

HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) FACT SHEET

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Introduction

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.

To date, HSCT represents one of the few therapies with proven, long-term benefit for some, but not all, MPS disorders. The MPS disorders benefiting most significantly from HSCT include severe MPS I (Hurler syndrome), MPS VI (Maroteaux-Lamy syndrome), and MPS VII (Sly syndrome). Unfortunately, a significant benefit from HSCT related to the nervous system and/or the skeletal system has not been definitively shown for MPS II (Hunter syndrome), MPS III (Sanfilippo syndrome) and MPS VI (Morquio syndrome).

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 sub-specialists who typically become involved in the pre- and post- transplant evaluation and management of individuals with MPS.

Evaluation of the Individual with MPS 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.). Also important is a disease-specific evaluation that provides insight into the stage of the disease process and its rate of progression. The specific details for such an evaluation will be included in the discussion of the particular MPS diseases. 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 happen more quickly using cord blood and may therefore be the best option.

The donor's enzyme activity level can and should be assessed as well. 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.

There are a number of relative advantages and disadvantages for each type of blood stem cell, bone marrow, peripheral blood, or umbilical cord blood. Therefore, there is no "perfect" source of blood stem cells. It is important to note that successes have occurred following transplant with all types of blood stem cells. 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 MPS, the rate of MPS disease progression, and the potential for stabilization or reversal of various aspects of the MPS disease process.

Preparative Regimen and Supportive Care Measures

Many different regimens that have been used successfully in transplanting individuals with MPS disorders, including chemotherapy agents and radiation. 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) along with anti-infection and other medications. 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. The transplant-related complications 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.

MPS Disorders for which HSCT Is Effective

MPS I (Hurler syndrome): Successful HSCT has been performed for children with Hurler syndrome since 1980. The immediate benefits include correction of the enzyme deficiency and clearance of glycosaminoglycans (GAGs). Long-term benefits include the possibility of long-term survival by protecting the heart, lungs, and brain from the effects of progression of the MPS disorder. Other organs and tissues can also show benefits from the HSCT; these include the eyes and ears, liver, spleen, joints, airway, etc. However, it should be noted that many children are still requiring a variety of orthopedic surgeries despite a successful transplant. While the term "cure" should not be used, HSCT has the longest track record of any effective therapy for Hurler syndrome, including the ability to preserve cognitive function and development in the normal range. While intravenous enzyme therapy is now available for MPS I, it does not treat the brain. Treating the brain intrathecally using enzyme replacement therapy is being studied in clinical trials, but is not widely available. For this reason, in patients with Hurler syndrome, transplantation is the standard of care. There is also the opportunity to use enzyme therapy prior to transplant to clear much of the storage material prior to the transplant; this is offered by some centers, but is not universal.

MPS VI (Maroteaux-Lamy syndrome): The principal clinical features of children with MPS VI are bone abnormalities, severe short stature, corneal clouding, lung problems, liver and spleen enlargement, and heart valve abnormalities. Intelligence is felt to be preserved in most individuals. For over twenty years,

HSCT has been used successfully to treat MPS VI with resolution of liver and spleen enlargement, airway obstruction and sleep apnea, and improved joint mobility. There has also been prevention of further heart and lung deterioration. Visual acuity has improved in some individuals although corneal haze does not necessarily resolve. As in other MPS disorders, HSCT has not been able to treat effectively the skeletal abnormalities. Consequently, successfully transplanted children have still required orthopedic surgical interventions on the knees and hips. With the availability of enzyme replacement therapy (ERT) for MPS VI patients, discussions as to the relative risk of transplantation as opposed to ERT are important in determining therapy.

MPS VII (Sly syndrome): Use of HSCT for MPS VII is limited by the rarity of the disorder and tendency toward stillbirths, although there are also milder adult forms of this disease. In certain circumstances, MPS VII can be effectively treated by HSCT provided that the developmental and clinical status of the individual is good at the time of HSCT.

Evaluation Recommendations: An evaluation prior to HSCT should include, at a minimum, the following specialists: transplant, anesthesia, ENT, neuropsychology, neurology, pulmonology, and cardiology. Evaluations after HSCT should include all of the above specialists as well as endocrine (growth and hormone status), ophthalmology, hand surgery and general orthopedic surgery.

MPS disorders for which HCT has NOT been Effective

MPS II (Hunter syndrome, severe form): To date, there is no compelling data that HSCT for the severe form of MPS II has been able to help prevent the progressive development decline in these boys. Treating the brain intrathecally using enzyme replacement therapy is being studied in clinical trials, but is not widely available.

MPS II (Hunter syndrome, less severe or attenuated form): There is no established role of HSCT for these boys and men, as ERT is available for these patients. Intelligence and life expectancy can be

relatively preserved in these boys and men with enzyme replacement. (See the section “Alternative and Complementary Therapies” below).

MPS III (Sanfilippo syndrome): The published experience to date with HSCT for children with MPS III shows that all have experienced progressive deterioration in their neurodevelopmental status despite "successful" HSCT performed in a timely manner. While HSCT is occasionally performed on MPS III individuals, there is no published evidence that any form of HSCT has been successful in preventing this decline. Treating the brain intrathecally using enzyme replacement therapy is being studied in clinical trials, but is not widely available.

MPS IV (Morquio syndrome): HSCT has not been able to correct the severe skeletal deformities associated with some of the MPS disorders. HSCT is, therefore, not recommended for individuals with Morquio syndrome.

Alternative and Complementary Therapies

Aldurazyme™ (alpha-L-iduronidase) enzyme replacement therapy is approved by the FDA for the treatment of individuals with MPS I. Aldurazyme has been primarily used in individuals with the less severe or attenuated forms of MPS I (i.e., Hurler/Scheie and Scheie syndromes). Studies of the role of combination therapy (Aldurazyme and HSCT) for individuals with MPS I, specifically Hurler syndrome, are underway. MPS II enzyme replacement therapy, idursulfase (Elaprase™) was approved by the FDA in 2006. MPS VI galsulfase (Naglazyme™), enzyme replacement therapy, was approved by the FDA in 2005. MPS IVA elosulfase alfa (Vimizim™), enzyme replacement therapy, was approved by the FDA in 2014. All of the MPS disorders have alternative therapies being explored, including a variety of novel, experimental therapies under investigation; it may be important to determine what alternative therapies (stem cell transplant related or others) are available to you.

Summary and Conclusions

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