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Hematopoietic Stem Cells

Hematopoietic Stem Cell Transplantation is a process whereby diseased stem cells in the bone marrow are replaced with new stem cells. Hematopoietic stem cells have the ability to differentiate, or reproduce, into other cells of the blood and immune system. They give rise to: red blood cells which carry oxygen throughout the body; white blood cells which fight infections; and platelets which are necessary for clotting (Cord Blood Donor Foundation, n.d.).

Stem Cell Transplantation Process

During hematopoietic transplantation, stem cells are introduced into the body through an infusion, similar to a blood transfusion. Unlike a simple blood transfusion, hematopoietic transplantation involves the removal of the diseased cells prior to the introduction of healthy cells just as you might remove a diseased organ (kidney) and replace it with a healthy organ (kidney). The 'organ' in this case is the bone marrow where the stem cells reside. Removing the bone marrow is not a surgical option so a different mechanism is used; chemotherapy and radiation. The amount of chemotherapy and/or radiation treatment required to kill the diseased cells differs according to the specific diagnosis but the desired result during this 'conditioning' process is destruction of unhealthy cells and suppression of the immune system in preparation for the introduction of the healthy stem cells (Mayo Clinic, 2008).

Once the new cells have been infused, they migrate to the bone marrow and begin to produce blood cells. When the stem cells produce all three types of blood cells the transplant is said to be engrafted. Engraftment can take anywhere from several weeks to months, during which time the patient is at high risk for bleeding and infections (National Marrow Donor Program (NMDP), 2008a).

Development of Stem Cell Transplantation

Hematopoietic stem cell transplants became possible after the discovery of human histocompatibility antigens in 1958. Human leukocyte antigens (HLA) are proteins found on most cells in the body. These proteins are used as markers by the immune system to recognize cells and determine if they are inherent or foreign and need to be destroyed (NMDP, 2008b). A close match between recipient and donor HLA markers is essential to a successful transplant. Since HLA markers are inherited, half from the mother and half from the father, the best chance for a match is a sibling. Each sibling has a 25% chance of a match with another sibling (NMDP, 2008c).

Stem cells are obtained from live donors by three methods, each of which yields a slightly different product. Additionally, the stem cell donor can be the patient him/herself (autologous transplant) or another person (allogeneic transplant), depending on the illness.

The first successful stem cell (bone marrow) transplant was in 1959 when a physician at Columbia University used cells from an identical twin to extend the life of an end-stage leukemia patient (Melmed, 2006). Bone marrow aspiration is the method of removing stem cells directly from the donor's bone marrow. This is done under general anesthesia in an operating room. The marrow is most often collected by multiple needle aspirations from the posterior iliac crests (back of the pelvis). A small amount of marrow is removed through a needle in several locations until the required amount has been collected. Collections may also be done from the anterior iliac crests (front of the pelvis) and/or the sternum (breast bone) (American Association of Blood Banks (AABB), 2005).

Further developments in the identification of HLA markers resulted in the identification of six specific markers crucial to transplant success. It wasn't until

1968 that transplants from siblings other than twins were possible. In 1973, the first unrelated bone marrow transplant was performed.

Apheresis is a special method of collecting stem cells from the peripheral (circulating) blood. The donor is usually given a growth factor to increase the number of cells available (AABB, 2005). The whole blood is collected from the donor and separated in an instrument similar to a centrifuge. The stem cells are processed for transplantation and the remaining blood products are re-transfused back into the donor. The process takes several hours, usually on each of two days (Memorial Sloan-Kettering Cancer Center, 2003).

The first cord blood transplant took place in 1988 using umbilical cord blood from an HLA matched sibling. Cord blood is the blood remaining in the placenta or “afterbirth” after the umbilical cord is cut at the birth of a child. A rich source of stem cells, it is collected in the delivery room, usually after the placenta is delivered although it may be collected through the umbilical cord before placenta delivery (MNDP, 2008d). Despite skepticism that a sufficient amount of stem cells would be present in such a small amount of cord blood, the transplant was a complete success (Kurtzberg, Lyerly, & Sugarman, 2005).

It has since been determined that cord blood has a higher frequency of progenitor cells compared with adult peripheral blood or bone marrow and that cord blood has a higher growth/engraftment potential (Grewel, Barker, Davies, & Wagner, 2003). 1993 was the first year that unrelated-donor cord blood was used for stem cell transplantation.

Graft-Versus-Host-Disease (GVHD) is a serious complication associated with any stem cell transplant. GVHD occurs when T cells (immune system cells) from the donor engraft and react against the tissues of the recipient (AABB, 2005). The risk of GVHD is reported to be 43% to 70% in HLA matched (6 of 6 markers) bone marrow transplants and 63% to 95% in HLA mismatch of one marker (5 of 6 markers) (Grewal et al., 2003).

One of the outcomes noted during the early days of using cord blood for transplantation was that the incidence of GVHD was 10-fold lower than with HLA matched bone marrow obtained from a sibling (Kurtzberg et al., 2005). Data indicates that “the risk of developing acute and chronic GVHD after 1-2 antigen HLA-mismatched unrelated cord blood transplant is similar, or even lower, than that

reported with HLA-matched bone marrow transplantation” (Grewal et al, 2003, p. 4239).

Hematopoietic stem cell transplants have been used to treat (and often cure) a variety of life threatening illnesses including:

- Hematologic Malignancies (blood cancers)
 - Leukemia – overproduction of white blood cells
 - 44,270 estimated new cases in 2008
 - 21,710 estimated deaths in 2008
 - Non-Hodgkin’s lymphoma – cancers arising from lymphocytes (a type of white blood cell)
 - 66,120 estimated new cases in 2008
 - 19,160 estimated deaths in 2008

(American Cancer Society (ACS), 2008)

- Bone Marrow Failure Diseases
 - Severe Aplastic Anemia
 - Bone marrow stops making stem cells
 - Estimated 500-1,000 new cases per year
 - Fanconi Anemia – genetic disease with high risk of aplastic anemia, leukemia, and other cancers

(National Heart Lung and Blood Institute, n.d.)

- Immune Deficiency Diseases
 - A group of nearly 100 disorders caused by basic defects in immune function
 - Severe Combined Immune Deficiency (SCID)
 - Also known as “bubble-boy disease”
 - Genetic disease in which the immune system is completely inactive
 - Estimated incidence of 1:100,000 births

(Ismailov, 2002)

- Metabolic Diseases
 - Mucopolysaccharidoses –
 - Group of genetic diseases characterized by the absence of certain enzymes needed to break down long chains of sugar carbohydrates
 - Estimated incidence of 1:25,000 births
 - Hurler’s Disease (gargoylism)
 - Most severe type of mucopolysaccharidosis
 - Characterized by severe developmental delay, progressive mental decline, loss of physical and language skills, and death by age 10
 - Estimated incidence of 1:100,000 births

(National Institute of Neurological Disorders and Stroke, 2008)

Cord Blood vs. Bone Marrow Transplants

Cord blood transplantation is the most recent advance in hematopoietic stem cell transplant procedures. Among the advantages of using cord blood is the fact that it is easier to collect and store than bone marrow. The placenta is disposed as medical waste after delivery in most cases.

Collecting cord blood poses no risk to the donor unlike bone marrow aspiration which is painful and requires a surgical procedure be performed on the donor. The small amount of cord blood per donation is a limiting factor for use in many adult patients. The following table summarizes issues involved in selecting a stem cell medium.

Issue for Graft Selection	Bone Marrow	Cord Blood
Available Pool	Living, volunteer donors ~11 million worldwide	Preharvested, cryopreserved ~250,000 units
Acceptable donor-recipient HLA match	5 of 6 markers	4 of six markers
Median search time	Long, ~ 4 months	Shorter, < 1 month
Potential for second graft from same donor	Yes	No
Risk to donor	Uncommon (anesthesia related, surgical complication)	None
Major limiting factors	HLA-match; donor attrition/availability	Fixed cell content (especially for larger sized recipients)
Engraftment	2-4 weeks average	Slower and slightly lower incidence
GVHD	Higher incidence-- 43%-95% HLA-match dependent	Less severe

(Kurtzberg et al., 2005; Grewal et al., 2003)

Donor Registry

The National Marrow Donor Program (NMDP) began operations in 1986. As of May 26, 2008 it listed more than 4.8 million donors and is the largest single registry in the world. Additionally, it has access to more than 6 million donors through arrangements with international registries (Bone Marrow Donors Worldwide (BMDW), 2008). Unfortunately, only 25% to 50% of patients needing transplants find HLA matched donors. Minority patients, especially Black/African American patients, have a lower probability of finding a perfectly matched unrelated adult donor because of the greater diversity in their tissue types (Health Resources and Services Administration (HRSA), 2008).

Unlike bone marrow donations in which the HLA-typed donor must be located and available at the time the transplant is to take place, cord blood can be collected, processed, and stored for later use. The first cord blood bank was started in 1991 at the New York Blood Center (Kurtzberg et al., 2005). The American Association of Blood Banks currently lists (as of May 7, 2008) 22 accredited Cord Blood Facilities in the United States. Only one is located in Texas, the South Texas Blood & Tissue Center in San Antonio (AABB, 2008). The M.D. Anderson Cancer Center in Houston,

TX established a cord blood bank in 2005 and is in the process of expanding its operations (MD Anderson, 2007). Cord blood units are listed as available in the NMDP, but not all public cord blood banks participate in that program. The Bone Marrow Donors Worldwide registry lists eight (8) U.S. cord blood banks/registries in addition to the NMDP with 134,474 cord blood units available in the U.S. as of May 26, 2008 (BMDW, 2008).

The Stem Cell Therapeutic and Research Act of 2005 established the C.W. Bill Young Cell Transplantation Program as the successor to the National Bone Marrow Donor Registry. The purpose of this program is to “provide funds to a network of cord blood banks to: (1) build a racially diverse inventory of the highest quality cord blood units for transplantation (P.L. 109-129 establishes a target of 150,000 new units), and (2) make these and other units at participating cord blood banks available to physicians and patients for blood stem cell transplants through the C.W. Bill Young Cell Transplantation Program. The Program also will make cord blood units available for preclinical and clinical research, focusing on cord blood stem cell biology and the use of cord blood stem cells for human transplantation and cellular therapies” (HRSA, 2008).

References

- American Association of Blood Banks (AABB). (2005, July). *Circular of information for the use of cellular products*. Retrieved May 29, 2008, from http://www.aabb.org/Documents/About_Blood/Circulars_of_Information/coi_ct1005.pdf
- American Association of Blood Banks (AABB). (2008, May 7). *AABB accredited cord blood facilities*. Retrieved May 29, 2008, from http://www.aabb.org/Content/Accreditation/Cord_Blood/AABB_Accredited_Cord_Blood_Facilities/
- American Cancer Society, Inc. (2008). Estimated new cancer cases and deaths by sex, US, 2008. *Cancer Facts & Figures 2008*. Retrieved May 28, 2008 from http://www.cancer.org/downloads/STT/2008CAFFfinals_eured.pdf
- Bone Marrow Donors Worldwide (BMDW). (2008, May 27). *Number of donors/CBU's per registry in BMDW*. Retrieved May 29, 2008, from http://www.bmdw.org/index.php?id=number_donors
- Cord Blood Donor Foundation. (n.d.). *Diseases treated with cord blood*. Retrieved May 29, 2008, from http://www.cordbloodcenter.com/en/01_oc_li.htm
- Grewel, W., Barker, J., Davies, S., & Wagner, J. (2003). Unrelated donor hematopoietic cell transplantation: marrow or umbilical cord blood? *Blood*. 101:4233-4244. Retrieved May 29, 2008, from <http://bloodjournal.hematologylibrary.org/cgi/reprint/101/11/4233?maxtoSHOW=&HITS=10&hits=10&RESULTFORMAT=&fulltext=unrelated+donor+hematopoietic+cell+transplantation%3A+marrow+or+umbilical+cord+bl+o&searchid=1&FIRSTINDEX=0&sortspec=relevance&resourcetype=HWCIT>
- Health Resources and Services Administration (HRSA). (2008). *National Cord Blood Inventory*. Retrieved May 29, 2008, from <http://www.hrsa.gov/about/budgetjustification08/NationalCordBloodInventory.htm>
- Ismailov, R. (2002, July). *IL2RG and Severe Combined Immunodeficiency (SCID), a Primary Immunodeficiency Disease (PID)*. Retrieved May 29, 2008, from http://www.cdc.gov/genomics/hugenet/file/print/factsheets/FS_IL2RG_ScidPid.pdf
- Kurtzberg, J., Lyerly, A., & Sugarman, J. (2005). Untying the Gordian knot: policies, practices, and ethical issues related to banking of umbilical cord blood. *The Journal of Clinical Investigation*. 115:2592-2507. Retrieved May 29, 2008, from <http://www.pubmedcentral.nih.gov/articlerender.fcgi?to=ol=pmcentrez&artid=1236704>
- Mayo Clinic. (2008, April 11). *Stem cell transplant*. Retrieved May 29, 2008 from <http://www.mayoclinic.com/health/stem-cell-transplant/CA00067>
- M.D. Anderson Cancer Center. (2007). *Cord Blood Bank at M.D. Anderson Cancer Center Receives \$9 Million Grant*. Retrieved May 29, 2008, from <http://www.mdanderson.org/topics/bmatmda/display.cfm?id=3c75d60e-7167-49f3-9cf69430abee9122&method=displayfull&pn=00c8a30fc468-11d4-80fb00508b603a14>
- Melmed, G. (2006). The war on cancer: a report from the front lines. *Proc (Bayl Univ Med Cent)* 19:323-334. Retrieved May 29, 2008 from <http://www.pubmedcentral.nih.gov/articlerender.fcgi?to=ol=pmcentrez&artid=1618753>
- Memorial Sloan-Kettering Cancer Center. (2003). *The transplant process*. Retrieved April 23, 2008, from <http://www.mskcc.org/mskcc/html/15451.cfm>
- National Heart Lung and Blood Institute. (n.d.). *Who is at risk for Aplastic Anemia?* Retrieved May 29, 2008, from http://www.nhlbi.nih.gov/health/dci/Diseases/aplastic/aplastic_whoisatrisk.html
- National Institute of Neurological Disorders and Stroke. (2008, February). *Mucopolysaccharidoses Fact Sheet*. Retrieved May 29, 2008, from http://www.ninds.nih.gov/disorders/mucopolysaccharidoses/detail_mucopolysaccharidoses.htm
- National Marrow Donor Program (NMDP). (2008a). *Waiting for engraftment: Days 0-30*. Retrieved May 29, 2008, from http://www.marrow.org/PATIENT/Donor_Select_Tx_Process/Waiting_for_Engraftment_Days_0/index.html
- National Marrow Donor Program (NMDP). (2008b). *History of Marrow and Blood Cell Transplants*. Retrieved April 25, 2007 from <http://www.marrow.org/ABOUT/History/index.html>
- National Marrow Donor Program (NMDP). (2008c). *HLA Matching: Finding the Best Donor or Cord Blood Unit*. Retrieved May 29, 2008 from http://www.marrow.org/PATIENT/Donor_Select_Tx_Process/The_Search_Process/HLA_Matching_Finding_the_Best_/index.html
- National Marrow Donor Program (MNDP). (2008d). *How to donate cord blood*. Retrieved May 29, 2008, from http://www.marrow.org/DONOR/Donation_Transplant_Process/The_Donation_Procedure/CB_Donation/index.html
- Stem Cell Therapeutic and Research Act of 2005. Pub. L. No. 109-129, December 20, 2005. Retrieved May 29, 2008, from [http://www.nationalcordbloodprogram.org/cord%20blood%20public%20law%20109-129%20\(2\).pdf](http://www.nationalcordbloodprogram.org/cord%20blood%20public%20law%20109-129%20(2).pdf)