MUCOLIPIDOSIS, TYPE II (I-CELL DISEASE) AND HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

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Mucolipidosis, Type II (ML II, I-cell disease)
ML II is a rare, recessive disorder resulting from defective transport of lysosomal enzymes in cells throughout the body. The clinical features resemble those seen in children with severe MPS I syndrome and include coarse facial features, enlargement of the internal organs (specifically the liver and spleen), progressive heart and lung problems, hernias, significant and severe developmental delay, and complex bone deformities. Typically infants with ML II or I-cell disease have an earlier age of onset of these various problems than do children with MPS I. They also show over development of the gums (gum hypertrophy), developmental delay (particularly motor) and the absence of glycosaminoglycans (GAGs) in the urine

Hematopoietic Stem Cell Transplantation (HSCT)
Stem cells are cells with the ability to divide for indefinite periods in culture and to give rise to specialized cells. There are many different types of stem cells, such as embryonic (from a fertilized egg until the end of the eighth week of gestation), mesenchymal (from the immature embryonic connective tissue), nerve, muscle, etc. Hematopoietic refers to the blood; therefore, HSCT refers to a blood stem cell transplant. Possible sources of blood stem cells include bone marrow, peripheral blood, and umbilical cord blood. All of these cells sources have been shown to engraft, or "take" following transplant. In pediatric patients, bone marrow and umbilical cord blood are used most often as sources of stem cells. While there is a large amount of information regarding outcomes with HSCT in diseases such as Hurler syndrome, there is much less information regarding its effectiveness as therapy for ML II (I-cell disease). There was a manuscript published in the journal Bone Marrow Transplantation in 2003 by the group from the University of Minnesota that stated "Over the past 5 years, three patients (0.3-1.7 year of age at HCT) have been transplanted at the University of Minnesota. The early follow-up has shown good cardiopulmonary function in two patients while one has developed pulmonary hypertension. All children remain mildly to moderately neurodevelopmentally delayed and are receiving appropriate additional educational resources."

Evaluation of the Individual with ML II before HSCT
The pre-transplant evaluation should include a comprehensive assessment as would be performed for any potential HSCT recipient (e.g., history and physical examination, blood tests, cultures, kidney function evaluation, x-rays, heart and lungs evaluations, etc.). A disease-specific evaluation that provides insight into the stage of the disease process and its rate of progression as well is critically important. For many infants and children the I-cell disease process may have already caused too much injury to important organs and tissues for a successful outcome. The impact of I-cell disease on an infant's development can be particularly devastating. In summary, very careful consideration must be given to whether HSCT would ultimately be of benefit to a specific infant or child. Surgical placement of a central venous catheter (also known as a Central Line, Broviac or Hickman Catheter, Right Atrial Catheter) is necessary.

Selecting a Suitable Donor of Blood Stem Cells and Choosing the Source of Blood Stem Cells
Identifying a suitable donor of the blood stem cells will involve a blood test, also known as tissue typing, that is performed on family members as well as unrelated donors. The health of the prospective donor should be evaluated as well as whether it will be safe for that person to donate blood stem cells. If umbilical cord blood is used for the transplant, there is no need to do an evaluation on the donor, as the cord blood units have already been tested, and they are frozen and readily available. For this reason, often the transplant can take place more quickly using cord blood, and may therefore be the best option.

The best possible match will be sought and may include a matched brother or sister, a closely matched parent or relative, or fully or partially matched unrelated donors. Issues that will be considered include the dose of cells to be given with the transplant, the chemotherapy used as preparation for the transplant, and the medications to be used to reduce the likelihood and severity of graft-versus-host disease (GvHD). Consideration must be given to the stage of disease in the individual with ML II, the rate of disease progression, and the potential for stabilization of various aspects of the disease process.

Transplant Center and Multi-disciplinary Care
The transplant center should have demonstrated proficiency in providing the full spectrum of medical care necessary for a successful outcome. This applies not only to the transplant procedure but also to the various medical and surgical subspecialists who typically become involved in the pre- and post-transplant evaluation and management of such complicated patients.

Preparative Regimen and Supportive Care Measures
Many different regimens that have been used successfully in transplanting individuals with MPS disorders would be applicable to infants with ML II (I-cell disease). The specific chemotherapy agents will be presented as well as whether radiation is to be used. The intensity or strength of the preparation regimen for the transplant can vary across a wide spectrum. In general, “reduced intensity” transplant regimens may be easier and less toxic for the patient, as less intensive chemotherapy is used. However, there may be a higher risk that the donor cells may not “take”. Transfusion of blood products will be provided as needed (e.g., red blood cells, platelets), and anti-infection and other medications will also be given. Good hand washing practices will be emphasized and there will be special air filtration and isolation procedures.

Graft-versus-Host Disease (GvHD) Prevention and Treatment and Other Complications of the HSCT Process
GvHD is a well-recognized complication of transplantation, and all blood stem cell sources can lead to this complication. GvHD occurs when the donor cells (the “graft”) recognize the patient being transplanted (the “host”) as being foreign. This may be a mild reaction, but in some cases is severe. Transplant protocols have a strategy for the prevention of GvHD, and specific treatments for GvHD are available should GvHD develop. Hair loss, painful mouth sores, and infections are common side effects or complications associated with the HSCT process. A number of transplant-related complications are possible and can involve virtually any organ or tissue in the body. Of particular concern are serious side-effects to the brain, lungs, heart, kidneys and liver. If severe complications develop, the long-term survival rates can decrease markedly. However, efforts will be made to minimize these side-effects.

Engraftment, Recovery from the HSCT, and Follow-up

Following engraftment or growth of the donor's blood stem cells, there is recovery of the blood counts often between 3 to 4 weeks after the transplant. Discharge from the hospital is dependent upon a number of factors including: recovery of blood counts, absence of active infection, the individual's ability to take medications by mouth or through a tube going from the nose into the stomach (i.e., a nasogastric or NG tube) or directly into the stomach (a gastrostomy tube, or G-tube), and the transplanted individual being in overall stable medical condition. Follow-up in the HSCT clinic often includes frequent routine check-ups, blood tests, medications, blood product transfusions, etc. Since many organ systems can be affected by the underlying disease, as well as by effects of the HSCT, multi-disciplinary, comprehensive, coordinated long-term follow-up at a medical center that has an interest and experience with these complex diseases is at minimum highly desirable, and could be considered essential. Subsequent HSCT procedures may be required if the individual does not successfully engraft.

Summary and Conclusions

The effective use of HSCT for selected MPS disorders has been established over the past twenty or more years. However, there remains relatively little experience in the treatment of ML II with transplant. HSCT should be performed at centers with experience in offering comprehensive, multi-specialty care for individuals with ML II whose underlying diseases can be appropriately treated by transplant.