OUTCOME OF CORD-BLOOD TRANSPLANTATION FROM RELATED AND UNRELATED DONORS

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ABSTRACT

Background Cord-blood banks have increased the use of cord-blood transplantation in patients with hematologic disorders. We have established a registry containing information on the outcome of cord-blood transplantation.

Methods We sent questionnaires to 45 transplantation centers for information on patients receiving cord-blood transplants from 1988 to 1996. Reports on 143 transplantations, performed at 45 centers, were studied, and the responses were analyzed separately according to whether the donor was related or unrelated to the recipient.

Results Among 78 recipients of cord blood from related donors, the Kaplan–Meier estimate of survival at one year was 63 percent. Younger age, lower weight, transplants from HLA-identical donors, and cytomegalovirus-negative serologic results in the recipient were favorable prognostic factors. Graft-versus-host disease of at least grade II occurred at estimated rates of 9 percent in 60 recipients of HLA-matched cord blood and 50 percent in 18 recipients of HLA-mismatched cord blood. Neutrophil engraftment was associated with an age of less than six years ($P=0.02$) and a weight of less than 20 kg ($P=0.02$), and it occurred in 85 percent of patients receiving 37 million or more nucleated cells per kilogram of body weight. Among 65 patients who received cord blood from unrelated donors, the Kaplan–Meier estimate of survival at one year was 29 percent. Cytomegalovirus-negative serologic status in these recipients was associated with improved survival ($P=0.03$) and was the most important predictor of graft-versus-host disease ($P=0.04$). Neutrophil recovery occurred in 94 percent of the patients who received 37 million or more nucleated cells per kilogram from unrelated donors.

Conclusions Cord blood is a feasible alternative source of hematopoietic stem cells for pediatric and some adult patients with major hematologic disorders, particularly if the donor and the recipient are related. (N Engl J Med 1997;337:373-81.)

SINCE the first successful transplantation of umbilical-cord blood in a patient with Fanconi's anemia,[1] cord blood has been used as a source of hematopoietic stem cells for transplantation to treat a variety of malignant and nonmalignant hematologic disorders.[2-4] Cord-blood banks have developed worldwide.[5-9] Eurocord, a group of physicians, was organized to standardize methods of collecting, testing, and cryopreserving cord blood from both related and unrelated donors; to study the properties of cord-blood cells; and to manage a registry of cord-blood transplantation performed in Europe.[10] We analyzed 143 cord-blood transplantations performed from October 1, 1988, through December 31, 1996, at 45 centers.

METHODS

Data Collection and Characteristics of Patients

Using the data bases of the European Blood and Marrow Transplantation Group and the French Society of Bone Marrow Transplantation, we invited centers that had reported performing cord-blood transplantation to join Eurocord. In addition, nine non-European centers volunteered to enter the study (see the Appendix). Overall, 45 centers reported from 1 to 22 cases each. Questions about the disease and the outcome of transplantation were already included in the questionnaire of the European Blood and Marrow Transplantation Group; questions concerning the origin of the cord blood, its processing, the number of cells collected and infused, HLA typing, and hematologic reconstitution were added by Eurocord. A clinical coordinator verified the accuracy of the data provided by the centers. Of 148 transplantations reported before December 31, 1996, 5 were excluded from the study because the patients had received bone marrow in addition to cord blood. Seventy-eight patients received cord blood from a related donor, and 65 received cord blood from an unrelated donor. These two groups were analyzed separately with respect to all study end points.

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Conditioning and Prophylaxis against Graft-versus-Host Disease

The conditioning regimens varied according to the patient's diagnosis, previous treatment, and disease status. Patients who received a cord-blood transplant from an HLA-identical sibling had the conditioning ordinarily given before bone marrow transplantation. Total-body irradiation combined with cyclophosphamide or other chemotherapy was used in 60 patients; busulfan was used instead of total-body irradiation in 40 patients (mean age, 4 years; range, 0.2 to 11) who received cord blood from a related donor and in 24 patients (mean age, 8 years; range, 0.3 to 28) who received cord blood from an unrelated donor. In 49 patients receiving an HLA-mismatched transplant, antithymocyte globulin or a monoclonal anti–T-cell antibody was given before transplantation. Cyclosporine, alone or combined with prednisone or methotrexate, was given as prophylaxis against graft-versus-host disease (GVHD). Established GVHD was usually treated with prednisone. Granulocyte colony-stimulating factor (G-CSF) or granulocyte–macrophage colony-stimulating factor (GM-CSF) was given to 104 patients (73 percent) after transplantation, at various times and in various doses.

Characteristics of Infused Cord Blood

The methods of collecting, cryopreserving, storing, and thawing cord blood varied among the centers. Usually, whole blood was cryopreserved in 10 percent dimethyl sulfoxide and thawed according to the method used at the cord-blood bank in New York.[6,7] Cord blood was provided from cord-blood banks in New York (47 cases), Milan, Italy (14), Paris (11), Dusseldorf, Germany (6), and the vicinity of the center (65). The median volume collected was 99 ml (range, 37 to 360), the median number of nucleated cells was 1.08 billion (range, 130 million to 5.8 billion), the median number of CD34+ cells (in 31 cases) was 3.8 million (range, 0.02 million to 38 million), and the median number of granulocyte–macrophage colony-forming units (CFU-GM) (in 83 cases) was 440,000 (range, 1000 to 29.8 million). The properties of the cord blood collected from the related and the unrelated donors were similar. The median number of nucleated cells infused after thawing was 37 million per kilogram of body weight (range, 7 million to 300 million), the median number of CD34+ cells (in 67 cases) was 200,000 per kilogram (range, 0 to 4.5 million), and the median number of CFU-GM infused (in 104 cases) was 24,000 per kilogram (range, 0 to 2.2 million). HLA typing was performed by serologic testing in the case of class I HLA-A and HLA-B antigens and by low-resolution generic oligotyping in the case of DRB1. Among the 78 cord-blood transplantations from related donors, there were no mismatches in 60 (the donor was an HLA-identical sibling) and there were mismatches of one HLA antigen in 3, two antigens in 5, three antigens in 9, and four antigens in 1. Among the 65 transplantations from unrelated donors, there were no mismatches in 9, one mismatch in 43, two mismatches in 11, and three mismatches in 2.

End Points

Surrogate end points indicating engraftment were the times from transplantation to the recovery of neutrophil and platelet counts. Recovery of neutrophils was defined as the time needed to reach an absolute neutrophil count of at least 500 per cubic millimeter on three consecutive days. Failure of engraftment was defined by the absence of detectable engraftment at day 60, a second transplantation, or hematopoietic reconstitution with autologous cells (that is, the reappearance of cells with markers bearing the recipient's sex, ABO type, or HLA-antigen status). Platelet recovery was defined as the time needed to reach a sustained platelet count of at least 20,000 per cubic millimeter in the absence of platelet transfusions. Graft rejection was defined as engraftment followed by pancytopenia or GVHD without signs of myeloid engraftment. Data on patients in whom no engraftment occurred were censored if the patient died before day 60. Acute GVHD was scored on the basis of standard criteria.[11] Grades 0 and I GVHD were not counted as acute GVHD. In patients surviving more than 100 days, cases of GVHD were defined as chronic and coded as either limited or extensive.[12] Relapses, complications, and causes of death were also reported.

Statistical Analysis

Our findings are presented as of January 1, 1997, with regard to overall survival, and as of March 31, 1997, with regard to engraftment and GVHD. All data on the time to failure were calculated from the date of cord-blood transplantation to the date of the event (engraftment, acute GVHD, or death) and were estimated by the Kaplan–Meier method. The prognostic significance of base-line covariates was studied by two-sided log-rank tests. All variables found to have a P value of less than 0.10 by that test were included as binary covariates in a Cox proportional-hazards model, with the use of a stepwise procedure with a type I error of 0.05. Relative risks for the association between covariates and events were estimated with 95 percent confidence intervals. SAS software (SAS Institute, Cary, N.C.) was used.

RESULTS

Characteristics of the Patients

Table 1 shows the characteristics of the patients before transplantation. Of the 78 related donors of cord blood, 76 were siblings of the recipient, 1 was a cousin, and 1 was a child donating cord blood to the mother. Of the 143 recipients, 95 received transplants to treat hematologic cancers, 26 had a bone marrow failure syndrome, 8 had hemoglobinopathy, and 14 had some other type of genetic disease. Of 62 patients with acute leukemia, 37 received transplants during a first or second complete remission and 25 were in a more advanced stage; 10 had previously received a bone marrow transplant (autologous in 9 and allogeneic in 1).

Overall Results

The overall survival at one year for all 143 patients was 49 percent (Kaplan–Meier estimate) (Table 2). For recipients of cord blood from related donors, one-year survival was 63 percent, and for recipients of cord blood from unrelated donors, it was 29 percent ($P<0.001$ by the log-rank test) (Fig. 1A). In all 143 patients, variables associated with better survival were an age of less than six years ($P<0.001$ by the log-rank test), weight of less than 20 kg ($P<0.001$), infusion of at least 37 million nucleated cells per kilogram ($P=0.04$), HLA identity with the donor ($P<0.001$), and cytomegalovirus-negative serologic status in the recipient ($P<0.001$). Because the outcomes in recipients of cord blood differed considerably according to whether the donor was related or unrelated, we decided to analyze the two types of transplantations separately.

Survival

Among recipients of cord blood from related donors, overall survival at one year was 63 percent (Kaplan–Meier estimate) (Table 2), and the median duration of follow-up was 29 months (range,

1 month to 8 years). Overall survival at one year was 73 percent in recipients of HLA-matched cord blood and 33 percent in recipients of cord blood mismatched for one or more HLA antigens ($P=0.006$). Variables associated with better survival were an age of less than six years, weight of less than 20 kg, cytomegalovirus-negative serologic status in the recipient, and HLA identity with the donor (Table 2). From the Cox model we found that the most favorable factors for survival were weight of less than 20 kg (relative risk, 0.24; 95 percent confidence interval, 0.11 to 0.52; $P<0.001$) and cytomegalovirus-negative serologic status in the recipient (relative risk, 0.41; 95 percent confidence interval, 0.18 to 0.90; $P=0.02$).

Among recipients of cord blood from unrelated donors, the Kaplan–Meier estimate of survival at 1 year was 29 percent, and the median duration of follow-up was 10 months (range, 1 to 30). The number of HLA mismatches between the donor and the recipient did not influence the survival rate, probably because we did not use high-resolution molecular typing for class I and class II antigens. As compared with cytomegalovirus-positive serologic status in the recipient, cytomegalovirus-negative status was associated with longer survival (median, 72 vs. 295 days; $P=0.03$). Patients who received less than 37 million nucleated cells per kilogram had 22 percent survival at one year, whereas those who received at least 37 million nucleated cells per kilogram had 41 percent survival at one year ($P=0.07$).

TABLE 1. CHARACTERISTICS OF THE PATIENTS RECEIVING CORD-BLOOD TRANSPLANTS.

CHARACTERISTIC	RELATED DONORS (N=78)	UNRELATED DONORS (N=65)	ALL PATIENTS (N=143)
Age (yr)			
Median	5	9	6
Range	0.2–20	0.3–45	0.2–45
Weight (kg)			
Median	19	30	20
Range	5–50	4–90	4–90
		no. of patients	
Cancer	46	49	95
Acute lymphoblastic leukemia	24	16	40
1st or 2nd complete remission	11	12	23
Advanced disease*	13	4	17
Acute myeloblastic leukemia	8	14	22
1st or 2nd complete remission	5	9	14
Advanced disease*	3	5	8
Myelodysplastic syndrome	4	6	10
Chronic myeloid leukemia	6	11	17
First chronic phase	3	5	8
Advanced disease†	3	6	9
Non-Hodgkin's lymphoma	2	2	4
Neuroblastoma	2	—	2
Bone marrow failure syndromes	17	9	26
Severe aplastic anemia	6	1	7
Fanconi's anemia	8	8	16
Dyskeratosis congenita	1	—	1
Blackfan–Diamond anemia	2	—	2
Hemoglobinopathy	8	—	8
Sickle cell	3	—	3
Thalassemia	5	—	5
Inborn errors	7‡	7§	14
ABO compatibility with donor¶			
Matched	55	20	75
Minor incompatibility	8	20	28
Major incompatibility	15	24	39

*Advanced disease was considered present if the patient had a third or subsequent remission, a relapse, or a partial response or had refractory leukemia at the time of the cord-blood transplantation.

†Advanced disease was considered present if the patient was in a second or subsequent chronic phase, an accelerated phase, or a blast crisis at the time of the cord-blood transplantation.

‡These patients had Hurler's syndrome (three patients), leukocyte adhesion deficiency (one), Günther's disease (one), bare-lymphocyte syndrome (one), and severe combined immunodeficiency (one).

§These patients had osteopetrosis (two patients), inherited neuronal ceroid lipofuscinosis (one), familial erythrophagocytic lymphohistiocytosis (one), adrenoleukodystrophy (one), Langerhans'-cell histiocytosis (one), and severe combined immunodeficiency (one).

¶Data were missing for one patient with an unrelated donor.

Engraftment

Among all 143 patients, the median time needed to reach an absolute neutrophil count of at least 500 per cubic millimeter was 30 days (range, 8 to 56), and to reach a platelet count of at least 20,000 per cubic millimeter the median time was 56 days (range, 9 to 180). The probability of an absolute neutrophil count of at least 500 per cubic millimeter by day 60 after transplantation was 79 percent in recipients of cord blood from related donors and 87 percent in recipients of cord blood from unrelated donors (Table 3 and Fig. 1B). For platelets, the respective probabilities were 62 percent and 39 percent (Table 4 and Fig. 1C).

Among the 78 patients who received cord blood from related donors, 46 had cancer. Data on four of these patients were censored, and in seven the cord blood did not engraft (three later received autologous bone marrow transplants, one had reconstitution of hematopoiesis with his own cells obtained before transplantation, and three died with aplastic bone marrow). Among the 17 patients with bone marrow failure syndrome, 3 had censored data and in 3 the cord blood did not engraft (2 received second transplants, and 1 had aplastic bone marrow at the time of death). Five of eight patients with Fanconi's anemia remained alive, with signs that the transplanted cord blood had engrafted. Among eight patients with hemoglobinopathy, four had engraftment and four did not (of the latter, two received a second bone marrow transplant and two patients had hematopoietic reconstitution with their own cells obtained before transplantation). Among the seven patients with inborn metabolic errors, there was en-

TABLE 2. FACTORS ASSOCIATED WITH SURVIVAL AFTER CORD-BLOOD TRANSPLANTATION.*

FACTOR	RELATED DONORS (N=78)				UNRELATED DONORS (N=65)				ALL PATIENTS (N=143)			
	NO. STUDIED	NO. OF DEATHS	SURVIVAL AT 1 YR (%)	P VALUE	NO. STUDIED	NO. OF DEATHS	SURVIVAL AT 1 YR (%)	P VALUE	NO. STUDIED	NO. OF DEATHS	SURVIVAL AT 1 YR (%)	P VALUE
Entire group	78	30	63		65	38	29		143	68	49	
Diagnosis				0.15				<0.001				0.07
Cancer	46	22	55		49	27	31		95	49	44	
Bone marrow failure syndrome	17	6	65		9	8	0		26	14	44	
Hemoglobinopathy	8	0	100		—	—	—		8	0	100	
Inborn error	7	2	69		7	3	57		14	5	63	
Age				<0.001				0.13				<0.001
<6 yr	45	9	83		27	16	35		72	25	65	
6–15 yr	30	19	36		18	9	40		48	28	37	
>15 yr	3	2	33		20	13	16		23	15	19	
Weight				<0.001				0.18				<0.001
<20 kg	40	7	82		24	13	38		64	20	66	
20–45 kg	35	21	57		21	13	29		56	34	39	
>45 kg	3	2	33		20	12	28		23	14	26	
No. of nucleated cells infused/kg				0.29				0.07				0.04
<37 million	38	16	57		36	23	22		74	39	42	
≥37 million	40	14	68		29	15	41		69	29	57	
No. of HLA mismatches												
0	60	18	73		9	5	0		69	23	67	
1	3	1	67		43	25	36		46	26	38	
2	5	2	60		11	6	34		16	8	40	
3	9	8	11		2	2	0		11	10	9	
4	1	1	0		—	—	—		1	1	0	
0	60	18	73	0.006	9	5	0	0.77	69	23	67	<0.001
≥1	18	12	33		56	33	33		74	45	32	
Recipient and donor are same sex†				0.07				0.99				0.16
Yes	41	12	73		30	17	29		71	29	57	
No	36	17	53		32	18	37		68	35	45	
Cytomegalovirus serologic status‡				0.002				0.03				<0.001
Negative	40	9	74		26	11	42		66	20	71	
Positive	36	20	42		39	27	20		75	47	31	

*The number of deaths was calculated over the entire study period. Percentages shown are Kaplan–Meier estimates at one year.

†Data on sex were missing for four pairs of patients (recipient and donor).

‡Data on cytomegalovirus serologic status were missing for two patients.

graftment in five, data on one were censored, and in one the transplant did not engraft.

Among the 65 recipients of cord blood from unrelated donors, 49 had cancer, 7 had censored data, and in 5 the cord blood did not engraft (3 received second transplants, 1 had reconstitution of his own hematopoietic cells, and 1 had graft rejection). Among the nine patients with bone marrow failure syndrome, four of eight with Fanconi's anemia had censored data, engraftment did not occur in one (who died after a second cord-blood transplantation), and one is alive. Of seven patients with inborn metabolic errors, two had censored data and the transplant failed to engraft in one.

The factors associated with engraftment (as judged on the basis of the absolute neutrophil count and the platelet count 60 days after cord-blood transplantation) are shown in Tables 3 and 4. In the entire group, neutrophil engraftment was associated with the infusion of at least 37 million nucleated cells per kilogram, as compared with less than 37 million nucleated cells per kilogram ($P=0.001$) (Table 3); platelet engraftment was associated with a weight of at least 20 kg in the recipient ($P=0.02$), and with HLA identity as compared with any HLA mismatch ($P<0.001$) (Table 4). Among the recipients of cord blood from related donors, neutrophil engraftment was influenced by age ($P=0.02$), weight ($P=0.02$), and the number of nucleated cells infused per kilogram ($P=0.06$). In the Cox proportional-hazards analysis, an age of less than six years was associated with a higher likelihood of reaching an absolute neutrophil count of more than 500 per cubic millimeter before day 60 (relative risk, 0.5; 95 percent confidence interval, 0.2 to 0.9; $P=0.008$). For platelet recovery, the most important factor was HLA identity between the donor and the recipient ($P<0.001$). Among the recipients of cord blood from unrelated donors, recovery of the absolute neutrophil count and platelet engraftment were also associated with a higher number of nucleated cells infused per kilogram and with HLA identity.

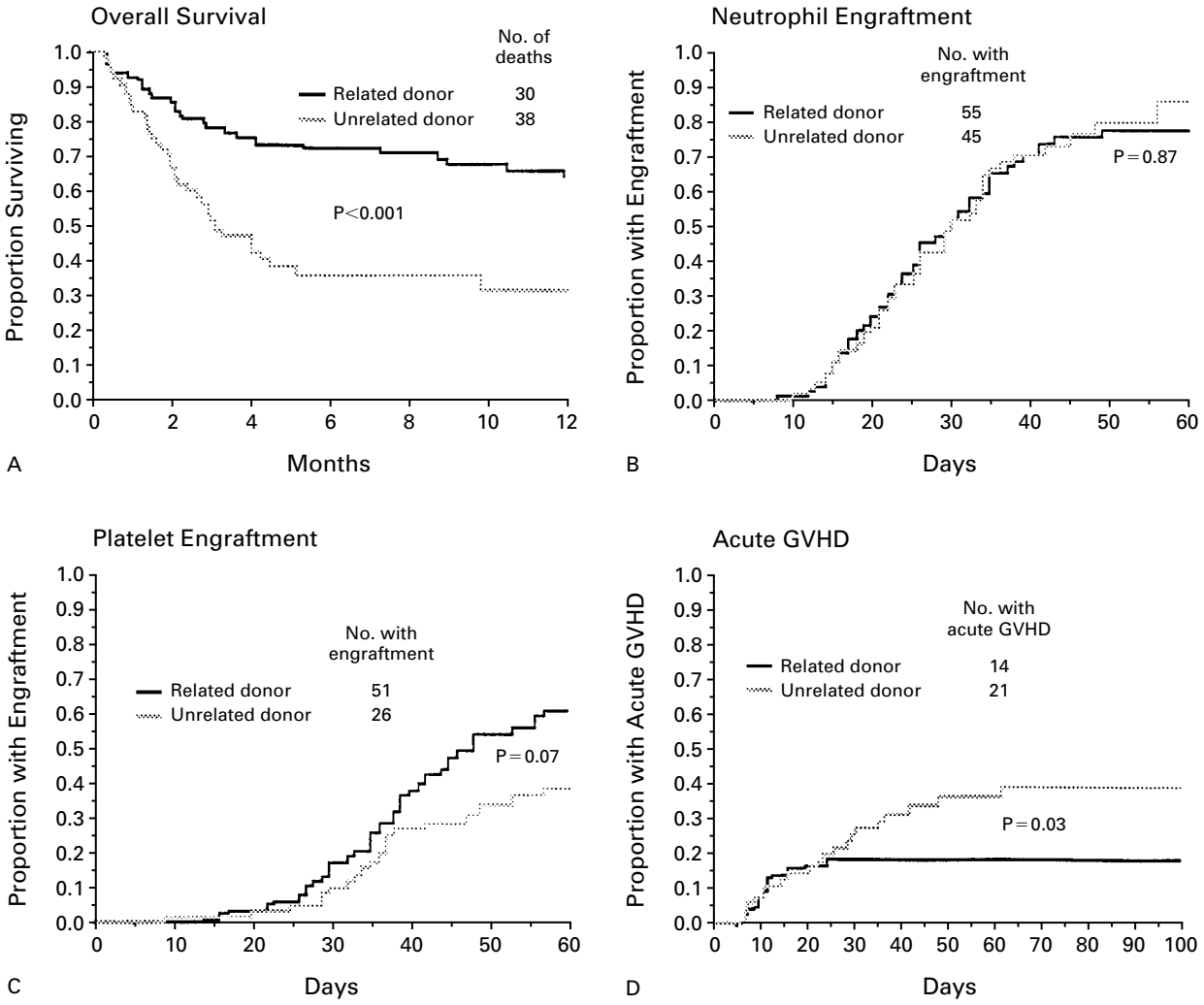

Figure 1. Kaplan–Meier Estimates of the Probability of Survival (Panel A), Engraftment of Neutrophils (Panel B) and Platelets (Panel C) at Day 60, and Acute Graft-versus-Host Disease (GVHD) (Panel D), According to Whether the Cord-Blood Transplant Originated from a Related or an Unrelated Donor.

Seventy-eight patients received cord blood from related donors, and 65 patients received cord blood from unrelated donors. Neutrophil engraftment was defined by an absolute neutrophil count of at least 500 per cubic millimeter, platelet engraftment by a count of at least 20,000 per cubic millimeter, and acute GVHD by disease of grade II or higher.

GVHD

Figure 1D shows the probability of acute GVHD among the recipients of cord blood from related and unrelated donors. Among the recipients of cord blood from related donors, acute GVHD of at least grade II was observed in 14 patients (grade II in 10, grade III in 3, and grade IV in 1). Chronic GVHD was observed in 8 of 56 patients who survived more than 100 days. Among the 65 recipients of cord blood from unrelated donors, acute GVHD was observed in 21 (grade II in 8, grade III in 9, and grade IV in 4). Among the 23 patients who survived more than 100 days, none had chronic GVHD. The factors associated with an increased risk of acute GVHD are shown in Table 5. Among patients who received cord-blood transplants from related donors, the number of HLA mismatches with the donor was the most important factor; the estimated incidence of acute GVHD was 9 percent in recipients of HLA-identical cord blood from related donors and 50 percent in recipients of HLA-mismatched cord blood from related donors ($P<0.001$). In the Cox proportional-hazards analysis, HLA mismatching was the only factor that was associated with an increased risk of GVHD (relative risk, 7.7; 95 percent confidence interval, 2.5 to 23; $P<0.001$).

In recipients of cord blood from unrelated donors, the incidence of acute GVHD was not affected

TABLE 3. FACTORS ASSOCIATED WITH NEUTROPHIL ENGRAFTMENT WITHIN 60 DAYS AFTER CORD-BLOOD TRANSPLANTATION.*

FACTOR	RELATED DONORS (N=78)				UNRELATED DONORS (N=65)				ALL PATIENTS (N=143)			
	NO. STUDIED	NO. WITH ENGRAFTMENT	%	P VALUE	NO. STUDIED	NO. WITH ENGRAFTMENT	%	P VALUE	NO. STUDIED	NO. WITH ENGRAFTMENT	%	P VALUE
Entire group	78	55	79		65	45	87		143	100	82	
Diagnosis				0.30				0.96				0.41
Cancer	46	35	84		49	37	91		95	72	87	
Bone marrow failure syndrome	17	11	78		9	4	66		26	15	75	
Hemoglobinopathy	8	4	50		—	—	—		8	4	50	
Inborn error	7	5	83		7	4	62		14	9	71	
Age				0.02				0.71				0.05
<6 yr	45	38	88		27	20	91		72	58	88	
6–15 yr	30	15	67		18	13	88		48	28	76	
>15 yr	3	2	67		20	12	76		23	14	74	
Weight				0.02				0.12				0.01
<20 kg	40	34	88		24	19	92		64	53	88	
20–45 kg	35	20	75		21	16	85		56	36	81	
>45 kg	3	1	33		20	10	69		23	11	62	
No. of nucleated cells infused/kg				0.06				0.008				0.001
<37 million	38	24	73		36	21	76		74	45	74	
≥37 million	40	31	85		29	24	94		69	55	89	
No. of HLA mismatches												
0	60	44	86		9	6	84		69	50	86	
1	3	1	33		43	30	87		46	31	80	
2	5	4	80		11	7	70		16	11	73	
3	9	6	70		2	2	100		11	8	83	
4	1	0	0		—	—	—		1	0	0	
0	60	44	86	0.04	9	6	84	0.03	69	50	86	0.03
≥1	18	11	62		56	39	87		74	50	78	
Recipient and donor are same sex†				0.42				0.22				0.88
Yes	41	31	85		30	20	85		71	51	84	
No	36	24	75		32	23	89		68	47	82	
Cytomegalovirus serologic status‡				0.22				0.69				0.45
Negative	40	31	82		26	18	83		66	49	82	
Positive	36	23	76		39	27	85		75	50	81	

*The number of engraftments was calculated over the entire study period. Percentages shown are Kaplan–Meier estimates at 60 days.

†Data on sex were missing for four pairs of patients (recipient and donor).

‡Data on cytomegalovirus serologic status were missing for two patients.

by the number of HLA mismatches. Cytomegalovirus-negative serologic status was associated with a lower risk of acute GVHD than was cytomegalovirus-positive status ($P=0.04$).

Other Complications, Relapses of Leukemia, and Causes of Death

Relapses of the original cancer were observed in 22 of the 95 patients with cancer. Of the 46 patients who received cord-blood transplants from related donors to treat cancer, 10 of 38 who had leukemia relapsed (4 with acute myeloblastic leukemia, 5 with acute lymphoblastic leukemia, and 1 with chronic myeloid leukemia); 5 remained alive after a second bone marrow transplant or after donor lymphocyte transfusions, and 5 (2 with neuroblastoma and 3 with myelodysplastic syndrome) died of resistant disease. Of the 49 patients who received cord-blood transplants from unrelated donors to treat cancer, 7 relapsed (3 with acute myeloblastic leukemia, 3 with acute lymphoblastic leukemia, and 1 with chronic myeloid leukemia). Two of the seven remained alive after treatment.

Thirty of the 78 recipients of cord blood from related donors died; the primary causes of death were relapse in 11, rejection in 8, infection in 5, veno-occlusive liver disease in 2, GVHD in 1, cardiac failure in 1, and multiorgan failure in 2. Thirty-eight of the 65 patients who received cord blood from an unrelated donor died; the primary causes of death were relapse in 5, interstitial pneumonitis in 7, acute respiratory distress syndrome in 2, veno-occlusive liver disease in 3, cardiac failure in 2, GVHD in 4, rejection in 4, infection in 10, and hemorrhage in 1.

DISCUSSION

The clinical advantages of cord blood as a source of allogeneic hematopoietic stem cells for transplantation may reflect differences between fetal and adult hematopoietic stem cells.[13,14] As compared with hematopoietic stem cells from adults, hematopoietic stem cells in cord blood have distinctive pro-

TABLE 4. FACTORS ASSOCIATED WITH PLATELET ENGRAFTMENT WITHIN 60 DAYS AFTER CORD-BLOOD TRANSPLANTATION.*

FACTOR	RELATED DONORS (N=78)				UNRELATED DONORS (N=65)				ALL PATIENTS (N=143)			
	NO. STUDIED	NO. WITH ENGRAFTMENT	%	P VALUE	NO. STUDIED	NO. WITH ENGRAFTMENT	%	P VALUE	NO. STUDIED	NO. WITH ENGRAFTMENT	%	P VALUE
Entire group	78	51	62		65	26	39		143	77	52	
Diagnosis				0.94				0.52				0.69
Cancer	46	31	59		49	21	34		95	52	46	
Bone marrow failure syndrome	17	11	67		9	2	44		26	13	68	
Hemoglobinopathy	8	4	60		—	—	—		8	4	60	
Inborn error	7	5	67		7	3	71		14	8	68	
Age				0.15				0.46				0.06
<6 yr	45	37	71		27	12	45		72	49	62	
6–15 yr	30	13	47		18	9	48		48	22	48	
>15 yr	3	1	33		20	5	20		23	6	22	
Weight				0.04				0.18				0.02
<20 kg	40	34	73		24	11	44		64	45	63	
20–45 kg	35	16	48		21	11	56		56	27	51	
>45 kg	3	1	33		20	4	13		23	5	17	
No. of nucleated cells infused/kg				0.23				0.02				0.01
<37 million	38	22	56		36	10	26		74	32	42	
≥37 million	40	29	67		29	16	56		69	45	62	
No. of HLA mismatches												
0	60	44	74		9	6	79		69	50	74	
1	3	1	0		43	15	32		46	16	30	
2	5	3	40		11	4	35		16	7	41	
3	9	3	22		2	1	50		11	4	27	
4	1	0	0		—	—	—		1	0	0	
0	60	44	74	<0.001	9	6	79	0.009	69	50	74	<0.001
≥1	18	7	25		56	20	34		74	27	31	
Recipient and donor are same sex†				0.25				0.19				0.08
Yes	41	30	63		30	15	41		71	45	54	
No	36	21	62		32	10	35		68	31	51	
Cytomegalovirus serologic status‡				0.26				0.55				0.14
Negative	40	31	74		26	13	45		66	44	63	
Positive	36	19	45		39	13	34		75	32	40	

*The number of engraftments was calculated over the entire study period. Percentages shown are Kaplan–Meier estimates at 60 days.

†Data on sex were missing for four pairs of patients (recipient and donor).

‡Data on cytomegalovirus serologic status were missing for two patients.

liferative advantages, including the capacity to form more colonies in culture, a higher cell-cycle rate, autocrine production of growth factors, and longer telomeres.[15,16] All these properties should favor the engraftment and growth of cord-blood hematopoietic stem cells. Moreover, the relative immaturity of lymphocytes in cord blood may reduce the risk and severity of GVHD, which in turn could permit more HLA mismatching between donor and recipient than is usually acceptable with transplants of blood or marrow hematopoietic stem cells from adults.

Cord-blood banks have developed worldwide, and a considerable effort has been made to standardize banking procedures.[6,7] There are several advantages to these banks, including the availability of hematopoietic stem cells, the low rate of viral infection at birth, and the possibility of collecting cord blood from ethnic groups not well represented in registries of bone marrow donors. There are potential legal and ethical problems, including the provision of informed consent and the follow-up of the donor to detect the possible transmission of genetic or infectious diseases.[17-20]

The limited number of nucleated cells in cord blood arouses concern about engraftment. In the 143 patients we studied, the median number of nucleated cells found in cord blood, whether it was obtained from related or unrelated donors, was 1.1 billion cells per unit. We found that the number of nucleated cells infused per kilogram was a major factor in the recovery of neutrophil and platelet counts. Among the recipients of cord blood from related donors, those who received less than 37 million nucleated cells per kilogram took a median of 35 days (range, 8 to 49) to reach an absolute neutrophil count of at least 500 cells per cubic millimeter and a median of 53 days (range, 16 to 180) to reach a platelet count of at least 20,000 per cubic millimeter. By contrast, among the patients who received 37 million or more nucleated cells per kilogram, the median time to neutrophil recovery was 25 days (range, 14 to 41) and the median time to platelet recovery was 45 days (range, 14 to

TABLE 5. FACTORS ASSOCIATED WITH ACUTE GRAFT-VERSUS-HOST DISEASE AFTER CORD-BLOOD TRANSPLANTATION.*

FACTOR	RELATED DONORS (N=78)				UNRELATED DONORS (N=65)				ALL PATIENTS (N=143)			
	NO. STUDIED	NO. OF EVENTS	%	P VALUE	NO. STUDIED	NO. OF EVENTS	%	P VALUE	NO. STUDIED	NO. OF EVENTS	%	P VALUE
Overall	78	14	18		65	21	40		143	35	27	
Diagnosis				0.14				0.71				0.08
Cancer	46	12	27		49	18	42		95	30	34	
Bone marrow failure syndrome	17	2	13		9	1	20		26	3	14	
Hemoglobinopathy	8	0	0		—	—	—		8	0	0	
Inborn error	7	0	0		7	2	36		14	2	16	
Age				0.02				0.52				0.76
<6 yr	45	7	16		27	11	45		72	18	26	
6–15 yr	30	5	18		18	5	33		48	10	23	
>15 yr	3	2	67		20	5	41		23	7	43	
Weight				0.04				0.07				0.06
<20	40	4	10		24	9	42		64	13	21	
20–45 kg	35	9	27		21	10	53		56	19	37	
>45 kg	3	1	33		20	2	18		23	3	19	
No. of nucleated cells infused/kg				0.18				0.38				0.61
<37 million	38	9	25		36	10	39		74	19	30	
≥37 million	40	5	13		29	11	40		69	16	24	
No. of HLA discrepancies												
0	60	5	9		9	3	42		69	8	12	
1	3	0	0		43	14	38		46	14	35	
2	5	3	60		11	2	21		16	5	34	
3	9	6	67		2	2	100		11	8	76	
4	1	0	0		—	—	—		1	0	0	
0	60	5	9	<0.001	9	3	42	0.67	69	8	13	0.001
≥1	18	9	50		56	18	38		74	27	41	
Recipient and donor are same sex†				0.75				0.71				0.94
Yes	41	7	18		30	10	37		71	17	25	
No	36	7	20		52	10	40		68	17	28	
Cytomegalovirus serologic status‡				0.87				0.04				0.08
Negative	40	7	18		26	5	23		66	12	19	
Positive	36	7	21		39	16	51		75	23	35	

*The number of patients with acute graft-versus-host disease was calculated over the entire study period. Percentages shown are Kaplan–Meier estimates at 100 days.

†Data on sex were missing for four pairs of patients (recipient and donor).

‡Data on cytomegalovirus serologic status were missing for two patients.

139). Recipients of cord blood from unrelated donors who received less than 37 million nucleated cells per kilogram took a median of 34 days (range, 14 to 48) to reach an absolute neutrophil count of at least 500 per cubic millimeter and a median of 134 days (range, 30 to 180) to reach a platelet count of at least 20,000 per cubic millimeter, whereas among the patients who received 37 million or more nucleated cells per kilogram, the median times were 25 days (range, 10 to 56) and 47 days (range, 9 to 85), respectively.

In a series of 25 children who received cord blood from unrelated donors, Kurtzberg et al. found a median dose of 30 million nucleated cells per kilogram (range, 7 million to 110 million).[3] Among 22 of these patients the cord blood engrafted, with a median of 22 days needed to reach an absolute neutrophil count greater than 500 per cubic millimeter. All the patients received filgrastim (granulocyte colony-stimulating factor) to accelerate engraftment, however. The International Cord Blood Registry[2] reported the results in 44 children who received cord-blood transplants from related and unrelated donors. The median number of nucleated cells infused was 52 million per kilogram (range, 10 million to 330 million). The median time to neutrophil recovery was 22 days, and the probability of engraftment was 0.82. There was no correlation among the number of cells infused, the use of hematopoietic growth factors, and engraftment. The same group reported results in 18 other patients; the median number of nucleated cells per kilogram was 41 million (range, 14 million to 400 million), and the cord blood engrafted in all 13 patients who survived for more than 30 days; it took a median of 24 days to reach an absolute neutrophil count of more than 500 per cubic millimeter. In the absence of prospective studies, it is difficult to recommend an optimal number of cells needed for long-term engraftment. Moreover, the cell dose is not the only factor associated with engraftment; we found that HLA mismatching between donor and recipient also increased the risk of delayed engraftment.

Cord-blood cells, which are immunologically im-

mature, may decrease the incidence and severity of acute GVHD.[21] As in previously published series, the GVHD we observed was not life-threatening, and the incidence of chronic GVHD was low. In the case of recipients of cord blood from related donors, the incidence of acute GVHD increased with the number of HLA mismatches. We cannot draw any conclusion about the role of HLA mismatches in recipients of cord blood from unrelated donors in the absence of high-resolution HLA typing, the importance of which has been shown in recent analyses of the transplantation of bone marrow from unrelated donors.[22-24]

This report shows that cord blood is an alternative source of hematopoietic stem cells for children and some adults with malignant and nonmalignant hematologic diseases. With other technical developments in hematopoietic-stem-cell transplantation, we may be able to identify a donor for any patient needing a transplant. This new situation calls for carefully planned prospective studies of the clinical efficacy of strategies of donor selection.

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APPENDIX

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