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Umbilical Cord Blood Transplantation in Children with Acute Leukemia: Impact of Conditioning on Transplantation Outcomes

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A B S T R A C T

The Blood and Marrow Transplant Clinical Trials Network (BMT CTN 0501) randomized children with hematologic malignancies to transplantation with 1 or 2 cord blood units (UCB) between 2006 and 2012. While the trial concluded that survival was similar regardless of number of units infused, survival was better than previously reported. This prompted a comparison of survival of trial versus nontrial patients to determine the generalizability of trial results and whether survival was better because of the trial treatment regimen. During the trial period, 396 recipients of a single UCB unit met trial eligibility but were not enrolled. Trial patients (n = 100) received total body irradiation (TBI) 1320 cGy, cyclophosphamide 120 mg/kg, and fludarabine 75 mg/m^2 (TCF). Nontrial patients either received the same regimen (n = 62; nontrial TCF) or alternative regimens (n = 334; nontrial regimens). Five-year survival between trial and nontrial patients conditioned with TCF was similar (70% versus 62%). However, 5-year survival was significantly lower with nontrial TBI-containing (47%; hazard ratio [HR], 1.97; $P = .001$) and chemotherapy-only regimens (49%; HR, 1.87; $P = .007$). The results of BMT CTN 0501 appear generalizable to the population of trial-eligible patients. The survival difference between the trial-specified regimen and other regimens indicate the importance of conditioning regimen for UCB transplantation.

INTRODUCTION

Most children and adolescents with acute leukemia can be cured by conventional chemotherapy. However, a subset of patients is at particularly high risk of disease recurrence and is frequently offered allogeneic hematopoietic cell transplantation (HCT) as a treatment option. For those without an HLA-matched related or unrelated donor, partially HLA-matched umbilical cord blood (UCB) is a suitable alternative for HCT. A study by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN 0501, NCT00412360) randomized children with hematologic malignancies to transplantation with1 or 2 UCB units between December 2006 and February 2012 [1]. While it was hypothesized that transplantation of 2 UCB units would result in better survival based on higher cell doses, survival was similar in the 2 treatment arms ($P = .17$). However, survival in both arms was higher than that reported in prior large studies. For example, survival was substantially better in single UCB transplantation patients enrolled in the BMT CTN 0501 trial relative to those in a similar high-risk pediatric malignancy population in an earlier multicenter trial of Cord Blood Transplantation (73% versus 57% at 1 year, respectively, $P = .01$) [2,3]. Notable differences between the trials included transplantation conditioning, immunoprophylaxis for graft-versus-host disease (GVHD), and transplantation period. The BMT CTN 0501 conditioning

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regimen consisted of total body irradiation (TBI) 1320 cGy, cyclophosphamide 120 mg/kg, and fludarabine 75 mg/m^2 (TCF) and cyclosporine and mycophenolate for GVHD prophylaxis [1]; the transplantation-conditioning regimen for the phase II trial [2] consisted of 1350 cGy of TBI, cyclophosphamide 120 mg/kg, and antithymocyte globulin (ATG, equine) 90 mg and cyclosporine and methylprednisolone for GVHD prophylaxis. Lastly, patients in BMT CTN 0501 were enrolled between 2006 and 2012 as compared to 1999 and 2003 in the prior study.

Examination of nontrial single–UCB unit transplantations reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) during the trial period (December 2006 to February 2012), revealed that 80% met the broad eligibility criteria for BMT CTN 0501 (ie, ages 1 to 21 years, high-risk acute leukemia, performance score ≥70). The potentially improved survival in recipients of BMT CTN 0501 compared with survival in prior studies in children who underwent transplantation with a single UCB unit prompted a comparison of trial versus nontrial treatment outcomes to determine the generalizability of treatment offered on trial and whether trial participation per se or some other aspect, such as the trial-specified transplantation conditioning regimen, led to the apparent improved survival reported for patients in BMT CTN 0501.

MATERIALS AND METHODS

Data Source

The CIBMTR is a working group of transplantation centers that contributes data on consecutive allogeneic and autologous transplantations. Participating centers report consecutive transplantations and compliance is monitored by on-site audits. The CIBMTR, together with the EMMES Corporation and the National Marrow Donor Program, serves as the data coordinating center for the BMT CTN. Consent is sought from patients enrolled on BMT CTN trials for data sharing with the CIBMTR for the conduct of research and for longitudinal follow-up beyond the trial period. The institutional review board of the National Marrow Donor Program approved the study.

Patients

Eligibility criteria for BMT CTN 0501 included ages 1 to 21 years, high-risk leukemia, performance score of 70 or higher, adequate organ function, and availability of 2 cord blood units with adequate cell dose (precryopreservation total nucleated cell ≥2.5×10^7/kg in recipients of a single unit) and HLA matched to the patient and each other at least 4 of 6 HLA loci (ie, HLA match score of 6/6, 5/6, or 4/6) considering HLA-A and -B at the antigen level and HLA-DRB1 at the allele level.

The current study population includes 2 cohorts of patients with acute myeloid or lymphoblastic leukemia for whom data were retrieved from the CIBMTR's database: patients treated on the single-UCB arm of the BMT CTN 0501 protocol (n = 100 of 113 enrolled, 28 centers) and those who underwent single–UCB unit transplantation during the study period (n = 396, 72 centers) in the United States and Canada (Figure 1). Twenty-five of these 72 centers (35%) also enrolled patients on BMT CTN 0501. Excluded were 13 patients on BMT CTN 0501 randomized to receive a single UCB unit (1 did not proceed to transplantation after randomization and 12 had other malignant diseases with too few nontrial patients for comparison).

Based on information reported to the CIBMTR, the comparator group of 396 patients met inclusion criteria for BMT CTN 0501. Although information on organ function was not collected on CIBMTR data collection form, the HCT-Specific Comorbidity Index, with known effect on survival after transplantation [4,5], was used as surrogate. The HCT-Specific Comorbidity Index for nontrial patients was comparable to that for patients enrolled on BMT CTN 0501.

Outcomes

Definitions for each outcome are detailed in the BMT CTN 0501 study protocol [1]. The primary outcome for this analysis was overall survival; death from any cause was considered an event and surviving patients were censored at last follow-up. Secondary outcomes were leukemia-free survival (relapse or death as cause of treatment failure), nonrelapse mortality (death in continuous remission), relapse (morphologic or cytogenetic evidence of acute myeloid leukemia [AML] or acute lymphoblastic leukemia [ALL] consistent with pretransplantation features), hematopoietic recovery (neutrophil recovery ≥$.5 \times 10^9$/L and platelets ≥20×10^9/L unsupported for 7 days), and acute [6] and chronic [7] GVHD.

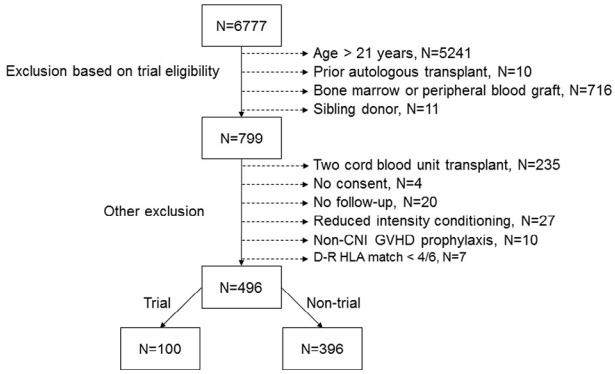

Figure 1. Consort diagram.

Statistical Methods

The characteristics of patients who received a single UCB unit on trial and the nontrial groups were compared using the chi-square test for categorical variables. The probabilities of hematopoietic recovery, infection, and GVHD were calculated using the cumulative incidence estimator to accommodate competing risks [8]. Comparison of overall survival, treatment failure, nonrelapse mortality, and relapse between treatment groups, adjusting for variables associated with outcomes, were performed using the Cox proportional hazards model [9]. The probabilities of leukemia-free and overall survival, relapse, and nonrelapse mortality were generated from final Cox regression models [10,11].

Variables considered included treatment regimen (trial TCF, nontrial TCF, and nontrial alternative regimens that did or did not include TBI), age (≤10 versus >10 years), sex (male versus female), performance score (90 and 100 versus 70 and 80), recipient cytomegalovirus (CMV) serostatus (positive versus negative), disease (AML versus ALL), disease status (first complete remission [CR] versus second CR versus relapse), and cytogenetic risk (intermediate versus poor risk). Models were built using step-wise forward selection and variables that met a significance level of ≥.05 were held in the final model. The variable for treatment type was held in all steps of model building, regardless of level of significance. All variables met the assumption of proportional hazards and there were no first-order interactions between the variable for treatment type and other variables held in the final model. Transplantation center effect was tested using the frailty model and a P value ≤.01 was considered significant [12]. All P values are 2-sided. All analyses were done using SAS version 9.3 (Cary, NC).

RESULTS

Patient and Disease Characteristics

Table 1 shows patients, disease, and transplantation characteristics of patients treated on BMT CTN 0501 (n = 100), those who received the trial regimen (nontrial TCF, n = 62) and those who received different myeloablative transplantation-conditioning regimens (with or without TBI, n = 334). The patient and disease characteristics of those treated on BMT CTN 0501 and nontrial TCF regimen were similar except that nontrial TCF patients were more likely to report performance scores of 80 or 70 (11% versus 24%, $P = .04$) and more likely to have undergone transplantation while in relapse (5% versus 18%, $P = .02$). The patient and disease characteristics of those treated on BMT CTN 0501 and nontrial alternative regimens were also similar except for age with recipients of nontrial regimens being more likely to be ages 1 to 10 years (53% versus 76%, $P < .0001$). For ALL transplantations that occurred beyond CR1, the duration of CR1 was <36 months for 74% of patients on trial, 70% of those who received the TCF regimen off trial, and 84% of those who received nontrial regimens. There were no differences in cytogenetic risk across treatment groups. For AML transplantations, 9 of 41 (22%)