Chapter 29

Hematopoietic Stem Cell Transplantation

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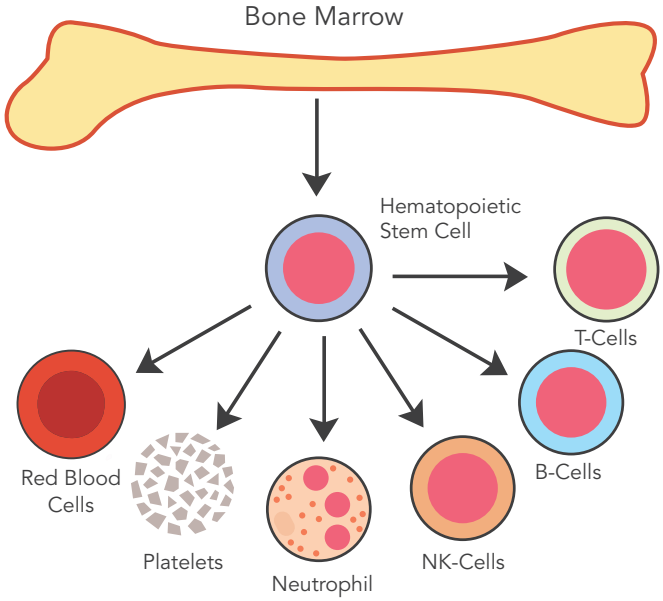
Primary immunodeficiency diseases (PI) cause a wide spectrum of symptoms with varying severity. Some forms of PI are mild and don't cause significant harm, or may be effectively treated with agents like immunoglobulin (Ig) replacement therapy. Other forms of PI are so severe that individuals have a very poor quality of life or can die as a result of their disease. When PI is likely to cause significant harm or death to someone, allogeneic hematopoietic stem cell transplantation (HSCT) may be the best treatment option. Some common indications for allogeneic HSCT include Severe Combined Immunodeficiency (SCID), Wiskott-Aldrich Syndrome (WAS), Chronic Granulomatous Disease (CGD), Leukocyte Adhesion Deficiency (LAD), Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked (IPEX) syndrome, X-linked Lymphoproliferative Disease (XLP), Hyper IgM Syndrome, Combined Immune Deficiency (CID), and Hemophagocytic Lymphohistiocytosis (HLH). Allogeneic HSCT can also be considered for other forms of PI. The following will review the basics of allogeneic HSCT for PI.

Overview

Immune system cells develop from special cells that live in the bone marrow called hematopoietic stem cells. Hematopoietic stem cells produce all blood cells including red blood cells, platelet-producing cells, and immune system cells such as neutrophils, T cells, B cells, and NK cells (Figure 29:1).

Hematopoietic stem cells can be transferred from one person to another person. This requires a very specialized procedure called an allogeneic HSCT. The person who receives the stem cells is called a recipient of HSCT. The term, allogeneic, indicates that the stem cells given to the recipient came from someone else, the hematopoietic stem cell donor. If an allogeneic HSCT is successful, the donor's hematopoietic stem cells will replace the recipient's own cells. The donor cells will live in the recipient's bone marrow and make blood and immune system cells.

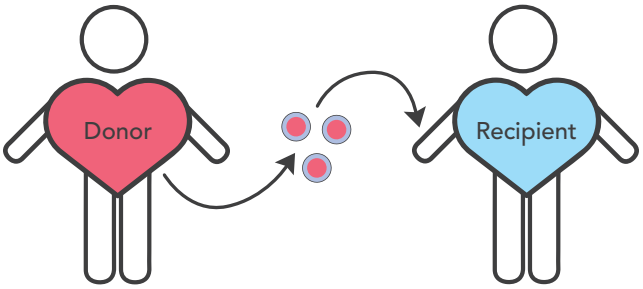
Figure 29:1 Hematopoietic Stem Cell Produces All Blood Cells



People with PI essentially have broken pieces in their immune system. Immune system cells may be missing or just not work properly. An allogeneic HSCT can replace an individual's own hematopoietic stem cells with stem cells that will produce normal immune system cells. In this way, a person's immune system can be fixed. Allogeneic HSCT also fixes any problems with other blood cells. For example, platelets will be fixed in those with WAS who have a successful allogeneic HSCT. Unfortunately, problems outside of the blood or immune system will not be fixed. For instance, if an individual with IPEX has diabetes before transplant, they will still have diabetes after transplant, because the cells in the pancreas that make insulin have been destroyed by this disease, and HSCT cannot replace pancreatic cells.

Hematopoietic stem cells may be collected from the bone marrow, the peripheral blood, or from umbilical cord blood, so HSCT procedures may be called bone marrow transplants, peripheral blood stem cell transplants, or cord blood transplants depending on the source of the stem cells. The transplant itself does not require surgery for the recipient, as the hematopoietic stem cells are typically infused into a large vein in the same way that a patient receives a blood transfusion. (Figure 29:2)

Figure 29:2 Hematopoietic Stem Cell Transplantation (HSCT)

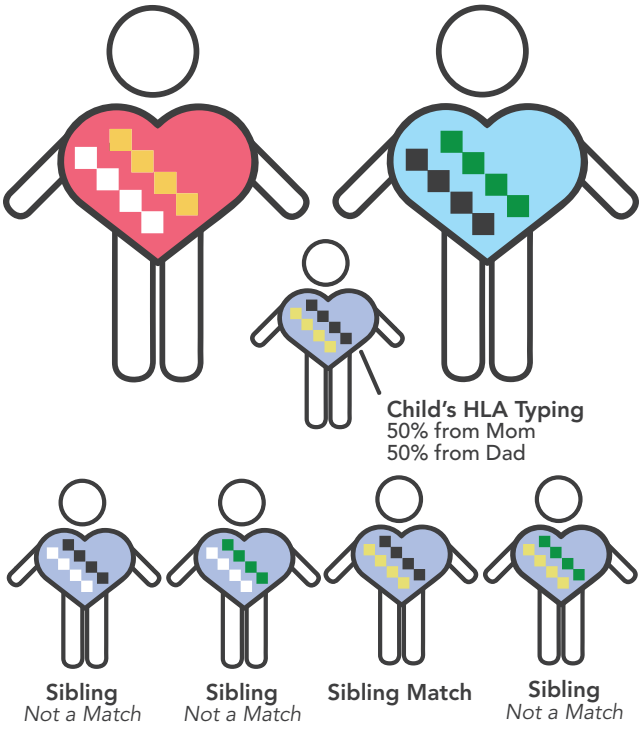


Finding a Donor

Before having a transplant, a suitable donor must be found. Finding a donor can take several weeks or months. The first thing that happens is a blood test is done to learn about a person's human leukocyte antigen (HLA) typing. The immune system uses HLA proteins on cells to help determine which cells belong to the body and which don't, so HLA matching increases the chances of transplanted donor cells being successfully incorporated into the recipient's body. A donor must be found who has the same or almost the same HLA typing results. HLA-matched donors are the best donors because when HLA typing is the same between a donor and recipient, the chances of complications, such as graft rejection and graft versus host disease (GVHD), are low. Transplant providers typically look at 8 to 12 HLA alleles (markers) or genes when trying to find a matched donor. A fully matched donor would be an 8/8, 10/10, or 12/12 (depending on the testing lab) HLA matched donor.

If the individual with PI has siblings, the brothers and sisters will have HLA typing done to determine if they are a match. Everyone has two sets of HLA genes. One set is inherited from the mother, and the other set is inherited from the father. Typically, each full brother or sister (same mother and same father as the recipient) has a 25% chance of being a full match to their affected sibling (Figure 29:3). It is important that potential sibling donors are evaluated for PI before being used as donors.

Figure 29:3 Example of Human Leukocyte Antigen (HLA) Typing in a Family



If there are no sibling donors available, the search will move to several national and international donor registries to look for a matched unrelated donor. If there are no matched donors, a mismatched donor may be considered. If only one HLA allele is different between the person with PI and the donor, that would be noted as a 7/8, 9/10, or 11/12 HLA mismatch. Having an HLA mismatch increases the risks of graft rejection and GVHD—the greater the mismatch, the greater the risks of rejection or GVHD.

Sometimes, a parent may be used as a donor. Parents are typically only a half match to their children, so this type of transplant is called a haploidentical transplant. This type of transplant must be done in a special way because there is a high risk of graft rejection or acute GVHD. Donor T cells must be removed from the graft or otherwise destroyed to decrease the risk of severe GVHD.

Graft Sources

Hematopoietic stem cells can come from three sources: bone marrow grafts, cord blood grafts, and peripheral blood stem cell grafts. Bone marrow grafts are harvested from the pelvic bones of donors using large needles after the donor is put to sleep. Cord blood grafts are collected from the umbilical cord at the time of a baby's birth, and processed in a special way to allow the cord blood to be frozen and stored until it is used. Peripheral blood stem cell grafts are collected from a donor's veins after the donor receives several days of a special medicine that causes stem cells to leave the bone marrow and circulate in the bloodstream. A central venous line or large intravenous lines (IVs) are placed in the donor's veins, a machine is used to remove and collect the stem cells from the blood, and the blood minus the stem cells is then returned to the donor. This process takes several hours. Sometimes more than one peripheral blood stem cell collection is performed in order to get more stem cells.

Preparing for Allogeneic HSCT

Some individuals with PI may be fortunate enough to be able to have an allogeneic HSCT at their nearby hospital, but many will have to travel to specialized centers for transplantation. This can be difficult for families and can be emotionally and financially challenging. Individuals with PI and their families will usually meet members of the transplant team, which can include physicians, nurse practitioners, social workers, psychologists, nurses, and financial counselors. These team members can help prepare recipients and their families for the impact the transplant will have on family life, and they can help provide support and assistance with all aspects of the transplant. Staff at the hospital, in collaboration with the families, will often work with insurance companies to get approval for the transplant.

The time spent at a transplant center can vary from center to center, and it also varies from person to person. However, recipients and families can generally expect to stay at the transplant center for at least three to six months before returning home. Allogeneic HSCT are generally performed in the hospital, but once recipients are healthy enough, they can be discharged from the hospital and return to the transplant clinic several times a week.

Pre-transplant Evaluations

Recipients typically have a large battery of tests and procedures done before transplant to make sure they are healthy enough to have a transplant. Healthcare providers may find hidden problems that need to be addressed prior to transplant, such as infections or organ function problems. Immunologists and transplant providers will typically order many blood tests as well as imaging studies, such as computerized tomography (CT) scans, ultrasounds, and/or magnetic resonance imaging (MRI). Special tests of kidney function will be done. The heart will be evaluated with an echocardiogram (ECG, EKG), an ultrasound of the heart. If recipients are old enough, pulmonary function testing will be done. Some may need procedures such as a bone marrow biopsy, lumbar puncture, bronchoalveolar lavage, or gastrointestinal endoscopy prior to allogeneic HSCT. All of these tests usually take a few weeks to complete.

Consent for Transplant

Before having a transplant, a recipient and/or family must give consent to proceed with the transplant. Members of the transplant team will meet with the recipient and/or family to go over the process and the risks and benefits in detail. Recipients and families should ask questions and be sure that they understand the proposed treatment before proceeding.

The Transplant

HSCT is different than organ transplants, for example of liver, lung, or kidney, in several ways. As mentioned before, the transplant itself is not a surgery, because the stem cells are given in the vein similar to a transfusion. Also, HSCT recipients need special preparation to receive the stem cells that solid organ patients don't need. The process of replacing the stem cells in the bone marrow requires an inpatient stay of about six to eight weeks. This inpatient stay is what most people think of as the transplant. After discharge, full recovery of the immune system to a normal immune system occurs as an outpatient, and is a process that takes many months, up to a year. Unlike solid organ transplant

recipients, HSCT recipients are able to wean off of immune suppressive medications if all goes well because the new immune system becomes accustomed or tolerant to the patient's body.

Most need a long-term central venous line placed prior to transplant. This ensures that venous access will be available for chemotherapy, stem cell infusion, medications, IV fluids, and lab work that will be done throughout the transplant process. It also avoids the need for repeated IV placement and venipuncture. Central lines are usually placed in large veins in the chest or neck, and recipients and parents can learn to take care of them.

What happens during the inpatient hospitalization can be thought of as similar to what happens if you replant a garden. If you imagine that the immune system is a garden that has weeds in it, instead of healthy plants, first you need to use some weed killer to get rid of the weeds. For stem cell transplant, the weed killer is what is called a conditioning regimen, in other words a combination of different medications to destroy the patient's own immune and bone marrow cells to prepare for receiving the donor stem cells. Conditioning regimens vary from center to center and from person to person. In general, conditioning regimens may consist of chemotherapy and serotherapy, and the regimen is given over many days prior to receiving the hematopoietic stem cells. Chemotherapy medications are given to essentially kill the recipient's own hematopoietic stem cells. This helps to make space in the bone marrow for the donor's stem cells to grow. Common chemotherapy agents include busulfan, fludarabine, melphalan, cyclophosphamide, and thiotepa, but other agents may be used. Serotherapy medications are antibody therapies, often monoclonal antibodies that are toxic to immune system cells. These agents can help prevent graft rejection, and they also help prevent GVHD. Common serotherapy agents include alemtuzumab and anti-thymocyte globulin. Different conditioning regimens have different intensities, which refers to how strong the chemotherapies are and how effectively they kill a person's bone marrow. Higher intensity regimens are very effective and are called myeloablative regimens. Lower intensity regimens, such as partial myeloablative regimens, may be less effective, but they are associated with fewer risks. The choice of conditioning regimen depends on each individual and the individual's diagnosis. In certain situations, conditioning may not be given. This is particularly true for some individuals with SCID and depends on the type of donor.

After the conditioning regimen is completed, the hematopoietic stem cells are given. The planned day of stem cell infusion is called Day 0. Stem cells are given through the central line like a blood transfusion. After Day 0, recipients typically remain in the hospital for several weeks while doctors wait for the new stem cells to grow. Similar to the garden analogy, once the weeds are gone, you can plant the seeds, but there is a period of time when the garden is empty because it takes time for the healthy plants to grow. During this time, there are no blood cells being produced by the bone marrow, so it is common to need blood and platelet transfusions. Recipients will be watched closely for any signs of infection, and they may need pain medicines, medicines for nausea, and fluid and nutrition support. Frequent blood tests will be performed to monitor for any signs of organ dysfunction. Most will receive medications to help prevent GVHD. These medications suppress the immune system. Common examples include cyclosporine or tacrolimus. Transplant teams will monitor the recipient's blood counts with a blood test called a complete blood count (CBC). When the stem cells start to work, the numbers of particular blood cells will start to rise; this is called engraftment. Once there are signs of engraftment, a special blood test will be done to determine what percentage of the cells are from the donor, called an engraftment or chimerism study. Once the blood counts recover to a safe level, recipients may be able to transition to outpatient care at the transplant center. Recipients will have a lot of oral medications, and many will need some IV medications, IV fluids, or IV nutrition during the early outpatient treatment phase. Home healthcare services, depending upon an individual's insurance coverage, may be utilized to help with these needs.

Early Transplant Complications

Allogeneic HSCT can have many complications. It is difficult to estimate the risks for each individual, but common complications are noted below.

Mucositis and Nausea, Vomiting, Diarrhea:

Chemotherapy can damage the lining of the mouth, throat, stomach, and intestines. This can be very mild or more problematic depending on the intensity of the conditioning regimen. Recipients may have ulcers, nausea, pain, vomiting, diarrhea, and sometimes bleeding. This improves as the blood counts start to recover a few weeks after transplant. Recipients may need pain medications, anti-nausea

medications, and nutrition and fluid support. These symptoms improve once the recipient engrafts with donor cells.

Graft Failure: If donor stem cells don't grow (primary graft failure) or don't last (secondary graft failure), a recipient is said to have graft failure. An individual will often have a second transplant if this occurs.

Graft Rejection: Sometimes graft failure is suspected to occur because a recipient's immune system attacked it. This is called graft rejection. An individual will often have a second transplant if this occurs.

Anemia: Recipients usually require blood transfusions early after transplant. After successful engraftment, the recipient changes blood type from their blood type to the blood type of the donor. Once the donor marrow is producing a good amount of red blood cells, the recipient will generally no longer need transfusions.

Bleeding: Recipients have low platelet counts and are prone to bleeding after transplant. They often receive platelet transfusions for several weeks after transplant to prevent bleeding. After successful engraftment, they generally no longer need transfusions.

Mixed Chimerism: If a donor's stem cells grow, but the recipient's stem cells also grow after transplant, an individual is said to have mixed chimerism. This will be evident on the engraftment study. Mixed chimerism is more likely to happen with lower intensity conditioning regimens. In general, mixed chimerism is okay for many individuals with many types of PI, as long as there are enough donor cells to keep the individual healthy. The level of donor cells needed and type of donor cells needed, depends on the disease for which that the individual was treated.

Acute Graft Versus Host Disease (GVHD): In the first few months after transplant, a donor's immune system may recognize a recipient's as being foreign, and mount an attack against the recipient's own tissues, just as it would fight an infection. For this reason, HSCT recipients take immune suppressive medicines for approximately six months after transplant to prevent GVHD. Sometimes despite the preventative medications, GVHD still occurs. The most common signs of acute GVHD are rash or diarrhea. It can also affect the liver or other organs. Acute GVHD can be mild or severe. It is usually treated with steroids and other immune suppressive medications.

Chronic GVHD: Chronic GVHD typically occurs later than acute GVHD and can last a long time. It can affect several organs including the skin, mouth, gastrointestinal tract, eyes, lungs, and genitourinary tract. It is usually treated with steroids and other immune suppressive medications.

Infections: Individuals with PI are prone to infections prior to allogeneic HSCT, but the risk goes up further with transplant. Recipients are monitored very closely for infections during and after transplant. Several anti-microbial medications are given to prevent infections, and Ig replacement therapy may be given regularly. Recipients are treated aggressively for any sign of infection. It is important that the recipient or caregivers call immediately if the recipient has a fever or other signs of infection after discharge from the hospital after undergoing an allogeneic HSCT.

Organ toxicity: Chemotherapy can damage organs such as the liver and lungs. Certain transplant medications can damage the kidneys. Organ function is another thing that will be closely monitored after transplant.

Transplant-associated thrombotic microangiopathy (TMA): TMA is characterized by injury to little blood vessels during or after transplant. This can lead to blood clotting in the little blood vessels and organ dysfunction.

Death: Even though transplant outcomes are now very good for most individuals with PI, survival is not 100%. As a gross estimation, chances of survival can be considered to be approximately 80% for most individuals with PI. However, if a matched (HLA) sibling is available as a donor, survival data is closer to almost 100%. Chances of survival may be higher or lower depending on several factors such as diagnosis, age, pre-existing complications, donor relation, and HLA match, as well as other variables.

Hospital Discharge

Once a recipient's donor cells are producing enough neutrophils and platelets to keep the patient safe, they may be ready for discharge. Recipients must not have fevers or bleeding, and they need to be able to take their medications as prescribed. Recipients and/or caregivers must be comfortable taking care of the central line, and they may also need to learn to give IV fluids, IV nutrition, and even some IV medications

outpatient. Once a recipient is discharged, they will usually come back to the transplant clinic several times a week for lab work, examinations, and infusions. Often recipients are discharged to housing that is close to the transplant center, particularly if their own homes are some distance away. Recipients can still develop complications after discharge, including infections, organ toxicities from medications, and GVHD.

By Day +100, some recipients are ready to return to their own homes and can usually just continue to follow up just with their local healthcare providers. Recipients often still need to take several medications for the first year after transplant, including immune suppressive medications to prevent GVHD. Until they have full recovery of immune cell numbers and are successfully weaned off of immune suppressive medications, they should still remain isolated. Neutrophils recover just a few weeks after transplant, but T cells require many months and B cells may take one to two years. Healthcare providers can do blood tests to see how an individual's immune system is recovering and make recommendations about when it is safe to stop isolation. Once the immune system is fully recovered, recipients should receive routine re-vaccination following transplant.

Long-Term Follow Up

By one to two years post-transplant, most recipients have good immune system recovery and do not need frequent follow up. It is generally recommended that an individual should return for follow up yearly or every other year, as this long term follow up is important to monitor them for late complications of transplant. These late complications are mostly related to the conditioning medications given to prepare the recipient for transplant, but they may also be related to organ damage caused by infection or immune dysregulation before the transplant. The severity and likelihood of late complications related to allogeneic HSCT is variable. Some complications include endocrine problems such as thyroid function, growth, or puberty issues. Fertility may be affected. Individuals who develop chronic GVHD need special long-term follow up. The transplant team can tell recipients and caregivers more about what long-term monitoring may be needed.

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