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Second Allogeneic Hematopoietic Cell Transplantation for Patients with Fanconi Anemia and Bone Marrow Failure

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A B S T R A C T

A second allogeneic hematopoietic cell transplantation (HCT) is the sole salvage option for individuals who develop graft failure after their first HCT. Data on outcomes after second HCT in patients with Fanconi anemia (FA) are scarce. Here we report outcomes after second allogeneic HCT for FA (n = 81). The indication for second HCT was graft failure after the first HCT. Transplantations were performed between 1990 and 2012. The timing of the second HCT predicted subsequent graft failure and survival. Graft failure was high when the second HCT was performed less than 3 months from the first. The 3-month probability of graft failure was 69% when the interval between the first HCT and second HCT was less than 3 months, compared with 23% when the interval was longer ($P < .001$). Consequently, the 1-year survival rate was substantially lower when the interval between the first and second HCTs was less than 3 months compared with longer (23% vs 58%; $P = .001$). The corresponding 5-year probability of survival was 16% and 45%, respectively ($P = .006$). Taken

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together, these data suggest that fewer than one-half of patients with FA undergoing a second HCT for graft failure are long-term survivors. There is an urgent need to develop strategies to reduce the rate of graft failure after first HCT.

INTRODUCTION

Fanconi anemia (FA) cells are characterized by defects in DNA repair and cell cycle checkpoints, which play prominent roles in the genomic instability characteristic of this disease. This instability leads to increased apoptosis and bone marrow failure, as well as evolution to myelodysplastic syndrome or acute leukemia in some patients [1-5]. Allogeneic hematopoietic cell transplantation (HCT) is currently the only curative modality for the treatment of bone marrow failure and clonal disorders in patients with FA, with excellent outcomes particularly in recipients of HLA-matched related donor HCT [6-21].

Nonetheless, graft failure is a major complication associated with a dismal prognosis, particularly in recipients of alternative donor HCT. Second HCT is the only potential salvage modality, although great caution must be exercised because patients with FA may experience pronounced toxicity and higher mortality owing to their underlying genomic instability. Available data on the outcomes of patients with FA after second HCT are limited [12,13,16,22-24]; therefore, we studied 81 patients with FA who underwent a second HCT for graft failure.

PATIENTS AND METHODS

Data Source

The Center for International Blood and Marrow Transplant Research is a voluntary network of more than 450 transplantation centers worldwide that contribute detailed data on consecutive allogeneic and autologous HCT. Onsite audits ensure compliance and data quality. Patients are followed longitudinally until death or loss to follow-up. Patients, legal guardians, or both provided written informed consent for research participation. The Institutional Review Boards of the Medical College of Wisconsin and the National Marrow Donor Program approved this study.

Patients

To be eligible, patients with FA had to have undergone a second HCT for graft failure after their first HCT. The indication for the initial transplantation was marrow failure. All HCTs were performed between 1990 and 2012. Patients with FA with acute leukemia or myelodysplastic syndrome or with abnormal clones before either the first or second HCT were excluded. A total of 533 patients with FA underwent allogeneic HCT, including 432 who underwent first HCT for marrow failure. Among these 432 transplant recipients, 137 experienced either primary or secondary graft failure, and of these, only 81 underwent a second HCT (the population for the present analysis). The remaining 56 patients with graft failure after the first HCT did not proceed to a second HCT; all succumbed to their disease, with a median time to death of 1 month. The decision to offer a second HCT was at the discretion of the transplantation center and the treating physicians.

End Points

The primary outcome was survival. Neutrophil recovery was defined as the first of 3 consecutive days with an absolute neutrophil count (ANC) of 0.5×10^9/L. Primary graft failure was defined as failure to achieve neutrophil recovery, and secondary graft failure was defined as sustained loss of ANC ($<0.5 \times 10^9$/L) after initial recovery. Platelet recovery was defined as achieving an ANC of 20×10^9/L unsupported by platelet transfusions for at least 7 days. Acute and chronic graft-versus-host disease (GVHD) were graded using published criteria [25,26].

Statistical Analyses

The probability of overall survival was calculated using the Kaplan-Meier estimator [27]. The probabilities for hematopoietic recovery and acute and chronic GVHD were calculated using the cumulative incidence estimator, with death as the competing risk [28]. The 5-year probabilities of overall survival were estimated for the all patients, by the interval between the first HCT and second HCT ($\leq$3 vs >3 months), age at transplantation ($\leq$10 vs >10 years), performance score (90 to 100 vs <90), donor type (related vs unrelated), same versus different donor for second HCT, and transplantation period (before 2000 vs 2000 and after). A P value $\leq$ .05 was considered significant; all P values are 2-sided. Analyses were performed using SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

Patient, Disease, and Transplant Characteristics

Patient and transplant characteristics are listed in Table 1. The median age at second HCT was 11 years, with most of the second HCTs (69 of 81; 85%) occurring within 6 months of the first HCT. Five patients were older than 21 years. Only 22% of the patients reported a performance score of 90 or 100, and one-third of the patients reported a score of 60, 70, or 80. Five patients were reported to have renal impairment, 3 patients had infection, and 3 patients had hepatic toxicity (elevated transaminases) after veno-occlusive disease from the first HCT. Most transplant recipients received non–irradiation-containing regimens. Only 8% of recipients received irradiation-containing regimens for both the first and second HCTs. Fludarabine was included in the conditioning regimen for one-third of the HCTs. The predominant stem cell source was an unrelated donor, accounting for approximately 60% of transplants. Bone marrow was the predominant graft source (47 of 81; 58%); 17 transplants used peripheral blood (21%), and 17 used umbilical cord blood (21%). One-third of second HCTs (n = 27) used a different donor from that used in the first HCT. Of these, 6 used a graft from a related donor, and 21 used a graft from an unrelated donor. Of note, 14 of the 27 recipients who received their graft from a different donor had received umbilical cord blood for their first HCT.

Most GVHD prophylaxis regimens included cyclosporine with another agent; in vivo T cell depletion (antithymocyte globulin [ATG]) was used for 62% of the second HCTs. The median follow-up from the second HCT was 62 months (range, 3 to 117 months).

Approximately 60% of second HCTs were performed within 3 months of the first HCT; characteristics of these transplantations are presented in Table 2. Patients undergoing HCT within 3 months of their first HCT were more likely to report a performance score <90, less likely to have received a fludarabine-containing regimen, and more likely to have received their transplants from a donor different from their first transplant. Most second HCTs with a different donor used an unrelated donor for the first and second transplants, with cord blood as the predominant stem cell source.

Hematopoietic Recovery and Overall Survival

For the entire study population, the day 28 probability of neutrophil recovery was 37% (95% confidence interval [CI], 27% to 48%) and the day 100 probability of platelet recovery was 30% (95% CI, 19% to 40%). The rate of primary graft failure was high (48 of the 81 HCTs), and secondary graft failure occurred in 4 patients. Neutrophil and platelet

Table 1
Patient and Transplantation Characteristics for Second HCT

Characteristic	Value
Number of patients	81
Age at HCT, n (%)	
2-10 yr	38 (47)
11-21 yr	38 (47)
22-36 yr	5 (6)
Sex, n (%)	
Male	54 (67)
Female	27 (33)
Performance score, n (%)	
≤50	30 (37)
60-80	26 (32)
90-100	18 (22)
Missing	7 (9)
Interval between first and second HCTs, n (%)	
<3 mo	50 (62)
3-4 mo	10 (12)
5-6 mo	9 (11)
≥7 mo	12 (15)
Conditioning regimens	
Radiation-containing regimens, n (%)	
Total body irradiation + fludarabine	9 (11)
Total body irradiation + cyclophosphamide	2 (3)
Total body irradiation + ATG	4 (5)
Total body irradiation alone	2 (3)
Total lymphocyte irradiation + cyclophosphamide	1 (1)
Non–radiation-containing regimens, n (%)	
Fludarabine + cyclophosphamide + ATG	15 (19)
Fludarabine and ATG	7 (9)
Fludarabine and cyclophosphamide	4 (5)
Fludarabine alone	4 (5)
Cyclophosphamide alone	8 (10)
ATG alone	14 (16)
None	11 (13)
Recipient CMV status, n (%)	
Negative	25 (31)
Positive	38 (47)
Missing/not tested	18 (22)
Donor type, n (%)	
HLA-identical sibling (cord blood, n = 3)	17 (20)
Other mismatched relative	15 (19)
Unrelated donor HLA-matched (cord blood, n = 1)	15 (19)
Unrelated donor HLA-mismatched (cord blood, n = 16)	34 (42)
Year of HCT, n (%)	
1990-1999	27 (33)
2000-2012	54 (67)
GVHD prophylaxis, n (%)	
Ex vivo T cell depletion	12 (15)
In vivo T cell depletion	8 (10)
Tacrolimus-containing	5 (6)
Cyclosporine-containing	50 (62)
Post-transplantation cyclophosphamide	1 (1)
None	5 (6)
Follow-up of survivors, mo, median (range)	62 (3-117)

CMV indicates cytomegalovirus.

recovery rates were higher when the interval between the first and second HCTs exceeded 3 months (Table 3 and Figure 1). Among the 50 patients who underwent retransplantation within 3 months of the first HCT, 48 did so owing to primary graft failure and 2 did so for secondary graft failure. Only 14 of these 50 patients achieved sustained neutrophil recovery. Five of these 14 patients were alive at the time of this report; the 9 deaths were attributed to infection, GVHD, multiorgan failure, graft rejection, and hemorrhage. In contrast, 19 of 31 patients who underwent HCT beyond 3 months achieved sustained neutrophil recovery. Twelve patients were alive at the last follow-up, and 7 patients died from transplantation-related complications (2 from graft rejection, 2 from GVHD, 2 from multiorgan failure, and 1 from interstitial pneumonitis).

Table 2
Patient and Transplantation Characteristics by Interval between First and Second HCTs

Characteristic	Interval	
	<3 mo	≥3 mo
Number of patients	50	31
Performance score, n (%)		
≤50	22 (44)	8 (26)
60-80	17 (34)	9 (29)
90-100	6 (12)	12 (39)
Missing	5 (10)	2 (6)
Interval between first and second HCTs, n (%)		
<3 mo	50 (100)	0
3-4 mo	0	10 (32)
5-6 mo	0	9 (29)
≥7 mo	0	12 (39)
Transplantation conditioning regimen, n (%)		
Radiation and fludarabine-containing	4 (8)	5 (16)
Nonradiation regimen with fludarabine	7 (14)	10 (32)
Radiation-containing without fludarabine	7 (14)	3 (10)
Nonradiation regimen without fludarabine	32 (64)	13 (42)
Different donor, n (%)		
Yes	20 (40)	7 (23)
No	30 (60)	24 (77)

The 1-year and 5-year probabilities of overall survival for patients undergoing retransplanted within 3 months of their first HCT were 23% and 16%, respectively (Table 3 and Figure 2). The corresponding probabilities for patients undergoing retransplantation beyond 3 months were higher (58% and 45%; Table 3). As expected, the 1-year and 5-year survival rates were 17% and 13%, respectively, for patients with a performance score <90, but 83% and 72% for those with a performance scores of 90 or 100 ($P < .0001$). The transplantation period was also associated with survival. The 5-year probability of survival was 7% (95% CI, 1% to 21%) for patients undergoing HCT in 1990 to 1999 and 38% (95% CI, 25% to 50%) for those undergoing HCT in 2000 to 2012 ($P < .0001$). We specifically tested for effects of age at second HCT, same versus different donor for second HCT, and related versus unrelated donor, and found none. We were unable to test for an effect of graft type, because bone marrow was the predominant graft. Only 3 of 17 cord blood recipients were alive at the time of this report.

Most deaths occurred within the first year after the second HCT in both groups, 38 of 41 (93%) among those undergoing retransplantation within 3 months of the first HCT

Table 3
Results of Univariate Analysis after Second HCT by Interval between First and Second HCTs (<3 vs ≥3 mo)

Outcome	<3 mo		≥3 mo		*P* value
	N	Probability (95% CI), %	N	Probability (95% CI), %	
ANC >0.5 × 10^9/L	50		31		.002
At 28 d		24 (13-37)		58 (38-73)	
Graft failure (primary or secondary)	45		26		
At 28 d		33 (20-47)		8 (1-22)	.004
At 3 mo		69 (53-80)		23 (9-40)	<.001
Platelets ≥20 × 10^9/L	45		26		
At 100 days		13 (5-25)		58 (37-74)	<.001
Overall survival	50		31		
At 1 yr		23 (13-36)		58 (39-73)	.001
At 3 yr		19 (9-31)		45 (27-61)	.013
At 5 yr		16 (8-28)		45 (27-61)	.006

N indicates number evaluable.

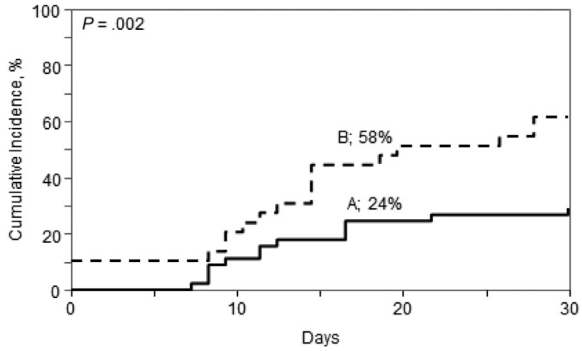

Figure 1. The day 28 cumulative incidence of neutrophil recovery was 24% (95% CI, 13% to 37%) for patients undergoing HCT within 3 months of their first HCT (A) and 58% (95% CI, 38% to 73%) for those undergoing HCT beyond 3 months after their first HCT (B).

and 15 of 20 (75%) among those undergoing retransplantation later. Although graft failure after the second HCT was the predominant cause of death in both groups (n = 42), there were 5 GVHD-related deaths, 3 deaths from infection, 1 death from interstitial pneumonitis, 1 death from hemorrhage, and 2 deaths from multiorgan failure. The cause of death was not reported in 1 patient.

Acute and Chronic GVHD

The day 100 cumulative incidence of grade II-IV acute GVHD was 16% (95% CI, 9% to 26%), including grade II in 4 patients and grade III-IV in 7 patients. The 5-year cumulative incidence of chronic GVHD was 11% (95% CI, 5% to 19%); it was limited in 3 patients and extensive in 5 patients. The low incidence of acute and chronic GVHD prevented further subset analyses.

Post-Transplantation Malignancy

One patient developed Epstein-Barr virus–associated lymphoproliferative disease malignancy at 2 months after the second HCT. This patient was alive at the last follow-up.

DISCUSSION

Graft failure represents a relatively infrequent but potentially lethal complication of allogeneic HCT. Data on the incidence of graft failure and subsequent management in patients with FA are limited. Early reports indicated a graft failure rate of 8% after HLA-matched related transplantation and conditioning with cyclophosphamide (20 mg/kg) and thoracoabdominal irradiation (500 cGy) [14]. Others have reported that the addition of ATG or the omission of radiation from the conditioning regimen did not change the incidence of graft failure, with rates varying between 7% and 13% [8,16,22,23].

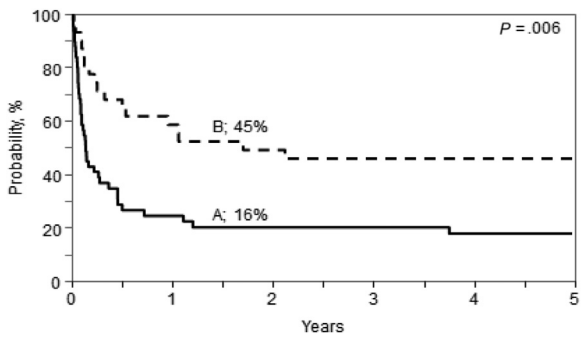

Figure 2. The 5-year probability of overall survival was 16% (95% CI, 8% to 28%) for patients undergoing HCT within 3 months of their first HCT (A) and 45% (95% CI, 27% to 61%) for those undergoing HCT beyond 3 months after their first HCT (B).

The decision to perform a second HCT after primary or secondary graft failure for FA is challenging. The underlying genomic instability of FA cells may render further cytotoxic conditioning detrimental and lead to poor survival. The present analyses identified 3 factors predictive for survival after second HCT. When the interval between the first and second HCTs was less than 3 months, survival was dismal. Poor performance score was also associated with poor survival; however, more than 75% of the patients who underwent retransplantation within 3 months of the first HCT had a performance score of $\leq$80, implying that performance score is a surrogate for the interval between first and second HCTs. Because the majority of patients in the present analysis underwent retransplantation for primary graft failure, the timing of the second HCT was at the discretion of the treating physician. Transplantation before the year 2000 was also associated with lower survival compared with transplantation more recent years. This effect of transplantation period can be attributed to advances in supportive care; however, approximately 40% of second HCTs done before 2000 were performed less than 3 months after the first HCT. Formal multivariate analysis was not undertaken owing to the limited sample size. Although comorbidity data were not systematically collected during the study period, most patients in the early retransplantation group had poor performance scores, a surrogate marker for the burden of comorbidities. Observations similar to ours regarding the timing of second HCT and performance scores have been reported for patients with severe aplastic anemia undergoing a second HCT for graft failure [29].

Given the superior survival rate in patients undergoing HCT beyond the 3-month period (1-year survival of 58% vs 23%), it might be prudent to provide supportive care and delay offering second HCT for at least 3 months after the first HCT. This strategy might allow for recovery from tissue damage suffered during the first HCT, although patients would be at risk of succumbing to infection. Overall survival after primary graft failure is low. The decision to offer a second HCT and the determination of the timing must be made after carefully weighing the risks and benefits.

One of the chief concerns when contemplating a second HCT is the choice of the most appropriate preparative regimen. Many regimens used for second HCTs have resulted in poor engraftment with high mortality. The introduction of fludarabine-based conditioning regimens for FA has improved engraftment and survival after first HCT [12,13,15,19,20,30]. Our small sample size prevented a more detailed analysis of the effects of the various conditioning regimens. It is noteworthy, however, that most second HCTs used nonirradiation regimens, and approximately one-half of the regimens used after a longer interval between the first and second HCTs included fludarabine. Similarly, our modest cohort size does not allow us to make strong recommendations regarding second HCT conditioning regimens. The choice of donor for second HCT was largely explained by whether the first donor was a related or an unrelated donor. With unrelated donor transplants, the donor for the second HCT was frequently different from that for the first HCT; this was unavoidable when the first HCT used cord blood as the graft source.

Although the present analysis shows that long-term survival is possible in approximately one-half of the patients undergoing retransplantation more than 3 months from the first HCT, repeated graft failure and transplantation-related complications are barriers to a more successful outcome. The significantly lower survival rate of <20% noted in patients with a shorter interval between the first and second HCTs raises questions regarding the justification for subjecting these patients to an early second HCT.

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