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Long-Term Survival and Late Effects among One-Year Survivors of Second Allogeneic Hematopoietic Cell Transplantation for Relapsed Acute Leukemia and Myelodysplastic Syndromes

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A B S T R A C T

We analyzed the outcomes of patients who survived disease-free for 1 year or more after a second allogeneic hematopoietic cell transplantation (HCT) for relapsed acute leukemia or myelodysplastic syndromes between 1980 and 2009. A total of 1285 patients received a second allogeneic transplant after disease relapse; among these, 325 were relapse free at 1 year after the second HCT. The median time from first to second HCT was 17

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and 24 months for children and adults, respectively. A myeloablative preparative regimen was used in the second transplantation in 62% of children and 45% of adult patients. The overall 10-year conditional survival rates after second transplantation in this cohort of patients who had survived disease-free for at least 1 year was 55% in children and 39% in adults. Relapse was the leading cause of mortality (77% and 54% of deaths in children and adults, respectively). In multivariate analyses, only disease status before second HCT was significantly associated with higher risk for overall mortality (hazard ratio, 1.71 for patients with disease not in complete remission before second HCT, $P < .01$). Chronic graft-versus-host disease (GVHD) developed in 43% and 75% of children and adults after second transplantation. Chronic GVHD was the leading cause of nonrelapse mortality, followed by organ failure and infection. The cumulative incidence of developing at least 1 of the studied late effects within 10 years after second HCT was 63% in children and 55% in adults. The most frequent late effects in children were growth disturbance (10-year cumulative incidence, 22%) and cataracts (20%); in adults they were cataracts (20%) and avascular necrosis (13%). Among patients with acute leukemia and myelodysplastic syndromes who receive a second allogeneic HCT for relapse and survive disease free for at least 1 year, many can be expected to survive long term. However, they continue to be at risk for relapse and nonrelapse morbidity and mortality. Novel approaches are needed to minimize relapse risk and long-term transplantation morbidity in this population.

INTRODUCTION

Disease relapse is the leading cause of treatment failure after allogeneic hematopoietic cell transplantation (HCT) for hematologic malignancy and occurs in approximately 20% to 60% of patients [1-5]. The outcome after disease relapse after first transplantation is poor, with survival rates less than 10% in some populations, and treatment options for these patients are limited [5-8]. Second HCT is a potentially curative option for selected patients and disease relapse is the most common indication for second allogeneic transplantation [9]. The decision to undergo a second transplantation is complex, given the heightened risks of disease recurrence, acute toxicity, post-transplantation late effects, and transplantation-related mortality.

Rates of overall survival after second allogeneic HCT range between 28% and 60%, with disease-free survival rates of 25% to 56% [1,2,9-15]. Studies of second transplantation in children have demonstrated more favorable survival, but are limited by small patient numbers [11,16]. Previous studies of second transplantation have been limited in sample size and, hence, have been inconsistent in identifying favorable factors for longer survival after second allogeneic HCT. Notwithstanding the limitation of small sample size, factors associated with superior survival include younger recipient age, longer duration of remission between transplantations, complete remission (CR) at second transplantation, bone marrow as the stem cell source, the use of a fully HLA-matched donor, the presence of acute and chronic graft-versus-host disease (GVHD), and transplant from a female donor [1,9-12,17,18]. An area of controversy has been the impact of the intensity of conditioning regimen on survival, as some studies have found reduced-intensity conditioning regimens to favorably impact survival, whereas others found survival to benefit from high-dose myeloablative regimens containing total body irradiation [2,12,15]. An additional area of discussion is the impact of using the same or alternate donor with the second transplantation.

Much attention has been paid to analyzing late effects after single allogeneic HCT. The Bone Marrow Transplant Survivor Study reported that 66% to 79% of long-term survivors of HCT suffered from at least 1 chronic health condition [19-21]. The rates of long-term survival and the incidence of late effects after second allogeneic transplantation have not been well described. Given the cumulative exposure to chemotherapy and radiation, recipients of 2 or more transplants may be at substantial risk for late complications.

In this study, we selected a cohort of patients who were alive and in remission for 1 year or more after a second allogeneic HCT for relapsed acute leukemia or myelodysplastic syndrome (MDS) to describe: (1) long-term survival and predictive factors for survival outcomes, and (2) cumulative incidence of late effects in this population.

MATERIALS AND METHODS

Data Source and Patients

Data for this study were obtained from the Center for International Blood and Marrow Transplant Research (CIBMTR). The CIBMTR is a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on hematopoietic cell transplantations to a statistical center at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program in Minneapolis. Participating centers are required to report all transplantation consecutively; compliance is monitored by on-site audits. Patients are followed longitudinally. Computerized checks for discrepancies, physicians' review of submitted data, and on-site audits of participating centers ensure data quality. Data are collected before transplantation, 100 days and 6 months after transplantation, and annually thereafter, or until death. 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.

Transplantation-essential data are collected for all patients participating in CIBMTR data collection. These includes demographic, disease type and stage, survival, relapse, graft type, the presence of GVHD, and cause of death data. A subset of CIBMTR participants are selected for comprehensive research level data collection by weighted randomization. Late effects data are collected from this group of patients. Transplantation centers report the presence of clinically significant organ impairment or disorder at 6 months and 1 year after transplantation and annually thereafter. Centers are specifically asked to report the presence of the following late effects: stroke/seizure, myocardial infarction, cirrhosis, gonadal dysfunction requiring hormone replacement, renal failure severe enough to warrant dialysis, avascular necrosis, cataracts, growth hormone deficiency/growth disturbance, hypothyroidism, and bronchiolitis obliterans.

Study Population

The study population included children (age $\leq$ 18 years) and adults (age $>$ 18 years) who had survived disease free for at least 1 year after their second allogeneic HCT for acute lymphoblastic leukemia, acute myelogenous leukemia, juvenile myelomonocytic leukemia (JMML), and MDS between January 1, 1980 and December 31, 2009. There was no exclusion based on type of conditioning regimen. The intensity of the conditioning regimen was based on the definitions published by Bacigalupo et al. [22]. All types of donor grafts were included with the exception of syngeneic twins. Patients who had an allogeneic HCT after autologous transplantation were not included in the analysis.