

Outcomes after Transplantation of Cord Blood or Bone Marrow from Unrelated Donors in Adults with Leukemia

Mary J. Laughlin, M.D., Mary Eapen, M.B., B.S., Pablo Rubinstein, M.D., John E. Wagner, M.D., Mei-Jei Zhang, Ph.D., Richard E. Champlin, M.D., Cladd Stevens, M.D., Juliet N. Barker, M.D., Robert P. Gale, M.D., Ph.D., Hillard M. Lazarus, M.D., David I. Marks, M.D., Ph.D., Jon J. van Rood, M.D., Andromachi Scaradavou, M.D., and Mary M. Horowitz, M.D.

ABSTRACT

BACKGROUND

Data regarding the outcome of cord-blood transplantation in adults are scant, despite the fact that these grafts are increasingly used in adults.

METHODS

We compared the outcomes of the transplantation of hematopoietic stem cells from unrelated donors in adults with leukemia who had received cord blood that was mismatched for one HLA antigen (34 patients) or two antigens (116 patients), bone marrow that had one HLA mismatch (83 patients), and HLA-matched bone marrow (367 patients). We used Cox proportional-hazards models to analyze the data.

RESULTS

Cord-blood recipients were younger and more likely to have advanced leukemia than were bone marrow recipients, and they received lower doses of nucleated cells. Hematopoietic recovery was slower with transplantation of mismatched bone marrow and cord blood than with matched marrow transplantations. Acute graft-versus-host disease (GVHD) was more likely to occur after mismatched marrow transplantation, and chronic GVHD was more likely to occur after cord-blood transplantation. The rates of treatment-related mortality, treatment failure, and overall mortality were lowest among patients who received matched marrow transplants. Patients who received mismatched bone marrow transplants and those who received mismatched cord-blood transplants had similar rates of treatment-related mortality ($P=0.96$), treatment failure ($P=0.69$), and overall mortality ($P=0.62$). There were no differences in the rate of recurrence of leukemia among the groups. There were no differences in outcome after cord-blood transplantation between patients with one HLA mismatch and those with two HLA mismatches.

CONCLUSIONS

HLA-mismatched cord blood should be considered an acceptable source of hematopoietic stem-cell grafts for adults in the absence of an HLA-matched adult donor.

From the Case Comprehensive Cancer Center and University Hospitals of Cleveland Ireland Cancer Center, Cleveland (M.J.L., H.M.L.); the International Bone Marrow Transplant Registry, Health Policy Institute, Medical College of Wisconsin, Milwaukee (M.E., M.-J.Z., M.M.H.); the National Cord Blood Program, New York Blood Center, New York (P.R., C.S., A.S.); the University of Minnesota Medical School, Minneapolis (J.E.W., J.N.B.); the M.D. Anderson Cancer Research Center, Houston (R.E.C.); the Center for Advanced Studies in Leukemia, Los Angeles (R.P.G.); the Adult Blood and Marrow Transplant Unit, United Bristol Health Care Trust, Bristol, United Kingdom (D.I.M.); and Leiden University Medical Center, Leiden, the Netherlands (J.J.R.). Address reprint requests to Dr. Horowitz at the International Bone Marrow Transplant Registry, Medical College of Wisconsin, 8701 Watertown Plank Rd., P.O. Box 26509, Milwaukee, WI 53226, or at marymh@mcw.edu.

N Engl J Med 2004;351:2265-75.

Copyright © 2004 Massachusetts Medical Society.

TREATMENT OF LEUKEMIA WITH TRANSPLANTATION of allogeneic bone marrow or stem cells from the peripheral blood is limited by the scarcity of HLA-matched related donors. Only 30 percent of otherwise eligible patients with leukemia in the United States have a related histocompatible donor and, of the remainder, only about 20 percent receive a transplant from an unrelated donor or an HLA-mismatched related donor.¹ The higher risk of acute and chronic graft-versus-host disease (GVHD) is an important drawback to be considered when grafts from unrelated donors or related donors with partially matched HLA antigens are used.²⁻⁵

Cord-blood grafts from unrelated donors have been used successfully, primarily in children.⁶⁻¹¹ In children, these grafts reconstitute hematopoiesis more slowly than do bone marrow grafts and thereby contribute to relatively high rates of post-transplantation infection and early death.¹¹⁻¹⁴ The incidence and severity of GVHD are not excessive, however, even with cord-blood grafts mismatched for more than one HLA antigen, and graft-versus-leukemia effects are well maintained.^{11-13,15} Reports of cord-blood transplantation in adults also suggest slower hematopoietic recovery and variable rates of leukemia-free and overall survival, but these studies have been small and did not compare cord-blood with bone marrow transplantation.¹⁴⁻¹⁸

We analyzed data on a large number of adult patients that were reported to the International Bone Marrow Transplant Registry (IBMTR) and the National Cord Blood Program (NCBP) of the New York Blood Center. We compared the outcomes after transplantation of hematopoietic stem cells from cord blood from unrelated donors that was mismatched for one or two HLA antigens (150 patients), from bone marrow that was mismatched for one HLA antigen (83 patients), or from HLA-matched bone marrow (367 patients).

METHODS

COLLECTION OF DATA

Data on patients who underwent bone marrow and cord-blood transplantation were obtained from the IBMTR and the NCBP of the New York Blood Center. The IBMTR is a working group of more than 400 transplantation centers worldwide. Participating centers register basic information on consecutive transplantations at a statistical center located at the Medical College of Wisconsin. Detailed dem-

ographic and clinical data are collected on a representative sample of patients in the registry. Centers that obtain cord-blood grafts from the NCBP are required, under the Investigational New Drug rules of the Food and Drug Administration, to report data on the outcome of transplantation procedures.

INCLUSION CRITERIA

The study included patients 16 to 60 years of age who had received either an HLA-matched marrow transplant or a marrow transplant with a single HLA mismatch from an unrelated donor or had received a cord-blood transplant with one or two HLA mismatches. HLA matching was performed with the use of serologic or low-resolution molecular typing methods for HLA-A and HLA-B and high-resolution molecular typing for HLA-DRB1. The matching process identified all specificities that were recognized by the World Health Organization at the time of transplantation. There were not enough transplantations performed with HLA-matched cord blood (5 patients) or cord blood with three mismatches (19 patients) to include these in the comparison. Also excluded were recipients of T-cell-depleted marrow, peripheral blood, reduced-intensity preparative regimens, ex vivo expanded grafts, or multiple cord-blood units and those in whom prior transplantation had failed. Transplantations were performed between January 1, 1996, and December 31, 2001, in various locations throughout the United States. Eligible for the study were 450 bone marrow recipients and 150 cord-blood recipients. The patients had been given a diagnosis of acute lymphoblastic leukemia, acute myeloid leukemia, chronic myeloid leukemia, or myelodysplastic syndrome.

END POINTS

Neutrophil recovery was defined by an absolute neutrophil count of at least 500 cells per cubic millimeter for three consecutive days; platelet recovery was defined by a count of at least 20,000 platelets per cubic millimeter, unsupported by transfusions, for seven days. The incidence of grade 2, 3, or 4 acute GVHD was determined in all patients,¹⁹ and the incidence of chronic GVHD was determined in patients who survived for at least 90 days.²⁰ Treatment-related death was defined as death during a continuous remission. Relapse was defined as a recurrence of leukemia; patients in whom a remission failed to occur after transplantation were considered to have had a recurrence at day 1. Leuke-

mia-free survival was defined as survival in a state of continuous complete remission.

STATISTICAL ANALYSIS

Variables related to patients, disease, and transplants were compared among the groups with the use of the chi-square statistic for categorical variables and the Kruskal–Wallis test for continuous variables. The probabilities of overall and leukemia-free survival were calculated with the use of the Kaplan–Meier estimator.²¹ For analyses of survival rates, death from any cause was considered an event, and data on patients who were alive at the last follow-up contact were censored. For leukemia-free survival, relapse or death (i.e., treatment failure) was considered an event, and data on patients who were alive and in continuous complete remission were censored at the last follow-up. The probabilities of neutrophil and platelet recovery, acute and chronic GVHD, treatment-related death, and relapse were calculated with the use of the cumulative-incidence–function method.²¹ For neutrophil and platelet recovery and for GVHD, death without an event (hematopoietic recovery or GVHD) was the competing event; for treatment-related mortality, relapse was the competing event; and, for relapse, treatment-related death was the competing event. Data on patients who were alive without an event were censored at the last follow-up.

Confidence intervals were calculated with the use of a log transformation.²¹ Adjusted probabilities of overall and leukemia-free survival were estimated with the use of the Cox proportional-hazards regression model, with consideration of the variables in the final multivariate models.²² Multivariate models were built with the use of stepwise forward selection, with a P value of 0.05 or less considered to indicate statistical significance; all variables met the proportional-hazards assumption. The primary objective was to compare outcomes according to graft type: HLA-matched bone marrow, single-antigen–mismatched bone marrow, and cord blood with one or two antigen mismatches. Results were expressed as hazard ratios — the relative rate of occurrence of the event with one graft type as compared with another.

Before comparing bone marrow and cord-blood grafts, we analyzed the effect of HLA matching in cord-blood transplantation. There were no statistically significant differences in outcome between patients who had received transplants with one antigen mismatch and those who received trans-

plants with two antigen mismatches, and these groups were combined for further analyses. The variable for graft type was retained in all steps of model building. Other variables that were considered were the age of the transplant recipient, the serologic status with respect to cytomegalovirus in both donor and recipient before transplantation, the type of leukemia and the status of the disease at transplantation, the sex of the recipient and the donor, the conditioning regimen (i.e., with irradiation vs. without it), the regimen for GVHD prophylaxis (e.g., treatment with cyclosporine and methotrexate vs. treatment with alternative regimens), and the total dose of nucleated cells (for each graft type separately). There were no first-order interactions between the graft type and the other variables studied. No statistically significant effects according to treatment center were noted.²³ P values are two-sided. Analyses were completed with the use of PROC PHREG in SAS software, version 8.2 (SAS Institute).

RESULTS

PATIENTS

Table 1 shows features of the patients, the types of leukemia they had, and the types of transplant they received. As compared with bone marrow recipients, cord-blood recipients were younger, were less likely to be white, were more likely to have acute leukemia, were more likely to have advanced leukemia at transplantation, and weighed less. The average total dose of nucleated cells for marrow recipients was generally 10 times as high as that for cord-blood recipients. All cord-blood grafts were HLA-mismatched — 23 percent for one antigen, and 77 percent for two antigens. The median period of follow-up for survivors after marrow and cord-blood transplantation was 48 months and 40 months, respectively. Completeness of follow-up for the study population was 91 percent.²⁴

NEUTROPHIL AND PLATELET RECOVERY

Among patients who had neutrophil and platelet recovery, the recovery times were longer after cord-blood transplantation than after bone marrow transplantation. Median times to neutrophil recovery were 18 days (95 percent confidence interval, 18 to 19) after HLA-matched bone marrow transplantation, 20 days (95 percent confidence interval, 18 to 22) after mismatched marrow transplantation, and 27 days (95 percent confidence interval, 25 to 29)

Table 1. Characteristics of Patients Who Received Bone Marrow or Cord-Blood Transplants from Unrelated Donors, 1996 to 2001.

Variable	Matched Bone Marrow (N=367)	Bone Marrow Mismatched for 1 Antigen (N=83)	Cord Blood Mismatched for 1 or 2 Antigens (N=150)	P Value
Sex — no. (%)				0.29
Male	206 (56)	52 (63)	78 (52)	
Female	161 (44)	31 (37)	72 (48)	
Age group — no. (%)				<0.001
16–20 yr	43 (12)	18 (22)	48 (32)	
21–30 yr	84 (23)	16 (19)	30 (20)	
31–40 yr	101 (27)	25 (30)	33 (22)	
41–50 yr	109 (30)	19 (23)	28 (19)	
51–60 yr	30 (8)	5 (6)	11 (7)	
Weight — kg				<0.001
Median	76	73	68	
Range	40–156	46–143	44–133	
Race — no. (%)*				<0.001
White	328 (89)	60 (73)	95 (64)	
Other	35 (10)	21 (25)	54 (36)	
Unknown	4 (1)	2 (2)	1 (<1)	
Disease — no. (%)				0.02
Acute myeloid leukemia	115 (31)	27 (33)	58 (39)	
Acute lymphoblastic leukemia	82 (22)	17 (20)	45 (30)	
Chronic myeloid leukemia	145 (40)	37 (45)	37 (25)	
Myelodysplastic syndrome	25 (7)	2 (2)	10 (6)	
Disease status — no. (%)†				<0.001
CR1, CP1, or RA	149 (40)	27 (33)	30 (20)	
≥CR2, CP2, or AP	112 (31)	35 (42)	48 (32)	
Relapse, PIF, BP, or RAEBT	106 (29)	21 (25)	64 (43)	
Missing	0	0	8 (5)	
Conditioning regimen — no. (%)				0.42‡
Cyclophosphamide, total-body irradiation with or without other agents	288 (78)	68 (82)	72 (48)	
Total-body irradiation with or without other agents	10 (3)	2 (2)	55 (37)	
Busulfan, cyclophosphamide with or without other agents	68 (19)	13 (16)	8 (5)	
Busulfan and melphalan	1 (<1)	0	13 (9)	
Unknown	0	0	2 (1)	
Prophylaxis against GVHD — no. (%)				<0.001
Cyclosporine with or without other agents	67 (18)	21 (25)	100 (67)	
Cyclosporine, methotrexate with or without other agents	295 (81)	56 (68)	15 (10)	
Tacrolimus with or without other agents	5 (1)	6 (7)	19 (13)	
Other	0	0	1 (<1)	
Unknown	0	0	15 (10)	

Table 1. (Continued.)

Variable	Matched Bone Marrow (N=367)	Bone Marrow Mismatched for 1 Antigen (N=83)	Cord Blood Mismatched for 1 or 2 Antigens (N=150)	P Value
Nucleated-cell dose/kg of body weight — $\times 10^{-8}$	2.4 (0.02–17)	2.2 (0.01–5.8)	0.22 (0.10–0.65)	<0.001
HLA compatibility — no. (%)§				
Matched	367 (100)	0	0	
One-antigen mismatch	0	83 (100)	34 (23)	
Two-antigen mismatch	0	0	116 (77)	
ABO compatibility — no. (%)¶				
Matched	123 (34)	37 (45)	52 (35)	0.09
Minor mismatch	95 (26)	15 (18)	44 (29)	
Major mismatch	82 (22)	21 (25)	34 (23)	
Bidirectional	27 (7)	5 (6)	13 (8)	
Unknown	40 (11)	5 (6)	7 (5)	
Donor–recipient sex match — no. (%)				
Male–male	133 (37)	26 (32)	35 (23)	0.004
Male–female	99 (27)	16 (19)	32 (21)	
Female–male	71 (19)	25 (30)	37 (25)	
Female–female	59 (16)	14 (17)	39 (26)	
Unknown	5 (1)	2 (2)	7 (5)	
Donor–recipient serologic status for cytomegalovirus — no. (%)				
Negative–negative	117 (32)	25 (30)	69 (46)	<0.001
Negative–positive	114 (31)	21 (25)	79 (53)	
Positive–negative	60 (16)	14 (17)	0	
Positive–positive	66 (18)	19 (23)	0	
Unknown	10 (3)	4 (5)	2 (1)	
Follow-up — mo				
Median	48	48	40	0.16
Range	12–85	12–78	4–82	

* Race was reported by the transplantation center.

† CR indicates clinical remission (numbers represent first or second remission), CP chronic phase (numbers represent first or second chronic phase), RA refractory anemia, AP accelerated phase, PIF primary induction failure, BP blast phase, RAEFT refractory anemia with excess blast in transformation, and GVHD graft-versus-host disease.

‡ The P value is for a conditioning regimen that involves total-body irradiation as compared with a regimen without irradiation (variable as tested in multivariate models).

§ Transplants were classified as matched or as having one or two antigen mismatches, according to the total number of antigen mismatches at HLA-A and HLA-B loci (defined by serologic or low-to-intermediate-resolution DNA typing) and the number of allele mismatches at HLA-DRB1 (defined by high-resolution DNA typing). HLA data for cord-blood and bone marrow transplantations as reported by the International Bone Marrow Transplant Registry were provided by the transplantation centers. Typing of cord-blood units from the National Cord Blood Program and the blood of recipients was done at the F.H. Allen Immunogenetics Laboratory of the New York Blood Center and, in most cases, also at the HLA laboratory of each transplantation center before transplantation. Among one-antigen-mismatched bone-marrow transplants, 38 were mismatched at the A locus, 27 at the B locus, and 18 at the DRB1 locus. Among one-antigen-mismatched cord-blood transplants, 17 were mismatched at the A locus, 18 at the B locus, and 7 at the DRB1 locus. Among two-antigen-mismatched cord-blood transplants, 21 were mismatched at the A and DRB1 loci, 33 at the B and DRB1 loci, 49 at the A and B loci, 2 at both DRB1 loci, and 1 at both B loci.

¶ Matched donors and recipients are of the same blood group (A, B, or O). A minor mismatch indicates that donor blood from group O has been used in patients with group A, B, or AB and that donor blood from group A or B has been used in patients with group AB. A major mismatch indicates that donor blood from group A, B, or AB has been used in patients with group O and that donor blood from group AB has been used in patients with group A or B. A bidirectional match indicates that donor blood from group A has been used in patients with group B and that donor blood from group B has been used in patients with group A.

after cord-blood transplantation ($P < 0.001$). Corresponding times to platelet recovery were 29 days (95 percent confidence interval, 27 to 30), 29 days (95 percent confidence interval, 27 to 34), and 60 days (95 percent confidence interval, 54 to 71), respectively ($P < 0.001$). Despite early differences, the cumulative incidence of neutrophil recovery at day 100 ($P = 0.29$) and that of platelet recovery at one

year ($P = 0.16$) were similar after transplantations of mismatched bone marrow and of cord blood. Corresponding cumulative incidence rates after transplantation of HLA-matched bone marrow were significantly higher ($P < 0.01$) (Fig. 1).

ACUTE AND CHRONIC GVHD

Acute GVHD of grade 2, 3, or 4 developed in 176 of 367 recipients of HLA-matched bone marrow, in 43 of 83 recipients of mismatched bone marrow, and in 61 of 150 recipients of mismatched cord blood. The rate of acute GVHD grade 2, 3, or 4 was similar between patients who received mismatched cord blood and those who received HLA-matched bone marrow (hazard ratio, 0.81; 95 percent confidence interval, 0.59 to 1.10; $P = 0.17$). However, acute GVHD was less likely after transplantation of mismatched cord blood than after that of mismatched bone marrow (hazard ratio, 0.66; 95 percent confidence interval, 0.44 to 0.99; $P = 0.04$).

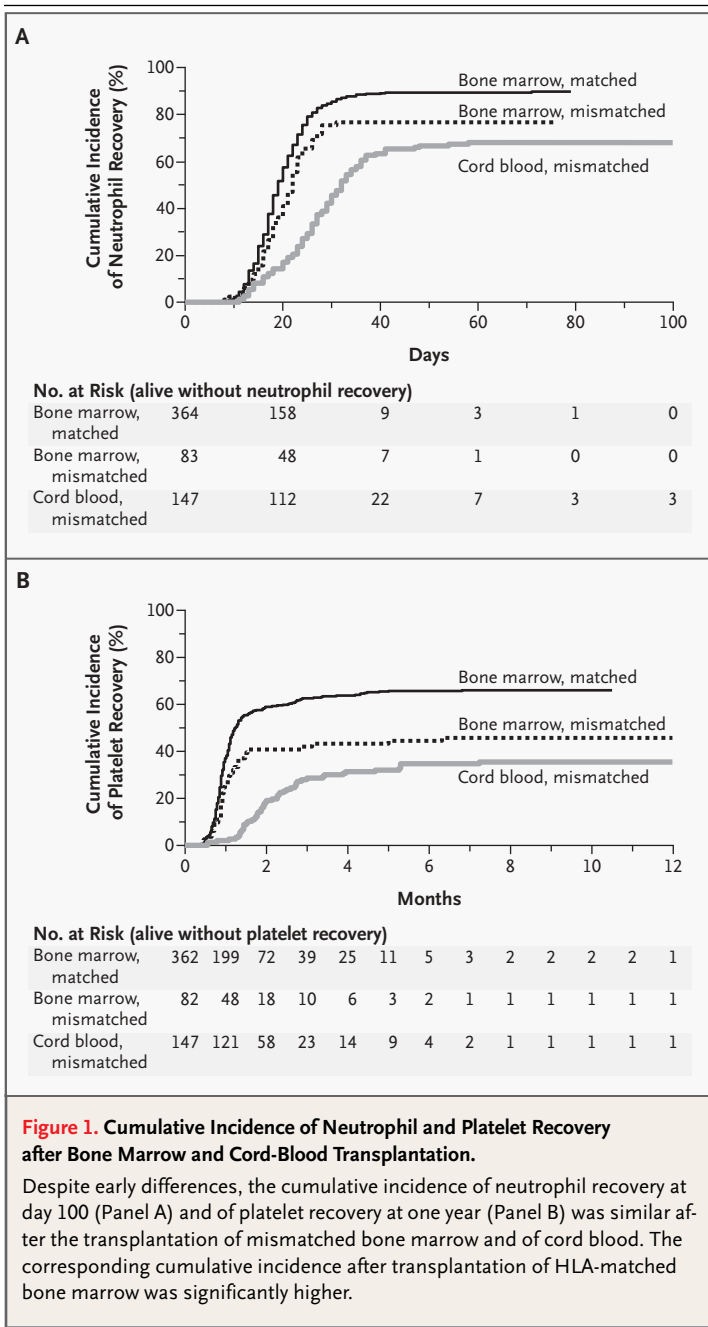
Among patients who survived for 90 days or longer, chronic GVHD developed in 86 of 243 recipients of HLA-matched bone marrow, in 17 of 43 recipients of mismatched bone marrow, and in 35 of 69 recipients of mismatched cord blood. The rate of chronic GVHD was higher among patients who received cord blood than among those who received HLA-matched marrow (hazard ratio, 1.62; 95 percent confidence interval, 1.08 to 2.42; $P = 0.02$) but similar to the rate among recipients of mismatched marrow (hazard ratio, 1.12; 95 percent confidence interval, 0.63 to 2.02; $P = 0.69$). Among patients with chronic GVHD, the proportion with extensive disease was lower among cord-blood recipients than among HLA-matched or mismatched marrow recipients, with rates of 33 percent, 52 percent, and 71 percent, respectively ($P = 0.03$).

TREATMENT-RELATED MORTALITY

Death from treatment-related complications occurred in 169 of 367 recipients of HLA-matched bone marrow, in 54 of 83 recipients of mismatched marrow, and in 95 of 150 recipients of cord blood. Rates of treatment-related death were similar among patients who received mismatched bone marrow and those who received mismatched cord blood; the rate was significantly lower among patients who received HLA-matched bone marrow (Table 2).

RELAPSE

Leukemia recurred after transplantation in 83 of 367 recipients of HLA-matched marrow, in 12 of



83 recipients of mismatched marrow, and in 26 of 150 recipients of mismatched cord blood. All of these rates were similar (Table 2).

LEUKEMIA-FREE SURVIVAL

Treatment failure (i.e., relapse or death) occurred in 252 of 367 recipients of HLA-matched marrow, in 66 of 83 recipients of mismatched marrow, and in 121 of 150 recipients of mismatched cord blood.

Rates of treatment failure were similar among patients who had received mismatched marrow and those who had received cord blood, but the rates were significantly lower among patients who had received HLA-matched marrow (Table 2). The probability of surviving for three years without a recurrence of leukemia, after adjustments were made for other significant factors, was 19 percent (95 percent confidence interval, 12 to 27 percent) for re-

Table 2. Results of Multivariate Analysis of Outcomes in 367 Recipients of Matched Marrow, 83 Recipients of Mismatched Marrow, and 150 Recipients of Mismatched Cord Blood.

Outcome	Hazard Ratio (95% CI)*	P Value
Treatment-related death†		
Mismatched marrow vs. matched marrow	1.91 (1.40–2.61)	<0.001
Mismatched cord blood vs. matched marrow	1.89 (1.45–2.48)	<0.001
Mismatched cord blood vs. mismatched marrow	0.99 (0.70–1.40)	0.96
Relapse‡		
Mismatched marrow vs. matched marrow	0.85 (0.46–1.57)	0.61
Mismatched cord blood vs. matched marrow	0.73 (0.46–1.14)	0.16
Mismatched cord blood vs. mismatched marrow	0.85 (0.43–1.70)	0.65
Treatment failure§		
Mismatched marrow vs. matched marrow	1.58 (1.20–2.08)	0.001
Mismatched cord blood vs. matched marrow	1.48 (1.18–1.86)	0.001
Mismatched cord blood vs. mismatched marrow	0.94 (0.69–1.28)	0.69
Death from any cause¶		
Mismatched marrow vs. matched marrow	1.66 (1.26–2.19)	<0.001
Mismatched cord blood vs. matched marrow	1.53 (1.21–1.94)	<0.001
Mismatched cord blood vs. mismatched marrow	0.92 (0.68–1.26)	0.62

* CI denotes confidence interval.

† Other significant variables were age, 16 to 40 years (baseline hazard ratio, 1.0) and more than 40 years (hazard ratio, 1.56; 95 percent confidence interval, 1.24 to 1.97; P<0.001); disease status, clinical remission (CR) 1, chronic phase (CP) 1, or refractory anemia (RA) (baseline hazard ratio, 1.0), CR2, CR3, or CR4, CP2, or accelerated phase (AP) (hazard ratio, 1.21; 95 percent confidence interval, 0.92 to 1.60; P=0.16), relapse, primary induction failure (PIF), blast phase (BP), refractory anemia with excess blasts (RAEB), or refractory anemia with excess blasts in transformation (RAEBT) (hazard ratio, 1.47; 95 percent confidence interval, 1.11 to 1.96; P=0.01); and donor–recipient serologic cytomegalovirus status, negative for donor and recipient (baseline hazard ratio, 1.0) and positive for donor, recipient, or both (hazard ratio, 1.58; 95 percent confidence interval, 1.24 to 2.01; P<0.001).

‡ Other significant variables were disease status, CR1, CP1, or RA (baseline hazard ratio, 1.0), CR2, CR3, or CR4, CP2, or AP (hazard ratio, 2.95; 95 percent confidence interval, 1.66 to 5.26; P<0.001), relapse, PIF, BP, RAEB, or RAEBT (hazard ratio, 7.71; 95 percent confidence interval, 4.48 to 13.27; P<0.001).

§ Other significant variables were age, 16 to 40 years (baseline hazard ratio, 1.0) and more than 40 years (hazard ratio, 1.43; 95 percent confidence interval, 1.17 to 1.74; P=0.001); disease status, CR1, CP1, or RA (baseline hazard ratio, 1.0), CR2, CR3, or CR4, CP2, or AP (hazard ratio, 1.47; 95 percent confidence interval, 1.15 to 1.88; P=0.002), relapse, PIF, BC, RAEB, or RAEBT (hazard ratio, 2.26; 95 percent confidence interval, 1.77 to 2.88; P<0.001); and donor–recipient serologic cytomegalovirus status, negative for donor and recipient (baseline hazard ratio, 1.0) and positive for donor, recipient, or both (hazard ratio, 1.58; 95 percent confidence interval, 1.28 to 1.94; P<0.001).

¶ Other significant variables were age, 16 to 40 years (baseline hazard ratio, 1.0) and more than 40 years (hazard ratio, 1.43; 95 percent confidence interval, 1.17 to 1.75; P=0.001); disease status, CR1, CP1, or RA (baseline hazard ratio, 1.0), CR2, CR3, or CR4, CP2, or AP (hazard ratio, 1.44; 95 percent confidence interval, 1.13 to 1.85; P=0.004), relapse, PIF, BC, RAEB, or RAEBT (hazard ratio, 2.25; 95 percent confidence interval, 1.76 to 2.87; P<0.001); and donor–recipient serologic cytomegalovirus status, negative for donor and recipient (baseline hazard ratio, 1.0) and positive for donor, recipient, or both (hazard ratio, 1.58; 95 percent confidence interval, 1.28 to 1.94; P<0.001).

recipients of mismatched marrow and 23 percent (95 percent confidence interval, 17 to 30 percent) for recipients of cord blood ($P=0.69$); the probability of such survival after transplantation with HLA-matched marrow was higher, at 33 percent (95 percent confidence interval, 28 to 37 percent; $P=0.001$) (Fig. 2A).

OVERALL MORTALITY

Death due to any cause after transplantation occurred in 247 of 367 recipients of HLA-matched marrow, in 65 of 83 recipients of mismatched marrow, and in 117 of 150 recipients of mismatched cord blood (Table 3). Mortality rates were similar after transplantation of mismatched marrow and of cord blood but significantly lower after transplantation of HLA-matched marrow (Table 2). Adjusted probabilities of three-year survival were 20 percent (95 percent confidence interval, 12 to 28 percent) for recipients of mismatched marrow, 26 percent (95 percent confidence interval, 19 to 32 percent) for recipients of cord blood ($P=0.62$), and 35 percent (95 percent confidence interval, 30 to 39 percent) for recipients of HLA-matched marrow ($P<0.001$) (Fig. 2B).

The proportion of deaths that occurred during the first 100 days after transplantation of mismatched marrow or cord blood was significantly higher than that after transplantation of HLA-matched marrow (70 percent vs. 50 percent, $P<0.001$). The proportion of deaths that were related to infections within 100 days after transplantation was significantly higher among recipients of mismatched cord blood than among recipients of either HLA-matched marrow or mismatched marrow (45 percent, 21 percent, and 24 percent, respectively; $P=0.01$). Beyond day 100, the proportions of infection-related deaths were similar in the three groups. Of the infection-related deaths, the proportions that resulted from bacteria, viruses, and fungi did not differ among the groups.

DISCUSSION

Our objective was to compare the effectiveness of hematopoietic stem-cell transplantation with the use of cord-blood grafts mismatched for one or two HLA antigens, HLA-matched bone marrow, and bone marrow mismatched for one antigen, all from unrelated donors, in adults with leukemia. Significant prognostic factors were older age (over 40 years), advanced leukemia, and positivity for cyto-

megalovirus in the donor, recipient, or both. After we adjusted for these factors, treatment-related mortality, the rate of treatment failure, and overall mortality were significantly lower after the transplantation of HLA-matched marrow than after the transplantation of HLA-mismatched marrow or cord blood. The rate of recurrence of leukemia was similar among the three groups. It is important to note that there were no significant differences in treatment-related mortality, the rate of treatment failure, or overall mortality between recipients of HLA-mismatched marrow and those who received mismatched cord blood despite the fact that 77 percent of cord-blood grafts were mismatched for two HLA antigens, whereas all mismatched-marrow grafts were mismatched for only one antigen. The relative efficacy of HLA-matched and mismatched bone marrow and cord-blood grafts did not differ according to age, type of leukemia, or other prognostic variables we studied.

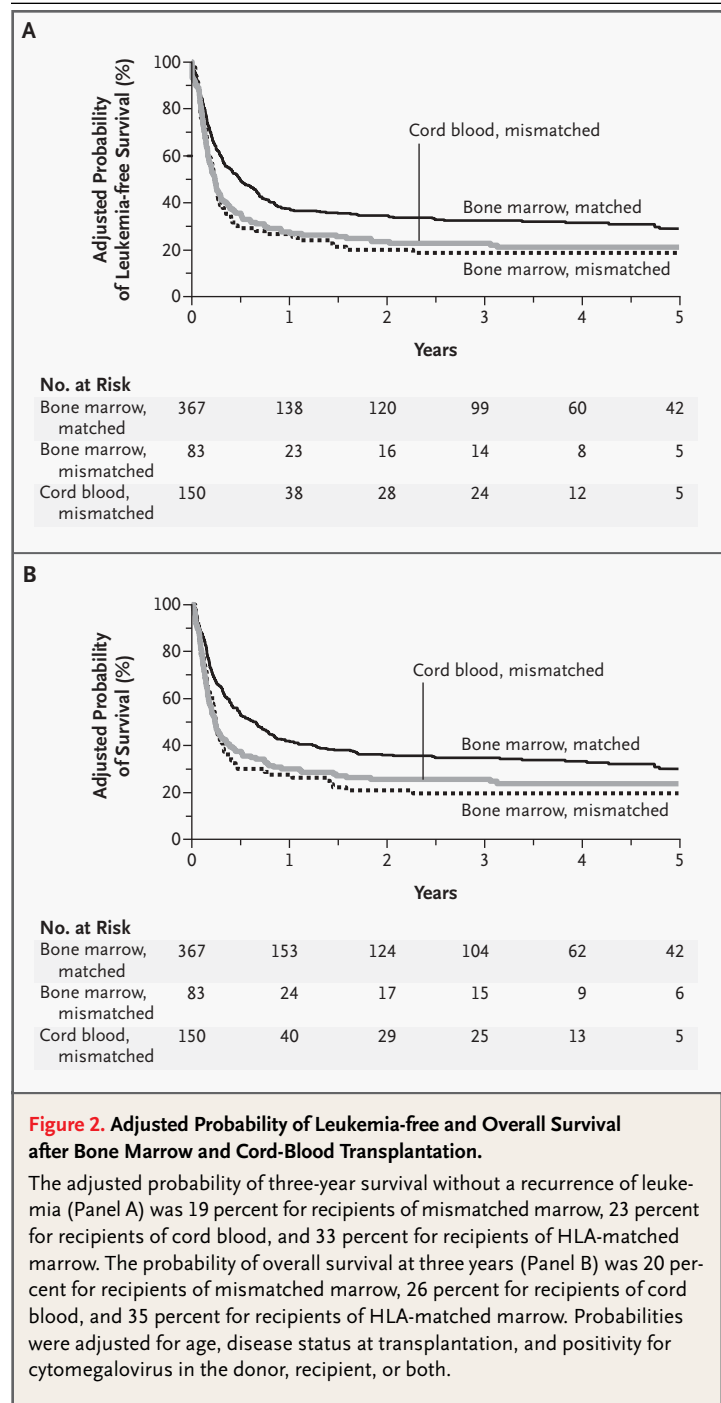
An HLA mismatch is perhaps the strongest risk factor for GVHD and other outcomes after bone marrow transplantation. The association of HLA disparity with GVHD after cord-blood transplantation is less clear.^{8-10,18} We did not observe differences in outcome between transplantations that involved cord blood mismatched for one and two HLA antigens; this finding contrasts with our recent analysis in which an increasing HLA disparity in children was associated with worse outcomes after transplantation of cord blood (unpublished data). However, in that study, overall outcomes were better, the number of patients was larger, doses of nucleated cells were higher, and the range of HLA disparity was wider (from 0 to 3 antigens). All of these factors may have produced an effect that was easier to detect. Most of the cord-blood grafts (77 percent) in the current study were mismatched at two HLA loci; the relatively small number mismatched at one HLA locus gave the study low statistical power to detect an effect of the number of mismatches. Moreover, the definition of an HLA match in this study included only six HLA loci and low-resolution typing for class I antigens. This is how cord-blood units were typed and selected during the study period, but bone marrow donors were often selected with the use of criteria that included high-resolution typing for 8 or 10 HLA antigens. It may be that undetected mismatches also decreased our ability to find an effect of the HLA matching. Further analysis of larger numbers of patients, with the use of more sensitive typing techniques, will be

necessary before we can conclude that increasing HLA disparity does not affect the outcome of cord-blood transplantation in adults.

A major limitation to the use of cord-blood grafts in adults is the concern that these grafts have an insufficient number of precursor cells as compared with bone-marrow grafts. Reports of cord-blood transplantation in adults suggest that hematopoietic recovery is faster with higher cell doses.¹⁶⁻¹⁸ The median dose of nucleated cells in our study was 2.2×10^7 per kilogram of body weight, which is similar to that reported in other studies, and the rates of neutrophil and platelet recovery were lower with cord blood than with bone marrow. However, we did not find a significant effect of the cell dose on the rates of mortality and treatment failure among cord-blood recipients. The range of doses was relatively narrow (80 percent of patients received a dose of less than 3.0×10^7 per kilogram), which may have precluded the detection of a cell-dose effect.

We observed, as others have, that the proportion of deaths related to infection was higher soon after cord-blood transplantation than after transplantation of HLA-matched and mismatched bone marrow — a difference that is possibly the result of slower myeloid recovery.^{14,15} Although infections were more common with transplantation of cord blood, the distribution of types of infection did not differ significantly among recipients of HLA-matched marrow, mismatched marrow, and cord blood. Others have also reported delayed neutrophil and lymphocyte recovery and higher rates of bacterial infections in the early post-transplantation period (i.e., less than 50 days) in the case of cord blood, with overall rates of infection at later times being similar to those for marrow transplantation.¹⁵ Several ongoing studies are attempting to improve hematopoietic recovery and thereby decrease infection in the early period after cord-blood transplantation.²⁵⁻²⁸

All aspects of the transplantation regimen, including the choice of graft type, were determined by the transplantation centers. A higher proportion of cord-blood recipients than marrow recipients had advanced leukemia at the time of transplantation, which probably reflects a practice of using these grafts in patients with limited treatment options. Any observational study that compares different interventions is subject to bias owing to the complex criteria for selection that underlie the choice of intervention, and our study is no exception. However, our ability to adjust for key risk fac-



tors made a controlled (though not randomized) comparison possible. The results support a standard of care in which transplantation of HLA-matched marrow is performed when a donor is available in a timely manner. In the absence of such a donor, cord blood mismatched for one or two antigens or

Table 3. Causes of Death, According to Type of Transplant.*

Cause	Early Death			Late Death		
	Mismatched Cord Blood (N=85)	Mismatched Marrow (N=46)	Matched Marrow (N=127)	Mismatched Cord Blood (N=32)	Mismatched Marrow (N=19)	Matched Marrow (N=120)
	<i>percent of patients</i>					
Primary disease	17	13	18	22	26	45
Graft-versus-host disease	8	15	19	9	11	11
Interstitial pneumonitis	5	22	13	6	26	8
Infection	45	24	21	35	26	20
Organ failure	14	13	19	19	11	8
Other	11	13	10	9	0	8

* Early death was defined as death that occurred during the first 100 days after transplantation, and late death as death more than 100 days after transplantation.

marrow grafts mismatched for one antigen are acceptable alternatives and have similar outcomes. The rapid availability of a unit of cord blood (i.e., after a median of 13.5 days)²⁹ may be a particular advantage for patients who require urgent transplantation. The slow rate of hematopoietic recovery remains a major deterrent to the use and success of cord-blood transplantation in adults, and novel strategies to overcome this obstacle are needed.

Supported by a Public Health Service grant (U24-CA76518) from the National Cancer Institute, the National Institute of Allergy and Infectious Diseases, the National Heart, Lung, and Blood Institute, the Abraham J. and Phyllis Katz Foundation, the Leukemia and Lymphoma Society of America, the American Society of Clinical Oncology, and the Children's Leukemia Research Association. Dr. Laughlin is a Leukemia Scholar in Clinical Research, the Leukemia and Lymphoma Society of America. Dr. Eapen is the recipient of a Clinical Research Career Development award from the American Society of Clinical Oncology.

Dr. Champlin reports having received consulting fees from StemCyte.

REFERENCES

- Bone marrow transplants: despite recruitment successes national programs may be underutilized. Washington, D.C.: General Accounting Office, 2002. (GAO publication no. GAO-03-182.)
- McGlave P, Bartsch G, Anasetti C, et al. Unrelated donor marrow transplantation therapy for chronic myelogenous leukemia: initial experience of the National Marrow Donor Program. *Blood* 1993;81:543-50.
- 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.
- Kernan NA, Bartsch G, Ash RC, et al. Analysis of 462 transplantations from unrelated donors facilitated by the National Marrow Donor Program. *N Engl J Med* 1993;328:593-602.
- Szydlo R, Goldman JM, Klein JP, et al. Results of allogeneic bone marrow transplants for leukemia using donors other than HLA-identical siblings. *J Clin Oncol* 1997;15:1767-77.
- Wagner JE, Rosenthal J, Sweetman R, et al. Successful transplantation of HLA-matched and HLA-mismatched umbilical cord blood from unrelated donors: analysis of engraftment and acute graft-versus-host disease. *Blood* 1996;88:795-802.
- 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.
- 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.
- 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.
- Locatelli F, Rocha V, Chastang C, et al. Factors associated with outcome after cord blood transplantation in children with acute leukemia. *Blood* 1999;93:3662-71.
- Rocha V, Wagner JE Jr, 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.
- 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.
- Barker JN, Davies SM, DeFor T, Ramsay NKC, 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.
- Saavedra S, Sanz GF, Jarque I, et al. Early infections in adult patients undergoing unrelated donor cord blood transplantation. *Bone Marrow Transplant* 2002;30:937-43.
- Hamza NS, Lisgaris M, Yadavalli G, et al. Kinetics of myeloid and lymphocyte recovery and infectious complications after unrelated HLA-mismatched allogeneic umbilical cord blood transplantation in adults. *Br J Haematol* 2004;124:488-98.
- Ooi J, Iseki T, Takahashi S, et al. A clinical comparison of unrelated cord blood transplantation and unrelated bone marrow trans-

- plantation for adult patients with acute leukaemia in complete remission. *Br J Haematol* 2002;118:140-3.
17. Sanz GE, Saavedra S, Planelles D, et al. Standardized unrelated donor cord blood transplantation in adults with hematologic malignancies. *Blood* 2001;98:2332-8.
18. 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.
19. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant* 1995;15:825-8.
20. Flowers ME, Kanasu E, Sullivan KM. Pathophysiology and treatment of graft-versus-host disease. *Hematol Oncol Clin North Am* 1999;13:1091-112.
21. Klein JP, Moeschberger ML. Survival analysis: techniques of censored and truncated data. New York: Springer-Verlag, 2003.
22. Cox DR. Regression models and life-tables. *J R Stat Soc [B]* 1972;34:187-220.
23. Andersen PK, Klein JP, Zhang M-J. Testing for centre effects in multi-centre survival studies: a Monte Carlo comparison of fixed and random effects tests. *Stat Med* 1999;18:1489-500.
24. Clark TG, Altman DG, De Stavola BL. Quantification of the completeness of follow-up. *Lancet* 2002;359:1309-10.
25. Barker JN, Weisdorf DJ, DeFor TE, Blazar BR, Miller JS, Wagner JE. Rapid and complete donor chimerism in adult recipients of unrelated donor umbilical cord blood transplantation after reduced-intensity conditioning. *Blood* 2003;102:1915-9.
26. Jaroscak J, Goltry K, Smith A, et al. Augmentation of umbilical cord blood (UCB) transplantation with ex vivo expanded UCB cells: results of a phase 1 trial using the AastromReplicell System. *Blood* 2003;101:5061-7.
27. Fernandez MN, Regidor C, Cabrera R, et al. Unrelated umbilical cord blood transplants in adults: early recovery of neutrophils by supportive co-transplantation of a low number of highly purified peripheral blood CD34+ cells from an HLA-haploidentical donor. *Exp Hematol* 2003;31:535-44.
28. Shpall EJ, Quinones R, Giller R, et al. Transplantation of ex vivo expanded cord blood. *Biol Blood Marrow Transplant* 2002;8:368-76.
29. Barker JN, Krepski TP, DeFor TE, Davies SM, Wagner JE, Weisdorf DJ. Searching for unrelated donor hematopoietic stem cells: availability and speed of umbilical cord blood versus bone marrow. *Biol Blood Marrow Transplant* 2002;8:257-60.

Copyright © 2004 Massachusetts Medical Society.

JOURNAL EDITORIAL FELLOW

The *Journal's* editorial office invites applications for a one-year research fellowship beginning in July 2005 from individuals at any stage of training. The editorial fellow will work on *Journal* projects and will participate in the day-to-day editorial activities of the *Journal* but is expected in addition to have his or her own independent projects. Please send curriculum vitae and research interests to the Editor-in-Chief, 10 Shattuck St., Boston, MA 02115 (fax, 617-739-9864), by January 15, 2005.