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Relationship between Mixed Donor–Recipient Chimerism and Disease Recurrence after Hematopoietic Cell Transplantation for Sickle Cell Disease

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Abstract

Mixed donor chimerism after hematopoietic cell transplantation for sickle cell disease (SCD) can result in resolution of disease symptoms, but symptoms recur when donor chimerism is critically low. The relationship between chimerism, hemoglobin S (HbS) level, and symptomatic disease was correlated retrospectively in 95 patients who had chimerism reports available at day 100 and at 1 and 2 years after transplantation. Recurrent disease was defined as recurrence of vaso-occlusive crises, acute chest syndrome, stroke, and/or HbS levels > 50%. Thirty-five patients maintained full donor chimerism (myeloid or whole blood) through 2 years. Donor chimerism was less than 10% (defined as graft failure) in 13 patients during this period. Mixed chimerism was reported in the remaining 47 patients (range, 10% to 94%). The lowest documented donor chimerism without symptomatic disease was 26%. Of 12 surviving patients with recurrent disease, 2 had recurrence of symptoms before documented graft failure (donor chimerism of 11% and 17%, respectively). Three patients underwent second transplantation for graft failure. None received donor leukocyte infusion to maintain mixed chimerism or prevent graft failure. We

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conclude stable donor chimerism greater than 25% is associated with resolution of SCD-related symptoms, and HbS levels in transplant recipients should be interpreted in context of the sickle trait status of the donors.

Keywords

Mixed chimerism; Disease symptoms; Transplant; Sickle cell disease

INTRODUCTION

Many patients with nonmalignant disorders are symptom-free long-term after hematopoietic cell transplantation (HCT) despite mixed donor–recipient chimerism [1–6]. It is difficult to (1) distinguish between patients with adequate/stable donor chimerism with continued long-term disease control and those with unstable engraftment that results in disease recurrence and (2) predict the level at which donor chimerism is too low to sustain a disease-free state. These parameters are variable and disease dependent.

The increased use of reduced-intensity conditioning (RIC) regimens to reduce toxicity in nonmalignant disorder transplants has led to a higher incidence of mixed chimerism post-HCT, resulting in the need to define adequate donor engraftment [2,4,7–9]. After HCT for hemoglobinopathy, disease control even in the presence of relatively low-level donor chimerism has been attributed to engraftment of donor erythrocytes [3,10]. The presence of high levels of donor erythropoiesis in this setting has been demonstrated by erythroid-specific chimerism analysis and hemoglobin electrophoresis mirroring that of the donor despite low donor chimerism levels detected by traditional analysis of whole peripheral blood samples [3,5,10].

In sickle cell disease (SCD), disease resolution has been described after HCT despite donor leukocyte chimerism as low as 11% to 20% [4,5,8,11,12]. The objective of the current study was to correlate donor cell chimerism at day +100 and at 1 and 2 years after HCT with disease recurrence as assessed by hemoglobin electrophoresis and/or disease symptoms.

METHODS

A retrospective review was performed in 95 patients with SCD who underwent related or unrelated donor HCT between 2002 and 2013 in the United States and had chimerism data available by day +100 and 1 and 2 years after transplantation as reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) or to the National Institutes of Health. Data on chimerism were not collected beyond 2 years for patients reported to the CIBMTR, but hemoglobin S (HbS) levels were collected beyond 2 years.

For this study patients were censored at death, at second transplantation, or at 2 years. Full donor chimerism was defined as ≥95% donor cells in myeloid or whole blood fractions and graft failure as less than 10%. Chimerism was defined as mixed when donor cells were 10% to 94%. The type of test performed was at the discretion of the transplant center, with 31 centers reporting whole blood chimerism on 51 patients and 1 center reporting myeloid

chimerism on 44 patients. Disease recurrence was defined as a HbS levels of 50% or higher irrespective of donor trait status, and/or return of SCD-related symptoms (stroke, vaso-occlusive crisis, acute chest syndrome), or resumption of chronic RBC transfusion therapy. The HbS level > 50% was chosen because no patient with adequate donor-derived erythropoiesis was expected to have an HbS level higher than 50%.

Transplants were classified as myeloablative or reduced intensity using previously described definitions [13]. To determine the effect of donor chimerism on disease symptoms, all available mixed chimerism values by day +100 and 1 and 2 years and the associated disease assessments at each of these time points were reviewed taking into consideration symptoms, HbS level, and confounders such as RBC transfusions in the 4-week period before chimerism assessment. The Institutional Review Board of the National Marrow Donor Program approved this study.

RESULTS

Demographics

Patient and transplant characteristics by donor chimerism groups (full donor, mixed chimerism and graft failure) for 95 patients are shown in Table 1. All patients were followed longitudinally. Ninety-five patients were assessable at day 100, 91 patients at 1 year, and 76 patients at 2 years. Most patients (61%) received bone marrow or peripheral blood grafts from HLA-matched siblings. Stroke alone or with vaso-occlusive crisis and acute chest syndrome was the predominant indication for HCT (Table 1). RIC regimens were more commonly used than myeloablative regimens in this study (66% versus 34%, $P = .002$). The median time to neutrophil and platelet recovery was 20 days (range, 8 to 54) and 17 days (range, 8 to 47), respectively.

Ninety-one patients were assessable for chimerism by day +100 (Table 1). Table 1 shows patient and transplant characteristics by donor chimerism at 1 and 2 years after HCT, and comparison between Tables 1 and 2 reflects the change in percentage of patients with full or mixed chimerism with time.

The median age at transplantation for the study population was 16 years (range, 2 to 65). The median age of those who experienced graft failure was 31 years. In contrast, the median age of patients with mixed chimerism and full donor chimerism was 11 and 14 years, respectively ($P = .020$).

Full Donor Chimerism

By day +100, 55 patients had achieved full donor chimerism. Their median chimerism was 100% (range, 95% to 100%). By 1 year 52 patients reported full donor chimerism. Ten of 55 patients (18%) with full chimerism by day +100 reverted to mixed chimerism at the 1-year time point. Eight patients with mixed chimerism by day +100 achieved full donor chimerism by their 1-year evaluation. At 2 years, 43 patients reported full donor chimerism. Seven patients who had full donor chimerism at 1 year reverted to mixed chimerism. Four patients with full donor chimerism at day +100 and 1 year were reported to be transfusion independent with HbS < 50% at 2 years; donor chimerism was not evaluated. One patient

with full donor chimerism died 14 months after transplantation from pulmonary failure as a transplant-related complication. No patient with full donor chimerism reported SCD-related symptoms post-transplant.

Graft Failure

Thirteen patients experienced graft failure before day +100. All patients received RIC regimens. Ten of 13 patients with graft failure at 1-year post-HCT were alive with disease at 2 years. One patient had a second transplant 7 months after the first. Two patients died 3 and 10 months after transplantation from sepsis from a contaminated platelet transfusion and from intracranial bleeding related to moyamoya disease, respectively. Patients with graft failure included 1 patient who received an unrelated umbilical cord blood graft and RIC regimen (fludarabine, melphalan, and alemtuzumab), 5 patients who received peripheral blood grafts from an HLA-matched sibling after a RIC regimen of alemtuzumab and total body irradiation (300 cGy), and 7 patients who received peripheral blood grafts from mismatched relatives (haploidentical donor) with a RIC regimen of alemtuzumab and total body irradiation of 400 cGy.

Mixed Donor Chimerism

There were 27 patients with mixed donor chimerism by day +100; median donor chimerism was 81% (range, 42% to 94%). All these patients achieved neutrophil and platelet recovery, and the median times to neutrophil and platelet recovery were 19 days (range, 12 to 46) and 17 days (range, 10 to 41), respectively. Of these, 1 patient with mixed chimerism (42%) by day +100 received a second transplant 11 months after the first transplant and was censored for further evaluation.

At the 1-year assessment, 29 patients reported mixed chimerism. This included 21 patients who had mixed chimerism by day +100 and an additional 8 patients with full donor chimerism at that evaluation but reverted to mixed chimerism at the 1-year time point. Conversely, 8 patients with mixed chimerism by day +100 converted to full donor chimerism at their 1-year assessment.

At the 2-year assessment, 23 patients reported mixed chimerism and included 3 patients with full donor chimerism by day +100 and 1 year who developed mixed chimerism at 2 years (89%, 94%, and 83%, respectively). Of the remaining 9 patients with mixed chimerism at 1 year, 4 achieved full donor chimerism at their 2-year assessment and chimerism was not reported for 5 patients (alive, asymptomatic and transfusion independent with HbS levels < 50% at 2 years). One of these 5 patients died 42 months after transplantation from an infection.

No disease recurrence or graft failure occurred in patients with mixed donor chimerism levels ranging between 51% and 94%. However, recurrent disease at a later time point was reported in 1 of 8 patients with chimerism levels between 26% and 50% as described below. However, it should be noted that this patient had undergone a second transplantation. All patients with donor chimerism ≤ 17% had recurrent disease.

The median donor chimerism in the absence of disease recurrence or rise in HbS level was 81% (range, 26% to 94%). Of note, the lowest level of donor chimerism in this asymptomatic group was 26% and reported in 3 patients (myeloid cell lineage tested in 2 and whole blood analysis performed in 1). None had increased HbS levels defined as greater than 50% or disease symptoms. In all patients with mixed chimerism who were asymptomatic, the HbS level was always <50%.

Recurrent Disease

The 13 patients with graft failure met our definition of recurrent disease, defined by either symptoms or HbS > 50%. Additionally, 2 patients with mixed chimerism (defined by us as having >10% but <95% donor engraftment) had donor chimerism levels of 11% (at 1-year post-HCT) and 17% (at 2-years post-HCT) also had disease recurrence. One of 2 patients had 51% HbS at the 1-year evaluation that increased to 54% at 2 years. At the 2-year time point, donor chimerism had decreased to 4% confirming graft failure. The other patient developed disease symptoms with 17% donor chimerism at the 2-year time point. There was a patient with donor chimerism of 33% at 2 years and a corresponding HbS level of 51.3% and although asymptomatic and transfusion independent, qualified as having disease recurrence by our definition. Longer follow-up eventually confirmed graft failure in this patient approximately 6 years after HCT, underscoring the importance of long-term surveillance. We hypothesize that the rising HbS level noted at 2 years was a harbinger of graft failure and is an important indicator. Overall, 3 of 23 patients with mixed chimerism ultimately failed to benefit from HCT.

Death

There were 3 deaths among the 95 patients (3%) within the 2-year period after HCT, at 3 (sepsis), 10 (intracranial bleeding related to moyamoya disease), and 14 months (pulmonary failure), respectively. There were 3 additional deaths beyond 2 years: 2 attributed to infection (without graft failure) and 1 to thrombocytopenia and gastrointestinal bleeding.

DISCUSSION

This descriptive report of donor cell engraftment after allogeneic transplantation for SCD revealed that as many as 41% of patients at 1 year and 36% at 2 years had mixed chimerism and yet the majority had no evidence of the SCD phenotype. Our objective was to describe the relationship between SCD-related symptoms, HbS level, and mixed chimerism in myeloid or whole blood analyses, especially in the absence of a standard widely accepted test for erythrocyte-specific engraftment. We observed amelioration of SCD-related symptoms when donor chimerism was ≥26% and resulted in HbS levels < 50%, unsupported by RBC transfusion. The single patient with a higher level of donor chimerism (33%) still had a higher level of HbS (51%) detected several years before graft failure or return of symptoms. These data make the case that the mere presence of mixed chimerism does not warrant an intervention such as donor lymphocyte infusion or a second transplant because each of these interventions can be associated with unnecessary toxicity. Such interventions could be a consideration if a sustained decline to 25% or lower is detected or there is clear

disease symptom progression in the presence of rising HbS levels, depending on the sickle cell trait status of the donors.

A limitation to this report is that insight into chimerism levels that may be considered predictive for eventual graft failure are restricted to the first 2 years after HCT because data on chimerism analysis is only collected for 2 years by the CIBMTR. In the 2-year follow-up period, most graft failures occurred early. Although we do not have chimerism beyond the 2-year time point in that cohort, this time point generally represents the period beyond withdrawal of immune suppression and should represent steady-state HbS levels in most. However, we have noted that 3 patients with full donor chimerism at 1 year reverted to mixed chimerism at 2 years, albeit with high donor engraftment. The registry continues to follow patients longitudinally beyond 2 years. The median follow-up of this cohort is now 4 years beyond year 2, and there have been no reports of disease-related symptoms, late donor lymphocyte infusions, or second transplants, which could be considered surrogate markers of graft failure. Although there was no clinical indication of late disease recurrence after established donor engraftment at 2 years in the cohort contributed by the registry, it is unclear what the required duration of follow-up should be in the setting of stable engraftment (with or without mixed chimerism) because of the small number of patients in this series. We recommend ongoing evaluation by hemoglobin electrophoresis on a yearly basis.

In transplantation for hemoglobinopathies, assessment of donor erythroid engraftment is more specific and tends to persist at a high level after successful transplantation even in the presence of low donor engraftment in cells of other lineages [10,14]. However, because erythroid engraftment analysis is not widely available, a combination of myeloid cell engraftment and hemoglobin electrophoresis can predict graft stability provided there is no RBC transfusion requirement. Our findings are similar to mathematical model predictions showing that 20% donor myeloid chimerism is needed to maintain an HbS level < 50% in recipients receiving grafts from donors with sickle trait [15]. This model was based on the differences between donor and recipient RBC half-lives. This number is higher than the previously reported 11% donor chimerism associated with an HbS level of 7% measured at 64 days after transplant; however, this 11% was measured from unfractionated whole blood so lymphocyte contribution may have affected this measure [5].

Our modest sample size prevented identification of donor and recipient factors that predisposed to mixed chimerism. Nevertheless, our observation that graft failure in a high proportion of HLA-mismatched related donor transplants (haploidentical transplants) after very low intensity conditioning that was designed to offset toxicity suggests that a modified approach is necessary to ensure successful engraftment defined as a donor chimerism level of ≥26% from these data. No recipient of myeloablative transplant conditioning regimen recorded donor chimerism less than 50% (Table 2).

The data extracted could not be used to correlate the kinetics of decreasing chimerism, graft failure, and return of disease symptoms in patients destined to eventually have recurrent disease. After graft failure, the interval between the rise in HbS levels and return of symptoms can be variable depending on the severity of the SCD, the trait status of the donor

where HbS levels could rise faster in the event of graft failure, and the severity of pre-existing vasculopathy. It is noteworthy that 2 of the 3 patients with donor chimerism levels of 26% had transplants from donors with traits and yet maintained donor levels of HbS and remained disease-free. This report also does not provide insight into the timing and potential interventions that might prevent graft failure. These interventions would be predicted to vary based on the conditioning, stem cell source, timing, and other variables [4,9,16].

In summary, the ability of mixed chimerism, if adequate, to control HbS levels and ameliorate disease symptoms is encouraging and lends support to the development of RIC regimens to transplant nonmalignant disorders such as SCD provided adequate and stable donor engraftment can be achieved. This report demonstrates that pre-emptive intervention for mixed chimerism is unnecessary post-transplant unless donor chimerism is unstable and approaches the critical threshold. We also provide here a chimerism threshold of 25% below which patients are at risk for eventual graft failure and disease recurrence. Hemoglobin S levels need to be interpreted carefully in context with donor sickle cell trait status. In addition, success in eradicating disease with mixed chimerism supports gene targeting or gene modification endeavors by providing a target level of engraftment of modified autologous cells to achieve a cure.

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Table 1

Characteristics of Patients with Donor Chimerism by Day +100, by 1 Year, and by 2 Years

	Chimerism		
	Full Donor N (%)	**Graft Failure N (%)**	**Mixed N (%)**
Donor chimerism by day +100 (n = 95)			
Number of patients	55	13	27
Median age at transplant, yr (range)	14 (2–53)	31 (14–57)	11 (2–65)
Donor and graft type			
HLA-identical sibling, bone marrow	21 (38)	0	7 (26)
HLA-identical sibling, peripheral blood	18 (33)	4 (31)	8 (30)
HLA-identical sibling, cord blood	4 (7)	0	6 (22)
Other relative, bone marrow	1 (2)	0	0
Other relative, peripheral blood	3 (5)	8 (62)	3 (11)
Unrelated donor, bone marrow	3 (5)	0	2 (7)
Unrelated donor, cord blood	5 (9)	1 (8)	1 (4)
Indication for transplantation			
Stroke, acute chest syndrome, vaso-occlusive crisis	3 (5)	3 (23)	2 (7)
Stroke, acute chest syndrome	1 (2)	0	2 (7)
Stroke, vaso-occlusive crisis	3 (5)	3 (23)	2 (7)
Acute chest syndrome, vaso-occlusive crisis	21 (38)	3 (23)	6 (22)
Stroke alone	7 (13)	1 (8)	4 (15)
Acute chest syndrome alone	4 (7)	0	1 (4)
Vaso-occlusive crisis alone	9 (16)	2 (15)	6 (22)
Not reported	7 (13)	1 (8)	4 (15)
Transplant conditioning regimen			
Myeloablative			
Busulfan + cyclophosphamide	20 (36)	0	8 (30)
Busulfan + fludarabine	4 (7)	0	0
Busulfan + cyclophosphamide + fludarabine	0	0	2 (7)
Reduced intensity			
Melphalan + fludarabine + alemtuzumab	7 (13)	1 (8)	4 (15)
Melphalan + fludarabine	1 (2)	0	1 (4)
Total body irradiation (200 cGy) + fludarabine + alemtuzumab	1 (2)	0	1 (4)
Total body irradiation (300/400 cGy) + alemtuzumab	21 (38)	12 (92)	11 (41)
Cyclophosphamide + alemtuzumab	1 (2)	0	0
Year of transplant			
1994–2005	11 (20)	0	4 (15)
2006–2013	44 (80)	13 (100)	23 (85)
Donor Chimerism at 1 Year (n = 91)[*]			
Number of patients	52	10	29
Median age at transplant, yr (range)	14 (2–53)	28 (14–57)	11 (2–65)

	Chimerism		
	Full Donor N (%)	**Graft Failure N (%)**	**Mixed N (%)**
Type of donor			
HLA-identical sibling, bone marrow	15 (29)	0	13 (45)
HLA-identical sibling, peripheral blood	18 (35)	2 (20)	7 (24)
HLA-identical sibling, cord blood	6 (12)	0	4 (14)
Other relative, bone marrow	1 (2)	0	0
Other relative, peripheral blood	2 (4)	7 (70)	4 (14)
Unrelated, bone marrow	4 (8)	0	1 (3)
Unrelated, cord blood	6 (12)	1 (10)	0
Indication for HCT			
Stroke, acute chest syndrome, vaso-occlusive crisis	3 (6)	2 (20)	2 (7)
Stroke, acute chest syndrome	1 (2)	0	2 (7)
Stroke, vaso-occlusive crisis	3 (6)	2 (20)	2 (7)
Acute chest syndrome, vaso-occlusive crisis	17 (33)	3 (30)	9 (31)
Stroke alone	7 (13)	1 (10)	4 (14)
Acute chest syndrome alone	2 (4)	0	3 (10)
Vaso-occlusive crisis alone	11 (21)	2 (20)	4 (14)
Not reported	8 (15)	0	3 (10)
Conditioning regimens			
Myeloablative			
Busulfan + cyclophosphamide	15 (29)	0	13 (45)
Busulfan + fludarabine	3 (6)	0	1 (3)
Busulfan + cyclophosphamide + fludarabine	2 (4)	0	0
Reduced intensity			
Melphalan + fludarabine + alemtuzumab	10 (19)	1 (10)	1 (3)
Melphalan + fludarabine	1 (2)	0	1 (3)
Total body irradiation (200 cGy) + fludarabine + alemtuzumab	1 (2)	0	1 (3)
Total body irradiation (300/400 cGy) + alemtuzumab	20 (38)	9 (90)	11 (38)
Cyclophosphamide + alemtuzumab	0	0	1 (3)
Year of transplant			
1994–2005	7 (2)	0	7 (24)
2006–2013	45 (98)	10 (100)	22 (76)
Donor chimerism at 2 years (n = 76)[†]			
Number of patients	43	10	23
Median age at transplant, yr (range)	14 (2–53)	28 (14–57)	14 (2–65)
Type of donor			
HLA-identical sibling, bone marrow	11 (26)	0	11 (48)
HLA-identical sibling, peripheral blood	17 (40)	2 (20)	7 (30)
HLA-identical sibling, cord blood	5 (12)	0	2 (9)
Other relative, peripheral blood	0	7 (70)	3 (13)
Unrelated, bone marrow	4 (9)	0	0

	Chimerism		
	Full Donor N (%)	**Graft Failure N (%)**	**Mixed N (%)**
Unrelated, cord blood	6 (14)	1 (10)	0
Indication for HCT			
Stroke, acute chest syndrome, vaso-occlusive crisis	2 (5)	2 (20)	3 (13)
Stroke, acute chest syndrome	3 (7)	0	0
Stroke, vaso-occlusive crisis	1 (2)	2 (20)	2 (9)
Acute chest syndrome, vaso-occlusive crisis	14 (33)	3 (30)	7 (30)
Stroke alone	5 (12)	1 (10)	4 (17)
Acute chest syndrome alone	2 (5)	0	2 (9)
Vaso-occlusive crisis alone	10 (23)	2 (20)	2 (9)
Not reported	6 (14)	0	3 (13)
Conditioning regimens			
Myeloablative			
Busulfan + cyclophosphamide	12 (28)	0	10 (43)
Busulfan + fludarabine	2 (5)	0	1 (4)
Busulfan + cyclophosphamide + fludarabine	2 (5)	0	0
Reduced intensity			
Melphalan + fludarabine + alemtuzumab	8 (19)	1 (10)	0
Melphalan + fludarabine	2 (5)	0	0
Total body irradiation (200 cGy) + fludarabine + alemtuzumab	0	0	1 (4)
Total body irradiation (300/400 cGy) + alemtuzumab	17 (40)	9 (90)	10 (43)
Cyclophosphamide + alemtuzumab	0	0	1 (4)
Year of transplant			
1994–2005	5 (11)	0	4 (17)
2006–2013	38 (88)	10 (100)	19 (82)

Values are number of patients with percents in parentheses unless otherwise defined.

*Four patients were censored between day +100 and 1 year: 2 patients with primary graft failure died, 1 patient with primary graft failure received a second transplant 7 months after first transplant, and 1 patient with mixed chimerism received a second transplant for graft failure 11 months after first transplant.

†Fifteen patients were censored between 1 and 2 years: 1 patient with full donor chimerism died at 14 months; 1 patient with full donor chimerism received a second transplant 14 months after first transplant for secondary graft failure; 4 patients with full chimerism at 1 year did not have chimerism test at 2 years but HbS level was <50%, RBC transfusion independent, and asymptomatic; 5 patients with mixed chimerism at 1 year did not have chimerism test at 2 years, but HbS level was <50%, RBC transfusion independent, and asymptomatic; and 4 patients with mixed chimerism were not followed beyond 1 year.

Table 2

Number of Patients with Full Donor Chimerism at Day +100 and 1 Year and 2 Years after Transplant and with Mixed Chimerism at Day +100 and 1 Year and 2 Years after Transplant Showing Donor Chimerism Levels

	Day +100		**Total**	**1 Year**		**Total**	**2 Years**			**Total**
Patients with full donor chimerism at day +100, 1 year, and 2 years after transplant										
Chimerism (%)	≥95		95	≥95		91	≥95			76
MAC	21		31	17		31	14			25
RIC	34		64	35		60	29			51
	Day +100		Total	1 Year		Total	2 Years			Total
Patients with mixed chimerism at day +100, 1 year, and 2 years after transplant										
Chimerism (%)	26–50	51–94	95	26–50	51–94	91	10–25	26–50	51–94	76
MAC	0	10	31	0	14	31	0	1	10	25
RIC	1	16	64	2	13	60	1	1	10	51

MAC indicates myeloablative conditioning; RIC, reduced intensity conditioning.