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Late Effects after Umbilical Cord Blood Transplantation in Very Young Children after Busulfan-Based, Myeloablative Conditioning

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A B S T R A C T

Infants and young children who undergo allogeneic cord blood transplantation (CBT) are at increased risk for late effects because of exposure of developing organs to chemotherapy and radiation therapy typically used in transplant conditioning regimens. Busulfan (Bu)-based myeloablative regimens were developed to eliminate radiation exposure in these young children with the hope that late effects would be minimized. We now describe the late effects in 102 consecutive patients surviving a minimum of 5 years (median follow-up, 12.9 years) post-CBT. Patients were conditioned with high-dose chemotherapy using Bu-containing regimens. No patient received total body irradiation. The median age at transplant was 1 year (range, .1 to 2). Diagnoses included inherited metabolic diseases (59.8%), leukemia (17.6%), congenital immune deficiency (20.2%), bone marrow failure/myelodysplastic syndrome (3.9%), and hemoglobinopathy (2%). Among patients surviving 5 years, the overall survival rate at 10 years post-CBT was 93% (95% CI, 84.9 to 96.8). Virtually all patients (98%) experienced at least 1 significant late effect. Most (83.3%) experienced 2 or more late effects, and more than half of the patients (64.7%) experienced 3 or more late effects. The most commonly observed late effects included dental problems (92.2%), short stature (55.9%), cognitive deficits (53.6%), pulmonary dysfunction (18.6%), and abnormal pubertal development (27.9%). This is the first report of late effects of Bu-based conditioning in a cohort of very young patients at the time of transplant. These results will inform clinical care guidelines for long-term follow-up and add to the growing information regarding outcomes of hematopoietic stem cell transplantation.

INTRODUCTION

Over the past 3 decades, hematopoietic stem cell transplantation (HSCT) using umbilical cord blood (CBT) has been established as an effective therapy for pediatric patients with life-threatening malignant and nonmalignant conditions [1]. Many CBTs have been performed in infants and young children, who are at increased risk for late effects because of organ immaturity at the time of transplantation. Because of improvements in cord blood banking, preparative regimens, and supportive care, more of these patients are now surviving into adulthood. To date, the late outcomes of these patients and late effects occurring as a result of their transplantation therapy have not been reported in a systematic fashion.

Late effects occur due to multiple factors, including age at transplant, primary diagnosis, comorbidities, pretransplant therapy, conditioning regimens, development of graft-versus-host disease (GVHD), and other transplant-related complications [2] Most reports of late effects to date have focused on outcomes in older children and adults [2-17]. Most information published to date regarding late effects after HSCT in children has focused on total body irradiation (TBI)-containing conditioning regimens, where the most commonly observed late effects include growth hormone deficiency and short stature, cognitive dysfunction, abnormal puberty, and thyroid dysfunction [2-7,9,11-15,18,19]. Over the past 2 decades, alternative busulfan (Bu)-based,

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myeloablative chemotherapy regimens have been used to eliminate radiation exposure and its consequences, particularly in very young patients.

There remains a paucity of data regarding late effects in very young children undergoing HSCT, particularly in those prepared for transplantation with myeloablative, non-TBI preparative regimens. Elucidating these effects will allow for the development of a strategic, evidence-based algorithm for surveillance and long-term care for these patients with the goal of preserving organ function to the fullest extent possible. We now report the results of a single-center, retrospective review of very young patients who underwent CBT using Bu-based conditioning regimens, describing the characteristics of the cohort, overall survival, and incidence of key late effects.

METHODS

Study Design

The study was designed as a single-center, retrospective study reviewing clinical data routinely collected by the Pediatric Blood and Marrow Transplant Program at Duke University Medical Center. Patients were selected from a cohort of consecutively transplanted patients, who each received a single umbilical cord blood unit at less than 2 years of age from September 1993 to August 2008 after chemotherapy-based cytoreduction.

Eligibility

Eligibility criteria included age 2 years or less at transplant, stem cell source related or unrelated umbilical cord blood, myeloablative Bu-based preparative regimen, survival to a minimum of 5 years post-transplant, and transplant date before August 2008. Criteria for exclusion included TBI-containing or reduced-intensity conditioning and non–cord blood graft sources. Three patients who had received craniospinal irradiation or later received TBI were excluded. All patients were enrolled in an Institutional Review Board–approved protocol or treatment plan for transplant, and written informed consent was obtained from the parents or legal guardians of all patients before the initiation of conditioning therapy. Institutional Review Board approval was also obtained for this retrospective review. Information regarding the transplantation, supportive care, and early transplant courses for a subset of these patients was previously reported in articles describing outcomes of the Cord Blood Transplantation Study (n = 24) and in other reports from Duke University Medical Center [20-25].

Data Collection

Patients were routinely evaluated for follow-up transplant care at Duke at a minimum of every 3 to 6 months for the first year, every 6 months for the second year, and then on an annual basis. Patients with active issues were seen more frequently. Medical records were reviewed to collate data from these follow-up visits, including physical examinations, and assessments of disease status, growth, and organ function were performed (Table 1).

Cord blood unit data were provided by the cord blood bank supplying the unit for transplantation and post-thaw characteristics and dosing by the Duke Stem Cell Transplant Laboratory. Confirmation of donor cell chimerism was performed using fluorescence in situ hybridization or restriction fragment length polymorphism. Grading of GVHD was performed according to conventional criteria [26,27]. Duration of steroid exposure was defined as the period during which patients received steroid doses of 1 mg/kg daily or higher. Pulmonary toxicity and neurocognitive deficits were graded according to the National Cancer Institute/National Institutes of Health Common Terminology Criteria for Adverse Events [28].

Precocious puberty was defined as Tanner stage $\geq$ 2 development by 7 years for females and 9.5 years for males. Delayed puberty was defined as Tanner stage 2 or less development by age 13 years for females and 14 years for males. Long-term sequelae of primary diseases but not transplantation were not included in scoring of late effects. Causes of death were coded according to the algorithm published in 2007 by Copelan, et al. [29].

Statistical Analysis

Descriptive statistics are presented for baseline characteristics and late effects including absolute and relative frequencies for categorical data and the 5-number summary for continuous data. A Kaplan-Meier survival estimate is presented at 10 years post-transplant. Cumulative incidence for observed late effects with death as a competing risk is presented. Further analyses explored associations between possible predictors and late effects. Predictors included age at transplant, gender, diagnosis (malignant or nonmalignant), Lansky performance score, duration of steroid therapy, duration of immunosuppressive therapy, and chronic GVHD (cGVHD) 2 years post-transplant (for late effects other than cGVHD at 5 years). Duration of steroid therapy was examined as both continuous and categorical, with cut-offs at 6 months, 1 year, and 2 years. Univariate Cox regression models explored individual associations between each predictor and late effect, where an event date was known. If there was evidence of significant univariate associations, a multivariate model was constructed to further examine these associations in the presence of other potential confounders. If the event date was unknown for a particular late effect, a logistic regression model was used to explore associations at the univariate and multivariate levels.

Multivariate models were then reduced using backward selection with selection criterion of $P < .05$. In general, $P < .05$ was considered to be statistically significant. For patients with nonmetabolic diagnoses, height data were evaluated by using growth charts provided by the World Health Organization (up to 2 years of age) and the Centers for Disease Control and Prevention (2 to 20 years of age). Median height standard deviation (SD) scores were calculated using the LMS method based on the use of Box-Cox transformations (http://www.cdc.gov/growthcharts/percentile_data_files.htm). Height SD scores were not calculated for patients with metabolic disorders because no published reference height ranges exist for inherited metabolic disease at this time. All analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC).

Table 1
Long-Term Follow-up Visit Evaluations

Studies Performed
Physical examination
Assessment of growth curve
Tanner staging
Complete blood count
Complete metabolic panel
Chimerism
Cellular and humoral immune reconstitution panels
Immunoglobulins
Thyroid hormone levels: thyroid-stimulating hormone, thyroxine (T_4), triiodothyronine (T_3)
Reproductive hormone levels: estradiol/testosterone, follicular-stimulating hormone, luteinizing hormone
Echocardiogram
Electrocardiogram
Spirometry
Diffusion capacity of carbon monoxide
Ophthalmologic examination
Audiologic evaluation
Dental examination
Neurocognitive testing
Additional disease-specific evaluations for malignancies: disease surveillance (ie, PCR)
Additional disease-specific evaluations for metabolic diseases: magnetic resonance imaging, electroencephalogram, electromyelogram, nerve conduction studies, brainstem auditory-evoked response, visual-evoked potentials

RESULTS

Study Population

In this study we report the late effects observed in 102 patients under 2 years of age treated at Duke University Medical Center from September 1993 to August 2008 who survived more than 5 years after CBT after cytoreduction with Bu-based myeloablative, non-TBI containing, preparative regimens. Patient, donor, and transplant characteristics of the study cohort are shown in Table 2. The median ages at transplant and follow-up were 1 year (range, .1 to 2) and 13.8 years (range, 7.7 to 23.8), respectively. Most patients underwent CBT for nonmalignant diseases (82.4%), and more than half of patients with nonmalignant diagnoses were transplanted for inherited metabolic diseases (59.8%). The most common inherited metabolic diseases were Krabbe disease (globoid cell leukodystrophy, n = 18) and mucopolysaccharidosis (n = 35), of which most cases were type 1