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GRAFT-VERSUS-HOST DISEASE IN CHILDREN WHO HAVE RECEIVED A CORD-BLOOD OR BONE MARROW TRANSPLANT FROM AN HLA-IDENTICAL SIBLING

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ABSTRACT

Background Umbilical-cord blood as an alternative to bone marrow for hematopoietic stem-cell transplantation may lower the risk of graft-versus-host disease (GVHD).

Methods We studied the records of 113 recipients of cord blood from HLA-identical siblings from the period from 1990 through 1997 and compared them with the records of 2052 recipients of bone marrow from HLA-identical siblings during the same period. The study population consisted of children 15 years of age or younger. We compared the rates of GVHD, hematopoietic recovery, and survival using Cox proportional-hazards regression to adjust for potentially confounding factors.

Results Recipients of cord blood were younger than recipients of bone marrow (median age, 5 years vs. 8 years; $P < 0.001$), weighed less (median weight, 17 kg vs. 26 kg; $P < 0.001$), and were less likely to have received methotrexate for prophylaxis against GVHD (28 percent vs. 65 percent, $P < 0.001$). Multivariate analysis demonstrated a lower risk of acute GVHD (relative risk, 0.41; $P = 0.001$) and chronic GVHD (relative risk, 0.35; $P = 0.02$) among recipients of cord-blood transplants. As compared with recovery after bone marrow transplantation, the likelihood of recovery of the neutrophil count and the platelet count was significantly lower in the first month after cord-blood transplantation (relative risk, 0.40 [$P < 0.001$], and relative risk, 0.20 [$P < 0.001$], respectively). Mortality was similar in the two groups (relative risk of death in the recipients of cord blood, 1.15; $P = 0.43$).

Conclusions Recipients of cord-blood transplants from HLA-identical siblings have a lower incidence of acute and chronic GVHD than recipients of bone marrow transplants from HLA-identical siblings. (N Engl J Med 2000;342:1846-54.)

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SINCE the first successful transplantation of hematopoietic stem cells from umbilical-cord blood 11 years ago,¹ banks have been established worldwide to supply cord blood as an alternative to bone marrow for transplantation. Globally, about 200 transplantations of cord blood from related donors and 1000 of cord blood from unrelated donors have been performed.²⁻⁷ The benefits of cord blood for transplantation are the immediate availability of cells, the absence of risk to the donor, and the low risk of transmitting infectious diseases. A potential advantage of cord blood over bone marrow is a lower risk of graft-versus-host disease (GVHD). The immunologic properties of lymphocytes from cord blood,⁸⁻¹² as well as experimental results^{13,14} and clinical experience,^{2,5} suggest that the risk of GVHD may be lower after cord-blood transplantation than after bone marrow transplantation. Because transplantation of umbilical-cord blood has not been compared with transplantation of bone marrow after adjustment for factors known to influence the risk of GVHD, the issue is controversial.

Using data from two registries, we studied hematopoietic stem-cell transplantation in 113 children who received cord-blood transplants from HLA-identical siblings and 2052 children who received bone marrow transplants from HLA-identical siblings during the same period. We used a multivariate Cox regression analysis to adjust for factors that could potentially influence the risk of GVHD.

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METHODS

Collection of Data

Data on children who underwent cord-blood transplantation were provided by the Eurocord–Cord Blood Transplant Group (CBTG) and the International Bone Marrow Transplant Registry. Data on children who underwent bone marrow transplantation were provided by the International Bone Marrow Transplant Registry. Overlapping cases were identified, and the accuracy of the data was verified by both registries.

Eurocord–CBTG is an international registry in Paris that operates on behalf of the European Group for Blood and Marrow Transplantation. Participation is open to European and non-European centers that perform cord-blood transplantation, although most centers are in Europe. For each recipient, the registry collects, by questionnaire, data on the reasons for transplantation, specific characteristics of the cord-blood transplant, and outcomes. More than 100 transplantation centers participate.⁶ Participating centers report consecutive transplantations directly to the Eurocord–CBTG registry or to the registry of the European Group for Blood and Marrow Transplantation. Entries in both registries are checked by Eurocord–CBTG physicians at six-month intervals to eliminate overlap and to monitor compliance. Patients are followed longitudinally, with follow-up every six months. Submitted data are reviewed by two physicians, and the quality of the data is ensured by computerized checks for errors.

The International Bone Marrow Transplant Registry is a working group of more than 300 transplantation centers worldwide that contribute detailed data on allogeneic hematopoietic stem-cell transplantations to a statistical center at the Health Policy Institute of the Medical College of Wisconsin (in Milwaukee).¹⁵ Participating centers are required to report all transplantations consecutively; compliance is monitored by on-site audits. Patients are followed longitudinally, with yearly follow-up. Computerized checks for errors, physicians' reviews of submitted data, and on-site audits of participating centers ensure the quality of the data.

Inclusion Criteria

Our study involved patients who received a first transplant of allogeneic cord blood or bone marrow that had not been depleted of T cells; who were reported to Eurocord–CBTG, the International Bone Marrow Transplant Registry, or both; who were 15 years of age or younger at the time of transplantation; whose donor was an HLA-identical sibling; and who underwent transplantation between January 1, 1990, and December 31, 1997. A total of 113 recipients of a cord-blood transplant and 2052 recipients of a bone marrow transplant at 207 transplantation centers satisfied these criteria. At most, 60 of these transplantations have been described previously.^{2,5,16}

Cord-Blood Transplantation

Patients

Table 1 shows the characteristics of the 113 children who underwent cord-blood transplantation. The median age was five years, and the median weight was 17 kg. Of the 61 of these children who underwent transplantation because of malignant disease, 47 had acute leukemia or chronic myelogenous leukemia. Of these, 21 percent had early leukemia (in first remission or first chronic phase), 60 percent had intermediate-stage leukemia (in second or subsequent remission or accelerated phase), and 19 percent had advanced leukemia (not in remission or in blast phase). The median length of time from diagnosis to transplantation was 25 months. The median period of follow-up was 27 months (range, 3 to 85).

Transplantations

Twenty-seven patients who underwent cord-blood transplantation received total-body irradiation as part of the conditioning regimen (Table 1). Prophylaxis against GVHD consisted mainly of cy-

closporine alone (58 percent) or in combination with glucocorticoids or other drugs, not including methotrexate (8 percent); 28 percent also received methotrexate. Methods of collection, cryopreservation, and storing of cord-blood units varied among centers. The median number of nucleated cells infused was 0.47×10^8 per kilogram of body weight (range, $<1.0 \times 10^8$ to 3.6×10^8 per kilogram). Data on the numbers of colony-forming cells, CD3+ cells, and CD34+ cells in the graft were not available.

Bone Marrow Transplantation

Patients

Table 1 shows the characteristics of the 2052 children who received bone marrow transplants. The median age was eight years, and the median weight was 26 kg. Of the 1262 children who underwent transplantation for malignant disease, 1081 had acute leukemia or chronic myelogenous leukemia. Of these, 44 percent had early leukemia, 44 percent had intermediate-stage leukemia, and 12 percent had advanced leukemia. The median time from diagnosis to transplantation was 10 months. The median period of follow-up was 45 months (range, 1 to 101).

Transplantations

A total of 705 children who underwent bone marrow transplantation received total-body irradiation (Table 1). Prophylaxis against GVHD consisted mainly of cyclosporine in combination with methotrexate, with or without glucocorticoids (65 percent). Twenty percent received cyclosporine alone. The median number of nucleated cells infused was 3.5×10^8 per kilogram (range, $<1.0 \times 10^8$ to 41×10^8 per kilogram).

End Points

Grade II, III, or IV acute GVHD was the primary end point of our study. Acute GVHD was diagnosed and graded with the use of standard criteria by the physicians who performed the transplantations at each center¹⁷; only patients who survived at least 21 days were evaluated. Chronic GVHD was diagnosed according to standard criteria¹⁸; only patients who survived at least 90 days with sustained engraftment were evaluated.

Neutrophil recovery and platelet recovery were analyzed separately in patients who survived for at least 21 days after transplantation. Indicators of recovery were a neutrophil count of at least 500 per cubic millimeter for three consecutive days and a platelet count of at least 20×10^3 per cubic millimeter that was maintained for seven consecutive days without platelet transfusions. Data on patients who underwent a second transplantation because of non-engraftment were censored at the time of conditioning for the second procedure or, if no additional conditioning was administered, at the time of the second transplantation. For analyses of survival, data on patients were censored at the time of the last follow-up visit.

Statistical Analysis

For both groups, we compared variables related to the transplant recipients, the underlying diseases, and the transplantation procedures, using the chi-square statistic for categorical variables and the Mann–Whitney test for continuous variables. The probability of survival was estimated by the Kaplan–Meier method; the log-rank test was used for univariate comparisons. Cumulative incidence curves were used to calculate the probability of acute GVHD, chronic GVHD, and neutrophil and platelet recovery.¹⁹ The associations of the type of graft with outcomes were evaluated in multivariate analyses, with the use of Cox proportional-hazards regression to adjust for differences in potentially confounding variables between the cohorts.

The variables considered were the recipient's age, weight, and status with respect to cytomegalovirus (determined by serologic testing); the sex of the recipient and the donor, and the degree of ABO matching; the type and duration of the underlying disease;

TABLE 1. CHARACTERISTICS OF THE RECIPIENTS OF CORD-BLOOD OR BONE MARROW TRANSPLANTS FROM HLA-IDENTICAL SIBLINGS.

| CHARACTERISTIC | CORD-BLOOD TRANSPLANT (N=113) | BONE MARROW TRANSPLANT (N=2052) | P VALUE* | CHARACTERISTIC | CORD-BLOOD TRANSPLANT (N=113) | BONE MARROW TRANSPLANT (N=2052) | P VALUE* |
|--|-------------------------------|---------------------------------|----------|---|-------------------------------|---------------------------------|----------|
| Patient-related | | | | Donor-related | | | |
| Age | | | | Sex of donor and recipient — no. (%) | | | <0.001 |
| Median — yr | 5 | 8 | | Male/male | 37 (34) | 674 (33) | |
| Range — yr | <1–15 | <1–15 | <0.001 | Female/female | 29 (26) | 371 (18) | |
| <10 yr — no. (%) | 101 (89) | 1280 (62) | <0.001 | Female/male | 25 (23) | 414 (20) | |
| 10–15 yr — no. (%) | 12 (11) | 772 (38) | | Male/female | 19 (17) | 585 (29) | |
| Male sex — no. (%) | 59 (52) | 1264 (62) | 0.46 | Extent of ABO match — no. (%)** | | | <0.001 |
| Weight — kg | | | | Match | 66 (62) | 1122 (67) | |
| Median | 17 | 26 | <0.001 | Minor mismatch | 13 (12) | 248 (15) | |
| Range | 5–46 | 4–109 | | Major mismatch | 28 (26) | 304 (18) | |
| Cytomegalovirus serologic status before transplantation — no. (%)† | | | 0.14 | Transplantation-related | | | |
| Negative | 57 (52) | 863 (43) | | Conditioning regimen — no. (%)†† | | | 0.07 |
| Positive | 53 (48) | 1153 (57) | | Regimen based on total-body irradiation | 27 (24) | 705 (34) | |
| Disease-related | | | | Chemotherapy | 86 (76) | 1345 (66) | |
| Type of disease — no. (%) | | | 0.11 | Prophylaxis against graft-versus-host disease — no. (%) | | | <0.001 |
| Malignant | 61 (54) | 1262 (62) | | Cyclosporine alone | 65 (58) | 412 (20) | |
| Nonmalignant | 52 (46) | 790 (38) | | Cyclosporine and glucocorticoids | 9 (8) | 282 (14) | |
| Diagnosis — no. (%) | | | <0.01 | Cyclosporine and other (not methotrexate) | 0 | 16 (1) | |
| Acute leukemia | 41 (36) | 991 (48) | | Cyclosporine and methotrexate | 29 (26) | 1232 (60) | |
| Chronic myelogenous leukemia | 6 (5) | 90 (4) | | Cyclosporine, methotrexate, and glucocorticoids | 2 (2) | 105 (5) | |
| Lymphoma | 2 (2) | 48 (2) | | Cyclosporine, methotrexate, and other | 0 | 5 (1) | |
| Myelodysplasia or other cancers | 12 (11) | 133 (6) | | Hematopoietic growth factors‡‡ | | | <0.001 |
| Aplastic anemia | 8 (7) | 290 (14) | | No | 64 (59) | 1611 (79) | |
| Congenital disorders of hematopoiesis‡ | 35 (31) | 385 (19) | | Yes | 45 (41) | 425 (21) | |
| Congenital immune deficiencies§ | 5 (4) | 54 (3) | | No. of nucleated cells infused — ×10 ⁻⁸ /kg | | | <0.001 |
| Other¶ | 4 (4) | 61 (3) | | Median | 0.47 | 3.5 | |
| | | | | Range | <1.0–3.6 | <1.0–41 | |
| | | | | Time from diagnosis to transplantation — mo | | | <0.001 |
| | | | | Median | 25 | 10 | |
| | | | | Range | 2–118 | <1–175 | |

*The chi-square test was used for categorical variables; the Mann-Whitney nonparametric test was used for continuous variables.

†Data were not available for 3 patients in the cord-blood group and 36 in the bone marrow group.

‡The congenital disorders of hematopoiesis were unclassified inherited abnormalities of the differentiation or function of erythrocytes (8 patients), Fanconi's anemia (106), Diamond-Blackfan anemia (15), β-thalassemia major (53), α-thalassemia major (3), β⁺-thalassemia major (104), β⁰-thalassemia major (111), hemoglobin E-β-thalassemia major (4), hemoglobin S-β-thalassemia major (2), sickle cell anemia (13), and amegakaryocytic thrombocytopenia (1).

§The congenital immune deficiencies were unspecified immune disorders (3 patients); severe combined immunodeficiency (SCID) and absence of T and B cells (11); SCID, absence of T cells, and normal B cells (4); reticular dysgenesis (1); bare lymphocyte syndrome (2); SCID and other deficiencies (4); Wiskott-Aldrich syndrome (18); chronic granulomatous disease (5); Chédiak-Higashi syndrome (1); X-linked lymphoproliferative syndrome (1); leukocyte adhesion deficiency (4); Kostmann's syndrome (2); and unspecified SCID (3).

¶Other diagnoses were unclassified inherited disorders of metabolism (6 patients), osteopetrosis (13), other inherited metabolic disorders (1), Hurler's syndrome (10), Hunter's syndrome (4), Sanfilippo's syndrome (1), Morquio's syndrome (1), Maroteaux-Lamy syndrome (1), Gaucher's disease (6), metachromatic leukodystrophy (3), adrenoleukodystrophy (2), globoid-cell leukodystrophy (1), Niemann-Pick disease (2), histiocytic disorder (8), familial erythrophagocytic lymphohistiocytosis (3), histiocytosis X (1), and other (2).

||Data were not available for three patients in the cord-blood group and eight in the bone marrow group.

**Data were not available for 6 patients in the cord-blood group and 378 in the bone marrow group.

††Data were not available for two patients in the bone marrow group.

‡‡Data were not available for 4 patients in the cord-blood group and 16 in the bone marrow group.

the conditioning regimen; the type of prophylaxis against GVHD; the use or nonuse of granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, or both to hasten the recovery of neutrophils; and the dose of nucleated cells infused. Only factors significantly associated with an outcome ($P < 0.05$) were retained in the final models. The absence of a factor from the final models indicates that there was no significant association with the risk of the outcome described.

For each outcome and covariate, the assumption of proportional hazards was tested with the use of time-dependent covariates. When the test indicated differential effects over time (nonproportional hazards), we constructed models in which the interval after transplantation was divided into two periods, and we used the maximized partial-likelihood method to find the most appropriate breakpoint.²⁰ For these variables, we determined the relative risks for each of the periods. A forward stepwise method of selecting variables at a significance level of less than 0.05 was used to identify covariates other than the type of graft that were associated with outcome. In each step, the covariate for the type of graft was included in the model. First-order interactions between the type of graft and significant covariates were considered. We tested the overall effects of covariates using Wald's test. To determine the effects of the transplantation center, we tested a random-effects model²¹; there was no evidence that center-related effects confounded our previous findings. All *P* values are two-sided.

RESULTS

Patients

Recipients of cord-blood transplants tended to be younger ($P < 0.001$) and weigh less ($P < 0.001$) than recipients of bone marrow transplants (Table 1). The proportion of patients with malignant or nonmalignant diseases was similar in both groups ($P = 0.11$). However, the proportion of patients with acute leukemia was smaller and the proportion with congenital disorders of hematopoiesis was larger in the cord-blood group ($P < 0.01$).

Transplantation

The interval between diagnosis and transplantation was longer for recipients of cord-blood transplants than for recipients of bone marrow transplants ($P < 0.001$). The cord-blood group had more pairs of female donors and female recipients and fewer pairs of male donors and female recipients than the bone marrow group ($P < 0.001$). The cord-blood group also had more donor–recipient pairs with major ABO mismatches ($P < 0.001$). Substantially fewer recipients of cord-blood transplants received methotrexate for prophylaxis against GVHD ($P < 0.001$). Hematopoietic growth factors were used more frequently after cord-blood transplantation ($P < 0.001$). Cord-blood grafts contained almost one log fewer nucleated cells than did the bone marrow grafts ($P < 0.001$).

Acute and Chronic GVHD

In the univariate analysis, which was not adjusted for differences among patients, the cumulative incidence of grade II, III, and IV acute GVHD was significantly lower after cord-blood transplantation: 14 percent (95 percent confidence interval, 8 to 22 percent), as compared with 24 percent (95 percent confidence

interval, 22 to 26 percent) after bone marrow transplantation ($P = 0.02$) (Fig. 1A). Acute GVHD was less severe in patients who received cord-blood transplants. Among 107 cord-blood recipients who could be evaluated (those who survived at least 21 days after transplantation), 18 had grade I acute GVHD (17 percent), 13 had grade II acute GVHD (12 percent), 2 had grade III acute GVHD (2 percent), and none had grade IV acute GVHD. In contrast, among 2012 bone marrow recipients who could be evaluated, 413 had grade I acute GVHD (21 percent), 314 had grade II acute GVHD (16 percent), 111 had grade III acute GVHD (6 percent), and 73 had grade IV acute GVHD (4 percent) ($P = 0.004$). Similar differences in severity were found when the manifestations of GVHD in the skin, gut, and liver were analyzed separately (data not shown).

Chronic GVHD affected 5 of 93 recipients of cord-blood transplants who survived more than 90 days (5 percent) and 257 of 1779 recipients of bone marrow transplants who survived at least 90 days (14 percent). The three-year cumulative incidence of chronic GVHD was 6 percent (95 percent confidence interval, 2 to 13 percent) after cord-blood transplantation and 15 percent (95 percent confidence interval, 13 to 17 percent) after bone marrow transplantation ($P = 0.02$) (Fig. 1B).

Results were similar in the multivariate analysis (Table 2). After adjustment for relevant risk factors, the risk of acute and chronic GVHD was significantly lower after cord-blood transplantation than after bone marrow transplantation. The relative risk of grade II, III, or IV acute GVHD and chronic GVHD in the cord-blood group, as compared with the bone marrow group, was 0.41 (95 percent confidence interval, 0.24 to 0.70; $P = 0.001$) and 0.35 (95 percent confidence interval, 0.14 to 0.85; $P = 0.02$), respectively. Other variables associated with a lower risk of acute GVHD were nonmalignant disease, a shorter interval between diagnosis and transplantation, absence of a major ABO mismatch, and the use of methotrexate in combination with cyclosporine for prophylaxis against GVHD. Other variables associated with a lower risk of chronic GVHD were an age of less than 10 years, nonmalignant disease, and the use of methotrexate in combination with cyclosporine for prophylaxis against GVHD.

Hematopoietic Recovery

The median number of days required for the neutrophil count to reach at least 500 per cubic millimeter after cord-blood transplantation was 26, as compared with 18 for bone marrow transplantation. The cumulative incidence of a neutrophil count of at least 500 per cubic millimeter 60 days after transplantation was 89 percent (95 percent confidence interval, 82 to 94 percent) after cord-blood transplantation and 98 percent (95 percent confidence interval,

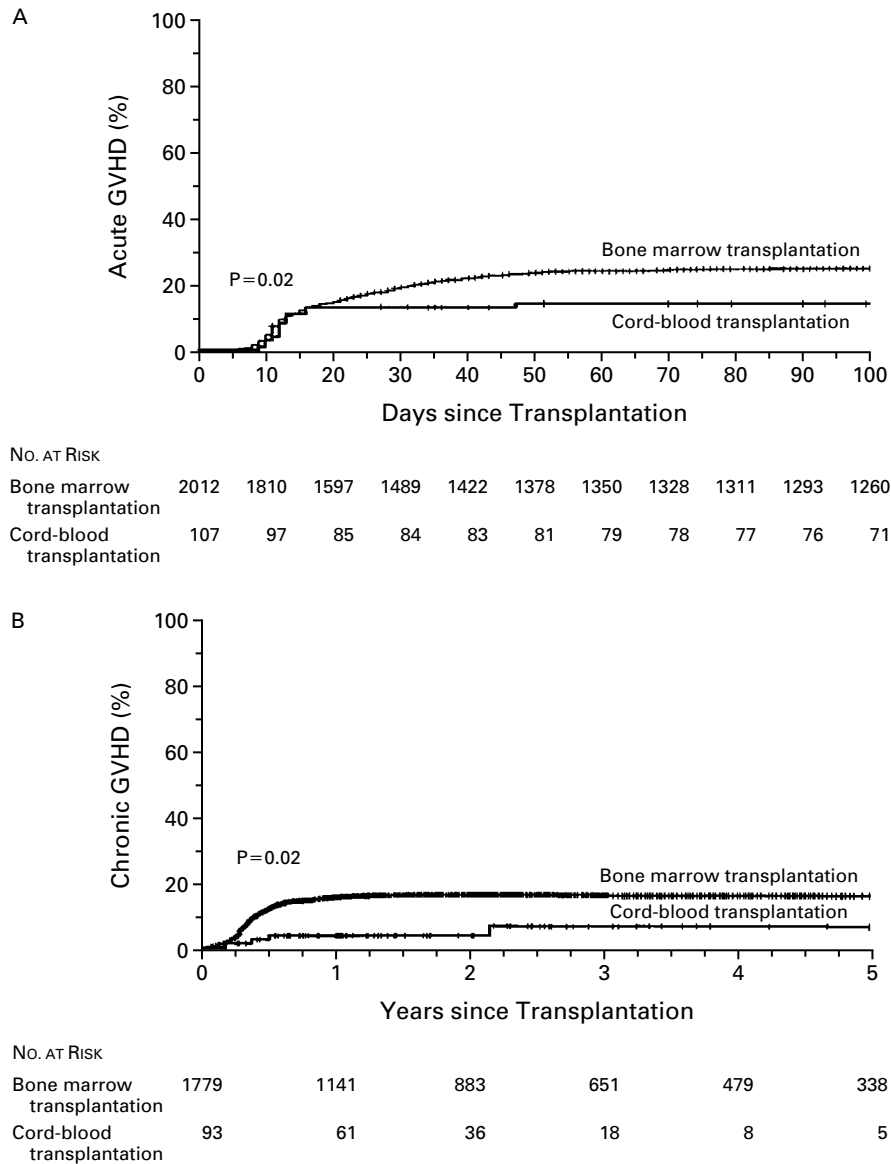


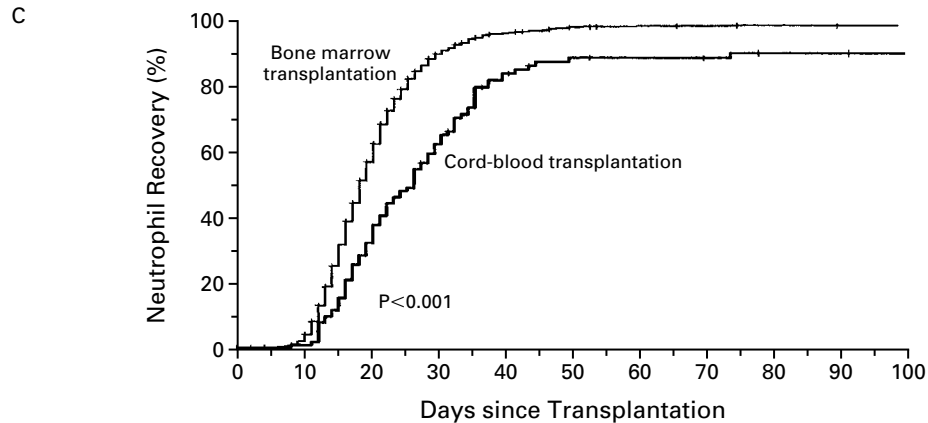
Figure 1. Outcomes among Recipients of a Cord-Blood Transplant from an HLA-Identical Sibling and Recipients of a Bone Marrow Transplant from an HLA-Identical Sibling.

The tick marks on the curves indicate censored data. Panel A shows the cumulative incidence of grade II, III, and IV acute graft-versus-host disease (GVHD). Panel B shows the cumulative incidence of chronic GVHD. Panel C shows the cumulative incidence of neutrophil recovery to more than 500 cells per cubic millimeter. Panel D shows the Kaplan–Meier estimate of survival according to the underlying disease.

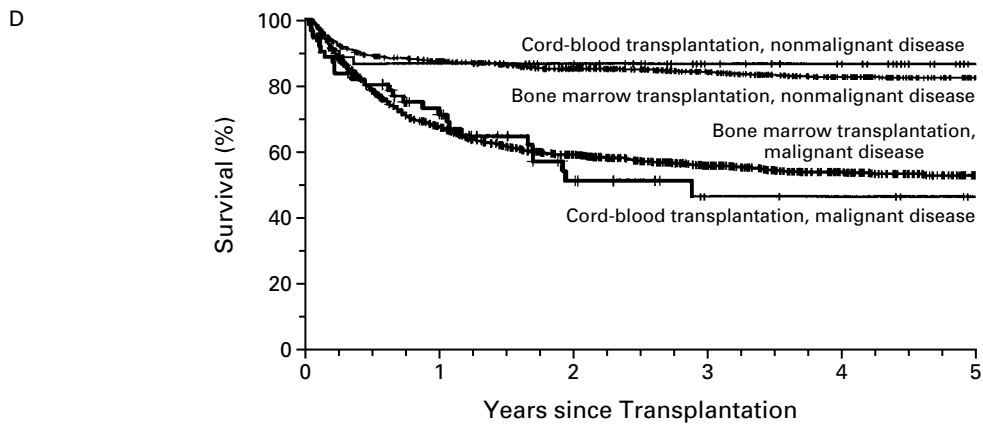
97 to 99 percent) after bone marrow transplantation ($P < 0.001$) (Fig. 1C). The median time required for the platelet count to reach at least 20×10^3 per cubic millimeter was 44 days after cord-blood transplantation and 24 days after bone marrow transplantation. The cumulative incidence of such a platelet count at day 180 was 86 percent (95 percent confidence interval, 78 to 92 percent) after cord-blood transplantation and 96 percent (95 percent confidence inter-

val, 94 to 97 percent) after bone marrow transplantation ($P < 0.001$).

In the multivariate analysis, the relative risk of neutrophil recovery in the first month after cord-blood transplantation as compared with bone marrow transplantation was 0.40 (95 percent confidence interval, 0.32 to 0.51; $P < 0.001$) (Table 2). Patients who received a cord-blood transplant had a significantly longer time to platelet recovery in the early period after



| No. AT Risk | | | | | | | | | | | |
|-----------------------------|------|----|----|----|----|----|----|----|----|----|----|
| Bone marrow transplantation | 2018 | 71 | 60 | 40 | 37 | 33 | 30 | 29 | 29 | 27 | 26 |
| Cord-blood transplantation | 106 | 15 | 12 | 11 | 10 | 11 | 8 | 7 | 7 | 7 | 7 |



| No. AT Risk | | | | | | |
|---|------|-----|-----|-----|-----|-----|
| Bone marrow transplantation, nonmalignant disease | 789 | 644 | 530 | 419 | 333 | 252 |
| Cord-blood transplantation, nonmalignant disease | 52 | 37 | 26 | 13 | 5 | 2 |
| Bone marrow transplantation, malignant disease | 1263 | 763 | 570 | 409 | 284 | 186 |
| Cord-blood transplantation, malignant disease | 61 | 35 | 16 | 10 | 5 | 4 |

transplantation than patients who received a bone marrow transplant (relative risk, 0.20; 95 percent confidence interval, 0.13 to 0.29; $P < 0.001$). However, among patients who lived 34 days after the procedure and still had thrombocytopenia, the likelihood that the platelet count would return toward normal was similar in both groups (relative risk, 0.98; 95 percent confidence interval, 0.73 to 1.32; $P = 0.92$) (Table 2). Other factors significantly associated with delayed

neutrophil recovery were malignant disease, female recipient, presence of a major ABO mismatch, use of cyclosporine and methotrexate as prophylaxis against GVHD, and no use of post-transplantation growth factors. Factors significantly associated with delayed platelet recovery were malignant disease, younger age of recipient, prophylaxis against GVHD with cyclosporine and methotrexate, and the use of post-transplantation growth factors.

TABLE 2. RESULTS OF MULTIVARIATE ANALYSES IN WHICH OUTCOMES WERE COMPARED BETWEEN RECIPIENTS OF CORD-BLOOD TRANSPLANTS AND RECIPIENTS OF BONE MARROW TRANSPLANTS.*

| OUTCOME | RELATIVE RISK (95% CI)† | P VALUE |
|---------------------------------|-------------------------|---------|
| Grade II, III, or IV acute GVHD | 0.41 (0.24–0.70) | 0.001 |
| Chronic GVHD | 0.35 (0.14–0.85) | 0.02 |
| Neutrophil recovery | 0.40 (0.32–0.51) | <0.001 |
| Platelet recovery | | |
| ≤34 days after transplantation | 0.20 (0.13–0.29) | <0.001 |
| >34 days after transplantation | 0.98 (0.73–1.32) | 0.92 |
| Mortality | 1.15 (0.81–1.65) | 0.43 |

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

†The relative risk is for transplantation with umbilical-cord blood as compared with transplantation with bone marrow.

Overall Survival

One hundred days after transplantation, the mortality rate was 14 percent (95 percent confidence interval, 8 to 22 percent) in the cord-blood group and 12 percent (95 percent confidence interval, 11 to 13 percent) in the bone marrow group ($P=0.36$). The three-year probability of survival was 64 percent (95 percent confidence interval, 53 to 74 percent) in the cord-blood group and 66 percent (95 percent confidence interval, 64 to 68 percent) in the bone marrow group ($P=0.93$). Among patients who received transplants for malignant disease, the three-year survival rate was 46 percent (95 percent confidence interval, 31 to 62 percent) for 61 patients given cord blood and 55 percent (95 percent confidence interval, 52 to 58 percent) for 1263 patients given bone marrow ($P=0.69$) (Fig. 1D). Among patients who underwent transplantation for nonmalignant diseases, the three-year survival rate was 86 percent (95 percent confidence interval, 75 to 94 percent) for 52 given cord blood and 84 percent (95 percent confidence interval, 81 to 87 percent) for 789 given bone marrow ($P=0.82$) (Fig. 1D).

In the multivariate analysis, there was no significant difference between the cord-blood group and the bone marrow group in terms of survival after transplantation (relative risk of death, 1.15; 95 percent confidence interval, 0.81 to 1.65; $P=0.43$) (Table 2). Covariates significantly associated with an increased risk of death in both cohorts were an age older than 10 years, malignant disease, and seropositivity for cytomegalovirus in the recipient.

Causes of Death

Thirty-one of 113 recipients of cord-blood transplants (27 percent) and 648 of 2052 recipients of bone marrow transplants (32 percent) died. Persistent or recurrent malignant disease was the most frequent-

ly reported primary cause of death in both groups (accounting for 48 percent of deaths in the cord-blood group and 49 percent in the bone marrow group). In the cord-blood group, there were two deaths from graft failure (6 percent of the deaths), seven deaths from infection (all in the first 100 days after transplantation) (23 percent), three deaths from hemorrhage (10 percent), and four deaths from unknown causes (13 percent). In the bone marrow group, there were 23 deaths from graft failure (4 percent), 72 deaths from GVHD (11 percent), 113 deaths from infection (61 of which were in the first 100 days after transplantation) (17 percent), 46 deaths from organ failure (7 percent), 24 deaths from hemorrhage (4 percent), and 54 deaths from other or unknown causes (8 percent). Deaths related to infection from any cause and hemorrhage were more common in the cord-blood group, whereas deaths related to GVHD, interstitial pneumonitis, and organ failure were more common in the bone marrow group ($P=0.05$ by Fisher's exact test). The numbers of relapse-related deaths were similar in the two groups.

DISCUSSION

Several reports have suggested that cord-blood transplantation is associated with a lower incidence of acute and chronic GVHD than is bone marrow transplantation.^{2,5,7,22} However, because the incidence of GVHD correlates strongly with age, and because most cord-blood transplantations are performed in children, it is not clear whether or by how much the incidence differs in comparable groups of recipients of bone marrow or cord-blood transplants. Comparing the risk of GVHD between recipients of cord-blood transplants and recipients of bone marrow transplants from unrelated donors is complicated by differences in donor–recipient histocompatibility that may not apply to sibling donor–recipient pairs and by the methods used to ascertain histocompatibility.

In this registry-based study, we found that after adjustment for factors that influence the risk of GVHD, the incidence of acute and chronic GVHD was lower after cord-blood transplantation than after bone marrow transplantation in children who received cells from HLA-identical sibling donors.

In our study, some of the differences between recipients of cord-blood transplants and recipients of bone marrow transplants, such as the length of time from diagnosis to transplantation, might not be expected to confound comparisons of the risk of GVHD. However, there were also differences in factors that influence this risk, such as the younger age of the recipients of cord blood (which would be expected to result in a decreased risk) or the fact that fewer patients in the cord-blood group than in the bone marrow group received a combination of methotrexate and cyclosporine as prophylaxis against GVHD (which would be expected to result in an increased risk).^{23,24}

We used multivariate regression models to take into account the independent effects of each potential prognostic factor. These analyses confirmed that the risk of GVHD was lower after transplantation with cord blood than after transplantation with bone marrow. The difference between cord blood and bone marrow may be due to immunologic properties of umbilical-cord T cells that reduce their capacity to induce GVHD.^{8,11,25-28}

In our study, overall survival did not differ significantly between recipients of cord-blood transplants and recipients of bone marrow transplants, regardless of the indication for transplantation and despite a slower rate of engraftment after cord-blood transplantation. Overall, the data suggest that umbilical-cord blood is as effective as bone marrow as a source of hematopoietic stem cells for children who receive transplants from HLA-identical siblings.

Few patients have umbilical-cord blood from an HLA-identical sibling available for transplantation; the real potential for this procedure lies in its use for unrelated recipients. Comparisons similar to those made in this study are needed for transplants of cord blood and bone marrow from unrelated donors, especially because the differences between such groups in terms of the characteristics of the patients may be even more pronounced than in the groups of patients who received transplants from related donors. Such comparisons will also require careful consideration of the degree of histocompatibility between donor and recipient.

In conclusion, children who received cord-blood transplants from HLA-identical siblings had a lower risk of acute and chronic GVHD and longer times to neutrophil and platelet recovery than children who received bone marrow transplants from HLA-identical siblings. These results justify the systematic collection of cord blood in families with a child affected by a disease that can be treated successfully by allogeneic transplantation of hematopoietic stem cells. The results also support further exploration of cord blood as a source of stem cells for transplants from unrelated donors.

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APPENDIX

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REFERENCES

1. Gluckman E, Broxmeyer HA, 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. Wagner JE, Kernan NA, Steinbuch M, Broxmeyer HE, Gluckman E. Allogeneic sibling umbilical-cord-blood transplantation in children with malignant and non-malignant disease. *Lancet* 1995;346:214-9.
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. 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.
5. Gluckman E, Rocha V, Boyer-Chamard A, et al. Outcome of cord-blood transplantation from related and unrelated donors. *N Engl J Med* 1997;337:373-81.
6. Gluckman E, Rocha V, Chastang C. Ham Wasserman Lecture: cord blood hematopoietic stem cells: biology and transplantation. *Hematology* 1998;1-14.
7. 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.
8. Harris DT, Shumacher MJ, Locascio J, et al. Phenotypic and functional immaturity of human umbilical cord blood T lymphocytes. *Proc Natl Acad Sci U S A* 1992;89:10006-10.
9. 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.
10. Roncarolo MG, Bigler M, Ciuti E, Martino S, Tovo PA. Immune responses by cord blood cells. *Blood Cells* 1994;20:573-85.
11. 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.
12. Garderet L, Dulphy N, Douay C, et al. The umbilical cord blood alpha T-cell repertoire: characteristics of a polyclonal and naive but completely formed repertoire. *Blood* 1998;91:340-6.
13. de La Salle V, Gluckman E, Bruley-Rosset M. Newborn blood can engraft adult mice without inducing graft-versus-host disease across non H-2 antigens. *Blood* 1996;87:3977-83.

14. *Idem*. Graft-versus-host disease and graft-versus-leukemia effect in mice grafted with peripheral newborn blood. *Blood* 1998;92:3968-75.
15. Horowitz MM, Bortin MM. The role of registries in evaluating the results of bone marrow transplantation. In: Trelaven JG, Barrett AJ, eds. *Bone marrow transplantation in practice*. London: Churchill Livingstone, 1992:367-77.
16. 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.
17. Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. *Transplantation* 1974;18:295-304.
18. Storb R, Prentice RL, Sullivan KM, et al. Predictive factors in chronic graft-versus-host disease in patients with aplastic anemia treated by marrow transplantation from HLA-identical siblings. *Ann Intern Med* 1983;98:461-6.
19. 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;18:695-706.
20. Klein JP, Moeschberger ML. *Survival analysis: techniques for censored and truncated data*. New York: Springer-Verlag, 1997:334-6.
21. Andersen PK, Klein JP, Zhang MJ. Testing for centre effects in multicentre survival studies: a Monte Carlo comparison of fixed and random effects tests. *Stat Med* 1999;18:1489-500.
22. Cairo MS, Wagner JE. Placental and/or umbilical cord blood: an alternative source of hematopoietic stem cells for transplantation. *Blood* 1997;90:4665-78.
23. Deeg HJ, Storb R, Thomas ED, et al. Cyclosporine as prophylaxis for graft-versus-host disease: a randomized study in patients undergoing marrow transplantation for acute nonlymphoblastic leukemia. *Blood* 1985;65:1325-34.
24. Ringdén O, Horowitz MM, Sondel P, et al. Methotrexate, cyclosporine, or both to prevent graft-versus-host disease after HLA-identical sibling bone marrow transplants for early leukemia? *Blood* 1993;81:1094-101.
25. Garban F, Ericson M, Roucard C, et al. Detection of empty HLA class II molecules on cord blood B cells. *Blood* 1996;87:3970-6.
26. Chalmers IM, Janossy G, Contreras M, Navarrete C. Intracellular cytokine profile of cord and adult blood lymphocytes. *Blood* 1998;92:11-8.
27. Truman JP, Garban F, Choqueux C, Charron D, Mooney N. HLA class II signaling mediates cellular activation and programmed cell death. *Exp Hematol* 1996;24:1409-15.
28. Truman JP, Choqueux C, Tschopp J, et al. HLA class II-mediated death is induced via Fas/Fas ligand interactions in human splenic B lymphocytes. *Blood* 1997;89:1996-2007.