Clinical Research: Alternative Donors

Factors Associated with Long-Term Risk of Relapse after Unrelated Cord Blood Transplantation in Children with Acute Lymphoblastic Leukemia in Remission

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A B S T R A C T

For pediatric patients with acute lymphoblastic leukemia (ALL), relapse is an important cause of treatment failure after unrelated cord blood transplant (UCBT). Compared with other donor sources, relapse is similar or even reduced after UCBT despite less graft-versus-host disease (GVHD). We performed a retrospective analysis to identify risk factors associated with the 5-year cumulative incidence of relapse after UCBT. In this retrospective, registry-based study, we examined the outcomes of 640 children (<18 years) with ALL in first complete remission (CR1; n = 257, 40%) or second complete remission (CR2; n = 383, 60%) who received myeloablative conditioning followed by a single-unit UCBT from 2000 to 2012. Most received antithymocyte globulin (88%) or total body irradiation (TBI; 69%), and cord blood grafts were primarily mismatched at 1 (50%) or 2+ (34%) HLA loci. Considering patients in CR1, the rates of 5-year overall survival (OS), leukemia-free survival (LFS), and relapse were 59%, 52%, and 23%, respectively. In multivariate analysis (MVA), acute GVHD (grades II to IV) and TBI protected against relapse. In patients in CR2, rates of 5-year OS, LFS, and the cumulative incidence of relapse were 46%, 44%, and 28%, respectively. In MVA, longer duration from diagnosis to UCBT (≥30 months) and TBI were associated with decreased relapse risk. Importantly, receiving a fully HLA matched graft was a strong risk factor for increased relapse in MVA. An exploratory analysis of all 640 patients supported the important association between the presence of acute GVHD and less relapse but also demonstrated an increased risk of nonrelapse mortality. In conclusion, the impact of GVHD as a graft-versus-leukemia marker

is evident in pediatric ALL after UCBT. Strategies that promote graft-versus-leukemia while harnessing GVHD should be further investigated.

INTRODUCTION

Modern risk-based chemotherapy regimens are curative for many children and adolescents with de novo acute lymphoblastic leukemia (ALL) [1]. An additional subset of patients can achieve long-term remission with allogeneic hematopoietic stem cell transplantation (HSCT), but outcomes are poor for those who relapse after HSCT. Current practice is to offer HSCT to patients with high-risk disease in first complete remission (CR1) or relapsed disease once a second complete remission (CR2) is achieved. The curative effect of HSCT is due to the use of high-dose chemotherapy with or without total body irradiation (TBI) along with the potential for the graft-versus-leukemia (GVL) effect. It is well established that the GVL effect, likely due to immune surveillance provided by donor natural killer and T cells, is important in eradicating leukemia after allogeneic HSCT [2-5], although the GVL effect in ALL may be weaker than in other malignancies [6-8]. Select clinical reports have demonstrated lower rates of relapse in pediatric patients with ALL who experience graft-versus-host disease (GVHD) after HSCT, providing indirect evidence of GVL actions in this disease [9-11].

For children and adolescents with ALL in need of HSCT, the use of unrelated donor cord blood (UCB) offers several benefits, including rapid procurement, more lenient HLA matching, and lower rates of GVHD [12]. Clinical reports have also demonstrated lower rates of relapse after UCB transplantation (UCBT) as compared with other donor sources [13-19]. The benefits of UCBT have historically been offset by higher nonrelapse mortality (NRM). Recent outcomes are similar to those seen with other donor sources [13,20,21]. Outcomes after UCBT for pediatric ALL have been described as part of larger prospective [9,16,22,23] and retrospective [18,24-26] studies, but a focused examination of factors influencing relapse in pediatric ALL recipients after UCBT is needed. In this report we describe the long-term outcomes of a collaborative effort between Eurocord, European Society of Blood and Marrow Transplantation (EBMT), and Duke University Pediatric Blood and Marrow Transplant Program to define risk factors associated with relapse and other outcomes after UCBT for pediatric ALL.

METHODS

Study Design

Eligible patients were <18 years old with a diagnosis of de novo ALL in morphologic CR1 or CR2. All patients received myeloablative conditioning followed by transplantation with a single, nonmanipulated UCB unit as their first graft. All UCBTs were performed from 2000 through 2012 to allow for long-term outcomes to be considered. Patients with diagnoses of biphenotypic leukemia, secondary or treatment-related leukemia, or with history of prior HSCT were excluded. Data on patient and graft characteristics and on outcomes were collected from the Eurocord or Duke University Pediatric Blood and Marrow Transplant Program clinical databases. All participating EBMT transplant centers received the synopsis of the study and gave their approval. The Institutional Review Boards of the Eurocord-Netcord scientific committee and Duke University approved this study. All patients gave informed consent for treatment and for data entry and use for analysis in accordance with the Declaration of Helsinki.

Definitions and Endpoints

The primary endpoint for this analysis was the cumulative incidence of relapse, defined as morphologic recurrence of leukemia at any site. Sec-

ondary endpoints included leukemia-free survival (LFS) defined as survival while in continuous CR, overall survival (OS), and NRM defined as death occurring while in remission.

Neutrophil recovery was defined as achieving an absolute neutrophil count $\geq .5 \times 10^9$/L for 3 consecutive days. Platelet recovery was defined as achieving a platelet count $\geq 20 \times 10^9$/L without transfusion support. Full donor chimerism was defined as ≥95% cells of donor origin and mixed chimera was between ≥5% and <95% donor cells, as measured using techniques according to the individual transplant center. The diagnosis and grading of acute (aGVHD) and chronic GVHD (cGVHD) was assigned by the transplant center using standard criteria [27,28]. Myeloablative conditioning was defined as containing either TBI with a dose > 8 Gy, a total dose of busulfan > 8 mg/kg orally, or intravenous equivalent.

HLA matching was assigned at the antigen level for class I –A and –B loci and at the allelic level for class II –DRB1. Cytogenetic findings were considered to be *high risk* if any of the following was present: BCR/ABL [t(9.22)], t(1,19), MLL rearrangements [t(4,11)], hypodiploid, or complex (>3 abnormalities); *intermediate* if abnormalities not considered high risk were present; *normal* if no abnormalities were detected; or *missing* if not available. Presence or absence of minimal residual disease (MRD) before UCBT was available for a subset of the cohort (n = 215) but was not considered in the analysis.

Statistical Approach

Separate analyses were performed for patients in CR1 and CR2 to account for the fact that disease status is a well-established predictor of outcomes after HSCT [23,29]. An exploratory analysis was also performed that included all patients in the study cohort. The probabilities of relapse, NRM, aGVHD, and cGVHD were estimated using the cumulative incidence function method in a competing risk setting treating death and relapse as competing events [30]. Differences between subgroups were compared using the Gray K-Sample test [31]. Probabilities of OS and LFS were calculated with the use of the Kaplan-Meier estimator, and differences between groups were compared using the log-rank statistics [32]. Cox proportional hazards regression was used to create prognostic multivariate models [33]. Factors known as potential prognostic factors and all factors associated with a $P < .10$ in the univariate analysis were included in the final models. The presence of aGVHD or cGVHD was considered as time-dependent variables. Statistical analyses were performed with SPSS 22 (SPSS Inc./IBM, Armonk, NY) and R 3.2.3 (R Development Core Team, Vienna, Austria) software packages.

RESULTS

Patient, donor, and transplantation characteristics are presented in Table 1. From 2000 to 2012, 640 children or adolescents (median age, 6.3 years) with ALL in either morphologic CR1 (n = 257; 40.2%) or CR2 (n = 383; 59.8%) underwent UCBT at an EBMT and Eurocord participating center (99 centers) or Duke University. Most patients were transplanted for B cell lineage ALL (79.2%). Patients and grafts were HLA matched (15.6%) or mismatched at 1 (50.1%) or ≥2 (34.3%) loci.

Most patients (68.8%) received TBI-containing regimens, most commonly TBI + cyclophosphamide (23.9%). Most TBI-containing regimens delivered total fractionated doses of 1200 to 1350 cGy (86%; range, 800 to 1500 cGy). The use of TBI-containing regimens was generally limited to children aged ≥ 3 years (94.5%), whereas 51.3% of patients who received chemotherapy-only regimens were younger than 3 years old. No infants (<12 months of age) received TBI. The most common chemotherapy-based regimen was busulfan + cyclophosphamide (15.8%), with most patients receiving a total busulfan dose of 16 mg/kg (data regarding busulfan pharmacokinetics not available). Most patients (88.0%) received antithymocyte globulin before UCBT. The median total nucleated cell dose was 5.0×10^7/kg (range, .3 to 35.4). GVHD prophylaxis was primarily cyclosporine-based with corticosteroids (72.3%) or