Allogeneic Hematopoietic Cell Transplantation for Fanconi Anemia in Patients With Pretransplantation Cytogenetic Abnormalities, Myelodysplastic Syndrome, or Acute Leukemia

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ABSTRACT

Purpose

Allogeneic hematopoietic cell transplantation (HCT) can cure bone marrow failure in patients with Fanconi anemia (FA). Data on outcomes in patients with pretransplantation cytogenetic abnormalities, myelodysplastic syndrome (MDS), or acute leukemia have not been separately analyzed.

Patients and Methods

We analyzed data on 113 patients with FA with cytogenetic abnormalities ($n = 54$), MDS ($n = 45$), or acute leukemia ($n = 14$) who were reported to the Center for International Blood and Marrow Transplant Research from 1985 to 2007.

Results

Neutrophil recovery occurred in 78% and 85% of patients at days 28 and 100, respectively. Day 100 cumulative incidences of acute graft-versus-host disease grades B to D and C to D were 26% (95% CI, 19% to 35%) and 12% (95% CI, 7% to 19%), respectively. Survival probabilities at 1, 3, and 5 years were 64% (95% CI, 55% to 73%), 58% (95% CI, 48% to 67%), and 55% (95% CI, 45% to 64%), respectively. In univariate analysis, younger age was associated with superior 5-year survival ($\leq v > 14$ years: 69% [95% CI, 57% to 80%] v 39% [95% CI, 26% to 53%], respectively; $P = .001$). In transplantations from HLA-matched related donors ($n = 82$), younger patients ($\leq v > 14$ years: 78% [95% CI, 64% to 90%] v 34% [95% CI, 20% to 50%], respectively; $P < .001$) and patients with cytogenetic abnormalities only versus MDS/acute leukemia (67% [95% CI, 52% to 81%] v 43% [95% CI, 27% to 59%], respectively; $P = .03$) had superior 5-year survival.

Conclusion

Our analysis indicates that long-term survival for patients with FA with cytogenetic abnormalities, MDS, or acute leukemia is achievable. Younger patients and recipients of HLA-matched related donor transplantations who have cytogenetic abnormalities only have the best survival.

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INTRODUCTION

Hematopoietic progenitor cells in Fanconi anemia (FA) are genetically unstable, leading to increased apoptosis and eventually to bone marrow failure,^{1,2} which is the main life-threatening problem in these patients.³⁻⁵ This defect also predisposes to an increased frequency of clonal cytogenetic abnormalities, myelodysplastic syndrome (MDS), and acute leukemia.⁵⁻¹² Development of any of these conditions is associated with poorer survival.¹²⁻¹⁵

Allogeneic hematopoietic cell transplantation (HCT) is the only curative modality for bone marrow failure in patients with FA. Excellent outcomes have been reported in recipients of HLA-matched related donor transplantations.¹⁶⁻¹⁹ Outcomes after HCT in patients with FA who have pretransplantation cytogenetic abnormalities, MDS, or acute leukemia are less certain.^{16,20-28}

We analyzed data from the Center for International Blood and Marrow Transplant Research (CIBMTR) to determine survival of patients with FA with cytogenetic abnormalities only, MDS, or acute

leukemia after HCT. Cumulative incidences of acute and chronic graft-versus-host disease (GVHD) and primary and secondary graft failure were evaluated.

PATIENTS AND METHODS

Database

The CIBMTR is a combined research program of the Medical College of Wisconsin and the National Marrow Donor Program. CIBMTR comprises a voluntary network of more than 450 transplantation centers worldwide that contribute detailed data on consecutive allogeneic and autologous HCT to a centralized Statistical Center. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected health information used in the performance of such research is collected and maintained in CIBMTR's capacity as a public health authority under the Health Insurance Portability and Accountability Act Privacy Rule. Additional details regarding the data source are described elsewhere.²⁹

Patients

Review of CIBMTR data from 1985 to 2007 identified 113 patients with FA and cytogenetic abnormalities, MDS, or acute leukemia before HCT. CIBMTR data were recorded as provided by the reporting centers; there was no central review of the cytogenetic abnormalities, MDS, or leukemia diagnoses.

End Points and Definitions

The primary outcome studied was survival. Patients were classified according to the presence of cytogenetic abnormalities, MDS, or acute leukemia, as reported by the transplantation center. Patients with cytogenetic abnormalities as well as MDS or acute leukemia were classified as MDS or acute leukemia, respectively.

Patients were considered to have an event at time of death from any cause; survivors were censored at last contact. Time to engraftment was calculated as the interval from transplantation to the first of 3 consecutive days with an absolute neutrophil count (ANC) of $\geq 500/\mu\text{L}$. Primary graft failure was defined as failure to achieve an ANC of $\geq 500/\mu\text{L}$ after HCT, and secondary graft failure was defined as sustained loss of ANC ($< 500/\mu\text{L}$) after initial recovery. Acute GVHD was graded using the International Bone Marrow Transplant Registry Severity Index.³⁰ Chronic GVHD was diagnosed using published criteria.³¹ Death without the event was considered a competing event for engraftment and GVHD.

Statistical Analyses

Probability of survival was calculated using the Kaplan-Meier method, with the variance estimated by the Greenwood formula. Engraftment incidence and the cumulative incidences of secondary graft failure and acute and chronic GVHD were estimated using the cumulative incidence function to accommodate for competing risks.³²

Proportions were compared using the χ^2 test, and continuous variables were compared using the Wilcoxon rank sum test. Univariate analysis of the correlation between 5-year survival and proposed prognostic factors was conducted. These factors include conditioning regimen, type of clonal disease before transplantation (cytogenetic abnormalities only, MDS, or acute leukemia), year of transplantation (before 2000 v in or after 2000), donor type,³³ and age at transplantation (the study population was divided into two groups based on the median age). Five-year survival probabilities were compared using the pointwise test. Survival curves were compared using the log-rank test. The association between acute and chronic GVHD and overall survival was examined in a univariate analysis. In this latter analysis, acute and chronic GVHD were entered in the model as time-dependent covariates.

Multivariate analysis was not feasible because of small sample size. SAS software, version 9.1 (SAS Institute, Cary, NC), was used in all analyses.

RESULTS

Patient characteristics are listed in Table 1. One hundred thirteen patients were reported from 46 centers worldwide. Fifty-four patients (48%) had cytogenetic abnormalities only, 45 (40%) had MDS, and 14 (12%) had acute leukemia. Patients in the cytogenetic abnormalities group were further classified as follows: complex abnormalities ($\geq$ three distinct abnormalities; $n = 18$); chromosome 1 abnormalities ($n = 8$); chromosome 3 abnormalities ($n = 1$); chromosome 5 abnormalities ($n = 3$); chromosome 7 abnormalities ($n = 4$); and other noncomplex abnormalities ($n = 20$). Twelve patients had acute myeloid leukemia (AML), and two patients had acute lymphoblastic leukemia (ALL). Data on pre-HCT chemotherapy for these patients were available in only seven patients; six patients (four with AML and two with ALL) received chemotherapy before HCT, and one patient with AML never received any chemotherapy before conditioning. Median age at transplantation was 14 years (range, 1 to 57 years); median age was 15 years for those with leukemia/MDS and 13 years for those with cytogenetic abnormalities. Fifty-three patients (47%) were male. The median follow-up of survivors was 84 months (range, 3 to 253 months).

Eighty-five patients (75%) received marrow stem cells (73 related and 12 unrelated), 13 patients received peripheral-blood stem cells (nine related and four unrelated), and 15 patients received umbilical cord blood grafts (two related and 13 unrelated).

Sixty-seven patients (60%) received radiation-based regimens. Forty-eight patients (42%) received total-body irradiation, and 19 patients (17%) received radiation as either total lymphoid irradiation or thoracoabdominal irradiation. Radiation dose ranged from 4 to 14 Gy, although the latter dose could not be verified. Thirty-one patients (27%) received fludarabine in their conditioning regimen, including 16 patients who received radiation-based conditioning. Antithymocyte globulin was given to 56 patients (50%). Most patients (80%) received cyclosporine-based GVHD prophylaxis (Table 1).

At the time of transplantation, three of 12 patients with AML were in first complete remission, one patient was in second complete remission, and four patients never achieved remission (one patient never received chemotherapy before HCT, whereas data on pre-HCT chemotherapy were missing for the remaining three patients). Data on the remission status of the remaining four patients were missing (data on pre-HCT chemotherapy were missing for all four cases). One patient with ALL was in first complete remission, and one patient never achieved remission. Classification of 31 patients with MDS was based on the French-American-British classification. Seventeen patients had early MDS (refractory anemia or refractory anemia with ringed sideroblasts), and 14 patients had advanced MDS (refractory anemia with excess blasts or refractory anemia with excess blasts in transformation).

Engraftment and GVHD

Seventy-eight percent of patients had neutrophil recovery by day 28 (95% CI, 70% to 85%) and 85% (95% CI, 78% to 91%) by day 100 (Appendix Table A1, online only). Cumulative incidence of secondary graft failure at 2 years after engraftment was 9% (95% CI, 4% to 15%; Appendix Table A2, online only). The small numbers of patients precluded detection of any correlation of graft failure with the studied variables (Appendix Tables A3 and A4, online only).

Table 1. Characteristics of 113 Patients Who Underwent Allogeneic HCT for Fanconi Anemia With Clonal Hematopoiesis From 1985 to 2007 Based on Clonal Disease Type

Variable	MDS		Acute Leukemia*		Cytogenetic Abnormalities	
	No. of Patients (n = 45)	%	No. of Patients (n = 14)	%	No. of Patients (n = 54)	%
Patient related						
Age, years						
Median	15		18		13	
Range	2-57		1-44		5-31	
Sex						
Male	19	42	5	36	29	54
Female	26	58	9	64	25	46
KPS						
< 90	16	36	5	36	11	20
≥ 90	28	62	9	64	43	80
Missing	1	2	0	0	0	0
Disease related						
Chromosomal aberrations in cytogenetic abnormalities group						
Complex abnormalities	—		—		18	33
Chromosome 1 abnormalities	—		—		8	15
Chromosome 3 abnormalities	—		—		1	2
Chromosome 5 abnormalities	—		—		3	6
Chromosome 7 abnormalities	—		—		4	7
Other	—		—		20	37
Transplantation related						
Donor age, years						
Median	24		35		18	
Range	<1-76		1-52		1-58	
Graft source						
Bone marrow	34	76	11	79	40	74
Peripheral blood	6	13	2	14	5	9
Umbilical cord blood	5	11	1	7	9	17
Conditioning regimen						
Radiation-based conditioning	32	71	8	57	27	50
Chemotherapy-based conditioning	13	29	6	43	27	50
Donor type						
Related	34	76	10	71	38	70
Unrelated	6	13	3	21	7	13
Umbilical cords	5	11	1	7	9	17
HLA matching						
HLA-identical sibling	26	58	7	50	30	56
Other related	7	16	3	21	5	9
Related unknown	1	2	0		3	6
URD well matched	3	7	1	7	1	2
URD partially matched	1	2	2	14	1	2
URD mismatched	1	2	0	0	3	6
URD TBD and unknown	1	2	0	0	2	4
Cord-sibling 6/6	1	2	0	0	1	2
Cord-unrelated 6/6	1	2	0	0	0	
Cord-unrelated 5/6	2	4	1	7	4	7
Cord-unrelated 4/6	1	2	0	0	3	6
Cord missing	0	0	0	0	1	2
GVHD prophylaxis						
Missing	0		0		1	2
T-cell depletion	8	18	2	14	6	11
FK506 + MTX + other	1	2	0	0	0	0
FK506 + other	0	0	1	7	1	2
CsA + MTX + other	16	36	6	43	21	39
CsA + other	20	44	4	29	24	44
Other†	0	0	1	7	1	2

(continued on following page)

Table 1. Characteristics of 113 Patients Who Underwent Allogeneic HCT for Fanconi Anemia With Clonal Hematopoiesis From 1985 to 2007 Based on Clonal Disease Type (continued)

Variable	MDS		Acute Leukemia*		Cytogenetic Abnormalities	
	No. of Patients (n = 45)	%	No. of Patients (n = 14)	%	No. of Patients (n = 54)	%
Year of HCT						
1985-1994	13	29	6		13	24
1995-1999	8	18	2		8	15
2000-2007	24	53	6		33	61
ATG use, yes	27	60	5	36	24	44
Follow-up of survivors, months						
Median	87		112		82	
Range	3.4-157		43-150		3-253	

NOTE. The completeness index follow-up at 1, 3, and 5 years is 96%, 93%, and 85%, respectively.

Abbreviations: ATG, antithymocyte globulin; CsA, cyclosporine; FK506, tacrolimus; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; KPS, Karnofsky performance score; MDS, myelodysplastic syndrome; MTX, methotrexate; URD, unrelated donor.

*Acute myeloid leukemia status before conditioning: primary induction failure (n = 4); first complete remission (n = 3); second complete remission (n = 1); and unknown (n = 4). Acute lymphoblastic leukemia status before conditioning: primary induction failure (n = 1) and first complete remission (n = 1).

†One patient is reported to have received MTX only; one patient is reported to have received MTX and corticosteroids.

Cumulative incidences of acute GVHD grades B to D and C to D at day 100 were 26% (95% CI, 19% to 35%) and 12% (95% CI, 7% to 19%), respectively. Cumulative incidences of chronic GVHD were 20% (95% CI, 13% to 29%), 23% (95% CI, 15% to 32%), and 23% (95% CI, 15% to 32%) at 1, 3, and 5 years, respectively. Nine patients developed limited chronic GVHD, and 12 patients developed extensive chronic GVHD (Table 2).

Survival

Survival probabilities at 1, 3, and 5 years were 64% (95% CI, 55% to 73%), 58% (95% CI, 48% to 67%), and 55% (95% CI, 45% to

64%), respectively (Table 2 and Figs 1 and 2). In univariate analysis, age at transplantation significantly correlated with 5-year survival ($\leq v > 14$ years: 69% [95% CI, 57% to 80%] v 39% [95% CI, 26% to 53%], respectively; $P = .001$; Table 3). Exclusion of patients with chromosome 1 abnormalities from the cytogenetic abnormalities group (which in some previous reports has not impacted outcome)¹⁵ did not change the results (data not shown). Additionally, the development of acute and chronic GVHD was associated with increased overall mortality; the univariate hazard ratio was 1.95 (95% CI, 1.10 to 3.44; $P = .02$) for grades B to D acute GVHD and 2.79 for chronic GVHD (95% CI, 1.23 to 6.34; $P = .01$).

In the cohort of recipients of HLA-matched related donor transplantations (n = 82), patients with cytogenetic abnormalities alone had better 5-year survival than did patients with MDS or acute leukemia (67% [95% CI, 52% to 81%] v 43% [95% CI, 27% to 59%], respectively; $P = .03$; Fig 3). A similar analysis for the unrelated donor recipients could not be carried out because of the small patient numbers. Younger age was also associated with significantly better 5-year survival in the related cohort ($\leq v > 14$ years: 78% [95% CI, 64% to 90%] v 34% [95% CI, 20% to 50%], respectively; $P < .001$).

Table 2. Engraftment, Acute and Chronic GVHD, and Survival			
Outcome	No. of Evaluable Patients	Probability (%)	95% CI (%)
ANC recovery	113		
At 28 days		78	70 to 85
At 100 days		85	78 to 91
Platelet recovery	102		
At 60 days		80	71 to 87
At 100 days		83	75 to 90
Secondary graft failure*	95		
At 2 years		9	4 to 15
At 3 years		9	4 to 15
Acute GVHD at 100 days	113		
Grades B to D		26	19 to 35
Grades C and D		12	7 to 19
Chronic GVHD	103		
At 1 year		20	13 to 29
At 3 years		23	15 to 32
At 5 years		23	15 to 32
Survival	113		
At 1 year		64	55 to 73
At 3 years		58	48 to 67
At 5 years		55	45 to 64

Abbreviations: ANC, absolute neutrophil count; GVHD, graft-versus-host disease.

*To be at risk, patients achieved successful engraftment initially; time to event was computed from date of ANC recovery.

Fig 1. Survival of all patients with Fanconi anemia with evidence of cytogenetic abnormalities, myelodysplastic syndrome, or leukemia at hematopoietic cell transplantation.

Fig 2. Survival of patients with Fanconi anemia according to the presence of cytogenetic abnormalities, myelodysplastic syndrome (MDS), or leukemia at hematopoietic cell transplantation.

Data on remission status after HCT for patients with leukemia were only available on five of the 14 patients (two of the five patients had experienced relapse and died after HCT). The most common cause of death in the entire cohort was infection (18%), followed by organ failure (13%).

DISCUSSION

The underlying genomic instability that characterizes FA cells promotes the evolution of abnormal hematopoietic cell clones; this, in time, may lead to the development of clonal cytogenetic abnormalities, MDS, and acute leukemia. The most frequently reported chromosomal abnormalities involve gains or deletions of 1q, 3q, 5q, or monosomy 7. Additional complex and noncomplex abnormalities have been reported.^{7,13,14} The biologic significance of the cytogenetic abnormalities has been unclear because of reports of cytogenetic fluctuation.^{7,34,35}

In patients without FA, MDS is a substantially heterogeneous disease, clinically and biologically, and it mostly affects older individuals,^{36,37} whereas in patients with FA, MDS and AML occur with the highest frequency during adolescence.³ However, diagnosing MDS in the bone marrow of patients with FA can be particularly challenging, because patients with FA may have dysplastic bone marrow morphology, which may be confused with MDS, and thus, the lack of central review is considered a major limitation in this multicenter study. Furthermore, the relationship between morphologic MDS and clonal cytogenetics is not well defined, although there is evidence that the development of cytogenetic aberrations is an adverse prognostic factor and may predict MDS/AML development and that some cytogenetic aberrations are more deleterious than others. Tonnie et al¹² reported that in a cohort of 25 patients with FA, those with 3q aberrations (18 patients) had an increased risk of MDS and AML development compared with those without the aberrations. Mehta et al¹⁵ also reported that chromosome 3 and 7 aberrations, but not gain of 1q alone, were associated with increased risk of developing MDS/AML. However, patients with FA with evidence of MDS are more likely to have cytogenetic abnormalities. In a cohort of 23 patients with FA and MDS, 20 had concomitant cytogenetic abnormalities,

Table 3. Univariate Analysis of Association of Prognostic Factors With 5-Year Overall Survival

Variable	No. of Evaluable Patients	5-Year Overall Survival (%) [*]	95% CI (%)	P†
Clonal disease prior to HCT				.27
Acute leukemia	14	36	14 to 62	
MDS	45	57	41 to 72	
Abnormal cytogenetics	54	58	45 to 71	
Clonal disease before HCT (related donor subgroup)				.03
Acute leukemia/MDS	44	43	28 to 59	
Abnormal cytogenetics	38	67	52 to 81	
Patient age at transplantation, years				.001
≤ 14	59	69	57 to 80	
> 14	54	39	26 to 53	
Patient age at transplantation, years (related donor subgroup)				< .001
≤ 14	20	85	66 to 97	
> 14	62	45	32 to 58	
Type of clonal disease stratified by age				.01
Acute leukemia and MDS, age ≤ 14 years	26	69	50 to 85	
Acute leukemia and MDS, age > 14 years	33	38	21 to 56	
Abnormal karyotype, age ≤ 14 years	33	69	52 to 83	
Abnormal karyotype, age > 14 years	21	41	21 to 63	
Fludarabine-based conditioning				.72
No	82	54	43 to 64	
Yes	31	58	38 to 76	
Radiation-based conditioning				.43
No	46	50	33 to 65	
Yes	67	57	45 to 69	
Year of transplantation stratified by donor type				.56
Before year 2000 (related donors)	41	47	31 to 62	
Before year 2000 (unrelated donors)	8	62	29 to 90	
In or after year 2000 (related donors)	43	62	46 to 77	
In or after year 2000 (unrelated donors)	20	55	33 to 76	

Abbreviations: HCT, hematopoietic cell transplantation; MDS, myelodysplastic syndrome.

^{*}Survival was calculated using the Kaplan-Meier product-limit estimate.

†Pointwise test.

and on follow-up, no patients demonstrated loss of any clones identified at initial presentation.¹⁴

Allogeneic HCT is the only curative modality for the bone marrow manifestations in patients with FA. HLA-matched related donor transplantations have been associated with an excellent outcome, with long-term overall survival of 80% to 85% in some studies.^{16,18,38-42} The outcomes of alternative donor transplantations have been less satisfactory, but the results have improved in recent years. The use of fludarabine-based protocols seems to have dramatically increased overall survival and lowered graft rejection rates.^{16,18,42-44}

Fig 3. Survival of patients with Fanconi anemia after related donor hematopoietic cell transplantation (HCT; n = 82) according to the presence of only clonal abnormalities, myelodysplastic syndrome (MDS), or acute leukemia before HCT.

Allogeneic HCT is also considered the only curative modality for MDS in patients without FA, but because MDS most commonly affects older individuals, the transplantation decision and outcome are influenced by the comorbid medical problems of the patients.⁴⁵⁻⁴⁷ Furthermore, there are currently multiple novel agents offering significant palliation for MDS in patients without FA who are not HCT candidates.⁴⁸⁻⁵⁰

Data on post-HCT outcomes for patients with FA with pretransplantation cytogenetic abnormalities, MDS, or acute leukemia are limited. Most investigators include these patients in HCT studies of the general FA population. Furthermore, the follow-up period for most studies is short. Available data, however, do suggest favorable outcome. Socié et al²⁰ reported five patients with FA and MDS (two also had abnormal cytogenetics) who were conditioned with cyclophosphamide (CY) and thoracoabdominal irradiation, four of whom are alive at 8 years. Ayas et al²¹ reported on 11 such patients (two with MDS with no cytogenetic abnormalities, eight with MDS and cytogenetic abnormalities, and one with AML with monosomy 7); 10 of 11 patients were alive without disease progression at a median follow-up of 46 months after HCT after conditioning with CY, antithymocyte globulin, and total-body irradiation. Bitan et al²⁶ reported survival with no active disease of three patients with FA and MDS (no cytogenetics reported) at 45, 50, and 96 months after HCT; patients were conditioned with CY, fludarabine, and antithymocyte globulin (one had graft failure and received salvage treatment with a second HCT).

The current study demonstrates that long-term survival is achievable in patients with FA and cytogenetic abnormalities, MDS, or acute leukemia after HCT and that younger age is associated with better outcome, even in patients with acute leukemia (Table 3). In our study, related donor HCT recipients had primary and secondary graft failure rates that are within the ranges previously reported in the general FA population.^{41-44,51} Because of small numbers, we cannot draw definitive conclusions on engraftment rates among unrelated donor and cord blood HCT recipients.

Our study demonstrates that, among matched related donor HCT recipients, patients with FA who only have cytogenetic abnormalities have better survival than patients who have MDS or leukemia (Fig 3). This observation is consistent with a report by

Alter et al¹³ on 41 patients with FA with cytogenetic abnormalities, MDS, or both. The presence of MDS had an adverse impact on survival, with an estimated 5-year survival of 9%, compared with 92% for patients who had not developed MDS. Cytogenetic abnormalities had a lesser impact and were associated with an estimated 5-year survival of 40% compared to 94% in patients without cytogenetic abnormalities. However, that study did not address the impact of HCT on survival among those patients.¹³

Although patients with FA fare better with low-intensity conditioning,^{17,24,39,40} earlier studies suggested that the presence of cytogenetic abnormalities, MDS, or leukemia required more intensive conditioning.^{16,21} In our analysis, however, the use of radiation therapy did not improve outcome. In a previous CIBMTR study, Pasquini et al⁴¹ similarly concluded that the use of radiation was not associated with improved outcomes in patients with FA. This is particularly pertinent in this patient population where radiation has been implicated in the development of new cancers after transplantation.^{11,19,52,53} In addition, the use of fludarabine, which has been suggested to improve HCT outcome for patients with FA in matched related and unrelated HCT,^{18,42-44,54,55} was not associated with a survival advantage in our study. However, these results should be interpreted with caution given the small sample size.

Despite its limitations, this is the largest study of transplantation outcomes in patients with FA and cytogenetic abnormalities, MDS, or leukemia. The data indicate that HCT can lead to long-term survival among these patients. Younger patients and recipients of HLA-matched related donor HCT who have cytogenetic abnormalities only have better long-term survival.

However, even with these encouraging results, the superior results of HCT in patients with FA without pretransplantation cytogenetic abnormalities, MDS, or leukemia suggest that the optimal timing of HCT in patients with FA should be when signs of bone marrow failure develop (eg, need for blood products support) and before the development of any cytogenetic abnormalities, MDS, or leukemia.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Appendix**Table A1.** Cumulative Incidence of 100-Day Neutrophil Recovery (considering death as a competing risk)

Donor Type	No. of Patients	Incidence (%)	95% CI (%)
Related donor recipients	82	90	82 to 96
Unrelated donor/cords recipients*	31	74	57 to 88

*Lumped together because of small numbers in each group.

Table A2. Two-Year (after initial neutrophil recovery) Cumulative Incidence of Secondary Graft Failure (considering death as a competing risk)

Donor Type	No. of Patients	Incidence (%)	95% CI (%)
Related donor recipients	73	7	2 to 14
Unrelated donor recipients	13	23	5 to 49
Cords recipients		0	

Table A3. Characteristics of Patients Who Developed Primary Graft Failure

Characteristic	Successful Engraftment		Primary Graft Failure	
	No. of Patients	%	No. of Patients	%
Disease				
MDS	34	40	7	41
AML	9	11	2	12
ALL	2	2	0	0
Abnormal cytogenetics only	39	46	8	47
Donor type				
Related	65	77	9	53
Unrelated	10	12	2	12
Umbilical cords	9	11	6	35
Fludarabine-based conditioning				
No	60	71	11	65
Yes	24	29	6	35
ATG				
No	46	55	8	47
Yes	38	45	9	53

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ATG, antithymocyte globulin; MDS, myelodysplastic syndrome.

Table A4. Characteristics of Patients Who Developed Secondary Graft Failure

Variable	Successful Engraftment		Secondary Graft Failure	
	No. of Patients	%	No. of Patients	%
Disease				
MDS	34	40	4	36
AML	9	11	1	9
ALL	2	2	0	0
Abnormal cytogenetics only	39	46	6	54
Donor type				
Related	65	77	8	73
Unrelated	10	12	3	27
Umbilical cords	9	11	0	0
Fludarabine				
No	60	71	10	91
Yes	24	29	1	9
ATG				
No	46	55	7	64
Yes	38	45	4	36

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ATG, antithymocyte globulin; MDS, myelodysplastic syndrome.