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专业资料

医学论坛

共享区

交流区

学习区

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### Cord-Blood Transplants from Unrelated Donors in Patients with Hurler's Syndrome

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#### ABSTRACT

Background Hurler's syndrome (the most severe form of mucopolysaccharidosis type I) causes progressive deterioration of the central nervous system and death in childhood. Allogeneic bone marrow transplantation before the age of two years halts disease progression and prolongs life, but many children lack a bone marrow donor. We investigated the feasibility of using cord-blood transplants from unrelated donors and a myeloablative preparative regimen that did not involve total-body irradiation in young children with Hurler's syndrome.

Methods Between December 1995 and October 2002, 20 consecutive children with Hurler's syndrome received busulfan, cyclophosphamide, and antithymocyte globulin before receiving cord-blood transplants from unrelated donors. The children were

subsequently evaluated for engraftment, adverse effects, and effects on disease symptoms.

Results Cord-blood donors had normal -L-iduronidase activity (mean number of cells, 10.53x107 per kilogram of body weight) and were discordant for up to three of six HLA markers. Neutrophil engraftment occurred a median of 24 days after transplantation. Five patients had grade II or grade III acute graft-versus-host disease; none had extensive chronic graft-versus-host disease. Seventeen of the 20 children were alive a median of 905 days after transplantation, with complete donor chimerism and normal peripheral-blood -L-iduronidase activity (event-free survival rate, 85 percent). Transplantation improved neurocognitive performance and decreased somatic features of Hurler's syndrome.

Conclusions Cord blood from unrelated donors appears to be an excellent source of stem cells for transplantation in patients with Hurler's syndrome. Sustained engraftment can be achieved without total-body irradiation. Cord-blood transplantation favorably altered the natural history of Hurler's syndrome and thus may be important to consider in young children with this form of the disease.

Hurler's syndrome (the most severe form of mucopolysaccharidosis type I), an autosomal recessive metabolic storage disease caused by a deficiency of -L-iduronidase, results in the accumulation of heparan and dermatan sulfate substrates (glycosaminoglycans) in various tissues.1,2 Severe phenotypes, in which symptoms begin by two years of age, are characterized by severe, progressive deterioration of the central

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nervous system, cardiac disease, skeletal abnormalities, corneal clouding, hepatomegaly, and death in childhood.<sup>1,2,3,4,5,6,7</sup> Bone marrow transplantation can prevent the progression of selected heritable enzyme deficiencies and provides maximal benefit when performed early in life.<sup>8</sup> More than 200 patients with Hurler's syndrome have undergone allogeneic bone marrow transplantation since 1980.<sup>3,4,7,8,9,10,11,12,13,14,15,16,17</sup> Donor stem cells deliver enzyme inside and outside the blood compartment, arresting the progression of the disease and improving overall survival.<sup>2,5,6,7,8,9,10,11,12,13,14,15,16,17</sup> Unfortunately, many children who might benefit from transplantation lack an appropriately matched donor.<sup>9,11,13,14,17</sup> Because banked umbilical-cord blood from unrelated donors with partial HLA mismatches can provide donor stem cells for children with cancer who lack suitable bone marrow donors,<sup>18,19,20</sup> we used cord blood from unrelated donors as the source of hematopoietic stem cells for transplantation in children with Hurler's syndrome.

#### Methods

##### Patients

Between December 28, 1995, and October 16, 2002, 20 consecutive children with Hurler's syndrome who were referred to Duke University Medical Center for transplantation and who lacked HLA-matched, related bone marrow donors who were not carriers of the disease received cord-blood transplants from unrelated donors. The diagnosis of Hurler's syndrome was confirmed on the basis of the activity of  $\alpha$ -L-iduronidase in peripheral-blood leukocytes and the clinical phenotype.<sup>21</sup> All patients were enrolled in a phase 1 and 2 study of cord-blood transplantation for the treatment of nonmalignant diseases approved by the institutional review board of Duke University. The parents of each patient provided written informed consent before enrollment.

##### Selection of Donors

Searches for cord-blood units from unrelated donors were conducted with the use of intermediate-resolution typing for HLA class I (A and B) and high-resolution typing for HLA-DRB1. The unit of cord blood with the highest number of nucleated cells (minimum,  $3 \times 10^7$  per kilogram of body weight) that matched at least three of six HLA loci was selected. Units were tested for leukocyte  $\alpha$ -L-iduronidase activity,<sup>22</sup> and those with high-normal activity were selected.

##### Transplantation Procedure

Cryopreserved units of cord blood were thawed and processed in a standard fashion.<sup>23</sup> The total numbers of nucleated cells, clonal hematopoietic progenitor cells, and CD34+ cells were counted; ABO and Rh typing was performed; the viability of the cells was assessed; and bacterial and fungal cultures were obtained before the infusion.

##### Conditioning Regimen

All patients were prepared for transplantation by receiving 16 doses of busulfan (20 to 40 mg per square meter of body-surface area orally, with the dose based on age) from days 9 through 6 before transplantation; 4 doses of cyclophosphamide (50 mg per kilogram of body weight given intravenously) from days 5 through 2 before transplantation; and 3 doses of antithymocyte globulin (PharmaciaUpjohn; 30 mg per kilogram given intravenously from days 3 through 1 before transplantation). The pharmacokinetics of busulfan were assessed after the first dose, and subsequent doses were adjusted to maintain a steady-state concentration of 600 to 900 ng per milliliter.<sup>24</sup> One patient required an increase in the dose, and 11 patients required a decrease. Patients received phenytoin for prophylaxis against seizures during treatment; busulfan and mesna were also given for prophylaxis against hemorrhagic cystitis during cyclophosphamide therapy. Radiation therapy was not used as part of the conditioning regimen.

##### Prophylaxis against and Treatment of Graft-versus-Host Disease

All children received cyclosporine for nine months and methylprednisolone for two to three months as prophylaxis against graft-versus-host disease (GVHD).<sup>18</sup> The severity of acute GVHD was scored with the use of standard criteria.<sup>25</sup> Patients with grade I acute GVHD were treated with topical creams, a small escalation in the dose of systemic methylprednisolone, or both. Patients with moderate acute GVHD received four pulsed doses of methylprednisolone (500 mg per square meter given intravenously every 12 hours) before treatment was switched to tacrolimus, alone or in combination with dacliximab (HoffmannLaRoche).

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## Supportive Care

All patients were kept in reverse isolation rooms with high-energy particulate air filtration. Standard prophylaxis against *Pneumocystis carinii*, viral, and fungal infections was used. Empirical treatment with broad-spectrum antibiotics was started with the first episode of febrile neutropenia and continued through engraftment. Intravenous immune globulin was administered weekly through day 100. A continuous infusion of low-dose heparin was used as prophylaxis against veno-occlusive disease. Patients received transfusions of leukocyte-depleted, irradiated, packed red cells and platelets. Filgrastim (Amgen; 10 µg per kilogram per day) was administered daily from the day of transplantation (day 0) through engraftment. Engraftment was defined by an absolute neutrophil count of at least 500 donor cells per cubic millimeter on three consecutive days.

## Post-Transplantation Evaluation

Patients were evaluated every 6 to 12 months by multiple pediatric subspecialists in developmental pediatrics, ophthalmology, audiology, cardiology (to obtain echocardiograms and provide follow-up), pulmonology, and orthopedics (to obtain hip and spine films and provide follow-up). The Cobb method was used to quantify the degree of kyphoscoliosis. Hip films were evaluated for subluxation, acetabular coverage, and dysplasia. The need for orthopedic surgery was determined on the basis of radiographic and clinical findings. Neurocognitive function was evaluated by the Program for the Study of Neurodevelopmental Function in Rare Disorders (Center for Development and Learning, University of North Carolina, Chapel Hill). Patients less than three years of age were assessed with the Bayley Scales of Infant Development, the Clinical Adaptive Test Clinical Linguistic Auditory Milestone Scale in Early Cognitive Assessment, and the Mullen Scales of Early Learning. Patients three years of age or older were assessed with the Mullen Scales of Early Learning and the Differential Abilities Scales. Standard scores, T scores, and developmental quotients were converted to age-equivalent scores to allow comparisons of results among various tests.

## Statistical Analysis

The probability of event-free survival was calculated according to the KaplanMeier method. The probabilities of all other events were calculated on the basis of their cumulative incidence, with engraftment, the occurrence of acute GVHD, and death as competing events.<sup>26</sup> Adverse events were defined as death, autologous recovery, and graft failure. Each patient's developmental course was assessed with the use of the hierarchical linear model, which depicts changes in cognitive function over time. This type of model allows for missing data and irregular evaluation times. The contribution to the estimate of the slope and intercept is greater for patients with more data points than for those with fewer data points. Linear and quadratic polynomial terms are included to allow for nonlinear changes. The cutoff date for data analysis was September 1, 2003.

## Results

### Characteristics of the Patients

From December 1995 through October 2002, 20 children (10 boys and 10 girls) received cord-blood transplants from unrelated donors. The median weight of the children was 12 kg (range, 5 to 15). The median age was 11 months (range, prenatal to 29 months) at diagnosis and 16 months (range, 2 to 33) at transplantation (Table 1). Five patients required ventriculoperitoneal shunts before transplantation, but none required them after transplantation.

Table 1. Characteristics of the Children and the Unrelated Donors.

### Selection of Units for Transplantation

Units of umbilical-cord blood were matched to the patient's HLA phenotype at three to six loci (Table 1). Ten patients received units with major ABO-blood-group incompatibilities. The mean number of nucleated cells in units selected for transplantation (before cryopreservation) was  $10.53 \times 10^7$  per kilogram (range,  $3.38 \times 10^7$  to  $20.95 \times 10^7$ ), whereas the mean number of cells infused (after thawing) was  $8.34 \times 10^7$  per kilogram (range,  $1.91 \times 10^7$  to  $20.90 \times 10^7$ ), and the mean number of CD34+ cells infused was  $2.51 \times 10^5$  per kilogram (range,  $0.66 \times 10^5$  to  $104.75 \times 10^5$ ) (Table 1).

### Engraftment

Neutrophil and platelet engraftment occurred a median of 24 days (range, 10 to 39) and 56 days (range, 28 to

216), respectively, after transplantation (Table 2 and Figure 1A and Figure 1B). Red-cell and platelet transfusions were no longer required after a median interval of 48 days (range, 20 to 67) and 55 days (range, 20 to 113), respectively, with patients requiring a median of 10 transfusions of packed red cells and 28 platelet transfusions in the interim. As of the last follow-up evaluation, all 17 surviving patients continued to have complete donor chimerism and normal peripheral-blood  $\alpha$ -L-iduronidase activity (Table 2).

Table 2. Engraftment, Chimerism, Incidence of GVHD, and Event-free Survival after Transplantation.

Figure 1. Cumulative Incidence of Neutrophil (Panel A) and Platelet (Panel B) Engraftment after Cord-Blood Transplantation and KaplanMeier Estimates of the Probability of Event-free Survival (Panel C).

In Panel A, myeloid engraftment was defined by an absolute neutrophil count of at least 500 per cubic millimeter on three consecutive days. The one patient who remained aplastic after the first cord-blood transplantation received a second cord-blood transplant on day 63. Myeloid engraftment occurred on day 26 after the second transplantation. In Panel B, platelet engraftment was defined by a platelet count of at least 50,000 per cubic millimeter without the need for transfusion for at least seven consecutive days. In Panel C, event-free survival was defined by survival with full (greater than 99 percent) donor chimerism. Tick marks indicate the most recent follow-up visit for each patient.

#### Immune Reconstitution

Cellular and humoral immune function was assessed quarterly for the first year after transplantation and yearly thereafter. CD4+ cell counts exceeded 100 per cubic millimeter at three months, 200 per cubic millimeter at six months, and 400 per cubic millimeter at nine months. The degree of proliferation in response to phytohemagglutinin and the absolute lymphocyte count were normal by nine months after transplantation. All children were immunized with age-appropriate killed- and live-virus vaccines after normalization of immune function, without adverse reactions.

#### Graft-versus-Host Disease

The overall probability of moderate-to-severe acute GVHD was 25 percent a median of 11 days (range, 8 to 35) after transplantation (Table 2). Limited, chronic GVHD of the skin developed in two patients, whereas none had extensive chronic GVHD.

#### Survival

As of September 1, 2003, a median of 905 days after transplantation (range, 333 to 2817), 17 of 20 patients were alive, for an overall event-free survival rate of 85 percent (Table 2 and Figure 1C). One child died of idiopathic hyperammonemia on day 32 after transplantation, one of central nervous system hemorrhage related to cytomegalovirus infection on day 90, and one, who received two cord-blood transplants, died of cytomegalovirus pneumonia 210 days after the first transplantation. Five children had serious adverse effects from which they recovered: hemolytic anemia in one, pulmonary hemorrhage in one, gallbladder hydrops in one, and ventriculoperitoneal-shunt infection in two. The median hospital stay was 39 days (range, 32 to 104).

#### Genetic Evaluation

Extremely low or undetectable concentrations of  $\alpha$ -L-iduronidase, as determined by immunoquantification,<sup>27</sup> were found in all 20 children before transplantation, which is consistent with the phenotype of Hurler's syndrome. Although some common mutations have now been identified that are consistently associated with the phenotype, many children with severe disease have other rare or unidentified mutations. Two children in our series have been identified as homozygotes and seven as compound heterozygotes for common mutations associated with the severe phenotype. Two previously unreported mutations have been identified in two other patients.

#### Follow-up

All children were evaluated serially to document the late effects of cord-blood transplantation on Hurler's syndrome. Longitudinal growth was closely monitored, and within one year after transplantation, growth velocity was normal in the majority of patients and remained so (Figure 2). Four of the children have required spinal fusion for kyphosis, six have had a spontaneous decrease in the degree of kyphosis after transplantation, kyphosis has not developed in two, and five have stable, mild kyphosis. One child has required hip surgery,

and none have undergone carpal-tunnel or knee surgery to date. No child has had clinically significant cardiac dysfunction. All children had either stable or improved neurocognitive function after transplantation (Figure 3A). Although the children quickly fell behind in development in the immediate post-transplantation period (slope = 0.56 at 24 months), by 54 months of age the developmental slope had increased to 0.81, and by 72 months they appeared to be gaining cognitive skills at a slightly slower rate (slope = 0.95) than the mean for unaffected children (Figure 3B).

Figure 2. Growth of Boys (Panel A) and Girls (Panel B) from the Age of Two Years until the Last Follow-up Visit.

Most of the children had normal growth velocity within one year after transplantation. The gray curves represent standard growth curves (5, 10, 25, 50, 75, 90, and 95 percentiles), and the black lines represent individual patients.

Figure 3. Neurocognitive Performance of Children with Hurler's Syndrome after Cord-Blood Transplantation (Panel A) and as Compared with That of Unaffected Children (Panel B).

We used age-equivalent scores for comparisons and to monitor the children's developmental progress. Panel A shows the cognitive trajectories achieved by plotting developmental age against chronologic age for each child over time. A slope of 1.0 (the straight red line) indicates normal developmental velocity. Panel B shows the mean cognitive growth curve for all surviving patients plotted against the mean typical cognitive growth curve for unaffected children. The two thin black lines indicate the 95 percent confidence interval for the patients. The shaded area indicates the variability ( $\pm 2$  SD) in typical cognitive development. Only two of the patients (three observations) had data recorded before six months of age, and these observations were not included in the final analysis, because they could have overly influenced the estimates.

#### Discussion

We describe the outcome in 20 children with Hurler's syndrome who received cord-blood transplants from unrelated donors after the administration of a chemotherapy-based preparative regimen. Eighty-five percent of the children survived with complete donor chimerism and normal peripheral-blood -L-iduronidase activity. In contrast, after bone marrow transplantation, graft failure has been reported in 28 to 37 percent of such patients, despite the use of total-body irradiation,<sup>9,10,11,13,14,17</sup> and mixed chimerism with decreased -L-iduronidase activity has also been observed.<sup>10,11,13</sup>

The limited availability of donors is a major obstacle to bone marrow transplantation, with no suitable adult stem-cell donor identified in a timely fashion in more than 50 percent of patients. Banked umbilical-cord blood is prospectively HLA typed, screened for infections and other risk factors, and readily available for transplantation. In our study, the average time from the initiation of a search for a donor to the identification of a compatible unit of cord blood (including an assessment of -L-iduronidase activity) was 15 days. The time from the initiation of a search to the beginning of the conditioning regimen for transplantation was 41 days (31 days among patients who underwent transplantation after 2000). In a disease in which the time from diagnosis to definitive treatment may represent a crucial period in which to prevent further disease progression, a readily available source of stem cells is extremely desirable.

An additional advantage of the use of umbilical cord blood is that HLA matching does not have to be as close as that necessary for bone marrow grafts; this allows a donor to be identified for virtually all patients. Despite mismatching at one to three HLA loci in most donorrecipient pairs in our series, engraftment and immune reconstitution were complete, and the rates of acute and chronic GVHD were low. No deaths were attributable to GVHD, and none of the children had extensive chronic GVHD. By contrast, among children with Hurler's syndrome who receive bone marrow transplants from unrelated donors, the rates of GVHD have been reported to be 30 and 55 percent and to account for up to half of transplantation-associated mortality.<sup>11,17</sup>

Hematopoietic stem-cell transplantation arrests the progression of Hurler's syndrome, averting death from cardiac causes and liver disease, improving growth and development, and prolonging survival.<sup>3,4,7,8,9,10,11,12,13,14,15,16,17</sup> Untreated children with Hurler's syndrome have severe growth failure by the age of two years, achieving a maximal height of 110 cm.<sup>1</sup> After cord-blood transplantation, the children in our study had normal growth velocities. Hurler's syndrome is associated with skeletal abnormalities, including kyphosis, hip dysplasia, and carpal tunnel syndrome, which cause serious complications and often

require surgical correction.<sup>28,29</sup> Previous data regarding the effect of hematopoietic stem-cell transplantation on skeletal abnormalities have been inconclusive.<sup>28,29</sup> Some clear benefits have been recognized, such as the correction of odontoid dysplasia.<sup>30</sup> In our series, five children required orthopedic intervention, whereas the remainder have had stabilization or regression of bony disease after transplantation, obviating the need for surgical intervention. Since the median age of these children is currently 4.5 years (range, 11 months to 10 years), additional long-term follow-up is needed to determine the full effect of cord-blood transplantation on the progression of the skeletal manifestations of Hurler's syndrome.

Fifteen of the 17 surviving children were serially evaluated by the neurodevelopmental team before and after transplantation. After the initial post-transplantation period of developmental delay, neurocognitive function stabilized or improved in all the children, and all have continued to gain skills. Three of the four oldest children have average-to-high IQs, although their genotypes and the results of protein analysis would predict them to have severe disease with rapid neurocognitive decline. Although results at 54 months were available for only four patients (24 percent of the group) and are therefore inconclusive, there was a trend toward increasing cognitive skills, with the mean scores of the sample falling within the normal range by 66 months of age.

Enzyme-replacement therapy with intravenous  $\alpha$ -L-iduronidase has ameliorated some manifestations of disease in patients older than six years who were less severely affected than our patients.<sup>31,32</sup> Such patients form nonneutralizing antibodies that do not appear to interfere with the efficacy of treatment.<sup>33</sup> Enzyme-replacement therapy is now being tested in limited numbers of more severely affected infants and younger children. Since the enzyme is unlikely to be able to cross the blood-brain barrier, transplantation therapy will continue to be used in children with Hurler's syndrome. Because of possible clinical gains with earlier exposure to enzyme, it is tempting to consider instituting enzyme-replacement therapy in patients with Hurler's syndrome while they are being prepared for transplantation. However, it is difficult to predict the nature of the antibody response and its possible influence on the efficacy of transplantation. Therefore, the pretransplantation use of enzyme-replacement therapy in the most severely affected patients with Hurler's syndrome should be tested in a controlled clinical trial and used with caution.

The children in this series underwent cord-blood transplantation at a median age of 16 months. In previous studies of bone marrow transplantation in patients with Hurler's syndrome, the median age was older — 19 to 24 months.<sup>9,11,13,14</sup> Children who undergo transplantation at a younger age may derive more benefit, regardless of the source of the stem cells. Additional studies are needed to determine whether the positive outcomes in this study are related to the stem-cell source, the age at transplantation, or both.

In summary, we found that hematopoietic stem-cell transplantation with banked cord blood from partially HLA-matched, unrelated donors favorably altered the natural history of Hurler's syndrome. Engraftment and full donor chimerism were achieved and maintained without the use of radiation therapy. The incidence of acute GVHD was low, and extensive chronic GVHD did not occur. Donors were readily and rapidly available. The overall event-free survival rate was 85 percent after a median follow-up of more than two years. Although long-term follow-up is needed to determine the full effect of cord-blood transplantation on the natural history of Hurler's syndrome, patients appear to derive important benefits from this therapy. It may prove to be a therapeutic option for young patients with Hurler's syndrome who lack an HLA-matched, related bone marrow donor who is not a carrier of the disease.

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#### Source Information

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