# Outcomes after Hematopoietic Stem Cell Transplantation for Children with I-Cell Disease

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A B S T R A C T

Mucolipidosis type II (MLII), or I-cell disease, is a rare but severe disorder affecting localization of enzymes to the lysosome, generally resulting in death before the 10th birthday. Although hematopoietic stem cell transplantation (HSCT) has been used to successfully treat some lysosomal storage diseases, only 2 cases have been reported on the use of HSCT to treat MLII. For the first time, we describe the combined international experience in the use of HSCT for MLII in 22 patients. Although 95% of the patients engrafted, overall survival was low, with only 6 patients (27%) alive at last follow-up. The most common cause of death post-transplant was cardiovascular complications, most likely due to disease progression. Survivors were globally delayed in development and often required complex medical support, such as gastrostomy tubes for nutrition and tracheostomy with mechanical ventilation. Although HSCT has demonstrated efficacy in treating some lysosomal storage disorders, the neurologic outcome and survival for patents with MLII were poor. Therefore, new medical and cellular therapies should be sought for these patients.



## INTRODUCTION

Mucolipidosis type II (MLII), or I-cell disease, is a rare autosomal recessive disorder caused by mutation in the *GNPTAB* gene on chromosome 12. This gene encodes the α/β subunits of the enzyme *N*-acetylglucosamine-1-phosphotransferase (GNPT), which acts to couple phosphate groups to mannose residues (mannose-6-phosphate [M6P] moieties) on enzymes destined to be targeted to the lysosome. Mutation in *GNPTAB*, with resultant abnormal GNPT function, can lead to inappropriate trafficking of lysosomal enzyme to the extracellular compartment. Pathologically, dense and dark granules, visible on phase-contrast microscopy, fill the cytoplasm of cultured fibroblasts, so-called inclusion cells, or I-cells. A complete absence of GNPT activity results in the severe storage disease, MLII, characteristically evident in infancy or even prenatally.

Clinical findings include coarse facial features, dysostosis multiplex, growth failure, global development delay, generalized hypotonia but stiff joints, and recurrent respiratory infections progressive. Death often occurs in the first decade of life from cardiopulmonary disease [1-3]. For patients with lysosomal storage disorders, HSCT aims to provide donor-derived hematopoietic cells that produce lysosomal enzymes with M6P moiety, allowing for intracellular uptake with appropriate trafficking to the lysosomal for substrate degradation. This "cross-correction" provided by transplanted cells has been used successfully for treatment of several enzyme-specific lysosomal storage disorders, notably mucopolysaccharidosis type I (MPSI-H), Gaucher disease, and α-mannosidosis [4-11]. However, in the case of I-cell disease, the gene product is not a soluble enzyme capable of internalization through binding to M6P receptors on the cell surface. The use of hematopoietic stem cell transplantation (HSCT) to treat I-cell disease has not been previously reported beyond 2 case reports [12,13]. We now describe the largest collection of outcome data on 22 patients with I-cell disease who underwent HSCT.

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## METHODS

### Data Collection

Patient-, disease-, and transplant-related data were obtained from the Center for International Blood and Marrow Transplant Research (CIBMTR), a voluntary working group of more than 450 transplantation centers that contribute detailed data on consecutive allogeneic and autologous transplantations to a Statistical Center at the Medical College of Wisconsin in Milwaukee or the National Marrow Donor Program in Minneapolis. Participating centers are required to report all transplants consecutively, and compliance is monitored by on-site audits. Patients are followed longitudinally until death or until lost to follow-up. All patients provided written informed consent for data submission and research participation. The study was approved by the institutional review boards of the Medical College of Wisconsin and the National Marrow Donor Program.

### Inclusion Criteria

Patients were identified by query of the CIBMTR database for the diagnoses "mucolipidosis, type II" or "I-cell disease." Records were reviewed to verify the molecular or enzyme-based diagnosis. All patients undergoing first or second allogeneic HSCT for MLII were considered.

### Outcomes

The primary endpoint was overall survival. Other outcomes studied were time to neutrophil engraftment (defined as the first day achieving an absolute neutrophil count $\geq .5 \times 10^9$/L for 3 consecutive measurements), platelet engraftment (defined as the first day when platelets remained $\geq 20 \times 10^9$/L without transfusions for 7 days), incidence of acute graft-versus-host disease (GVHD), and chronic GVHD. Acute and chronic GVHD were defined using standard criteria [14,15].

## RESULTS

### Patient and Graft Characteristics

We identified 22 patients, 12 girls and 10 boys, reported to the CIBMTR who underwent allogeneic HSCT for MLII or I-cell disease (summarized in Table 1). Patients were transplanted at a median age of 9 months (range, 2 to 23 months) and at a median of 3 months after diagnosis (range, 2 to 20 months). Most patients had Lansky performance scores of 80 or higher at transplantation. Cell sources varied, with 14 patients receiving unrelated umbilical cord blood; most of these were 5/6 or 6/6 HLA matched to the recipient. Of the remaining 8 patients, 3 patients received HLA-matched sibling bone marrow (carrier status was unknown), 1 patient received bone marrow from the mother, another received bone marrow from the father, and 3 patients received bone marrow from unrelated adult donors (1 HLA matched, 2 HLA mismatched).

Preparative regimens varied. Most were busulfan based and myeloablative in intent, although 5 patients received a reduced-intensity regimen. GVHD prophylaxis consisted largely of cyclosporine and steroids, although other regimens were also used.

Thirteen of 22 patients had documented DNA mutation analysis confirming the diagnosis of MLII. Interestingly, 3 patients (patients 4, 9, and 17) were found to have a genotype consistent with the less severe intermediate MLII/MLIII. It has been reported that these affected patients have mutations in the same *GNPTAB* gene as MLII, although retain some GNTP activity and have a milder phenotype [16]. However, 1 of these 3 patients died of organ failure more than 2 years after transplant, which suggests mortality in this case resulted from underlying disease. On the other hand, 1 of these 3 patients also died of pneumonitis shortly after transplant, a complication likely due to the transplant procedure itself.

### Outcomes

Primary engraftment was obtained in 19 of 22 patients with a median time to neutrophil and platelet engraftment of 17 days and 37.5 days, respectively. Engraftment status was not known in 2 patients; however, both died within 6 months. One patient had early secondary graft failure defined as sustained loss of neutrophil recovery in the absence of infection. This patient (patient 6) received a second transplant within 2 months from the first transplant and a third transplant 15 months after the second transplant. The donor source was adult unrelated donor. This patient is alive, approximately 10 years from first transplantation. Another patient (patient 9) developed a post-transplant lymphoma in the liver and was treated with surgical resection and 2 infusions (1 month apart) of sibling donor lymphocytes at 10.5 and 11.5 months post-transplant with resolution of her post-transplant lymphoma. Five of the 6 survivors listed in Table 1 had 100% donor chimerism at 1 to 2 years post-HSCT (no chimerism data were available for patient 21).

Grades I to II acute GvHD was documented in 9 patients. Grade III acute GVHD was seen in only 1 patient. Three patients had documented chronic GVHD, and all had been previously diagnosed with grade II acute GVHD. The probability of 5-year overall survival was 33% (95% confidence interval, 15% to 55%) with a median follow-up of 67 months (Figure 1); 27% of patients ($n = 6$) were alive at last contact. The median time to death was 27.6 months. The most common cause of death given was "organ failure" (6 patients) followed by primary disease progression (3 patients) and interstitial pneumonia (3 patients).

Although numerous reports have provided increasing amounts of information regarding survival and transplant-related outcomes for lysosomal storage disorders, the prevalence and severity of developmental delays associated with these disorders have been more difficult to measure. Consistent neuropsychiatric measures used across multiple centers are ideal in these assessments but were not available in this cohort of patients. We attempted a basic functional evaluation by sending a simple questionnaire to transplant centers to inquire as to the status of surviving patients and received information on 6 patients, 1 of whom had genetic testing indicating an intermediate form of MLII/MLIII (Table 2). The significant morbidity in these post-transplant MLII patients was likely related to their underlying disease, because they were described as requiring gastrostomy tubes for nutrition and ventilatory support per tracheostomy, having an impaired ability to ambulate, and being very delayed in speech and learning. Although these data are far from comprehensive, they document that a high degree of medical support was required for children with MLII post-transplant and that much of this support appears to be related to the underlying disease rather than to the transplant procedure.

## DISCUSSION

In the article we describe the largest series of patients undergoing HSCT for MLII, or I-cell disease. HSCT has been used for the metabolic "cross-correction" of lysosomal storage diseases for over 30 years, with most patients having severe MPSI-H. From these patients we learned that HSCT can arrest the fatal neurodegeneration of MPSI-H and allow patients to live significantly longer with improved function and quality of life. Patients undergoing HSCT for MPSI-H earlier

**Table 1**
Patient and Transplant Characteristics

| Patient No. | Year of Transplant | Time from Diagnosis to Transplant (mo) | Age at Transplant (mo) | Sex | Performance Score at Transplant | HLA Match and Graft Source | Conditioning Regimen | GVHD Prophylaxis | Acute GVHD Grade Gluksberg | Chronic GVHD | HSCT to Last Contact (mo) | Status | Cause of Death | *GNTPAB* Mutation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 2005 | n/a | 9 | Female | 100 | 5/6 UCB | ATG, Bu, Cy (MAC) | Steroids + CSA | 2 | No | 8.5 | Dead | Organ failure | Diagnosed by enzyme testing, no molecular data |
| 2 | 2006 | n/a | 4 | Male | 100 | 6/8 unrelated BM | ATG, Bu, Cy (MAC) | ATG, CSA, MTX | 3 | No | 54.1 | **Alive** | | Diagnosed by enzyme testing, no molecular data |
| 3 | 2007 | n/a | 13 | Male | 90 | 5/6 UCB | Mel, Clof, 200 cGy TBI (RIC) | CSA, MMF | 0 | No | 62 | **Alive** | | Frameshift detected, second mutation not detected by standard sequencing |
| 4 | 2000 | n/a | 14 | Male | 90 | 4/8 unrelated BM | Bu, Cy (MAC) | TCD, ATG, Steroids, CSA | 0 | No | 27.6 | Dead | Organ failure | Frameshift + missense mutations giving a diagnosis of either intermediate MLII or MLIII |
| 5 | 2002 | n/a | 4 | Female | 70 | 6/6 UCB | ATG, Bu, Cy (MAC) | Steroids, CSA | 2 | Yes | 5.5 | Dead | Interstitial pneumonia | Diagnosed by enzyme testing, no molecular data |
| 6 | 2002 | n/a | 13 | Male | 60 | 6/6 unrelated BM | Campath, Flu (RIC) | Tacrolimus | 2 | Yes | 117.4 | **Alive** | | Diagnosed by enzyme testing, no molecular data |
| 7 | 2007 | | 19 | Female | 100 | 6/6 UCB | ATG, Bu, Cy (MAC) | Tacrolimus, MMF | 0 | No | 62.8 | **Alive** | | Compound heterozygous frameshift mutation + nonsense mutation |
| 8 | 1999 | 3 | 4 | Male | n/a | HLA match unknown UCB | ATG, Bu, Mel (MAC) | Steroids, CSA | n/a | | 6.1 | Dead | Organ failure | Diagnosed by enzyme testing, no molecular data |
| 9 | 1997 | 20 | 20 | Female | 80 | Sibling BM | Bu, Cy, 750 cGy TBI (MAC) | TCD | 2 | No | 171.1 | **Alive** | | Frameshift + a splice change giving a milder than expected phenotype, intermediate MLII/MLIII |
| 10 | 2000 | 2 | 4 | Male | ≥80 | 5/6 related BM from mother | ATG, Bu, Cy (MAC) | Steroids, CSA | 0 | No | 40.1 | Dead | Primary disease | Compound heterozygous frameshift mutations |
| 11 | 2004 | 3 | 23 | Female | n/a | 6/6 UCB | ATG, Bu, Cy (MAC) | Steroids, CSA | 0 | n/a | 98 | Dead | Unknown | Compound heterozygous frameshift mutation + nonsense mutation |
| 12 | 2005 | 3 | 6 | Female | ≥80 | 5/6 UCB | ATG, Cy (RIC) | CSA, MMF | 2 | No | 57.2 | Dead | Infection | Compound heterozygous frameshift mutation + nonsense mutation |
| 13 | 2005 | 5 | 18 | Female | ≥80 | 6/6 UCB | ATG, Cy (RIC) | CSA, MMF | 0 | No | 90 | Dead | Primary disease | Homozygous frameshift mutation |
| 14 | 1991 | n/a | n/a | Male | n/a | Other related BM | Cy, TBI (MAC) | CSA | n/a | n/a | 2.9 | Dead | Unknown | Diagnosed by enzyme testing, no molecular data |
| 15 | 1996 | 2 | 9 | Male | 90 | Sibling BM | ATG, Bu, Cy (MAC) | CSA, MTX | 1 | No | 31.7 | Dead | Interstitial pneumonia | Diagnosed by enzyme testing, no molecular data |
| 16 | 2008 | 3 | 15 | Male | 90 | 5/6 UCB | ATG, Bu, Cy (MAC) | CSA, MMF | 2 | Yes | 22.7 | Dead | Organ failure | Frameshift + a splice change giving a milder than expected phenotype, intermediate MLII/MLIII |
| 17 | 2008 | 10 | 10 | Female | 100 | 5/6 UCB | Campath, Bu, Cy (MAC) | Tacrolimus, MTX | 0 | No | 0.6 | Dead | Interstitial pneumonia | Diagnosed by enzyme testing, no molecular data |
| 18 | 2008 | 8 | 8 | Female | n/a | 5/6 UCB | ATG, Bu, Flu (MAC) | Steroids, CSA | 2 | No | 5.3 | Dead | Organ failure | Compound heterozygous frameshift mutation + nonsense mutation |
| 19 | 2010 | 3 | 3 | Female | 100 | 6/6 UCB | Campath, Mel, Clof, 200 cGy TBI (RIC) | CSA, MMF | 0 | No | 8.3 | Dead | Primary disease | Homozygous nonsense mutation |
| 20 | 2010 | 2 | 2 | Female | 100 | Sibling BM | ATG, Bu, Flu (MAC) | CSA | 0 | No | 5.4 | Dead | Organ failure | Compound heterozygous frameshift mutation + nonsense mutation |
| 21 | 2010 | 10 | 10 | Male | 100 | 5/6 UCB | ATG, Bu, Cy (MAC) | Steroids, CSA | 2 | No | 89 | **Alive** | | No response from center |
| 22 | 2011 | 5 | 5 | Female | 90 | 4/6 UCB | ATG, Bu, Cy (MAC) | Steroids, CSA | 0 | No | 26 | Dead | Pulmonary failure | Homozygous frameshift mutation |

Bold text indicates survivors.
n/a indicates not available; UCB, umbilical cord blood; BM, bone marrow; Clof, clofarabine; TBI, total body irradiation; TCD, T-cell depletion; Campath, Alemtuzumab.
Performance scores are given as Lansky scores. Chemotherapy regimens consisted of antithymoglobulin (ATG), busulfan (Bu), Cytoxan (Cy), melphalan (Mel), fludarabine (Flu) and the conditioning intent classified as either myeloablative (MAC) or reduced-intensity conditioning (RIC). Graft-versus-host prophylaxis was as follows: cyclosporine A (CSA), mycophenolate mofetil (MMF), and methotrexate (MTX).

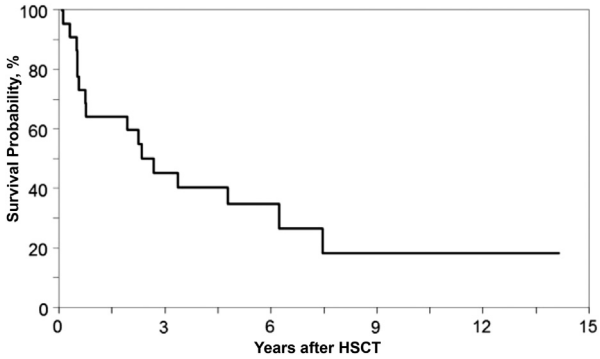


**Figure 1.** Kaplan-Meier estimate of overall survival in patients with I-cell disease after transplant.

in life (ideally before age 2 years) have been shown to lose less developmental ground and perform better. However, although HSCT may help alleviate visceral and neurologic disease associated with MPSI-H, its impact on orthopedic and cardiac valve pathology may be limited [8,17-19].

The overall survival at last follow-up in our cohort is strikingly low at 27%, with the median time to death of 27.6 months. This suggests these fatalities were not due to peritransplant-related toxicity but rather to disease-related complications not alleviated with transplantation. Specifically, although several reported causes of death were listed as "organ failure," because these occurred later after transplant, we presume some were due to progressive disease. Because MLII is rare, its natural history is documented mainly as case reports or small case series. These reports suggest that most patients do not survive past the first decade and die from cardiorespiratory complications [3,20]. Although our data show 2 patients post-transplant over age 10 (patients 6 and 9), patient 9 (who has the longest follow-up) was later determined to have an intermediate form of MLII/MLIII on review of her mutation. Interestingly, patient 9 was one of the first case reports of HSCT for I-cell disease [12].

The correlation of phenotype to genotype was reported by Cathey et al. [16], who described, for the first time, 61 patients with mutations in *GNPTAB* and found that some mutations fell into clinical separations of MLII (I-cell), MLIII, and an intermediate form of MLII/MLIII. On this basis, we cannot conclude that HSCT favorably changed the clinical outcome of patient 9, because her survival and neurologic status are not clearly different from that of an intermediate MLII/III patient. Compared with classic MLII, intermediate MLII/III patients tend to be taller, develop complications at a later age, and have less pronounced skeletal issues, less severe neurocognitive deficits, and a greater life span [16]. Furthermore, on evaluation of the available molecular mutations for patients in this cohort, 3 patients had mutations consistent with a milder phenotype than the classic MLII (Table 1).

Our limited neurologic follow-up showed that after transplant, many children are still severely affected by their disease, requiring significant medical interventions. It is unclear if they displayed any "true" improvement in neurologic development. HSCT has been attempted for several lysosomal storage diseases, although not all diseases are improved after HSCT. Also, HSCT outcomes are generally poor for patients who are in an advanced neurologic decline before transplant. We can speculate on several reasons for poor outcome after HSCT. It is believed that delivery of lysosomal enzymes by donor-derived hematopoietic cells requires the M6P moiety to allow targeting to the lysosome. In the case of MLII, disruption of the pathway by which the M6P signal is associated with the enzyme affects not just 1 but numerous enzymes. This results in inappropriate secretion and insufficient delivery of multiple enzymes to the lysosome. The outcome is the accumulation of macromolecular substrates that create inclusions in cells (giving rise to the namesake I-cells), ultimately making MLII a very severe form of lysosomal storage disease because of insufficient activity of most lysosomal enzymes. Evaluation of lysosomal enzyme activity in MPSI-H patients can show correction toward normal after HSCT, but in MLII patients the inappropriate plasma secretion of several enzymes (β-galactosidase, β-hexosaminidase A, α-mannosidase, β-mannosidase, β-glucoronidase, α-glucosaminidase, α-L-fucosidase) remains significantly elevated months to years after successful HSCT (personal observation). One could speculate this represents an incomplete lysosomal correction of disease by HSCT insufficient to prevent continued pathologic consequences.

In conclusion, we have little to no evidence that HSCT leads to improved clinical/neurologic outcomes in MLII. Overall patient survival is poor, as is quality of life among those who do survive. New modifications to HSCT or complementary therapies such as gene therapy, enzyme replacement, or

**Table 2**
Summary of Results of Questionnaire to Assess Neurologic Status in MLII Patients after Transplantation

| Patient No. | Gastrostomy Tube | Tracheostomy | Wheelchair Use | Can They Walk? | Speech? | Chronologic Age | In School? | Potty-Trained | Status |
|---|---|---|---|---|---|---|---|---|---|
| 3 | Yes | Yes | Yes | Never | No | 7 yr | Functions at a 6- to 9-month-old level | No | Alive |
| 7 | Yes | Yes | Yes | | | 8 yr | Never in school, homebound teacher 1 day per week | | Alive |
| 9 | No | No | Sometimes | Yes | Some | 18 yr | Functions at a 4-year-old level | Yes | Alive |
| 13 | Yes | Yes | Yes | Never | No | 9 yr | No | No | Died |
| 21 | Yes | Yes | No | No, and no wheelchair | 4 yr | | No | | Alive |
| 22 | Yes | No | Custom wheelchair | Never walked | No | 2.5 yr | Never achieved age for education | No | Dead |

Patient 9 had a molecular diagnosis consistent with intermediate MLII/III. Two patients died soon after the assessment was taken.

substrate reduction are needed to improve outcomes in this population of children.

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