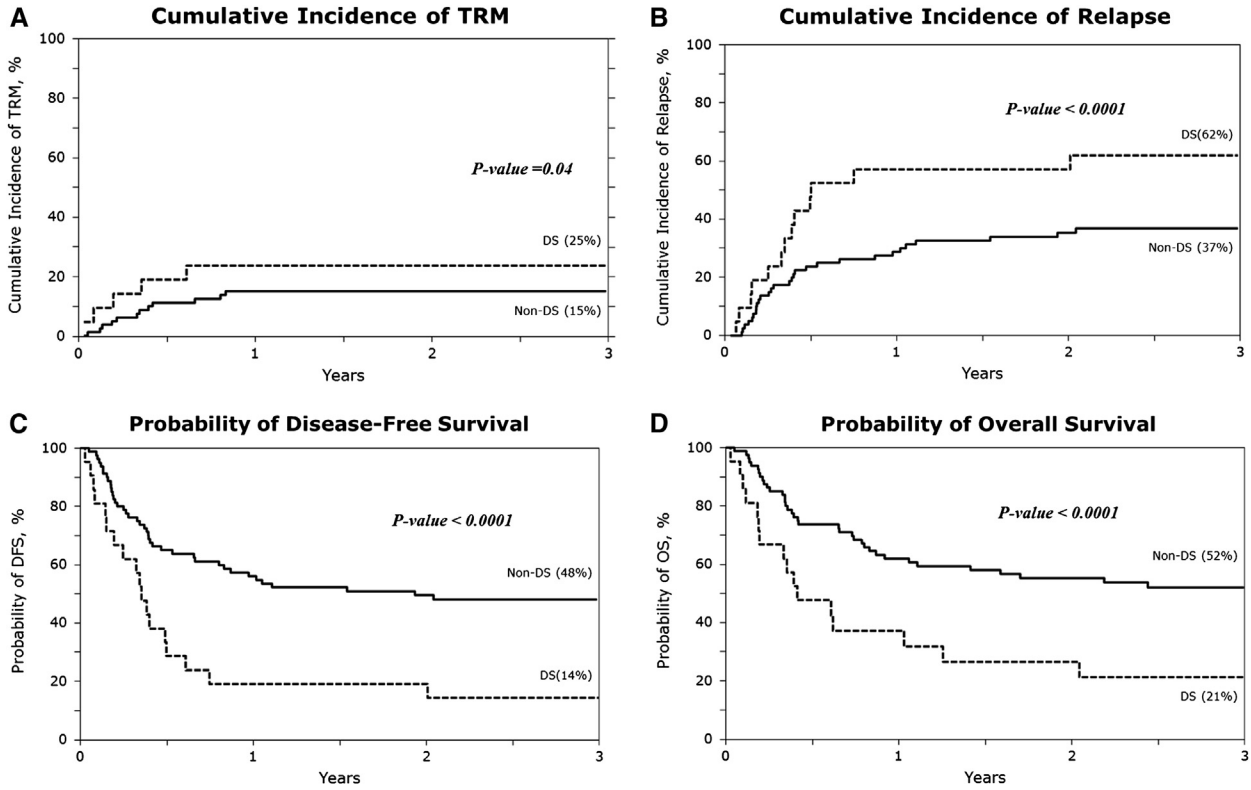

Figure 1. (A) The 3-year probabilities of TRM: 24% (95% CI, 9% to 44%) and 15% (95% CI, 8% to 24%) for DS-AML and non-DS AML, respectively ($P = .04$). (B) The 3-year probabilities of relapse: 62% (95% CI, 41% to 81%) and 37% (95% CI, 27% to 48%), for DS-AML and non-DS AML, respectively ($P < .001$). (C) The 3-year probabilities of DFS: 14% (95% CI, 3% to 32%) and 48% (95% CI, 37% to 59%) for DS-AML and non-DS AML, respectively ($P < .001$). (D) The 3-year probabilities of overall survival: 21% (95% CI, 6% to 42%) and 52% (95% CI, 41% to 63%), for DS-AML and non-DS AML, respectively ($P < .001$).

transplantation in a relatively large contemporary cohort of patients with DS-AML and our findings confirm that high rates of TRM and relapse both play a role. Confirmation of this observation was strengthened by the additional matched pair analyses of DS-AML and non-DS AML patients that adjusted for risk factors associated with transplantation outcomes. High rates of treatment failure led to an overall survival rate of only 21% after transplantation for DS-AML compared to 52% for non-DS AML.

It is tempting to attribute high relapse rates in our DS-AML cohort to the 39% of patients whose leukemia was active at transplantation. However, results from our matched pair comparison do not support this notion. Therefore, the reported overall favorable prognosis of DS-AML at time of original diagnosis appears to reflect outcomes in 2 different risk settings: one where over 80% of patients achieve long-term remission with lower intensity chemotherapy alone [5-7], and a smaller percentage, who respond poorly to up front therapy [23] as manifested by early relapse and inability to achieve complete remission after a relapse.

Table 4
Results of Multivariate Analysis of DS-AML and Non DS-AML Matched Pair

	Relative Risk (95% CI)	*P* value
Transplant-related mortality		
DS-AML versus non DS-AML*	2.52 (1.06-6.00)	.04
Time from diagnosis to transplantation ≤12 mo versus 13 to 36 mo*	2.17 (0.75-6.25)	.15
Relapse		
DS-AML versus non DS-AML*	2.84 (1.75-4.59)	<.001
Time from diagnosis to transplantation ≤12 mo versus 13 to 36 mo*	1.43 (0.76-2.63)	.27
Treatment failure		
DS-AML versus non DS-AML*	2.75 (1.75-4.31)	<.001
Time from diagnosis to transplantation ≤12 mo versus 13 to 36 mo*	1.59 (0.92-2.78)	.10
Overall mortality		
DS-AML versus non DS-AML*	2.86 (1.77-4.64)	<.001
Time from diagnosis to transplantation ≤12 mo versus 13 to 36 mo*	1.89 (1.05-3.45)	.03

* Reference group.

The current analysis used data reported to a transplant registry. A significant limitation is the heterogeneity of the patients with respect to their disease status at transplantation and transplant-conditioning regimen. However, we were able to perform a carefully controlled analysis adjusting for the known risk factors that influence transplantation outcomes. The observed poor outcome may be attributed to differences in the biology of DS-AML and/or the intensity of front-line chemotherapy regimens used in these patients compared to non-DS AML patients. Another plausible explanation could be the presence of minimal residual disease (MRD) at transplantation; data on MRD were not collected during the study period and is a limitation.

Our data suggest a reduction in TRM remains desirable, but the data also highlight the importance of leukemia recurrence as a major cause of treatment failure. Therefore, the decision to offer transplant for DS-AML must consider the excess risk of leukemia recurrence after transplantation even for those who attain remission after an initial relapse in addition to TRM risks. One strategy to improve survival could focus on carefully selecting transplant candidates such as those in morphological remission and who are

MRD negative. Other strategies include planned post-transplantation therapy to ensure better leukemia control posttransplantation. Lowering TRM risks remains a challenge in these patients; full intensity regimens, which offer leukemia control, are offset by life-threatening infections and/or organ toxicity.

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