Biol Blood Marrow Transplant 23 (2017) 1327–1334

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Survival and Late Effects after Allogeneic Hematopoietic Cell Transplantation for Hematologic Malignancy at Less than Three Years of Age

Lynda M. Vrooman [1,*], Heather R. Millard [2], Ruta Brazauskas [2,3], Navneet S. Majhail [4], Minoo Battiwalla [5], Mary E. Flowers [6], Bipin N. Savani [7], Görgün Akpek [8], Mahmoud Aljurf [9], Rajinder Bajwa [10], K. Scott Baker [6], Amer Beitinjaneh [11], Menachem Bitan [12], David Buchbinder [13], Eric Chow [6], Christopher Dandoy [14], Andrew C. Dietz [15], Lisa Diller [1], Robert Peter Gale [16], Shahrukh K. Hashmi [17], Robert J. Hayashi [18], Peiman Hematti [19], Rammurti T. Kamble [20], Kimberly A. Kasow [21], Morris Kletzel [22], Hillard M. Lazarus [23], Adriana K. Malone [24], David I. Marks [25], Tracey A. O'Brien [26], Richard F. Olsson [27,28], Olle Ringden [27], Sachiko Seo [29], Amir Steinberg [24], Lolie C. Yu [30], Anne Warwick [31], Bronwen Shaw [2], Christine Duncan [1]

[1] *Department of Pediatric Oncology, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, Massachusetts*
[2] *Center for International Blood and Marrow Transplant Research, Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin*
[3] *Division of Biostatistics, Institute for Health and Society, Medical College of Wisconsin, Milwaukee, Wisconsin*
[4] *Blood and Marrow Transplant Program, Cleveland Clinic Taussig Cancer Institute, Cleveland, Ohio*
[5] *Hematology Branch, National Heart, Lung and Blood Insititute, Bethesda, Maryland*
[6] *Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington*
[7] *Division of Hematology/Oncology, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee*
[8] *Stem Cell Transplantation and Cell Therapy, Department of Internal Medicine, Rush University Medical Center, Chicago, Illinois*
[9] *Department of Oncology, King Faisal Specialist Hospital Center and Research, Riyadh, Saudi Arabia*
[10] *Division of Hematology/Oncology/BMT, Nationwide Children's Hospital, Columbus, Ohio*
[11] *Division of Hematology and Oncology, University of Miami, Miami, Florida*
[12] *Department of Pediatric Hematology/Oncology, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel*
[13] *Division of Hematology, Children's Hospital of Orange County, Orange, California*
[14] *Division of Bone Marrow Transplant and Immune Deficiency, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio*
[15] *Division of Hematology, Oncology and Blood and Marrow Transplantation, Children's Hospital Los Angeles, University of Southern California, Los Angeles, California*
[16] *Hematology Research Centre, Division of Experimental Medicine, Department of Medicine, Imperial College London, London, United Kingdom*
[17] *Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota*
[18] *Division of Pediatric Hematology/Oncology, Department of Pediatrics, Washington University School of Medicine in St. Louis, St. Louis, Missouri*
[19] *Division of Hematology/Oncology/Bone Marrow Transplantation, Department of Medicine, University of Wisconsin Hospital and Clinics, Madison, Wisconsin*
[20] *Division of Hematology and Oncology, Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, Texas*
[21] *Division of Hematology-Oncology, Department of Pediatrics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina*
[22] *Division of Hematology, Oncology and Stem Cell Transplant, Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois*
[23] *Division of Hematology and Oncology, Seidman Cancer Center, University Hospitals Cleveland Medical Center, Cleveland, Ohio*
[24] *Division of Hematology/Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, New York*
[25] *Adult Bone Marrow Transplant, University Hospitals Bristol NHS Trust, Bristol, United Kingdom*
[26] *Blood and Marrow Transplant Program, Kids Cancer Centre, Sydney Children's Hospital, Sydney, Australia*
[27] *Division of Therapeutic Immunology, Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden*
[28] *Centre for Clinical Research Sormland, Uppsala University, Uppsala, Sweden*
[29] *National Cancer Research Center, East Hospital, Kashiwa, Chiba, Japan*
[30] *Division of Hematology/Oncology, The Center for Cancer and Blood Disorders, Children's Hospital/Louisiana State University Medical Center, New Orleans, Louisiana*
[31] *Department of Pediatrics, Uniformed Services University of the Health Sciences, Bethesda, Maryland*

Financial disclosure: See Acknowledgments on page 1333.

* Correspondence and reprint requests: Lynda M. Vrooman, MD, Department of Pediatric Oncology, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, 450 Brookline Avenue, Boston, MA 02215-5450.
E-mail address: lynda_vrooman@dfci.harvard.edu (L.M. Vrooman).

http://dx.doi.org/10.1016/j.bbmt.2017.04.017

Article history:
Received 12 December 2016
Accepted 16 April 2017

Key Words:
Hematopoietic cell transplantation (HCT)
Survival
Infants
Pediatric
Late effects
Hematologic malignancy
Relapse
Total body irradiation
Graft-versus-host disease

A B S T R A C T

Very young children undergoing hematopoietic cell transplantation (HCT) are a unique and vulnerable population. We analyzed outcomes of 717 patients from 117 centers who survived relapse free for ≥1 year after allogeneic myeloablative HCT for hematologic malignancy at <3 years of age, between 1987 and 2012. The median follow-up was 8.3 years (range, 1.0 to 26.4 years); median age at follow-up was 9 years (range, 2 to 29 years). Ten-year overall and relapse-free survival were 87% (95% confidence interval [CI], 85% to 90%) and 84% (95% CI, 81% to 87%). Ten-year cumulative incidence of relapse was 11% (95% CI, 9% to 13%). Of 84 deaths, relapse was the leading cause (43%). Chronic graft-versus-host-disease 1 year after HCT was associated with increased risk of mortality (hazard ratio [HR], 2.1; 95% CI, 1.3 to 3.3; $P = .0018$). Thirty percent of patients experienced ≥1 organ toxicity/late effect >1 year after HCT. The most frequent late effects included growth hormone deficiency/growth disturbance (10-year cumulative incidence, 23%; 95% CI, 19% to 28%), cataracts (18%; 95% CI, 15% to 22%), hypothyroidism (13%; 95% CI, 10% to 16%), gonadal dysfunction/infertility requiring hormone replacement (3%; 95% CI, 2% to 5%), and stroke/seizure (3%; 95% CI, 2% to 5%). Subsequent malignancy was reported in 3.6%. In multivariable analysis, total body irradiation (TBI) was predictive of increased risk of cataracts (HR, 17.2; 95% CI, 7.4 to 39.8; $P < .001$), growth deficiency (HR, 3.5; 95% CI, 2.2 to 5.5; $P < .001$), and hypothyroidism (HR, 5.3; 95% CI, 3.0 to 9.4; $P < .001$). In summary, those who survived relapse free ≥1 year after HCT for hematologic malignancy at <3 years of age had favorable overall survival. Chronic graft-versus-host-disease and TBI were associated with adverse outcomes. Future efforts should focus on reducing the risk of relapse and late effects after HCT at early age.

INTRODUCTION

Hematopoietic cell transplantation (HCT) is an important treatment modality in infants and young children with very-high-risk and relapsed or refractory leukemias [1-3]. Infants and very young children may be at particular risk for morbidities after HCT, including those from transplantation-related exposures, such as total body irradiation (TBI) [4,5]. There are, however, few reports focusing on survival and morbidities after HCT for hematologic malignancy in the first years of life [4-8]. A comprehensive characterization of outcomes following HCT for hematologic malignancy at a very young age would help to inform the care of this potentially vulnerable population.

In a retrospective, international, multicenter cohort of patients reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) between 1987 and 2012, we sought to characterize the survival and late effects of patients who underwent allogeneic myeloablative HCT for hematologic malignancy before the age of 3 years and who were alive and relapse free for at least 1 year after HCT. We aimed to report overall and disease-free survival, causes of death, risk factors for mortality, and the frequency and cumulative incidence of organ toxicities and late effects.

MATERIALS AND METHODS

Data Collection

We obtained data from the CIBMTR, a voluntary working group of more than 450 international transplantation centers. Centers contribute detailed pre- and post-HCT data to the Statistical Center at the Medical College of Wisconsin in Milwaukee, Wisconsin and the National Marrow Donor Program in Minneapolis, Minnesota. Computerized checks for discrepancies, physicians' review of submitted data, and on-site audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed under guidance of the institutional review board of the National Marrow Donor Program and are in compliance with all applicable federal regulations pertaining to the protection of human research participants.

The CIBMTR data repository includes information about patient demographics, disease type, survival, relapse, graft type, the presence of graft-versus-host disease (GVHD), and cause of death. A subset of CIBMTR participants is selected for more comprehensive research level data collection by weighted randomization. Late effects data were collected from this group of patients. Transplantation centers report the occurrence of clinically significant organ impairment or disorders at 6 months and 1 year following transplantation and annually thereafter, or until death. Centers report the presence of the following specific organ toxicities and late effects: avascular necrosis, cataracts, congestive heart failure, diabetes, gonadal dysfunction/infertility requiring hormone replacement, growth hormone deficiency/growth disturbance, hemorrhagic cystitis, hypothyroidism, myocardial infarction, pancreatitis, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, renal failure severe enough to warrant dialysis, stroke/seizures, bronchiolitis obliterans, pulmonary hemorrhage, cryptogenic organizing pneumonia, interstitial pneumonitis/idiopathic pneumonia syndrome, noninfectious liver toxicity, and new malignancy. This report focuses on organ impairment and disorders following 1 year after HCT.

Study Population

The study population consisted of patients who underwent allogeneic myeloablative HCT for hematologic malignancy at less than 3 years of age between January 1, 1987 and December 31, 2012 (Figure 1). Patients included in this analysis survived, relapse free, at least 1 year after HCT. Underlying diagnoses included acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), myelodysplastic syndrome, chronic myelomonocytic leukemia, and juvenile myelomonocytic leukemia. Twin donor and multiple donor cases were excluded. Stem cell sources included bone marrow, peripheral blood, or umbilical cord blood; patients who received multiple stem cell sources were excluded. Myeloablative conditioning regimens were defined as previously described [9]. Patients for whom baseline or day 100 forms were unavailable were excluded. Also excluded were those for whom the CIBMTR completion team index (demonstrating the ratio of observed versus expected follow-up) was less than 80% at 5 years after HCT.

Statistical Analysis

Descriptive statistics for categorical variables are presented as frequencies and percentages. Median and range were used to summarize continuous variables. The primary endpoint was overall survival. Secondary endpoints included relapse-free survival (survival without relapse), relapse, transplantation-related mortality, and occurrence of organ toxicities/late effects. Overall and relapse-free survival were estimated using Kaplan-Meier methodology. The cumulative incidence of relapse, transplantation-related mortality, organ toxicities, and late-effects were estimated using the cumulative incidence function to account for competing risks. Analyses of organ toxicities and late effects were limited to those experienced at least 1 year after HCT. Summaries of aggregated organ toxicities/late effects include items specified on CIBMTR reporting form fields, as noted above. Proportional hazard models were developed to explore potential risk factors for overall mortality (in the full cohort) and for the most frequently occurring late effects (limited to those undergoing HCT after the year 1994) including assessment by age at HCT, sex, underlying diagnosis, interval from diagnosis to HCT, disease status at HCT, donor type, graft type, exposure to TBI, exposure to corticosteroid for GVHD prophylaxis, history of chronic GVHD at 1 year after HCT, and year of HCT. Analyses were performed using SAS, version 9.3 (SAS Institute, Cary, NC) [10].

RESULTS

Patient and Transplantation Characteristics

Patient selection and exclusions are summarized in Figure 1. Of 1737 patients potentially eligible based on age