Biol Blood Marrow Transplant 23 (2017) 1695–1700

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Clinical Research: Pediatric

A Multicenter Retrospective Analysis Stressing the Importance of Long-Term Follow-Up after Hematopoietic Cell Transplantation for β-Thalassemia

Sonali Chaudhury *, M. Ayas, Colleen Rosen, Madeline Ma, M. Viqaruddin, Suhag Parikh, Sandhya Kharbanda, K.Y. Chiang, Ann Haight, Monica Bhatia, Greg Guilcher, Alexis Thompson, Shalini Shenoy

Pediatric Hematology/Oncology Stem Cell transplant, Childrens Memorial Hospital, Chicago, Illinois

Article history:
Received 11 April 2017
Accepted 8 June 2017

Key Words:
Thalassemia
Transplant
Late effects

A B S T R A C T

Allogeneic hematopoietic cell transplantation (HCT) is curative in patients with β-thalassemia major. However, most reports on HCT outcomes lack long-term follow-up data with the exception of single-center reports. An international multicenter retrospective data collection and analysis was conducted in 176 β-thalassemia patients who were 1 year or beyond after first HCT to evaluate follow-up methods and outcomes at 7 centers. Median age at HCT was 5.5 years (range, .6 to 18.5), and median follow-up was 7 years (range, 1 to 20). HCT was predominantly from HLA-matched related donors (91%) with bone marrow as stem cell source (91%) and myeloablative conditioning regimens (88%). Late mortality or persistent chronic graft-versus-host disease (GVHD) was rare (<2%). Graft rejection was reported in 23% (24% of these occurred beyond 1 year) post-HCT. Of 119 patients with donor chimerism results available for ≥4 years post-HCT, 50% had >95%, 22% had 50% to 95%, 7% had 20% to 50% and 25 (21%) had <20% donor chimerism. Organ dysfunction was identified in 10% pre-HCT and in 20% post-HCT even without complete clinical details on all patients. Hypogonadism and elevated creatinine for age were most commonly reported and significantly higher in recipients ≥ 7 years at the time of HCT ($P = .007$) and in those with pre-existing morbidity before HCT ($P = .02$). Outcomes were unaffected by pre-HCT ferritin or GVHD. Mean z scores for height and weight were low at baseline and remained low post-HCT (79%), confirming that growth impairment from disease lacked recovery post-HCT during this follow-up period. HCT for β-thalassemia has a high rate of cure and low mortality, especially in the young and from HLA-matched related donors. Half of the number of recipients live with mixed chimerism that requires continued follow-up because of a risk of late graft rejection (14%). Organ function after HCT when <7 years of age was generally preserved. Hypogonadism, renal dysfunction, and growth impairment that failed to correct were late complications identified most frequently in older transplant recipients. Systematic follow-up of individual organs such as lung and heart were inadequate but important. These data support the development of simple measures of uniformly tracking long-term HCT outcomes and organ functions in children and adolescents who undergo HCT for thalassemia, allowing for systematic identification and implementation of standardized surveillance strategies and interventions.

© 2017 American Society for Blood and Marrow Transplantation.

INTRODUCTION

β-Thalassemia major is a genetic disorder characterized by little or absent β-globin production, hemolysis from resulting unstable α-globin tetramers, ineffective erythropoiesis, and severe anemia that is fatal in the absence of life-long RBC transfusions [1]. First reported approximately 3 decades ago, allogeneic hematopoietic cell transplantation (HCT) remains the only widely available curative option for β-thalassemia [2]. In the absence of curative therapy, anemia and transfusion-related iron accumulation over time contribute to end-organ damage, morbidity, and mortality in patients often despite iron chelation. Based on these observations, the Pesaro group identified risk groups in children under 16 years and stratified HCT outcomes using hepatomegaly, liver fibrosis, and inadequate iron chelation as risk factors for mortality [3]. Recently, improvement in the knowledge of iron

Financial disclosure: See Acknowledgments on page 1699.

* Correspondence and reprint requests: Sonali Chaudhury, MD, Pediatric Hematology/Oncology Stem Cell Transplant, Childrens Memorial Hospital, 225 E Chicago Avenue, Box 30, Chicago, IL 60610.
E-mail address: schaudhury@luriechildrens.org (S. Chaudhury).

http://dx.doi.org/10.1016/j.bbmt.2017.06.004
1083-8791/© 2017 American Society for Blood and Marrow Transplantation.

pathophysiology has implicated tissue-reactive iron species in organ toxicity supported by environmental factors such as infections, supporting continued chelation of toxic iron before and after HCT for best results [4]. HCT has been increasingly applied worldwide, achieving thalassemia-free survival rates of 62% to 84%; survival has improved with time and modern interventions [5-11]. Other than the risk score, extensive experience with transplant has revealed additional prognostic factors that affect outcomes such as advancing age in childhood and hepatomegaly [12-14].

Outcomes of HCT for β-thalassemia generally report on survival. However, late follow-up and long-term effects after HCT are scarce and limited to single centers and focused organs [15-21]. This international report on long-term follow-up after HCT for β-thalassemia was undertaken to evaluate late follow-up efforts and outcomes in patients surviving beyond 1-year post-HCT and compiles data obtained from 7 contributing centers.

METHODS

Deidentified data describing outcomes of children with β-thalassemia surviving ≥ 1 year post-HCT were collected from HCT centers in the United States (Chicago, Atlanta, New York, San Francisco, and North Carolina) and internationally (United Arab Emirates and Canada) after approval from respective institutional review boards using a common case report form. Data from completed forms were collated for this report. Outcomes of interest included engraftment, chimerism studies, graft rejection, graft-versus-host disease (GVHD), ferritin, growth velocity (z scores), and measures of organ function.

Endpoints

The primary outcome was overall survival beyond 1-year post-HCT. Death from any cause after 1 year was considered an event, and surviving patients were censored at last contact. Only graft rejection was reported from all time points post-HCT because of relevance to outcomes. Primary (early) graft rejection was defined as failure to obtain neutrophil engraftment by day 42 or absolute neutrophil count < $.5 \times 10^9$/L, retransplantation within 42 days of first transplant, donor chimerism < 10%, or resumption of regular RBC transfusions. Secondary (late) graft rejection was defined as occurrence of these events after initial hematopoietic recovery [17].

The presence of GVHD beyond 1 year was described according to National Institutes of Health criteria and symptoms [22,23]. Impaired organ function included low left ventricular ejection fraction by echocardiogram (heart) compared with normal for age, low pulmonary function tests (forced expiratory volume in 1 second < 80% or adjusted diffusing capacity of the lungs for carbon monoxide < 60%), impaired renal function defined as proteinuria/elevated serum creatinine for age, and osteoporosis if detected by dual-energy x-ray absorptiometry (DEXA) scan or by susceptibility to fractures. Additional organ dysfunction of medical concern was to be reported if present and included abnormal hepatic function and visual or auditory impairment. Endocrine function assessment included levels of thyroid (free T_4, thyroid-stimulating hormone) and gonadal (follicle-stimulating hormone, luteinizing hormone, and testosterone in children aged > 10 years) hormones. Height and weight were plotted as z scores to eliminate variability of age and gender. Iron accumulation was evaluated by serum ferritin, liver biopsy, or magnetic resonance imaging (MRI) criteria [24]. Details on post-HCT malignant disorders were requested if diagnosed. Data were collated from the pre-HCT and most recent follow-up visit report beyond the first year after HCT for each patient.

Statistical Analysis

The probability of overall survival, disease-free survival, and event-free (graft failure/death) survival was calculated using the Kaplan-Meier estimator from time 0 [25]. Time zero (study entry) was 1 year from first transplant because only those who survived beyond the first year were included in the analysis. The incidence of late effects was calculated using the cumulative incidence estimator with death as the competing risk. Chi-square test of independence or Fisher's exact test was used for categorical covariates; 2-sample *t*-test was used for continuous covariates when comparing groups [26]. Variables tested were age (<7 and ≥7 years, <10 versus ≥10 years), pre-HCT ferritin (<1500 and ≥1500 ng/mL, <2000 versus ≥2000 ng/mL), presence of pre-HCT organ dysfunction, and occurrence of acute GVHD in the first year post-HCT. Chronic GVHD was extremely rare and hence not included.

RESULTS

Patient, Disease, and Transplant Characteristics

Table 1 shows characteristics of patients and transplantation. The median age at HCT was 5.5 years (range, .6 to 18.5). All patients were erythrocyte transfusion dependent before HCT; 87% were documented to have received regular chelation: 9 (5%) had no chelation and 14 (8%) had no chelation data available. Despite chelation in most patients, the median pre-HCT ferritin was 1638 ng/mL (range, 152 to 5001), and iron content calculated from MRI or biopsy was 4.1 mg/g dry weight or 6.5 mg/g dry weight, respectively. Pre-HCT organ dysfunction was documented in 18 patients (10%). Pre-HCT z scores for height and weight were lower than average for age in 75% and were −1.2 (20th percentile). Data on cytomegalovirus serostatus, performance scores, measurement of hepatomegaly, and quantitation of erythrocyte transfusions pre-HCT were not available for most patients because they had never been documented systematically.

Most patients (91%) received bone marrow grafts from HLA-matched siblings. Myeloabalative doses of busulfan with cyclophosphamide and cyclosporine were the most common preparative and GVHD regimens used, respectively (88%). Almost all patients (96%) received transplants from a HLA-matched familial donor.

Table 1
Patient and Transplant Characteristics (N = 176)

Variable	N (%) or Median (Range)
Age at HCT , yr	5.5 (.6-18.5)
<7 yr/<14 yr	114 (80)/168 (95)
>7 yr/>14 yr	62 (20)/8 (5)
Male	81 (47)
HCT at non-US centers	135 (77)
Pretransplant iron status	
Ferritin, abnormal > 1000 μg/L	92/122 (75), median 1638 ng/mL (157-5512)
Liver MRI, abnormal (iron >3 mg/g dry weight)	11/12 4.1 mg/g dry weight (1.5-12)
Liver biopsy	14/14 iron overload, fibrosis 3, median iron 6.5 mg/g dry weight (2-22)
Cardiac MRI, abnormal T2 < 20	1/9 median T2 29.7 ms (9.9-39)
Conditioning regimen	155 (88)
Myeloablative	
Busulfan + cyclophosphamide	149 (85)
Missing	1 (<1)
T cell serotherapy	94 (53)
Antithymocyte globulin	
Alemtuzumab	14 (8)
Unknown/none	68 (39)
GVHD prophylaxis	159 (90)
Cyclosporine A based	
Tacrolimus based	14 (8)
Missing	3 (2)
Donor HLA matching	161 (91)
HLA matched related donor	
HLA matched unrelated donor	9 (5)
HLA mismatched donor	6 (4)
Donor cell source	162 (+umbilical cord blood 2) (92)
Bone marrow	
Peripheral blood	3 (2)
Umbilical cord blood	11 (6)
Year of HCT	24 (14)
1995-2000	
>2000-2005	39 (22)
>2005-2010	61 (35)
>2010	51 (29)
Missing	1 (<1)
Median follow-up of survivors, yr	7 (1-20)

Download English Version:

https://daneshyari.com/en/article/5524055

Download Persian Version:

https://daneshyari.com/article/5524055

Daneshyari.com