Biol Blood Marrow Transplant 21 (2015) 1266–1272

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Outcomes after Second Hematopoietic Stem Cell Transplantations in Pediatric Patients with Relapsed Hematological Malignancies

Swati Naik [1,*], Caridad Martinez [1], Kathryn Leung [1], Ghadir Sasa [1], Ngoc-Yen Nguyen [2], Meng-Fen Wu [3], Stephen Gottschalk [1], Malcolm Brenner [1], Helen Heslop [1], Robert Krance [1]

[1] Center for Cell and Gene Therapy, Baylor College of Medicine, Texas Children's Hospital and Houston Methodist Hospital, Houston, Texas
[2] Department of Pharmacy, Texas Children's Hospital, Houston, Texas
[3] Biostatistics Shared Resource, Dan L. Duncan Cancer Center, Baylor College of Medicine, Houston, Texas

Article history:
Received 2 December 2014
Accepted 24 February 2015

Key Words:
Hematopoietic stem cell transplantation
Second transplantation
Relapse
Pediatric
Hematological malignancies
Remission status

A B S T R A C T

Relapse of hematological malignancies after hematopoietic stem cell transplantation (HCT) is associated with poor prognosis. A second HCT represents one of the few therapeutic options for these high-risk patients. For children undergoing second HCT, the outcome data are particularly limited. We, therefore, conducted a retrospective single-institution study and report the outcomes and prognostic variables associated with overall survival (OS) and relapse in 43 pediatric patients who underwent a second HCT between 2000 and 2013. Eleven of the 43 patients who underwent transplantation remain alive and disease-free at a median follow-up of 49 months (range, 5 to 127 months). The 5-year probability of OS for the entire cohort was 24%. Patients who had early relapse (<6 months) after first HCT had significantly worse OS than those who relapsed late (>6 months), with 5-year OS at 11% versus 34%, respectively (hazard ratio [HR], 2.24; 95% confidence interval [CI], 1.21 to 4.93; $P = .013$). Active disease at time of second HCT was also associated with a significantly increased risk of relapse (subdistribution hazard ratio [SHR], 2.36; $P = .049$) for the entire cohort and relapse was the most frequent cause of death (23 of 32; 72%). On subgroup analysis for the 34 patients with leukemia alone, presence of active disease was associated both with a significant decrease in OS (SHR, 2.28; 95% CI, 1.02 to 5.09; $P = .044$) and significant increase in the rate of relapse (SHR, 2.46; $P = .046$). By contrast, underlying disease, donor source, conditioning regimen, or development of GVHD did not modify OS or rate of relapse. Hence, a second HCT appears to be a useful therapeutic option in children with relapsed hematological malignancies that is most likely to benefit those individuals with late onset of relapse and with low disease burden at the time of transplantation.

INTRODUCTION

Although hematopoietic stem cell transplantation (HCT) can cure hematological malignancy, the relapse rate after treatment can be as high as 70% [1-3]. The treatment of patients who relapse after HCT is challenging and of variable success. These patients may be treated by withdrawal of immune suppression to harness a graft-versus-leukemia effect, infusion of donor lymphocytes, or by further chemotherapy with or without a second HCT [3-5]. The choice of treatment depends upon underlying clinical factors, such as primary diagnosis, disease status, organ function, and presence of graft-versus-host disease (GVHD) and other associated comorbidities.

For select patients, a second HCT may be curative. The overall survival (OS) for patients who undergo second HCTs has been reported to be as low as 0% and as high as 67% [6,7]. For adults undergoing a second HCT, several prognostic factors correlate with survival, including remission status at second HCT and duration between first transplantation and relapse [1,2,7]. For children, however, prognostic data are limited [8-10]. We, therefore, conducted a retrospective single-institution study to determine the outcome for pediatric patients who received a second HCT for relapsed hematological malignancies to identify prognostic factors and the patients who are most likely to benefit from this intervention.

Financial disclosure: See Acknowledgments on page 1271.

* Correspondence and reprint requests: Dr. Swati Naik, Baylor College of Medicine, 1102 Bates Avenue, Feigin Center Suite 1640.16, Houston, TX 77030.
E-mail address: sxnaik@txch.org (S. Naik).

http://dx.doi.org/10.1016/j.bbmt.2015.02.024
1083-8791/

Table 1
Disease and Transplantation Characteristics

Characteristic	First HSCT	Second HSCT
Age at transplantation, median (range), yr	7 (1-18)	8 (2-20)
Diagnosis		
ALL	14 (32.6)	13 (30.2)
AML	19 (44.2)	21 (48.8)
MDS	7 (16.3)	6 (14.0)
JMML	1 (2.3)	1 (2.3)
CML	1 (2.3)	1 (2.3)
Hodgkin's	1 (2.3)	1 (2.3)
Disease status at HSCT		
CR1	11 (25.6)	0 (0)
CR2	12 (27.9)	12 (27.9)
CR3	0 (0)	7 (16.3)
Relapse 1	6 (14.0)	12 (27.9)
Relapse 2	0 (0)	11 (25.6)
Relapse 3	0 (0)	0 (0)
Primary refractory disease	7 (16.3)	0 (0)
MDS	7 (16.3)	1 (2.3)
Site of relapse		
BM	34 (79)	33 (76.7)
Extramedullary	3 (6.9)	4 (9.3)
BM/extramedullary	6 (13.9)	6 (13.9)
Conditioning		
MAC	37 (86.0)	13 (30)
RIC	6 (14.0)	28 (65.1)
None	0 (0)	2 (4.6)
TBI		
TBI	31 (79.5)	18 (41.9)
No TBI	12 (27.9)	25 (58.1)
GVHD prophylaxis		
CNI/MTX	25 (58.1)	8 (18.6)
CD34 selection	9 (20.9)	21 (48.8)
Tacrolimus alone	4 (9.3)	8 (18.6)
Other	3 (7.0)	2 (4.7)
None	2 (4.7)	4 (9)
Donor type		
Auto	2 (4.6)	0 (0)
MSD	10 (23.2)	1 (2.3)
MMRD	4 (9.3)	3 (6.9)
MUD	12 (27.9)	13 (30.2)
MMUD	8 (18.6)	5 (11.6)
Haplo-identical	7 (16.3)	21 (48.8)
Stem cell source		
BM	28 (65.1)	18 (41.9)
PBSCT	12 (27.9)	25 (58.1)
Cord	3 (6.9)	0 (0)

JMML indicates juvenile myelomonocytic leukemia; CML, chronic myeloid leukemia; CR, complete remission; BM, bone marrow; TBI, total body irradiation; CNI/MTX, calcineurin inhibitor/methotrexate; MSD, matched sibling donor; MMRD, mismatched related donor; MUD, matched unrelated donor; MMUD, mismatched unrelated donor; PBSCT, peripheral blood stem cell transplantation.
Data presented are n (%), unless otherwise indicated.

METHODS

Study Design and Inclusion Criteria

This study was a retrospective chart review, which was approved by the institutional review board. Between January 1, 2000 and August 30, 2013, 43 patients underwent a second HCT for relapse and all were included in this analysis.

Definitions

The following data were collected: engraftment status, acute and chronic GVHD, transplantation-related mortality, relapse, disease-free survival (DFS), and OS. *Engraftment* was defined as an absolute neutrophil count> 500/μL for 3 consecutive days in those surviving at least 28 days after second HCT. GVHD was defined using standard published criteria [11]. *Relapse* was defined by morphological or cytogenetic evidence of disease at any site. *Active disease* was defined as morphologic or cytogenetic evidence of disease at any site at time of transplantation. *Nonrelapse mortality* (NRM) was defined as death occurring while in continuous remission. *DFS* was defined as survival without evidence of recurrent disease. *OS* was evaluated as the outcome from second HCT to last follow-up or death.

Table 2
Outcomes after Second HSCT

Outcome	Value
Days to engraftment, median (range)	16 (8-22)
Acute GVHD	
Grade II to III	6 (75%)
Grade IV	2 (25%)
Chronic GVHD	
Limited, n (%)	5 (100%)
Extensive, n (%)	0 (0%)
Five-year cumulative incidence of relapse	55%
Median time to relapse, (range), d	95 (13-755)
Five-year cumulative incidence of NRM	20%
Median time to NRM, (range), d	188 (5-1938)
Five-year DFS	25%
Five-year OS	
Entire cohort	24%
Early relapse (<6 mo)	11%
Late relapse (>6 mo)	34%
Subgroup with leukemia with active disease	12%
Subgroup with leukemia in remission	35%

Statistical Analysis

Descriptive statistics were calculated to summarize disease and transplantation characteristics. We analyzed OS and DFS using the Kaplan-Meier method and made comparisons between groups using the log-rank test. We used univariate Cox regression analysis to identify factors significantly associated with OS and DFS. Cumulative incidences were estimated for engraftment, relapse, and NRM, with death or relapse as a competing risk. We used univariate competing risk regression analysis to assess the impact of transplantation variables on relapse and NRM [12].

RESULTS

Patient and Disease Characteristics

Forty-three patients made up the study cohort, of whom 26 were male. The median age was 7 years (range, 1 to 18) at first HCT and 8 years (range, 2 to 20) at second HCT. Acute myeloid leukemia (AML) was the most common diagnosis at both the first (19 of 43) and second HCT (21 of 43). There were 21 patients with AML at time of second HCT compared with 19 at first HCT as 2 patients (1 with myelodysplastic syndrome [MDS] at first HCT and 1 with acute lymphoblastic leukemia [ALL] at first HCT) developed secondary AML. More than one half of the patients (24 of 43, 56%) had evidence of active disease going into their second HCT. The majority of patients received a second HCT for bone marrow relapses (33 of 43). Disease characteristics are summarized in Table 1.

Transplantation Procedures

Transplantation characteristics for first and second HCTs are summarized in Table 1. The median time between the first and second HCTs was 14 months (range, 5 to 57 months). Two patients had undergone an autologous HCT as the first HCT, 1 patient with Hodgkin's lymphoma and the other with acute promyelocytic leukemia, but all patients received an allogeneic HCT for their second HCT. Donor types, stem cell sources, and conditioning regimens used at first and second HCT are summarized in Table 1. The choice of donor and conditioning regimen at second HCT was dependent upon donor availability and clinical status of the patient. For 33 of the 43 patients, a different donor was identified for the second HCT. The 2 patients who did not receive any conditioning at the second HCT underwent transplantation with the same donor.

Engraftment

Two patients died before engraftment. Of the 41 evaluable patients, 39 patients engrafted (95%). The median time to engraftment was 16 days (Table 2). The 2 patients who did