Birth Order and Transplantation Outcome in HLA-Identical Sibling Stem Cell Transplantation: An Analysis on Behalf of the Center for International Blood and Marrow Transplantation

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Christiane Dobbelstein [1,*], Kwang Woo Ahn [2], Michael Haagenson [3],
Gregory A. Hale [4], Jon J. van Rood [5], David Miklos [6], Edmund K. Waller [7],
Stephen R. Spellman [3], Marcelo Fernandez-Vina [6], Arnold Ganser [1],
Mahmoud Aljurf [8], Martin Bornhaeuser [9], Vikas Gupta [10], Susan R. Marino [11],
Marilyn S. Pollack [12], Vijay Reddy [13], Matthias Eder [1], Stephanie J. Lee [14]

[1] Department of Hematology, Hemostasis, Oncology, and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany
[2] Center for International Blood and Marrow Transplant Research, Division of Biostatistics, Medical College of Wisconsin, Milwaukee, Wisconsin
[3] Immunobiology and Observational Research, Center for International Blood and Marrow Transplant Research, Minneapolis, Minnesota
[4] Pediatric Hematology, Oncology, and Blood and Marrow Transplant, All Children's Hospital, St. Petersburg, Florida
[5] Europdonor Foundation, Leiden University Medical Center, Leiden, The Netherlands
[6] Blood and Marrow Transplant, Stanford School of Medicine, Stanford, California
[7] Bone Marrow and Stem Cell Transplant Center, Emory University, Atlanta, Georgia
[8] Department of Oncology, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia
[9] Department of Medicine I, University Hospital Carl Gustav Carus, Dresden, Germany
[10] Department of Hematology, Princess Margaret Hospital, Toronto, Ontario, Canada
[11] Department of Pathology, University of Chicago Medical Center, Chicago, Illinois
[12] Department of Pathology, University of Texas Health Science Center, San Antonio, Texas
[13] Department of Hematology/Oncology, Florida Center for Cellular Therapy, Orlando, Florida
[14] Clinical Transplant Research, Fred Hutchinson Cancer Research Center, Seattle, Washington

ABSTRACT

Allogeneic stem cell transplantation (SCT) is the most effective treatment option for many hematologic malignancies, but graft-versus-host disease (GVHD) remains a major cause of treatment failure. Along with well-established risk factors for transplantation outcomes, recent single-center studies have identified a birth order effect in HLA-identical sibling SCT, with lower rates of acute and chronic GVHD and improved overall survival when the donor is younger than the recipient. One hypothesized mechanism for this effect is microchimerism due to fetomaternal and transmaternal sibling cell trafficking during pregnancy as the donor is exposed to recipient antigens in utero. The aim of the present study was to validate previously reported single-center data in a large, multicenter cohort provided by the Center for International Blood and Marrow Transplantation. All adult and pediatric patients (n = 11,365) with a hematologic malignancy who underwent allogeneic SCT with a graft from an HLA-identical sibling donor between 1990 and 2007 were included. When donors were younger than recipients, there was a significantly lower rate of acute GVHD grade II-IV and chronic GVHD in children, as well as a lower rate of chronic GVHD in adolescents. However, the hypothesized overall positive effect of lower relapse and better survival when donors are younger than recipients was not observed. Our data suggest that if otherwise equally matched, a graft from a younger sibling may be superior to a graft from an older sibling for children and adolescents undergoing SCT.

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INTRODUCTION

Allogeneic stem cell transplantation (SCT) is a curative treatment option for many hematologic malignancies. However, relapse and graft-versus-host-disease (GVHD) remain the most important causes of treatment failure [1]. Given that HLA disparity between donor and recipient is the most critical factor governing the incidence and severity of GVHD, the donor search focuses on HLA-identical siblings first [2]. Along with well-established risk factors for transplantation

outcome, an impact of birth order in HLA-identical sibling transplantation has been described in recent retrospective analyses [3,4].

The mechanism behind this birth order effect may include microchimerism by fetomaternal cell trafficking during pregnancy, leading to exposure to nonself antigens in both mother and child [5-7]. This early perinatal exposure and resultant microchimerism in the mother or siblings may result in B cell and T cell sensitization and the induction of T regulatory cells, which could affect the activation of donor lymphocytes in response to later antigen (re)exposure after SCT [8,9]. In the context of pregnancy and SCT immunology, an increased risk of GVHD after transplantation from parous female donors compared with nulliparous donors has been observed in HLA-identical SCT [10-14]. In the haploidentical setting, maternal grafts are superior in terms of disease-free survival (DFS), relapse incidence, and mortality, perhaps

owing to previous exposure of the maternal donor and her children [15,16]. To further evaluate the impact of recipient and donor birth order on the outcome of sibling SCT, we performed a retrospective analysis using the database of the Center for International Blood and Marrow Transplantation (CIBMTR).

PATIENTS AND METHODS

The aim of this study was to validate previously reported single-center data in a multicenter cohort provided by the CIBMTR. This multicenter analysis included patients who underwent an HLA-identical sibling SCT recorded in the CIBMTR database between 1990 and 2007. Only HLA-identical sibling transplantations were included, because birth order effects would not be expected with unrelated donors.

Adult and pediatric patients with a diagnosis of acute leukemia, myelodysplastic syndrome, or chronic myelogenous leukemia undergoing a first allogeneic SCT were included. Patients with nonmalignant disorders were excluded, given our interest in examining effects on relapse. Cord blood recipients, recipients age <2 years (because there were only a few patients in this cohort), and donor–recipient pairs in which the age difference was reported as >15 years apart or <1 year apart were excluded, to improve the homogeneity of the cohort. Disease stage was categorized according to CIBMTR conventions as early (acute leukemia in first complete remission, refractory anemia, refractory anemia with ringed sideroblasts, or chronic myelogenous leukemia in first chronic phase) or late (relapsed or refractory disease). All other disease types and stages were classified as intermediate. Patients were assigned to 1 of 2 groups: recipient older than donor (R>D) or donor older than recipient (D>R).

Outcomes were analyzed in terms of OS, relapse rate and mortality, DFS, treatment-related mortality, acute GVHD (aGVHD), and chronic GVHD (cGVHD).

Statistical analyses were performed with SAS 9.2 (SAS Institute, Cary, NC), comparing differences between the R>D and D>R groups using the χ^2 test, t-test, or nonparametric tests as appropriate. Probabilities of OS and DFS were calculated using Kaplan-Meier estimates. The log-rank test was used for univariate comparisons. Risk factors for outcomes were evaluated in multivariate analyses, using Cox proportional hazard models. All models included the main effect of interest (R>D versus D>R), as well as other covariates with a statistical significance level of $P < .05$. Potential covariates included donor–recipient sex match, cytomegalovirus (CMV) status, race, pre-transplantation performance status, disease and stage, time from diagnosis to transplantation, conditioning intensity, graft type, GVHD prophylaxis, antithymocyte globulin (ATG), and year of SCT. Recipient age and donor age were tested in separate models because of their correlation with birth order.

RESULTS

This retrospective analysis included a total of 11,365 patients who underwent allogeneic SCT from HLA-identical sibling donor (5870 in the R>D group and 5,495 in the D>R group). Patient characteristics are summarized in Table 1. The median age of patients at SCT was 35 years (range, 2 to 75 years) in the R>D group, compared with 31 years (range, 2 to 72 years in the D>R group ($P < .0001$). Acute myelogenous leukemia was the most common indication for SCT (38% in both groups). Bone marrow was the predominant stem cell source (72% in the R>D group and 73% in the D>R group). Most patients had early-stage disease at the time of SCT (80% in the R>D group and 81% in the D>R group; $P = .14$). The conditioning regimen was myeloablative in more than 90% of the recipients in each group. In both groups, most patients received a calcineurin inhibitor-based GVHD prophylaxis regimen. Few patients had ATG exposure (4% in the R>D group and 3% in the D>R group); these patients were excluded from analysis. Because exposure to CMV increases with age, the D>R group was more likely than the R>D group to be donor CMV-positive/recipient CMV-negative (14% versus 8%) and less likely to be donor CMV-negative/recipient CMV-positive (12% versus 20%).

Once it was determined that patient age interacted with birth order, patient age was divided into 3 groups, to reduce

Table 1
Recipient and Donor Characteristics

Variable	R>D Group	D>R Group	P Value
Number of patients	5870	5495	
Age at SCT, yr, median (range)	35 (2-75)	31 (2-72)	<.0001
Age at SCT, yr, n (%)			<.0001
Children (0-9)	319 (5)	542 (10)	
Adolescents (10-19)	814 (14)	911 (17)	
Adults (20+)	4737 (81)	4042 (74)	
Male sex, n (%)	3296 (56)	3248 (59)	.001
KPS ≥90 pre-SCT, n (%)	4546 (77)	4237 (77)	.67
Disease at SCT, n (%)			<.0001
Acute myelogenous leukemia	2234 (38)	2091 (38)	
Acute lymphoblastic leukemia	1244 (21)	1399 (25)	
Chronic myelogenous leukemia	1898 (32)	1608 (29)	
Myelodysplastic syndrome	494 (8)	397 (7)	
Stem cell source, n (%)			.27
Bone marrow	4244 (72)	4024 (73)	
Peripheral blood stem cells	1626 (28)	1471 (27)	
Conditioning regimen, n (%)			
Myeloablative	5440 (93)	5152 (94)	.02
Reduced-intensity/nonmyeloablative	430 (7)	343 (6)	
GVHD prophylaxis, n (%)			.67
Calcineurin inhibitor + MTX, other	4420 (75)	4167 (76)	
Calcineurin inhibitor other (no MTX)	1125 (19)	1043 (19)	
T cell depletion	325 (6)	285 (5)	
Donor-recipient sex match, n (%)			.21
Female-male	1490 (25)	1452 (26)	
All other	4380 (75)	4043 (74)	
Donor age, yr, median (range)	30 (<1-69)	37 (3-79)	<.0001
Year of SCT, n (%)			.16
1990-1994	2504 (43)	2426 (44)	
1995-1999	1756 (30)	1639 (30)	
2000-2004	1086 (19)	933 (17)	
2005-2009	524 (9)	497 (9)	
Survivor follow-up, mo, median (range)	80 (1-233)	83 (0.6-228)	.49

KPS indicates Karnofsky Performance Score; MTX, methotrexate.