Outcome of Unrelated Donor Bone Marrow Transplantation in 40 Children With Hurler Syndrome

By Charles Peters, Michael Balthazor, Elsa G. Shapiro, Roberta J. King, Craig Kollman, Janet D. Hegland, Jean Henslee-Downey, Michael E. Trigg, Morton J. Cowan, Jean Sanders, Nancy Bunin, Howard Weinstein, Carl Lenarsky, Peter Falk, Richard Harris, Tom Bowen, Thomas E. Williams, Guy H. Grayson, Phyllis Warkentin, Leonard Sender, Valerie A. Cool, Mary Crittenden, Seymour Packman, Paige Kaplan, Lawrence A. Lockman, James Anderson, William Krivit, Kathryn Dusenbery, and John Wagner

Long-term survival and improved neuropsychological function have occurred in selected children with Hurler syndrome (MPS I H) after successful engraftment with genotypically matched sibling bone marrow transplantation (BMT). However, because few children have HLA-identical siblings, the feasibility of unrelated donor (URD) BMT as a vehicle for adoptive enzyme therapy was evaluated in this retrospective study. Forty consecutive children (median, 1.7 years; range, 0.9 to 3.2 years) with MPS I H received high-dose chemotherapy with or without radiation following by BMT between January 27, 1989 and May 13, 1994. Twenty-five of the 40 patients initially engrafted. An estimated 49% of patients are alive at 2 years; 63% alloengrafted and 37% autoengrafted. The probability of grade II to IV acute graft-versus-host disease (GVHD) was 30%, and the probability of extensive chronic GVHD was 18%. Eleven patients received a second URD BMT because of graft rejection or failure. Of the 20 survivors, 13 children have complete donor engraftment, two children have mixed chimeric grafts, and five children have autologous marrow recovery. The BM cell dose was correlated with both donor engraftment and survival. Thirteen of 27 evaluable patients were engrafted at 1 year following URD BMT. Neither T-lymphocyte depletion (TLD) of the bone marrow nor irradiation appeared to influence the likelihood of engraftment. Ten of 16 patients alive at 1 year who received a BM cell dose greater than or equal to $3.5 \times 10^8$ cells/kg engrafted, and 62% are estimated to be alive at 3 years. In contrast, only 3 of 11 patients receiving less than $3.5 \times 10^8$ cells/kg engrafted, and 24% are estimated to be alive at 3 years ($P = 0.05$). The mental developmental index (MDI) was assessed before BMT. Both baseline and post-BMT neuropsychological data were available for 11 engrafted survivors. Eight children with a baseline MDI greater than 70 have undergone URD BMT (median age, 1.5 years; range, 1.0 to 2.4 years). Of these, two children have had BMT too recently for developmental follow-up. Of the remaining six, none has shown any decline in age equivalent scores. Four children are acquiring skills at a pace equal to or slightly below their same age peers; two children have shown a plateau in learning or extreme slowing in their learning process. For children with a baseline MDI less than 70 (median age, 2.5 years; range, 0.9 to 2.9 years), post-BMT follow-up indicated that two children have shown deterioration in their developmental skills. The remaining three children are maintaining their skills and are adding to them at a highly variable rate. We conclude that MPS I H patients with a baseline MDI greater than 70 who are engrafted survivors following URD BMT can achieve a favorable long-term outcome and improved cognitive function. Future protocols must address the high risk of graft rejection or failure and the impact of GVHD in this patient population.

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The mucopolysaccharidoses (MPS) are a family of heritable disorders caused by deficiency of lysosomal enzymes needed to degrade glycosaminoglycans. Hurler syndrome (MPS I H) is a progressive autosomal recessive inborn error that leads to premature death usually by 5 years of age. Deficiency of a-L-iduronidase enzyme activity and the consequent accumulation of heparan sulfate and dermatan sulfate substrates contribute to the characteristic facial features, hepatosplenomegaly, cardiac disease, severe skeletal abnormalities, hydrocephalus, and progressive mental retardation.

The discovery of lysosomal storage disease by Baudhuin et al. was accompanied by the optimistic prediction that exogenously administered enzymes would reach lysosomes by endocytosis. In the early 1970s, Di Ferrante et al. infused large quantities of plasma or leukocytes into patients with Hurler or Hunter syndrome. Disappointing results from these attempts as well as from intravascular enzyme infusion prompted the search for a procedure that would provide a renewable source of lysosomal enzymes. Mutual metabolic correction of fibroblasts grown in coculture from patients with Hurler and Hunter syndrome provided a rationale for transplantation of amniotic epithelial membranes and fetal fibroblasts; however, neither amnion nor fibroblast transplantation was efficacious.

In contrast, bone marrow transplantation (BMT) has provided a method for correcting enzymatic deficiencies in several lysosomal and peroxisomal disorders. Hobbs et al. reported that allogeneic BMT could dramatically improve the somatic features of MPS I H. They observed donor levels of serum and leukocyte alpha-L-iduronidase, normalization of urinary excretion of glycosaminoglycans, and decreased hepatosplenomegaly in a 1-year-old MPS I H child after BMT. Since this original report, hundreds of children with storage diseases including 163 patients with MPS I H have received allogeneic BMTs worldwide. Matched sibling donor BMT has resulted in metabolic correction and either resolution or amelioration of many clinical features such as hepatosplenomegaly and obstructive sleep apnea. Accumulated substrates decrease to normal levels after replacement of deficient enzyme on the basis of histologic and biochemical evaluations.

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analyses of hepatocytes, tonsils, conjunctiva, BM, urine, and spinal fluid. Nevertheless, despite stable engraftment, skeletal and corneal abnormalities progress necessitating surgical interventions. While neuropsychological capabilities vary widely after matched sibling BMT, selected patients have maintained their rate of learning with low normal intelligence. However, most children do not have a genotypically matched sibling marrow donor. Consequently, we report The Storage Disease Collaborative Study Group retrospective experience using unrelated donor (URD) BMT for 40 children with MPS I H.

MATERIALS AND METHODS

Eligibility. From January 27, 1989 to May 13, 1994, 40 consecutive patients deficient in leukocyte α-L-iduronidase enzyme activity received high-dose chemotherapy with or without radiation followed by URD BMT. Unrelated BM donors were identified through either the National Marrow Donor Program or the Iowa Bone Marrow Donor Registry. The procedures and policies of the National Marrow Donor Program (NMDP) have been described previously. Initially, mixed lymphocyte culture (MLC) testing was performed at each BMT center (data available upon request). More recently, HLA-DRB1 molecular oligonucleotide typing has been used. Criteria employed for selection of an URD included: (1) phenotypic matching of HLA-DR loci and (2) phenotypic matching of three or four of 4 HLA-A and -B loci. Parental consent was obtained for all patients and protocols were approved by institutional review boards.

Engraftment. Engraftment was assessed by measuring leukocyte α-L-iduronidase enzyme activity and/or semiquantitative restriction fragment length polymorphism (RFLP) analysis of monocytes and/or neutrophils (data available upon request). Engraftment at 1 year following URD BMT was confirmed by using corrected presence of at least 25% of normal α-L-iduronidase enzyme activity and/or presence of at least 10% donor cell chimerism by RFLP (Table 1). These differing percentages were chosen because of the varying methodologies. Specific enzyme activity levels performed by three different laboratories for patients surviving at least 1 year from BMT are reported as well (Table 2).

Prophylaxis and grading of graft-versus-host disease (GVHD). T-lymphocyte depletion (TLD) of the BM graft was performed for 18 of the 40 BMTs (Table 1). The methods included: antibody + complement, elutriation, antibody + ricin, and soybean lectin + sheep erythrocyte rosetting. Seven different GVHD prophylaxis regimens were used; agents included: cyclosporin, methotrexate, antithymocyte or lymphocyte globulin, corticosteroid, or anti-CD5 ricin A chain conjugated immunotoxin. Acute GVHD was diagnosed and graded according to Glucksberg et al; chronic GVHD was diagnosed andgraded according to Shulman et al. Moderate to severe acute GVHD was defined as acute GVHD ≥ grade II. Patients were considered at risk for acute GVHD if they survived 28 days and for chronic GVHD if they survived 100 days following BMT.

Survival. Vital status was ascertained for all patients on September 1, 1994. When applicable, the date and cause of death were recorded for all nonsurvivors.

Neuropsychological testing. A battery of standardized neuropsychological tests was used in The Storage Disease Collaborative Study Group to assess the child’s developmental or intellectual level, adaptive behavior, academic readiness or performance, and neuropsychological functioning in several domains (language, perception, memory, attention, and executive functions), and emotional and social functioning. Testing performed pre-BMT served as a baseline; subsequent tests were administered annually post-BMT.

Tests used in the battery changed according to the emerging cognitive abilities of the child. Increasingly specific functions can be measured as the child develops. The battery for the youngest children was used before BMT. This battery included the Bayley Scales of Infant Development (BSID) (mental, motor, and behavior scales), a measure of adaptive behavior (Vineland Adaptive Behavior Scales), a measure of developmental level in several areas (Minnesota Child Development Inventory), a measure of receptive and expressive language (Receptive-Expressive Emergent Language scale), and a videotape sample of behavior for assessment of emotional and social behavior using the Minnesota Preschool Affect Rating Scales. For this study, only the results of the developmental and intelligence tests are reported.

Most children were tested within a 6-month span before BMT. Following BMT, age-appropriate tests were administered. For those children who were chronologically or developmentally less than 30 months, the BSID was readministered. For some children over 2 years, the Stanford Binet Intelligence Scale-4th edition could be used. For children over 3 years, either the Stanford Binet Intelligence Scale or the McCarthy Scales of Children’s Abilities were administered.

Mental developmental indices (MDIs) were calculated at baseline for all children from the normative tables to determine if they fell above or below 70.

Age equivalent scores are used for monitoring developmental status over time. Use of age equivalent scores provides a mechanism for comparing results across developmental tests and provides information about whether a child is losing mental ability, plateauing in learning, gaining more slowly than normally expected or progressing at an appropriate rate. Because a number of children fell below the floor of the normative tables (MDI ≤ 50), MDIs could not be used for longitudinal assessment.

RESULTS

Forty URD BMTs were performed at 14 centers in North America: nine (64%) of the centers performed one to two transplantations, four (29%) centers performed three to five transplantations, and one center performed 13 transplantations. All but one were first transplants; one patient received a second transplant from an URD after rejecting an HLA-DR-matched BMT from her mother. Twenty-eight grafts (70%) were phenotypically matched at six of six HLA A, B, and DR loci, while 12 grafts (30%) were matched at five of six loci. The median follow-up for all patients and for survivors was 1.3 years and 2.8 years, respectively.

Preparative regimen. Patients received a variety of preparative regimens determined by the individual transplantation centers (Table 1). Regimens used high-dose chemotherapy such as oral busulfan (Bu), intravenous cyclophosphamide (Cy), cytosine arabinoside (Ara-C), etoposide (VP-16), with or without irradiation. Specific preparative regimens included Bu (range, 16 to 24 mg/kg in divided doses every 6 hours over 4 days)/Cy (range, 200 to 240 mg/kg in two divided doses over 2 days) with or without antithymocyte globulin (ATG); Bu/Cy and total lymphoid irradiation (TLI); reduced dose Bu (10 mg/kg in divided doses every 6 hours over 4 days)/Cy (100 mg/kg in two divided doses over 2 days) and total body irradiation (TBI); Cy (100 mg/kg in two divided doses over 2 days)/Ara-C (18 g/m² in six divided doses over 3 days), and TBI. Irradiation...
Table 1. Patient Engraftment and Vital Status Following Unrelated Donor BMT According to Marrow Cell Dose

<table>
<thead>
<tr>
<th>BM Cell Dose (&lt;10^6/kg)</th>
<th>Engraft</th>
<th>Vital Status</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM cell dose ≥ 3.5 x 10^6 cells/kg of recipient body weight</td>
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</tr>
</tbody>
</table>

30 Bu, Cy 13.8/No Yes Alive
28 Bu, Cy 8.3/Yes No Dead MPS
6 VP-16, Cy, Ara-C, TBI: 1200 8.1/Yes Yes Dead CMV IP
34 Bu, Cy 7.8/No No Dead Graft failure
9 Bu, Cy 7.4/No No Alive (MPS)
3 VP-16, Cy, Ara-C, TBI: 1200 7.0/Yes No Alive (MPS)
13 Bu, Cy 5.4/No Yes Dead CP arrest
11 Bu, Cy 5.2/No No Dead GVHD, CMV
5 Bu, Cy 5.1/No Yes Alive
7 Cy, Ara-C, TBI: 1400 5.1/Yes Yes Alive
15 Bu, Cy, ATG 5.1/No Yes Alive
4 Bu, Cy 5.0/No Yes Alive
10 Bu, Cy, ATG 5.0/No No Alive (MPS)
25 Bu, Cy, ATG 5.0/No No Alive (MPS)
1 VP-16, Cy, Ara-C, TBI: 1200 4.5/Yes Yes Alive
14 Cy, Ara-C, TBI: 1400 4.2/Yes Yes Alive
19 Bu, Cy, ATG 4.1/No Yes Alive
27 Bu, Cy 3.7/No Yes Alive*
23 Bu, Cy 3.6/No Yes Alive
28 Bu, Cy 3.5/No Yes Alive
18 Bu, Cy 3.5/No Yes Dead GVHD

Pts: (+) TBI/TLD: 5 Median: Yes: 14 Alive: 10
21 (-) TBI/TLD: 16 5.1 No: 7 MPS: 3 Dead: 8

BM cell dose < 3.5 x 10^6 cells/kg of recipient body weight

12 VP-16, Cy, Ara-C, TBI: 1200† 3.3/Yes No Dead Sepsis
22 Cy, Ara-C, TBI: 1400 3.2/Yes Yes Alive
24 Bu, Cy 3.2/No No Alive (MPS)
2 Bu, Cy, TLI: 1000† 3.1/No No Dead GVHD
35 Bu, Cy 3.1/No Yes Dead GVHD
16 Bu, Cy 2.7/No Yes Dead RF, GVHD
31 Bu, Cy 2.7/No Yes Dead IP
40 Bu, Cy, ATG 2.6/No No Alive (MPS)
21 Bu, Cy 2.0/No No Dead VOD, GVHD
8 Cy, Ara-C, TBI: 1400 1.7/Yes Yes Alive
37 0.5Bu, 0.5Cy, TBI: 750 1.5/Yes Yes† Alive
38 0.5Bu, 0.5Cy, TBI: 750 1.5/Yes Yes Alive
33 Bu, Cy 1.3/Yes No Dead Resp, GVHD
17 Cy, Ara-C, TBI: 1400 1.2/Yes Yes Dead PCP
29 Bu, Cy 1.2/Yes No Dead IP, LF, RF
36 0.5Bu, 0.5Cy, TBI: 750 1.1/Yes Yes Dead CP arrest
39 Cy, Ara-C, S, TBI: 1332 1.0/Yes Yes Dead Viral infections
20 Bu, Cy, TLI: 600 0.8/Yes No Dead H, Sepsis
32 Bu, Cy 0.5/Yes Yes Alive

Pts: (+) TBI/TLD: 10 Median: Yes: 11 Alive: 5
19 (-) TBI/TLD: 9 1.7 No: 8 MPS: 2 Dead: 12

BM cell dose (x10^6/kg)/TLD: BM cell dose expressed as 10^6 cells per kilogram of recipient body weight/T lymphocyte depletion.

Abbreviations: PI, patient identifier, assigned in chronological order according to date of first URD BMT; Ara-C, cytosine arabinoside; Bu, busulfan; Cy, cyclophosphamide; VP-16, etoposide; TBI, total body irradiation; TLI, total lymphoid irradiation; ATG, antithymocyte globulin; 0.5, denotes half dose; Alive (MPS), alive with mucopolysaccharidosis IH; CMV IP, CMV interstitial pneumonitis; CP arrest, cardiopulmonary arrest; GVHD, graft-versus-host disease; H, hemorrhage; IP, interstitial pneumonitis etiology unknown; LF, liver failure; MPS, mucopolysaccharidosis; PCP, pneumocystis carinii pneumonitis; Resp, respiratory failure; RF, renal failure; VOD, veno-occlusive disease.

* Died following cervical subluxation injury after ascertainment date.
† TLI dose, spleen omitted; TBI dose, linear accelerator used instead of cobalt.
+ Graft rejection and second URD occurred after ascertainment date.
UNRELATED DONOR BMT FOR MPS I H

Table 2. Alpha-L-iduronidase Enzyme Activity Levels of MPS I H Patients Surviving at Least 1 Year Following URD BMT

<table>
<thead>
<tr>
<th>Pt</th>
<th>WBC α-L-iduronidase Enzyme Activity*</th>
<th>Years Post-BMT at Enzyme Determination</th>
</tr>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>28.0t</td>
<td>6.5</td>
</tr>
<tr>
<td>5</td>
<td>439t</td>
<td>5.2</td>
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<tr>
<td>7</td>
<td>205t</td>
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<td>22</td>
<td>632.4t</td>
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<td>1</td>
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<td>41t</td>
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<tr>
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<tr>
<td>27</td>
<td>467t</td>
<td>1.0</td>
</tr>
<tr>
<td>30</td>
<td>417t</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Enzyme activity levels of patients not engrafting after first URD BMT

* Reference ranges for enzyme activity are specified according to sample.
† Control, 39.7 ± 13.8 nmol/mg protein/h; disease, 0.0 to 1.0 nmol/mg protein/h.
‡ Control, 503.7 ± 885.3 pmol/mg protein/min; disease, 10.07 to 30.01 pmol/mg protein/min.
§ Control, 39 ± 15 nmol/mg protein/h.
|| Patient alive after second unsuccessful BMT.
† Patient died after second URD BMT.
# Patient alive after first unsuccessful URD BMT.
** Subsequent RFLP analysis documented autologous bone marrow recovery.
‖ Following second URD BMT.

was employed in 15 BMTs. TBI was used for 13 patients (range, 750 to 1400 cGy, single dose: three patients). TLI was administered in two cases (range, 600 to 1500 cGy, single dose: one patient).

Engraftment. Thirteen of 27 evaluable patients were engrafted at 1 year following URD BMT. Neither TLD of the BM nor irradiation appeared to influence the likelihood of engraftment. Ten of 16 patients alive at 1 year who received a BM cell dose ≈3.5 × 10^9 cells/kg engrafted, while only 3 of 11 patients receiving a lower BM cell dose engrafted (Table 1). Twenty-one patients received a BM cell dose ≈3.5 × 10^9 cells/kg of recipient body weight; the median BM cell dose was 1.7 × 10^9 cells/kg (Table 1). Ten patients received a radiation-containing preparative regimen, while nine patients received no radiation. Eleven patients engrafted; eight did not engraft. There are five survivors and two patients alive with MPS I H.

Of the 15 patients who demonstrated autologous recovery, 11 patients received a second BMT; nine patients received a second URD BMT, one patient received marrow from a related donor, and one patient received an URD BMT after a failed related BMT (vide supra).

Thirteen of 20 survivors achieved complete donor engraftment; two children showed mixed donor/recipient chimerism; five children showed autologous marrow recovery.

Determination of α-L-iduronidase enzyme activity level in patients surviving 1 year from BMT confirmed their engraftment status (Table 2). Of the 21 patients surviving 1 year from BMT, seven patients showed normal levels of α-L-iduronidase enzyme activity up to 6.5 years post-BMT, while five patients showed greater than 50% of normal levels.

Toxicity and GVHD. Transplant-related complications included acute and chronic GVHD, infection, sepsis, cardiopulmonary arrest, pneumonia, and renal failure. Acute GVHD developed in 20 of 40 of patients (50%) following first URD BMT; moderate to severe acute GVHD developed in 12 patients. Preparative regimens that used both TLD of the BM and irradiation were associated with a somewhat lower incidence of moderate to severe acute GVHD (2 of 14 BMTs) than regimens that employed neither TLD nor irradiation (9 of 20 BMTs). Moderate to severe acute GVHD occurred in 6 of 13 BMTs employing cyclosporin/methotrexate GVHD prophylaxis and in 6 of 27 BMTs using other GVHD prophylaxis regimens. Chronic GVHD developed in 10 of 33 patients with six showing extensive disease.

Survival. Twenty patients are alive 0.3 to 5.6 years post-URD BMT. The overall actuarial survival at 2 years is 49.2% (Fig 1). The primary cause of death in 5 of 20 patients was GVHD (Table 1). Five of nine patients developing pneumonitis died; pneumocystis carinii or cytomegalovirus (CMV) was identified in two cases. Renal failure was the primary cause of death in two patients, while cardiopulmonary arrest occurred in two patients. Sepsis occurred in three patients

![Fig 1. Overall actuarial survival (—-) of 40 MPS I H patients treated with unrelated donor BMT and their survival according to BM cell dose: ≈3.5 × 10^9 cells/kg (-) and <3.5 × 10^9 cells/kg (—).](www.bloodjournal.org)
Table 3. AES of Engrafted Survivors Following URD BMT for MPS I H According to Premarrow Transplantation MDI

<table>
<thead>
<tr>
<th>PI</th>
<th>Pre-BMT MDI</th>
<th>Age at BMT</th>
<th>AES* pre-BMT/ Age at Testing</th>
<th>AES post-BMT/ Age at Testing</th>
<th>Post-BMT MDI</th>
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</thead>
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<tr>
<td></td>
<td></td>
<td>(yr)</td>
<td>AES*</td>
<td>AES post-BMT</td>
<td></td>
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<tr>
<td>Patients with Bayley Scales MDI &gt; 70 pre-BMT</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>114†</td>
<td>1.4</td>
<td>0.8/0.8</td>
<td>1.8/2.4</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>99</td>
<td>1.0</td>
<td>0.7/0.8</td>
<td>2.7/5.9</td>
<td>48</td>
</tr>
<tr>
<td>1</td>
<td>85</td>
<td>1.3</td>
<td>1.0/1.3</td>
<td>4.8/5.5</td>
<td>88</td>
</tr>
<tr>
<td>22</td>
<td>85</td>
<td>2.4</td>
<td>1.4/1.5</td>
<td>2.7/3.6</td>
<td>76</td>
</tr>
<tr>
<td>15</td>
<td>82</td>
<td>1.7</td>
<td>1.2/1.3</td>
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<td>88</td>
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<tr>
<td>Median 85</td>
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<tr>
<td>Patients with Bayley Scales MDI &lt; 70 pre-BMT</td>
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<td></td>
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<td></td>
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<tr>
<td>19</td>
<td>64</td>
<td>1.9</td>
<td>1.2/1.5</td>
<td>3.0/4.8</td>
<td>67</td>
</tr>
<tr>
<td>27</td>
<td>58</td>
<td>2.5</td>
<td>1.6/2.4</td>
<td>1.7/4.4</td>
<td>&lt;50</td>
</tr>
<tr>
<td>5</td>
<td>&lt;50</td>
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<td>1.0/2.5</td>
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<tr>
<td>8</td>
<td>&lt;50</td>
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<td>1.2/2.7</td>
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<td>&lt;50</td>
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<tr>
<td>23</td>
<td>&lt;50</td>
<td>0.9</td>
<td>0.4/0.8</td>
<td>1.3/3.6</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Median &lt;50</td>
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</tbody>
</table>

Abbreviation: AES, age equivalent score.

* Age equivalent score (in years) was derived from Bayley Scales of Infant Development, Stanford Binet Intelligence Scale, or McCarthy Scales of Children’s Abilities.
† Corrected for prematurity.

and resulted in one death. One patient died of each of the following causes: multiple viral infections, acute toxicity secondary to graft failure, veno-occlusive disease, hemorrhage, and progressive MPS I H following nonengraftment. The median BM cell dose was \(3.5 \times 10^8\) cells/kg. The estimated 3-year survival was 24% for patients who received less than \(3.5 \times 10^8\) cells/kg, while the estimated 3-year survival was 62% for patients who received BM cells greater than or equal to this dose \((P = .05, \text{Table 1, Fig 1})\).

Neuropsychological function. Eight children who received an URD BMT and are engrafted had a baseline MDI greater than 70 (Table 3). Of these, two children were transplanted too recently for developmental follow-up to occur. Of the remaining six children, none has shown decline in age equivalent scores. Five children are acquiring skills at a pace that is equal to or slightly below their same age peers. In contrast, one child has shown slowing in her learning skills. The rate of development varied from a gain of 23 months in a 62-month span to a 45-month developmental gain in 51 months. Figure 2 (left) shows trajectories of cognitive development over time for children with baseline MDI greater than 70.

For five children with a baseline MDI below 70 (Table 3), post-BMT follow-up indicated that two children have deteriorated developmentally (Fig 2 [right]). Not only are they failing to show developmental gains, but also they are losing previously acquired skills. The remaining three children are maintaining their skills and adding to them at a rate that is more variable than the group with a baseline MDI greater than 70. The correlation of the baseline MDI with the slope of the cognitive growth trajectory is 0.76 \((P < .005)\).

Importantly, children whose baseline MDIs were less than 70 had a median age at BMT of 31 months (range, 11 to 36 months), whereas the children whose baseline MDIs were greater than 70 had a median age at BMT of 17 months (range, 12 to 29 months). The correlation of age at BMT with the slope of the cognitive growth trajectory is \(-0.64\) \((P < .03)\).

**DISCUSSION**

Untreated MPS I H patients die at a median of 5 years and rarely survive beyond 10 years. Conversely, stably engrafted MPS I H BMT patients are long-term survivors; they do not succumb to classic complications of the syndrome such as heart failure, hydrocephalus, and/or pneumo-

Lack of a related donor should not preclude effective treatment with BMT. Specifically, URD BMT can achieve normal enzyme activity. We report the retrospective experience of The Storage Disease Collaborative Study Group performing URD BMT in 40 consecutive children at 14 transplant centers in the United States and Canada. The primary focus of this report is the URD BMT and neuropsychological outcome; post-BMT somatic changes including cardiac, skeletal, and audiologic, as well as the use of genotypically identical or partial matched related BM donors are the subjects of other reports.

A consensus regarding optimal myeloablative and immuno-

suppressive preparation for URD BMT in MPS I H and the timing of BMT has not been established. In the absence of a common protocol, transplant centers determined the preparative regimen: 68% (ie, 27 of 40) of URD BMTs for MPS I H used Bu/Cy at standard dosages. TLD of donor marrow was performed in 18 of 40 transplantations (45%). Irradiation was employed in 15 of 40 (38%) URD BMTs. Both TLD of the bone marrow and irradiation were used in 14 patients. The outcomes and BMT-related morbidity provide guidance for future management of these patients.

Failure to achieve stable engraftment in MPS I H patients was a major obstacle following URD BMT. Engraftment occurred in only 62% of patients (13 of 21) surviving at least 1 year from first URD BMT and compares unfavorably.
to an engraftment rate of >85% for URD BMT in patients with leukemia.46

In leukemia patients, the development of GVHD is associated with a lower incidence of relapse and may reflect graft versus leukemia activity.46 However, GVHD is of no recognized clinical benefit in patients with MPS; instead, this BMT-related complication only increases morbidity and mortality. Initially, MLC reactivity testing was the primary method used to assess histocompatibility between donor and recipient. More recently, because of data indicating that MLC testing was not predictive of GVHD the NMDP has required that HLA-DRB1 molecular oligonucleotide typing be used.28 Moderate to severe acute GVHD occurred in 12 of 40 of patients following URD BMT and contributed to both morbidity and mortality. Furthermore, because GVHD induces inflammatory reactions that could precipitate additional central nervous system (CNS) injury, this BMT-related complication might explain, in part, the variable neuropsychological outcome in these patients.47 Future approaches to URD BMT in MPS I H must seek to reduce both the incidence and severity of acute GVHD.

Manipulation of URD grafts with TLD has been associated with a reduction in the incidence and severity of GVHD,34,48-52 but with an increase in rejection.53,54 However, the experience of the consortium showed that TLD of the marrow did not apparently compromise either the rate of engraftment at 1 year or survival. We speculate that in this patient population, insufficient myeloablative and/or immunosuppressive therapy is the principle cause of graft rejection. Of note, clearance of busulfan can be accelerated in children,55,56 but systematic evaluation of busulfan pharmacokinetics was not performed in this retrospective study. The immunocompetence of these patients may also contribute to the high rate of graft rejection. Pretransplant preparative regimens that used both TLD of the BM and irradiation were associated with a somewhat lower incidence of moderate to severe acute GVHD compared with regimens employing neither TLD nor irradiation. The recent phase I experience using TLD by elutriation, reduced doses of Bu/Cy, and TBI (750 cGy) has been encouraging.27 There are 21 patients who survived at least 1 year post-BMT; of these, seven patients showed normal levels of α-L-iduronidase enzyme activity up to 6.5 years post-BMT, while five patients demonstrated greater than 50% of normal levels. These data support the contention that BMT is a vehicle for stable adoptive enzyme therapy for MPS I H.

The overall actuarial survival at 2 years following URD BMT in these 40 patients with MPS I H is 49.2%. The two leading causes of death were GVHD and pneumonitis (five deaths each). Graft failure is another major impediment to long-term survival. This pilot experience of The Storage Disease Collaborative Study Group in performing URD BMT for MPS I H patients will serve as the foundation for a future prospective, randomized study. A BM cell dose of at least 3.5 × 10^9 cells/kg was associated with a higher rate of engraftment and better long-term survival. With future increased use of elutriation as a methodology for TLD of the BM, the BM cell dose may become a less critical factor in achieving engraftment and long-term survival. Additional study is needed to address this issue.

Both baseline and post-BMT neuropsychological data are available for 11 of 15 engrafted survivors. While two children deteriorated after URD BMT, the remaining children have continued to learn, albeit at a slower rate for a few children. We have shown in previous data that children with MPS I H transplanted with an MDI less than 70 have shown a different trajectory of development with less favorable outcome.27 This experience formed the rationale for the anal-
ysis of neuropsychologic outcomes following URD BMT based on a baseline MDI of greater than or less than 70. Of those children who had a baseline MDI greater than 70, five of six children have maintained their rate of learning. The single child who showed slowing in learning, experienced significant BMT-related complications (i.e., grade II acute GVHD and extensive chronic GVHD). She shows poor neuropsychological function relative to peers, but continues to learn at a slow rate.

Of the six children who had a baseline MDI greater than 70, all were transplanted at or before 2.4 years of age. In contrast, within the group of children with a baseline MDI less than 70, only two of five children were less than or equal to 2.4 years. Thus, in children with a good initial developmental level who are less than or equal to 2.4 years at the time of BMT, the risk for cognitive deterioration appears relatively low. The findings are not restricted to children with URD BMT, but are consistent with results obtained with related donor transplant. Neupropsychological results indicated that for children less than or equal to 2.4 years whose baseline MDI was greater than 70 and who were engrafted survivors following URD BMT, long-term outcomes are favorable and cognitive functions seem stable. These results support the efficacy of BMT for children using unrelated donors to prevent the inevitable dementia associated with the MPS I H in comparison with historic controls who were not transplanted.

Stable, life-long normalization of α-L-iduronidase enzyme activity can be achieved by BMT. An elusive goal of gene transfer therapy is precise localization, expression, and long-term production of protein. Repeated administration of genetically engineered enzyme presents potential benefits as well as logistic and economic challenges to the patient and society. In conclusion, the proliferation of and enzyme production by BM-derived monocytes and macrophages represents a successful, therapeutic intervention.

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APPENDIX

The following centers participate in The Storage Disease Collaborative Study Group and cared for patients described in this report: Alberta Children’s Hospital; Children’s Hospital of Philadelphia; Dana Farber Cancer Center; Fred Hutchinson Cancer Research Center; Kaiser Permanente; University of Iowa Hospitals and Clinics; University of California, San Francisco; University of Cincinnati, Children’s Hospital of Cincinnati; University of Kentucky Medical Center; University of Louisville, Kosair Children’s Hospital; University of Minnesota Hospital and Clinic; University of Nebraska; University of South Carolina; University of Southern California, Children’s Hospital of Los Angeles; University of Texas at San Antonio, Santa Rosa Children’s Hospital.

Contributors to this work. Principal author: C.P.; bone marrow transplanters: J.H.-D., M.E.T., M.J.C., J.S., N.B., T.W., C.L., P.F., R.H., T.B., T.E.W., G.H.G., P.W., L.S., W.K., J.W.; NMDP: R.J.K., J.D.H.; neuropsychologists: M.B., E.G.S., V.A.C., M.C.; geneticists: C.B.W., S.P., P.K.; neurologist: I.A.L.; radiation therapist: K.D.; statisticians: C.K., J.A. Departments of Pediatrics, University of Iowa College of Medicine; University of Minnesota School of Medicine; National Marrow Donor Program; University of Kentucky School of Medicine; University of South Carolina; University of California, San Francisco; Fred Hutchinson Cancer Center, University of Washington School of Medicine; Children’s Hospital of Philadelphia; University of Pennsylvania; Dana Farber Cancer Institute, The Children’s Hospital Medical Center, Boston; Children’s Hospital of Los Angeles, University of Southern California; Kaiser Permanente of Southern California; Children’s Hospital of Cincinnati, University of Cincinnati; Alberta Children’s Hospital; Santa Rosa Children’s Hospital, University of Texas, San Antonio; University of Nebraska Medical Center, University of Nebraska; and University of Louisville.

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