

ORIGINAL ARTICLE

Transplants of Umbilical-Cord Blood or Bone Marrow from Unrelated Donors in Adults with Acute Leukemia

Vanderson Rocha, M.D., Ph.D., Myriam Labopin, M.D., Guillermo Sanz, M.D., William Arcese, M.D., Rainer Schwerdtfeger, M.D., Alberto Bosi, M.D., Niels Jacobsen, M.D., Tapani Ruutu, M.D., Marcos de Lima, M.D., Jürgen Finke, M.D., Francesco Frassoni, M.D., and Eliane Gluckman, M.D., for the Acute Leukemia Working Party of European Blood and Marrow Transplant Group and the Eurocord–Netcord Registry*

ABSTRACT

BACKGROUND

Promising results of cord-blood transplants from unrelated donors have been reported in adults.

METHODS

We compared outcomes in 682 adults with acute leukemia who received a hematopoietic stem-cell transplant from an unrelated donor: 98 received cord blood and 584 received bone marrow. The transplantations were performed from 1998 through 2002 and reported to Eurocord and the European Blood and Marrow Transplant Group.

RESULTS

Recipients of cord blood were younger than recipients of bone marrow (median, 24.5 vs. 32 years of age; $P < 0.001$), weighed less (median, 58 vs. 68 kg; $P < 0.001$), and had more advanced disease at the time of transplantation (52 percent vs. 33 percent, $P < 0.001$). All marrow transplants were HLA matched, whereas 94 percent of cord-blood grafts were HLA mismatched ($P < 0.001$). The median number of nucleated cells that were infused was 0.23×10^8 per kilogram of the recipient's body weight for cord blood and 2.9×10^8 per kilogram for bone marrow ($P < 0.001$). Multivariate analysis showed lower risks of grade II, III, or IV acute graft-versus-host disease (GVHD) after cord-blood transplantation (relative risk, 0.57; 95 percent confidence interval, 0.37 to 0.87; $P = 0.01$), but neutrophil recovery was significantly delayed (relative risk, 0.49; 95 percent confidence interval, 0.41 to 0.58; $P < 0.001$). The incidence of chronic GVHD, transplantation-related mortality, relapse rate, and leukemia-free survival were not significantly different in the two groups.

CONCLUSIONS

Cord blood from an unrelated donor is an alternative source of hematopoietic stem cells for adults with acute leukemia who lack an HLA-matched bone marrow donor.

From Hôpital Saint-Louis (V.R., E.G.), and Hôpital Saint Antoine (M. Labopin), Assistance Publique des Hôpitaux de Paris and Paris University, Paris; Hospital Universitario La Fe, Valencia, Spain (G.S.); Università Tor Vergata, Rome (W.A.); Deutsche Klinik für Diagnostik, Wiesbaden, Germany (R.S.); Ospedale di Careggi, Florence, Italy (A.B.); University Hospital for Internal Medicine, Rigshospitalet, Copenhagen (N.J.); Helsinki University Central Hospital, Helsinki (T.R.); M.D. Anderson Cancer Center, Houston (M. de Lima); University of Freiburg, Freiburg, Germany (J.F.); and Ospedale San Martino, Genoa, Italy (F.F.). Address reprint requests to Dr. Gluckman at Hôpital Saint-Louis, Hematology Bone Marrow Transplant Department, 1 Ave. Claude Vellefaux, 75475 Paris CEDEX 10, France, or at eliane.gluckman@sls.ap-hop-paris.fr.

*Other members of the Eurocord–Netcord Registry and the Acute Leukemia Working Party of European Blood and Marrow Transplant Group Registry are listed in the Appendix.

N Engl J Med 2004;351:2276-85.
Copyright © 2004 Massachusetts Medical Society.

UMBILICAL-CORD BLOOD IS CONSIDERED an alternative to bone marrow as a source of hematopoietic stem cells for transplantation,¹ and its use in adults with hematologic cancers is increasing.² There is considerable evidence that cord blood is a promising option for patients who lack an HLA-matched bone marrow donor.³⁻⁹ The advantages of cord blood are the immediate availability of cells, the absence of risk to the donor, and a lower need for HLA compatibility between the donor and the recipient.⁸⁻¹¹ A limiting factor is the low number of hematopoietic stem cells in a unit of cord blood. For this reason, cord blood has been transplanted into few adults until recently, when cord-blood banks began a policy of selecting units with high numbers of nucleated and CD34+ cells.¹²⁻¹⁷

METHODS

COLLECTION OF DATA

Eurocord and the European Blood and Marrow Transplant Group (EBMT) provided data on cord-blood and bone marrow recipients. Eurocord is an international registry that operates on behalf of EBMT. Participation is open to both European and non-European centers that conduct cord-blood transplantation. The EBMT registry includes more than 450 transplantation centers, which are required to file an annual report of all consecutive stem-cell transplants, with follow-up by Eurocord and EBMT physicians. Eurocord and EBMT databases were checked to verify compliance and detect overlapping reports. Centers not associated with EBMT were asked to report their cord-blood transplants if cord-blood units came from Netcord banks. Eurocord is in charge of the clinical evaluation of cord-blood units provided by Netcord. Netcord is an international organization of cord-blood banks, which are listed in the Appendix.

INCLUSION CRITERIA

Our study evaluated outcomes in patients who were at least 15 years of age at the time of transplantation; who had primary acute leukemia; who received a single cord-blood unit or HLA-matched bone marrow that had not been depleted of T cells; who underwent transplantation between January 1, 1998, and December 31, 2002; who underwent a myeloablative regimen before transplantation; and for whom there were adequate data on outcomes. Seventy-two patients who received bone marrow

and 8 who received cord blood were excluded owing to missing data; a total of 98 recipients of a cord-blood transplant and 584 recipients of a bone marrow transplant at 145 transplantation centers met the criteria.

END POINTS

The probability of neutrophil recovery was defined as the estimated time from transplantation to the first of three consecutive days with an absolute neutrophil count of at least 500 per cubic millimeter. Data on patients who received a second transplant because of nonengraftment of the first were censored at the time of the second transplant. Graft failure was defined as no sign of neutrophil recovery 60 days after transplantation.

The end point of acute graft-versus-host disease (GVHD) was diagnosed and graded according to published criteria¹⁸; patients were evaluated one day or more after transplantation. Chronic GVHD was diagnosed according to standard criteria¹⁹; patients who survived at least 100 days with sustained engraftment were evaluated.

Transplantation-related mortality was defined as death related to transplantation and not to relapse. Relapse was defined on the basis of morphologic evidence of leukemia in bone marrow or other sites. Survival was calculated from transplantation to death from any cause, and leukemia-free survival was defined as the time from transplantation to either first relapse or death in complete remission.

STATISTICAL ANALYSIS

The duration of follow-up was the time to the last assessment for survivors. Before 2002, 95 marrow recipients and 4 cord-blood recipients were lost to follow-up. With the use of the chi-square statistic for categorical variables and the Mann-Whitney test for continuous variables, we compared variables that were related to the patients, the underlying diseases, and the transplantation procedure. Cumulative incidence curves were used in a competing-risks setting, with death treated as a competing event, to calculate the probability of neutrophil recovery, acute GVHD, chronic GVHD, transplantation-related mortality, and relapse.²⁰ Probabilities of leukemia-free survival and overall survival were estimated by the Kaplan-Meier method; the log-rank test was used for univariate comparisons. The associations of the type of graft with outcomes were evaluated in multivariate analyses, with the use of Cox proportional-hazards regression to adjust

Table 1. Characteristics of the Recipients of Cord-Blood or Bone Marrow Transplants from Unrelated Donors.*

Characteristic	Unrelated Cord-Blood Transplant (N=98)	Unrelated Bone Marrow Transplant (N=584)	P Value†
Patient-related			
Age — yr			
Median	24.5	32	<0.001
Range	15–55	15–59	
Male sex — no. (%)	50 (51)	318 (54)	0.53
Weight — kg			
Median	58	68	<0.001
Range	38–92	40–108	
Positive cytomegalovirus serologic status before transplantation — no./total no. (%)	63/94 (67)	161/288 (56)	0.05
Disease-related			
Type of disease — no. (%)			0.12
Acute myeloblastic leukemia	45 (46)	317 (54)	
Acute lymphoblastic leukemia	53 (54)	267 (46)	
Status at transplant			<0.002
First complete remission	26 (27)	197 (34)	
Second complete remission	21 (21)	191 (33)	
More advanced phase	51 (52)	196 (34)	
Previous autologous transplant	19 (19)	44 (8)	<0.001
Disease classification — no./total no. (%)			
Acute lymphoblastic leukemia			
Phenotype			0.08
T-cell	12/43 (28)	26/161 (16)	
B-cell	31/43 (72)	135/161 (84)	
Cytogenetics			0.17
t(9;22)	16/26 (62)	36/79 (46)	
t(4;11)	1/26 (4)	3/79 (4)	
Others	9/26 (35)	40/79 (50)	
Acute myeloblastic leukemia			
French–American–British			0.98
M5, M6, M7	8/40 (20)	60/297 (20)	
Others	32/40 (80)	237/297 (80)	
Cytogenetics‡			0.27
Favorable	7/25 (28)	20/123 (16)	
Intermediate	17/25 (68)	90/123 (73)	
Poor	1/25 (4)	13/123 (11)	

for leukemia-free survival and overall survival and with the use of Fine and Gray’s proportional-hazards model for subdistribution of a competing risk for other outcomes.²¹

The variables considered were the age (median) and sex of the recipient and the donor; HLA com-

patibility, in the case of cord blood; the recipient’s serologic status (positive or negative) with respect to cytomegalovirus; the characteristics of the disease (acute lymphoblastic leukemia according to phenotype and cytogenetics, or acute myeloid leukemia according to French–American–British clas-

Table 1. (Continued.)

Characteristic	Unrelated Cord-Blood Transplant (N=98)	Unrelated Bone Marrow Transplant (N=584)	P Value†
Donor-related			
Age — yr			
Median	—	36	
Range	—	19–57	
Positive cytomegalovirus serologic status before transplantation — no./total no. (%)	—	117/287 (41)	
HLA compatibility — no./total no. (%)§			<0.001
6 of 6	6/95 (6)	584 (100)	
5 of 6	48/95 (51)	—	
4 of 6	37/95 (39)	—	
3 of 6	4/95 (4)	—	
Transplantation-related			
Year of transplantation			
Median	2000	1999	0.001
Range	1998–2002	1998–2002	
Conditioning regimen — no. (%)			
Regimen based on total-body irradiation	64 (65)¶	426 (73)	0.10
Regimen based on busulphan	34 (35)¶	158 (27)	0.10
Antithymocyte or antilymphocyte globulin	75 (77)	216 (37)	<0.001
Prophylaxis against graft-versus-host disease — no. (%)			<0.001
Cyclosporine alone	6 (6)	25 (4)	
Cyclosporine and corticosteroids	69 (70)	2 (0.3)	
Cyclosporine and methotrexate	9 (9)	554 (95)	
Other	14 (14)	3 (0.5)	
No. of nucleated cells infused — ×10 ⁸ /kg			
Median	0.23	2.9	<0.001
Range	0.09–0.6	<1.0–9	

* Percentages may not sum to 100 because of rounding.

† The chi-square test was used for categorical variables, and the Mann–Whitney nonparametric test for continuous variables.

‡ Cytogenetic features associated with a favorable risk were t(8;21), t(15;17), or inv(16), and with a poor risk were monosomy 7, 11q23 abnormalities, monosomy 5, del(5q), abnormal 3q, t(6;9), or a complex karyotype. The remaining cytogenetic abnormalities were classified in the intermediate-risk group.

§ HLA compatibility was defined by HLA-A and B by means of serology or low-resolution DNA typing and by HLA-DRB1 by means of high-resolution typing.

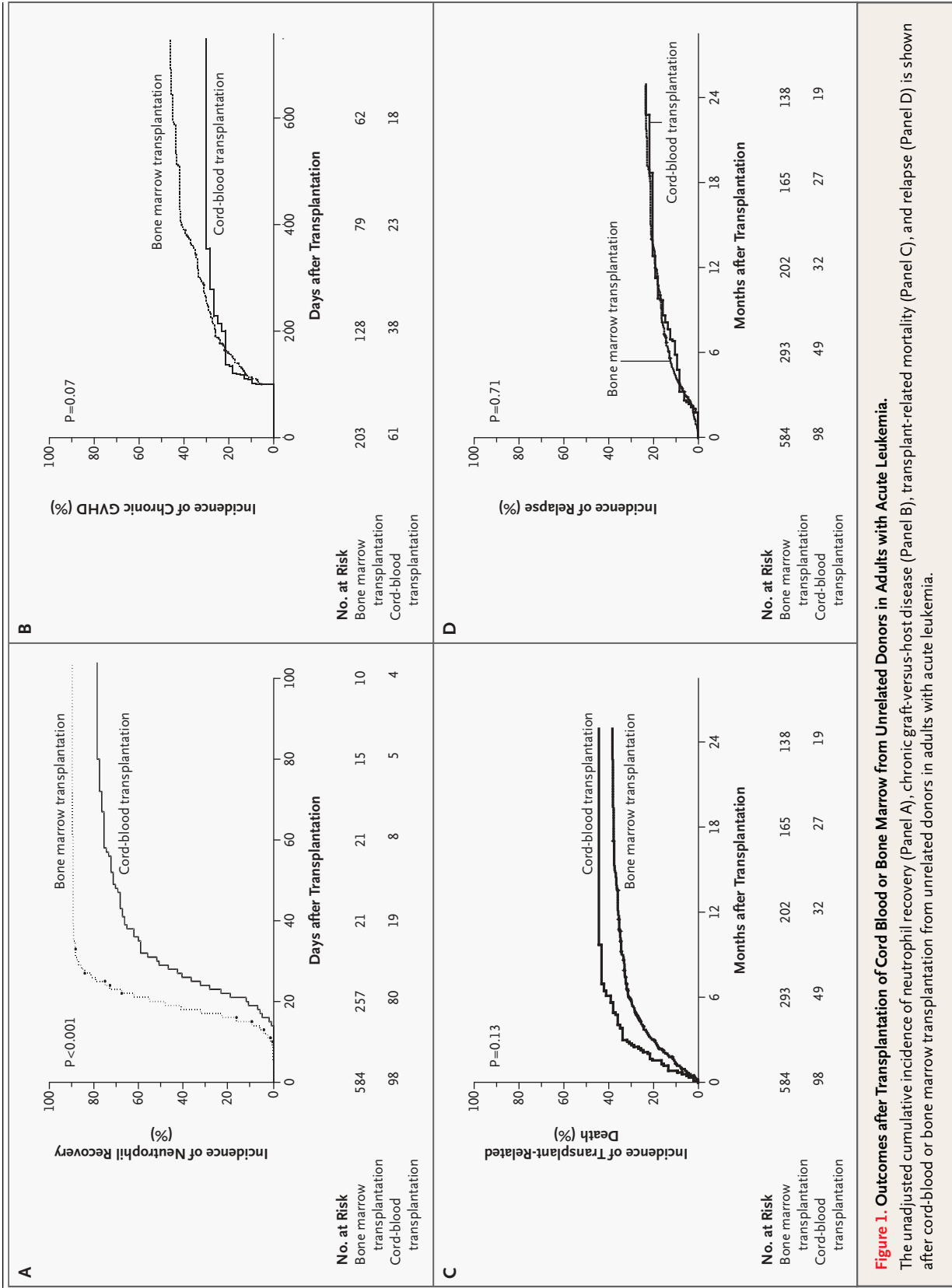
¶ In the cord-blood group, the regimen based on total-body irradiation included cyclophosphamide (22 patients), melphalan (3), or fludarabine alone (5) or in combination with two or more drugs (34); the regimen based on busulfan included cyclophosphamide (13 patients), melphalan (3), or cyclophosphamide plus thiotepea (17) or other drugs (1).

|| Other prophylaxes included regimens based on tacrolimus.

sification and cytogenetics); the status of the disease at the time of transplantation (e.g., first or second complete remission or more advanced disease); and the characteristics of transplantation, including the year of transplantation, receipt of a previous autologous transplant, the conditioning regimen, the type of prophylaxis against GVHD

(cyclosporine, cyclosporine and corticosteroids, or cyclosporine and methotrexate), and the dose of nucleated cells infused. Only factors differing in distribution between the two groups (P<0.10) and factors known to influence outcomes (such as type of leukemia) were included in the final models.

All P values are two-sided, with a type I error rate



fixed at 0.05. Statistical analyses were performed with SPSS and S-Plus (MathSoft) software.

RESULTS

PATIENTS

Table 1 shows the characteristics of the 98 adults who underwent cord-blood transplantation, their donors, and the grafts. The median times from diagnosis to transplantation for patients who received transplants in first and second complete remission were 18 months (range, 8 to 35) and 51 months (range, 19 to 182), respectively. The median period of follow-up was 27 months (range, 3 to 66).

Table 1 also shows the characteristics of the 584 adults who received a bone marrow transplant. The median times from diagnosis to transplantation for patients in first and second complete remission were 18 months (range, 6 to 79) and 59 months (range, 11 to 354), respectively. The median period of follow-up was 24 months (range, 1 to 76).

Cord-blood recipients were younger ($P < 0.001$) and weighed less ($P < 0.001$) than marrow recipients. The proportions of patients with acute myeloid leukemia and acute lymphoblastic leukemia were similar in the two groups ($P = 0.12$). Cord blood was transplanted into patients in a more advanced phase of leukemia than was bone marrow ($P = 0.002$), and more recipients of cord blood had previously received an autologous transplant ($P < 0.001$).

TRANSPLANTATION

All bone marrow transplants were HLA matched, whereas 94 percent of the recipients of cord blood were given an HLA-incompatible graft ($P < 0.001$). The median number of nucleated cells infused in recipients of cord blood was 0.23×10^8 per kilogram of the recipient's body weight (range, 0.09×10^8 to 0.6×10^8 per kilogram), about $1/10$ the number in bone marrow grafts, in which the median number was 2.9×10^8 per kilogram (range, $< 1.0 \times 10^8$ to 9.0×10^8 per kilogram; $P < 0.001$). The median number of CD34+ cells in the cord-blood grafts was 1.1×10^5 per kilogram (range, 0.08×10^5 to 8.8×10^5 per kilogram).

NEUTROPHIL RECOVERY

In the univariate analysis, neutrophil recovery was significantly delayed after cord-blood transplantation as compared with bone marrow transplantation. The median number of days required for the

Table 2. Results of Multivariate Analyses in Which Outcomes Were Compared between Recipients of Unrelated Cord-Blood Transplants and Recipients of Unrelated Bone Marrow Transplants.*

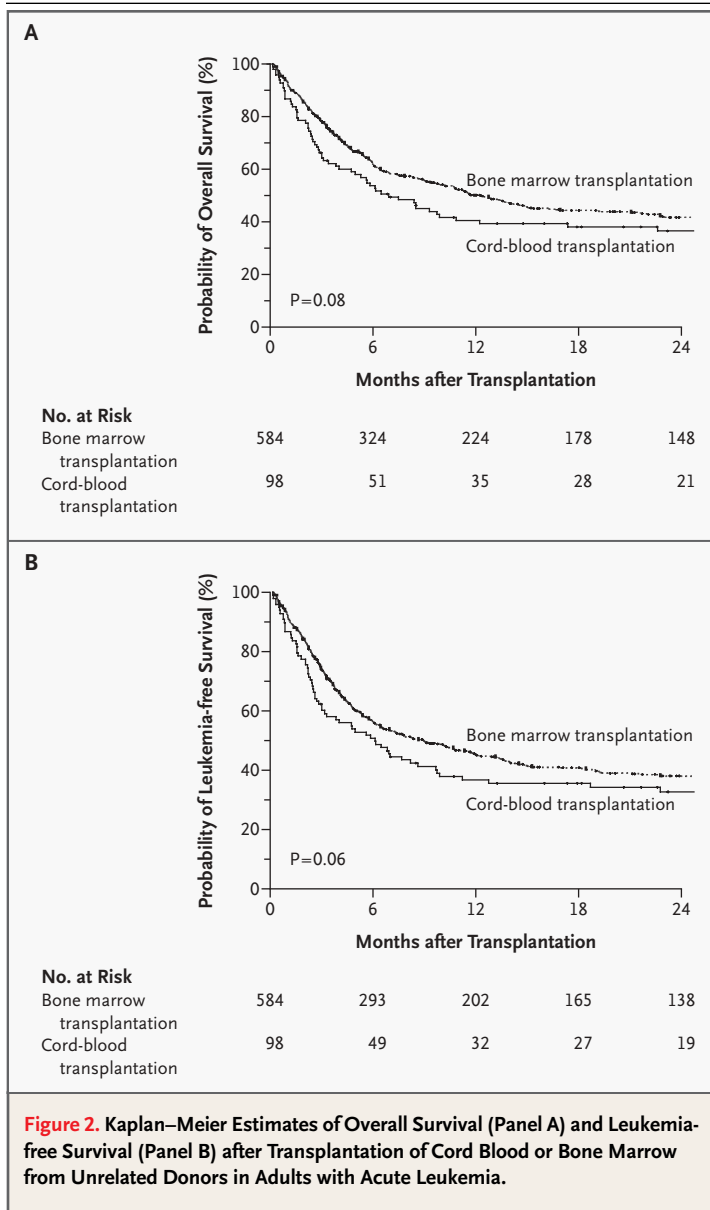
Outcome†	Number of Events (Recipients of Cord-Blood Transplants/Recipients of Bone Marrow Transplants)	Relative Risk (95% CI)‡	P Value
Neutrophil recovery	77/528	0.49 (0.41–0.58)	<0.001
Grade II, III, or IV acute GVHD	25/232	0.57 (0.37–0.87)	0.01
Chronic GVHD	18/94	0.64 (0.37–1.1)	0.11
Transplantation-related mortality	43/207	1.13 (0.78–1.64)	0.50
Relapse	24/136	1.02 (0.63–1.65)	0.93
Leukemia-free survival	67/343	0.95 (0.72–1.25)	0.70
Overall survival	62/320	0.95 (0.71–1.27)	0.75

*CI denotes confidence interval, and GVHD graft-versus-host disease.

† Another significant covariate associated with neutrophil recovery was advanced status of disease at transplantation (relative risk, 0.79; 95 percent confidence interval, 0.64 to 0.96; $P = 0.02$), with acute GVHD was a year of transplantation after 1999 (relative risk, 0.75; 95 percent confidence interval, 0.59 to 0.96; $P = 0.02$), with chronic GVHD was the use of total-body irradiation (relative risk, 0.59; 95 percent confidence interval, 0.39 to 0.88; $P = 0.01$), and with relapse was advanced status of disease at transplantation (relative risk, 2.06; 95 percent confidence interval, 1.39 to 3.05; $P < 0.001$). Other significant covariates associated with mortality were acute lymphoblastic leukemia (relative risk, 1.48; 95 percent confidence interval, 1.13 to 1.94; $P = 0.004$), advanced status of disease at transplantation (relative risk, 1.84; 95 percent confidence interval, 1.35 to 2.49; $P < 0.001$), and recipients older than 31 years of age (relative risk, 1.48; 95 percent confidence interval, 1.13 to 1.94; $P = 0.04$); with leukemia-free survival were second complete remission versus first complete remission (relative risk, 0.40; 95 percent confidence interval, 0.31 to 0.51; $P < 0.001$), advanced status of disease at transplantation (relative risk, 0.44; 95 percent confidence interval, 0.34 to 0.56; $P < 0.001$), patients older than 31 years of age (relative risk, 0.70; 95 percent confidence interval, 0.57 to 0.87; $P = 0.001$), and acute lymphoblastic leukemia (relative risk, 0.40; 95 percent confidence interval, 0.31 to 0.51; $P < 0.002$); and with overall survival were second complete remission versus first complete remission (relative risk, 0.39; 95 percent confidence interval, 0.31 to 0.51; $P < 0.001$), advanced status of disease at transplantation (relative risk, 0.45; 95 percent confidence interval, 0.35 to 0.57; $P < 0.001$), acute lymphoblastic leukemia (relative risk, 0.78; 95 percent confidence interval, 0.63 to 0.96; $P = 0.02$), and patients older than 31 years of age (relative risk, 0.77; 95 percent confidence interval, 0.62 to 0.96; $P = 0.02$).

‡ The relative risk is for transplantation with unrelated umbilical-cord blood as compared with transplantation with unrelated bone marrow (bone marrow group, relative risk of 1.00).

neutrophil count to reach at least 500 per cubic millimeter after cord-blood transplantation was 26 (range, 14 to 80), as compared with 19 (range, 5 to 72) after bone marrow transplantation ($P < 0.001$). The cumulative incidence of neutrophil recovery 60 days after transplantation was 75 percent (95 percent confidence interval, 66 to 84 percent) after cord-blood transplantation and 89 percent (95 per-



cent confidence interval, 87 to 91 percent) after bone marrow transplantation ($P < 0.001$) (Fig. 1A).

Graft failure occurred in 43 patients (7 percent) in the marrow group and 20 patients (20 percent) in the cord-blood group. In the marrow group, 3 of 43 patients who had autologous reconstitution were alive at 3, 18, and 23 months after transplantation, respectively; 4 patients who received a second transplant died. In the cord-blood group, 4 of 20 patients with graft failure survived, 1 after a second transplant 17 months after the first cord-

blood transplant, 1 after a second transplant at 40 months, and 2 with autologous reconstitution at 13 and 31 months, respectively. Secondary graft failure occurred in 4 of 528 marrow recipients and 1 of 77 cord-blood recipients. In the multivariate analysis, the relative risk of neutrophil recovery was significantly lower after cord-blood transplantation than after marrow transplantation (relative risk, 0.49; 95 percent confidence interval, 0.41 to 0.58; $P < 0.001$) (Table 2).

ACUTE AND CHRONIC GVHD

The cumulative incidence of grades II, III, and IV acute GVHD 100 days after transplantation was 26 percent (95 percent confidence interval, 14 to 38 percent) after cord-blood transplantation, which was significantly lower than that after bone marrow transplantation (39 percent; 95 percent confidence interval, 31 to 47 percent; $P = 0.008$). Severe acute GVHD (grades III and IV) occurred in 13 percent of cord-blood recipients and in 19 percent of marrow recipients ($P = 0.26$). In a multivariate analysis, the risk of acute GVHD was significantly lower after transplantation of cord blood than after transplantation of bone marrow (Table 2).

Among patients who survived more than 100 days, chronic GVHD affected proportionally fewer cord-blood recipients (18 of 61) than marrow recipients (94 of 203). The two-year cumulative incidence of chronic GVHD was 30 percent (95 percent confidence interval, 20 to 40 percent) after transplantation of cord blood and 46 percent (95 percent confidence interval, 44 to 48 percent) after transplantation of marrow ($P = 0.07$) (Fig. 1B). In the multivariate analysis, the risk of chronic GVHD was not significantly different between the two groups.

TRANSPLANTATION-RELATED MORTALITY

In the univariate and multivariate analyses, there was no significant difference in transplantation-related mortality between the two groups (two-year cumulative incidence, 44 percent with cord blood vs. 38 percent with bone marrow; $P = 0.13$) (Fig. 1C and Table 2).

RELAPSE

The cumulative incidence of relapse was not significantly different between the two groups (23 percent with cord blood vs. 23 percent with bone marrow, $P = 0.71$) (Fig. 1D). In a multivariate analysis, the risk for relapse was similar in the two groups;

only advanced disease was associated with an increased risk of relapse (Table 2).

OVERALL SURVIVAL AND LEUKEMIA-FREE SURVIVAL

The unadjusted two-year probabilities of overall survival and leukemia-free survival were similar in the two groups (36 percent in recipients of cord blood and 42 percent in recipients of bone marrow, P=0.08 [Fig. 2A]; and 33 percent in recipients of cord blood and 38 percent in recipients of bone marrow, P=0.06 [Fig. 2B]), and a multivariate analysis showed no significant difference in overall survival or leukemia-free survival between the groups (Table 2). Table 3 lists the unadjusted two-year probability of leukemia-free survival in recipients of cord blood and recipients of bone marrow according to the type of leukemia and disease status at the time of the transplantation.

CAUSES OF DEATH

Sixty-two of 98 recipients of cord-blood transplants (63 percent) and 320 of 584 recipients of bone marrow transplants (55 percent) died. Persistent or recurrent leukemia caused 19 (31 percent) of the deaths in the recipients of cord-blood and 118 (37 percent) of those in the recipients of bone marrow transplants. Table 4 lists the causes of death related to transplantation. Deaths related to toxicity were significantly more common in the cord-blood group (P<0.001), whereas deaths related to GVHD were significantly more common in the bone marrow group (P=0.02).

DISCUSSION

In this registry-based retrospective analysis, we found that adults with acute leukemia who underwent cord-blood transplantation had delayed neutrophil recovery and a lower incidence of acute GVHD, but other outcomes were similar to those in adults who underwent bone marrow transplantation. The main differences between the cord-blood group and the bone marrow group were the number of nucleated cells in the graft and HLA compatibility. A major factor that limits the use of cord blood is the number of nucleated cells and CD34+ cells in the graft. There is a consensus that a unit of cord blood should have at least 2.0×10 nucleated cells per kilogram at the time of freezing and no more than two disparities in the matching for HLA-A, B, or DRB1, alone or in combination, with

Table 3. Unadjusted Two-Year Probability of Leukemia-free Survival after Transplantation of Unrelated Umbilical-Cord Blood or Unrelated Bone Marrow in Adults with Acute Leukemia.

Variable	Probability (95% CI)*		P Value†
	Unrelated Cord-Blood Transplant (N=98)	Unrelated Bone Marrow Transplant (N=584)	
	percent		
Type of leukemia			
Acute myeloblastic leukemia	32 (25–39)	42 (39–45)	0.18
Acute lymphoblastic leukemia	34 (27–41)	33 (30–36)	0.21
Status of disease			
First complete remission	43 (33–53)	49 (45–53)	0.31
Second complete remission	44 (32–56)	47 (43–50)	0.64
Advanced	23 (17–29)	19 (16–22)	0.92

* CI denotes confidence interval.

† P values were determined by the log-rank test.

Table 4. Causes of Death after Transplantation of Unrelated Cord Blood or Unrelated Bone Marrow.

Mortality*	Unrelated Cord-Blood Transplant (N=62)	Unrelated Bone Marrow Transplant (N=320)
Related to relapse or progression — no. (%)	19 (31)	118 (37)
Related to transplantation — no. (%)	43 (69)	202 (63)
GVHD‡	5 (12)	63 (31)
Toxicity‡	15 (35)	13 (6)
Graft failure or hemorrhage	4 (9)	10 (5)
Infections§	18 (42)	82 (41)
Other or unknown	1 (2)	34 (17)

* The P value for overall causes of death is <0.001 and was determined by Fisher's exact test.

† GVHD denotes graft-versus-host disease.

‡ Death from toxicity in the cord-blood group included cardiac toxicity (three patients), acute respiratory distress syndrome or interstitial pneumonitis (six), and multiorgan failure (six).

§ Infections in the cord-blood group were bacterial (three patients), viral (five), fungal (seven), parasitic (one), and not determined (three).

the recipient.^{11,22,23} The delayed neutrophil recovery and the decreased incidence of acute GVHD in adult cord-blood recipients are similar to these outcomes in children^{8,9,24} and probably reflect the properties of the hematopoietic and lymphocytic components of cord blood.^{25–29} The relatively low incidence of GVHD after cord-blood transplanta-

tion, despite HLA incompatibility, is notable.³⁰⁻³² However, the role of HLA mismatches is difficult to analyze, since typing for class I HLA alleles is not routine with cord-blood transplants. The number of HLA disparities, found with low-resolution typing, has been associated with neutrophil and platelet recovery, grades III and IV GVHD, and relapse, but not with survival.²²

In our study, we included all cord-blood transplantations performed from 1998 through 2002, regardless of the number of HLA disparities, because during this period transplanting cord blood with as many as three HLA mismatches was a common practice. We have previously shown that transplant-related mortality at 100 days was higher after transplantation of cord blood than after transplantation of bone marrow in children with acute leukemia, because of delayed neutrophil recovery and a higher incidence of infections. In the present study, the risk of transplantation-related mortality was similar in the two groups, perhaps because transplantation centers have improved their criteria for selecting patients and units of cord blood. We ex-

pected more deaths related to infections in the cord-blood group owing to delayed neutrophil recovery and probably delayed immune recovery.^{14,33} However, causes of death were more frequently related to the toxicity of treatment, since cord-blood recipients underwent transplantation in a more advanced phase of leukemia than did recipients of bone marrow.

In conclusion, we believe that cord blood should be considered an alternative to bone marrow for transplantation in adults with acute leukemia. The choice of the source of hematopoietic stem cells will depend on the available number of cord-blood cells, on HLA compatibility, and on the urgency of the need for the transplant.

Supported by a grant from the European Commission (QLK3-CT-1999-00380, to Eurocord) and by grants from Programma Nazionale sulle Cellule Staminali 2003 and Progetto CARIGE Cellule Staminali (to Dr. Frassoni).

We are indebted to Dr. I. Ionescu and Dr. F. Garnier for collecting and validating clinical data from Eurocord, to Professor S. Chevret of the Biostatistical Medical Department of Hôpital Saint-Louis, to Mrs. Emmanuelle Polge for collecting data from the Acute Leukemia Working Party of European Blood and Marrow Transplant Group, and to the data managers from all the Eurocord–European Blood and Marrow Transplant Group centers.

APPENDIX

The authors are members of the following cooperative groups: **Eurocord–Netcord Registry** — V. Rocha, G. Sanz, W. Arcese, A. Bosi, M. de Lima, and E. Gluckman; **Acute Leukemia Working Party of European Blood and Marrow Transplant Group** — V. Rocha, M. Labopin, G. Sanz, W. Arcese, R. Schwerdtfeger, A. Bosi, N. Jacobsen, T. Ruutu, J. Finke, F. Frassoni, and E. Gluckman. In addition to the authors, other members of Eurocord, Netcord, and the European Blood and Marrow Transplant Group who participated in this study were as follows: **Netcord** — P. Wernet, G. Köegler, Düsseldorf Cord-Blood Bank, Düsseldorf, Germany; P. Rebutta and L. Lecchi, Italian Cord-Blood Bank Network (GRACE), Milan; J. Garcia and S. Querol, Barcelona Cord-Blood Bank, Barcelona, Spain; T. Takahashi and T. Nagamura-Inoue, Tokyo Cord-Blood Bank, Tokyo; P. Rubinstein, New York Blood Center, New York; M. Contreras and S. Armitage, London Cord-Blood Bank, London; Y. Beguin and, E. Baudoux, Belgium Cord-Blood Bank, Liege; V. Lapiere, French Cord-Blood Bank, Besançon, France; B. Dazey, French Cord-Blood Bank, Bordeaux, France; and the **Eurocord–European Blood and Marrow Transplant Group centers** — H. Greinix, University Hospital for Internal Medicine, Vienna; A. Bacigalupo, Ospedale San Martino, Genoa, Italy; A. Fauser, Klinik für Knochenmarktransplantation, Idar-Oberstein, Germany; L. Brinch, Rikshospitalet, Oslo; F. Rodeghiero, S. Bortolo Hospital, Vicenza, Italy; A. Vitek, Institute of Hematology and Blood Transfusion, Prague, Czech Republic; M. Falda, Azienda Ospedaliera S. Giovanni, Turin, Italy; S. Tura, Institute of Hematology and Medical Oncology Seragnoli, Bologna, Italy; U.W. Schaefer, University Hospital, Essen, Germany; T. Barbui, Ospedale Bergamo, Bergamo, Italy; J. Holowiecki, Silesian Medical Academy, Katowice, Poland; O. Ringden, Huddinge University Hospital, Huddinge, Sweden; H.-J. Kolb, Klinikum Grosshadern, Munich, Germany; S. McCann, St. James Hospital Trinity College, Dublin; J. Reiffers, Hôpital Haut Leveque, Pessac, France; G. Morgenstern, Christie NHS Trust Hospital, Manchester, United Kingdom; L. Kanz, Medizinische Klinik, Tübingen, Germany; P. Alessandrino, Policlinico San Matteo IRCCS, Pavia, Italy; A. Zander, University Hospital Eppendorf, Hamburg, Germany; V. Koza, Charles University Hospital, Pilsen, Czech Republic; I. Franklin, Glasgow Royal Infirmary, Glasgow, United Kingdom; J.P. Jouet, Hôpital Claude Huriez, Lille, France; A. Fassas, George Papanicolaou General Hospital of Thessaloniki, Exokhi, Greece; K. Kolbe, Johannes Gutenberg University, Mainz, Germany; C. Cordonnier, Hôpital Henri Mondor, Creteil, France; B. Simonsen, University Hospital, Uppsala, Sweden; R.E. Clark, Royal Liverpool University Hospital, Liverpool, United Kingdom; R. Scime, Ospedale V. Cervello, Palermo, Italy; Y. Beguin, University of Liege, Liege, Belgium; R. Arnold, Campus Virchow-Klinikum, Berlin, Germany; G. Ehninger, Universitätsklinikum Dresden, Dresden, Germany; A. Buzyn, Hôpital Necker, Paris; S. Giral, M.D. Anderson Cancer Center, Houston; S. Asano, Institute of Medical Science, University of Tokyo, Tokyo; N. Gratecos, Hôpital de l'Archet, Nice, France; G. Michel, Hôpital Pédiatrique de "La Timone," Marseille, France; S. Amadori, University Tor Vergata, St. Eugenio Hospital, Rome; K. Remes, Turku University Central Hospital, Turku, Finland; A. Torrez-Gomez, Cordoba Hospital, Cordoba, Spain; A. Iriondo, Hospital Universitario Marqués de Valdecilla, Santander, Spain; F. Guillot, Hôpital La Milétrie, Poitiers, France; B. Hertenstein, Medical School of Hannover, Hannover, Germany; D. Niederwieser, University of Leipzig, Leipzig, Germany; J. Ortega, Hospital M. Infantil Vall d'Hebron, Barcelona, Spain; N. Harhalakis, Evangelismos Hospital, Athens; M. Michallet, Hôpital E. Herriot, Lyon, France; N.H. Russell, Nottingham City Hospital, Nottingham, United Kingdom; D. Caballero, Hospital Clínico, Salamanca, Spain; S. Joerg, University of Saarland, Homburg, Germany; J. Apperley, Hammersmith Hospital, London; U. Schanz, University Hospital, Zurich; E. Carreras, Department of Hematology, Hospital Clinic, Barcelona, Spain; D. Bron, Institut Jules Bordet, Brussels; J.-Y. Cahn, Hôpital Jean Minjot, Besançon, France; V. Leblond, Hôpital Pitié-Salpêtrière, Paris; G. Gastl, University Hospital Innsbruck, Innsbruck, Austria; S.J. Proctor, Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom; M. Brune, Center for Hematopoietic-Cell Transplantation (CHECT), Goeteborg, Sweden; W. Siegert, Campus Charité Mitte, Berlin; E. Morra, Ospedale di Niguarda Ca' Granda, Milan; M. Freund, Universität Rostock Hospital, Rostock, Germany; F. Benedet-

ti, Policlinico G.B. Rossi, Verona, Italy; N. Ifrah, Centre Hospitalier Régional Universitaire, Nagers, France; A. Wahlin, Umea University Hospital, Umea, Sweden; G. Juliusson, Linköping University Hospital, Linköping, Sweden; G.J. Mufti, Guy's, Kings, and St. Thomas' School of Medicine, London; A. Gratwohl, Kantonsspital Basel, Switzerland; R. Willemze, Leiden University Hospital, Leiden, the Netherlands; N.C. Gorin, Hôpital Saint Antoine, Paris; B. Rio, Hôpital Hotel Dieu, Paris; D. Blaise, Institut Paoli Calmettes, Marseille, France; D.W. Milligan, Birmingham Heartlands Hospital, Birmingham, United Kingdom; G. Leone, Università Cattolica S. Cuore, Rome; J. Cornish, Bristol Royal Hospital for Children, Bristol, United Kingdom; R. Haas, Heinrich-Heine Universität, Düsseldorf, Germany; A. Poros, National Medical Center, Budapest, Hungary; S. Lenhoff, Lund University Hospital, Lund, Sweden; D. Hoelzer, Universität Frankfurt, Frankfurt, Germany; W. Linkesch, Karl Franzens University Graz, Graz, Austria; C. Craddock, University Hospital Birmingham NHS Trust, Birmingham, United Kingdom; D. Selleslag, A.Z. Sint-Jan, Brugge, Belgium; C. Vermeylen, Cliniques Universitaires St. Luc, Brussels; A.D. Ho, University of Heidelberg, Heidelberg, Germany; H.G. Sayer, Friedrich-Schiller-Universität Jena, Jena, Germany; H.-A. Horst, Christian Albrechts University, Kiel, Germany; P. Di Bartolomeo, Ospedale Civile, Pescara, Italy; L.F. Verdonck, University Medical Center, Utrecht, the Netherlands; G. Milone, Ospedale Ferrarotto, Catania, Italy; T. Littlewood, Oxford Radcliffe Hospital, Oxford, United Kingdom; P. Shaw, Children's Hospital at Westmead, Sydney; and J.P. Vannier, Hôpital Charles Nicolle, Rouen, France.

REFERENCES

1. Gluckman E, Broxmeyer HE, Auerbach AD, et al. Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical-cord blood from an HLA-identical sibling. *N Engl J Med* 1989;321:1174-8.
2. Netcord inventory and use Sept. 2004. (Accessed October 29, 2004, at <https://www.netcord.org/inventory.gif>.)
3. Kurtzberg J, Laughlin M, Graham ML, et al. Placental blood as a source of hematopoietic stem cells for transplantation into unrelated recipients. *N Engl J Med* 1996;335:157-66.
4. Gluckman E, Rocha V, Boyer-Chammard A, et al. Outcome of cord-blood transplantation from related and unrelated donors. *N Engl J Med* 1997;337:373-81.
5. Cairo MS, Wagner JE. Placental and/or umbilical cord blood: an alternative source of hematopoietic stem cells for transplantation. *Blood* 1997;90:4665-78.
6. Rubinstein P, Carrier C, Scaradavou A, et al. Outcomes among 562 recipients of placental-blood transplants from unrelated donors. *N Engl J Med* 1998;339:1565-77.
7. Gluckman E. Current status of umbilical cord blood hematopoietic stem cell transplantation. *Exp Hematol* 2000;28:1197-205.
8. Rocha V, Wagner JE, Sobocinski KA, et al. Graft-versus-host disease in children who have received a cord-blood or bone marrow transplant from an HLA-identical sibling. *N Engl J Med* 2000;342:1846-54.
9. Rocha V, Cornish J, Sievers EL, et al. Comparison of outcomes of unrelated bone marrow and umbilical cord blood transplants in children with acute leukemia. *Blood* 2001;97:2962-71.
10. Barker JN, Krepski TP, DeFor TE, Davies SM, Wagner JE, Weisdorf DJ. Searching for unrelated donor hematopoietic stem cell grafts: availability and speed of umbilical cord blood versus bone marrow. *Biol Blood Marrow Transplant* 2002;8:257-60.
11. Grewal SS, Barker JN, Davies SM, Wagner JE. Unrelated donor hematopoietic cell transplantation: marrow or umbilical cord blood? *Blood* 2003;101:4233-44.
12. Laughlin MJ, Barker J, Bambach B, et al. Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donors. *N Engl J Med* 2001;344:1815-22.
13. Sanz GF, Saavedra S, Planelles D, et al. Standardized, unrelated donor cord blood transplantation in adults with hematological malignancies. *Blood* 2001;98:2332-8.
14. Long GD, Laughlin M, Madan B, et al. Unrelated umbilical cord blood transplantation in adult patients. *Biol Blood Marrow Transplant* 2003;9:772-80.
15. Ooi J, Iseki T, Nagayama H, et al. Unrelated cord blood transplantation for adult patients with myelodysplastic syndrome-related secondary acute myeloid leukaemia. *Br J Haematol* 2001;114:834-6.
16. Ooi J, Iseki T, Takahashi S, et al. Unrelated cord blood transplantation for adult patients with de novo acute myeloid leukemia. *Blood* 2004;103:489-91.
17. Sanz G, Rocha V. Umbilical cord blood transplantation: current status and future directions. *Curr Opin Organ Transplant* 2003;8:109-17.
18. Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HLA-matched sibling donors. *Transplantation* 1974;18:295-304.
19. Shulman HM, Sullivan KM, Weiden PL, et al. Chronic graft-versus-host syndrome in man: a long-term clinicopathologic study of 20 Seattle patients. *Am J Med* 1980;69:204-17.
20. Gooley TA, Leisenring W, Crowley JA, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med* 1999;18:665-706.
21. Fine JP, Gray RJ. A proportional hazards model for subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496-509.
22. Gluckman E, Rocha V, Arcese W, et al. Factors associated with outcome of unrelated cord blood transplant: guidelines for donor choice. *Exp Hematol* 2004;32:397-407.
23. Wagner JE, Barker JN, DeFor TE, et al. Transplantation of unrelated donor umbilical cord blood in 102 patients with malignant and nonmalignant diseases: influence of CD34 cell dose and HLA disparity on treatment-related mortality and survival. *Blood* 2002;100:1611-8.
24. Barker JN, Davies SM, DeFor T, Ramsay NK, Weisdorf DJ, Wagner JE. Survival after transplantation of unrelated donor umbilical cord blood is comparable to that of human leukocyte antigen-matched unrelated donor bone marrow: results of a matched-pair analysis. *Blood* 2001;97:2957-61.
25. Lansdorp PM, Dragowska W, Mayani H. Ontogeny-related changes in proliferative potential of human hematopoietic cells. *J Exp Med* 1993;178:787-91.
26. Frassoni F, Podesta M, Maccario R, et al. Cord blood transplantation provides better reconstitution of hematopoietic reservoir compared with bone marrow transplantation. *Blood* 2003;102:1138-41.
27. Risdon G, Gaddy J, Stehman FB, Broxmeyer HE. Proliferative and cytotoxic responses of human cord blood T lymphocytes following allogeneic stimulation. *Cell Immunol* 1994;154:14-24.
28. Madrigal JA, Cohen SB, Gluckman E, Charron DJ. Does cord blood transplantation result in lower graft-versus-host disease? It takes more than two to tango. *Hum Immunol* 1997;56:1-5.
29. Lewis ID, Almeida-Porara G, Du J, et al. Umbilical cord blood cells capable of engrafting in primary, secondary, and tertiary xenogeneic hosts are preserved after ex vivo culture in a noncontact system. *Blood* 2001;97:3441-9.
30. Hansen JA, Gooley TA, Martin PJ, et al. Bone marrow transplants from unrelated donors for patients with chronic myeloid leukemia. *N Engl J Med* 1998;338:962-8.
31. Petersdorf EW, Gooley TA, Anasetti C, et al. Optimizing outcome after unrelated marrow transplantation by comprehensive matching of HLA class I and II alleles in the donor and the recipient. *Blood* 1998;92:3515-20.
32. Sasazuki T, Juji T, Morishima Y, et al. Effect of matching of class I HLA alleles on clinical outcome after transplantation of hematopoietic stem cells from an unrelated donor. *N Engl J Med* 1998;339:1177-85. [Erratum, *N Engl J Med* 1999;340:402.]
33. Klein AK, Patel DD, Gooding ME, et al. T-cell recovery in adults and children following umbilical cord blood transplantation. *Biol Blood Marrow Transplant* 2001;7:454-66.

Copyright © 2004 Massachusetts Medical Society.