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Unrelated Cord Blood Transplantation for Acute Leukemia Diagnosed in the First Year of Life: Outcomes and Risk Factor Analysis

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A B S T R A C T

Infant acute leukemia still has a poor prognosis, and allogeneic hematopoietic stem cell transplantation is indicated in selected patients. Umbilical cord blood (UCB) is an attractive cell source for this population because of the low risk of chronic graft-versus-host disease (GVHD), the strong graft-versus-leukemia effect, and prompt donor availability. This retrospective, registry-based study reported UCB transplantation (UCBT) outcomes in 252 children with acute lymphoblastic leukemia (ALL; n = 157) or acute myelogenous leukemia (AML; n = 95) diagnosed before 1 year of age who received a single-unit UCBT after myeloablative conditioning between 1996 and 2012 in European Society for Blood and Marrow Transplantation centers. Median age at UCBT was 1.1 years, and median follow-up was 42 months. Most patients (57%) received a graft with 1 HLA disparity and were transplanted in first complete remission (CR; 55%). Cumulative incidence function (CIF) of day 100 acute GVHD (grades II to IV) was 40% ± 3% and of 4-year chronic GVHD was 13% ± 2%. CIF of 1-year transplant-related mortality was 23% ± 3% and of 4-year relapse was 27% ± 3%. Leukemia-free-survival (LFS) at 4 years was 50% ± 3%; it was 40% and 66% for those transplanted for ALL and AML, respectively ($P = .001$). LFS was better for patients transplanted in first CR, regardless of diagnosis. In multivariate model, diagnosis of ALL ($P = .001$), advanced disease status at UCBT (<.001), age at diagnosis younger than 3 months ($P = .012$), and date of transplant before 2004 were independently associated with worse LFS. UCBT is a suitable option for patients diagnosed with infant acute leukemia who achieve CR. In this cohort, patients with AML had better survival than those with ALL.

INTRODUCTION

Acute leukemia diagnosed during the first year of life represents about 2.5% to 5% of acute lymphoblastic leukemia (ALL) and 6% to 14% of acute myelogenous leukemia (AML) in childhood [1]. At diagnosis, infant acute leukemia often occurs with hyperleukocytosis, central nervous system

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involvement (both ALL and AML), frequent *MLL* rearrangement (ALL), and extramedullary disease (AML) [2]. Although the results obtained in the treatment of acute leukemia in children over 1 year of age have improved over the last decades, infant acute leukemia remains an aggressive disease associated with poor outcome [3,4].

In view of the molecular/genetic characteristics of the leukemia clone and of the response to front-line therapy, about one-third of infants with ALL in first complete remission (CR1), one-third to one-half of infants with AML in CR1, and virtually all infants with acute leukemia in CR2 have an indication to receive allogeneic hematopoietic stem cell transplantation (HSCT) usually after a myeloablative conditioning regimen [2,5]. However, the use of myeloablative conditioning in these young and fragile, often previously heavily treated, patients raises concerns, considering their high risk of toxicity, morbidity, and mortality compared with older children [6]. Moreover, the role of HSCT for infant leukemia is still controversial [7].

Umbilical cord blood transplantation (UCBT) represents a suitable stem cell source for pediatric patients with hematologic malignancies, with results of UCBT comparable with those of HSCT using either bone marrow or peripheral blood stem cells in both children and adults [8,9]. Although the role of UCBT in children has been extensively discussed, only scarce data report its use in patients diagnosed in the first year of life (ie, infants) [1]. Thus, we analyzed results of UCBT in patients reported by participating transplant centers to Eurocord and the European Society for Blood and Marrow Transplantation (EBMT), with the objective of providing data on outcome of UCBT in children with infant ALL and AML.

METHODS

Study Design, Inclusion Criteria, and Data Collection

This is a retrospective registry-based study performed by Eurocord, in collaboration with the Pediatric Disease Working Party of EBMT. Patients with acute leukemia diagnosed within the first year of life who received unrelated single-unit UCBT (first transplant) after myeloablative conditioning in EBMT centers from 1996 through 2012 were considered for the study. A total of 252 patients meeting the above criteria were included in the analysis.

Demographic and clinical data were extracted from the Eurocord database and validated. Participating transplant centers were asked to provide missing information and correct discrepancies using a customized questionnaire.

Parents or legal guardians provided informed consent allowing data entry into the Eurocord and EBMT databases for research purposes. The study was conducted in compliance with the Declaration of Helsinki. The Internal Review Board of Eurocord reviewed and approved the study.

Endpoints, Definitions, and Statistical Analysis

The primary endpoint was leukemia-free survival (LFS), defined as being alive and in continuous CR at last follow up.

Secondary endpoints were overall survival (OS), time of neutrophil and platelet recovery, incidence of relapse, transplant-related mortality (TRM), and acute and chronic GVHD. Probabilities were calculated from date of transplantation until the event or censoring. Neutrophil engraftment was defined as achieving absolute neutrophil count $\geq .5 \times 10^9$/L for 3 consecutive days with no evidence of autologous recovery (<5% leucocytes of donor origin in peripheral blood or marrow). Full donor chimerism was defined as presence of ≥95% leucocytes of donor origin in peripheral blood or bone marrow.

Platelet engraftment was defined as achieving platelet count $\geq 20 \times 10^9$/L unsupported by platelet transfusions for 7 days. Acute and chronic GVHD were graded according to previously published criteria [10,11]. Probabilities of LFS and OS were calculated using the Kaplan-Meier estimates. Cumulative incidence functions (CIFs) were used to estimate incidence of relapse and TRM in a competing risks setting as death and relapse compete with each other. To estimate acute and chronic GVHD incidences, relapse and death were considered as competing events.

A comparison with 2-sided $P < .05$ was considered statistically significant. Variables reaching $P < .10$ in univariate analysis were included in Cox proportional hazard regression models using a backward stepwise selection. Analyses were performed with SPSS version 19 (Inc., Chicago, IL) and Splus software package (MathSoft, Inc., Seattle, WA).

Criteria for poor-risk cytogenetics for ALL were the presence of 1 or more of the following abnormalities: t(4;11), t(1;19), hypodiploidy (<44 chromosomes), and/or any 11q23 abnormality. For AML, poor-risk group was defined according to previously published reports [12,13]. Myeloablative conditioning was defined as a regimen containing either total body irradiation with a dose greater than 6 Gy, a dose of oral busulfan higher than 8 mg/kg, a dose of i.v. busulfan > 6.4 mg/kg, or a myeloablative dose of treosulfan (ie, ≥36 g/m^2 over 3 days). Donor–recipient HLA degree of matching was assessed at the antigen level for HLA-A and -B and at the allele level for HLA-DRB1.

RESULTS

Patient, Disease, and Transplant Characteristics

Patient, disease, and transplant characteristics are summarized in Table 1. Briefly, among the 252 patients included in the study, 95 (38%) were transplanted for AML and 157 (62%) for ALL. Median age at diagnosis and at UCBT was 5.6 months (range, 1 day to 12 months) and 1.1 years (range, .3 to 11 years), respectively. Overall, 138 patients (55%) were transplanted in CR1, 76 (30%) in CR2, and the remaining in

Table 1
Patient, Disease, and Transplant Characteristics (n = 252)

Variable	Value
Patient and disease	
Gender (male)	118 (47)
Disease	
ALL	157 (62)
AML	95 (38)
ALL disease status (assessable n = 154)	
CR1	84 (54)
CR2	50 (33)
>2nd CR	9 (6)
Advanced disease	11 (7)
AML disease status (assessable n = 93)	
CR1	54 (58)
CR2	26 (28)
>2nd CR	2 (2)
Advanced disease	11 (12)
Cytogenetic risk (assessable n = 205)	
Good risk	2 (.8)
Intermediate risk	79 (38)
Poor risk	124 (60)
MLL rearrangement (available for n = 157)	118 (75)
Age at initial diagnosis, mo, median (range)	5.6 (.03-12.0)
Age at diagnosis < 3 months of age, whole cohort	64 (25)
ALL patients	44 (28)
AML patients	20 (21)
Time from diagnosis to transplantation	
Patients in CR1, mo, median (range)	6.1 (2.8-20.7)
Patients in CR2, mo, median (range)	16.7 (5.7-111.6)
Patients beyond CR2, mo, median (range)	
Age at transplantation, yr, median (range)	1.1 (.3-11.0)
Weight at transplantation, kg, median (range)	9.5 (4.0-34.0)
Positive CMV serology	109 (48)
Previous autologous transplant	5 (2)
Transplantation characteristics	
Year of transplantation (assessable n = 252)	
<2004	56 (22)
≥2004	196 (78)
HLA compatibility (assessable n = 188)	
Identical	41 (22)
1 HLA disparity	107 (57)
≥2 HLA disparities	40 (21)
Gender mismatch patient–graft (assessable n = 245)	115 (47)
TNC at cryopreservation, $\times 10^7$/kg, median (range)	12.4 (3.0-44.3)
CD34+ cells at infusion, $\times 10^5$/kg, median (range)	3.9 (.2-323.6)

Values are total number of cases with percents in parentheses, unless otherwise noted.
CMV indicates cytomegalovirus; TNC, total nucleated cell dose collected.