

Blood and Marrow Stem Cell Transplantation

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Fighting Blood Cancers

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Introduction

This booklet provides information for patients and their families about blood or marrow stem cell transplantation for the treatment of leukemia lymphoma, myeloma, myelodysplastic syndromes or other cancers of the blood and marrow.

Between 1970, when the transplant registry began tracking data, and today, the number of patients with cancers of the blood and marrow receiving treatment with stem cell transplantation has increased from hundreds to thousands of patients transplanted per year. An estimated 18,720 people in North America had autologous or allogeneic stem cell transplantation for blood cancers in 2005, the most current data available (Source: *CIBMTR [Center for International Blood and Marrow Transplant Research] Newsletter*, Volume 13, Issue 2, December 2007.) The procedure continues to be improved in anticipation of making it a treatment option for even more patients each year.

Blood and Marrow Stem Cell Transplantation includes a glossary to help readers understand medical terms. Some of the medical terms used throughout this booklet may be synonyms for other words or phrases used by healthcare professionals. Check with your physician if you have questions about how the terms used in this booklet apply to you. We hope this information is of assistance and we welcome comments about the booklet.

This publication is designed to provide accurate and authoritative information about the subject matter covered. It is distributed as a public service by The Leukemia & Lymphoma Society (LLS), with the understanding that LLS is not engaged in rendering medical or other professional services.

Overview of Stem Cell Transplantation

Stem cell transplantation is a technique that can restore the marrow function of patients who have had severe injury to that site. Marrow injury can occur because of primary marrow failure, destruction of marrow by disease, or intensive chemical or radiation exposure. The source for the earliest transplants was the marrow of a healthy donor who had the same tissue (human leukocyte antigen [HLA]) type as the patient. Usually, the source was a brother or sister. Donor programs have been established to identify an unrelated donor who has a tissue type that matches that of a patient. This approach requires screening tens of thousands of people in order to find a suitable donor. The transplant succeeds because the infusion of donor stem cells is able to restore normal marrow function.

Stem Cell Sources for Transplantation. The cells used in transplants can come from three sources: marrow, peripheral blood and the blood in the umbilical cord after a baby's birth. Since blood and marrow are both good sources of stem cells for transplantation, the term "stem cell transplantation" has replaced "bone marrow transplantation" as the general term for this procedure. The acronym "BMT" is now used to represent blood and marrow transplant. Collecting stem cells from marrow is a surgical procedure. Peripheral blood is the most common source of stem cells for transplant. Peripheral blood stem cells (PBSCs) are released from the marrow into the bloodstream. Normally, the marrow releases only a small number of PBSCs into the blood; to obtain enough PBSCs for a transplant, a donor is given medication to move more blood-forming stem cells from the marrow to the blood. Cord blood stem cell transplantation is almost two decades old, yet is a relatively new procedure, especially for adults, in comparison to transplantation of peripheral blood or marrow stem cells. (See *Collecting Stem Cells for Transplantation or Infusion*, page 14.)

Types of Transplants. If a donor and recipient are identical twins, the transplant is called "syngeneic," the medical term for genetically identical. With a syngeneic transplant there is no immune difference and no likelihood of a host versus graft (graft rejection) or a graft versus host reaction. If the donor and recipient are not identical twins, the transplant is called "allogeneic." An allogeneic transplant means the donor is the same species and, in practice, nearly always a match in tissue type to the recipient. The term "matched unrelated" is applied to the donor who is not a family member, recruited by searching among a large pool of potential donors for the rare individual who is identical or very similar in HLA type to the recipient.

The important technique of collecting a patient's stem cells from marrow or blood, freezing the collection and returning it to the patient after he or she has received intensive chemotherapy and/or radiation therapy for the underlying disease is referred to as "autologous transplantation" or "autotransplant." This term is misleading since transplantation implies transferring tissue from one individual to another. This technique is better referred to as "autologous stem cell infusion."

Pretreatment (Conditioning). High-dose chemotherapy and/or radiation therapy prior to transplantation is necessary to

- Decrease the risk that the recipient's immune cells will reject the transplanted stem cells
- In cases involving marrow failure, to rid the recipient of the disordered lymphocytes that are often the cause of the condition (that is, an attack by the patient's own lymphocytes on developing blood cells). The transplant aids the patient's recovery by providing the donor's lymphocytes and blood cells to replace those of the patient.

In patients who have cancers of the blood and marrow, the radiation and/or chemotherapy work to eliminate any disease which might remain at the time of the transplant.

Some patients who receive an allogeneic stem cell transplant have a nonmyeloablative transplant. This type of transplant follows reduced-intensity conditioning that does not destroy the patient's immune system. After the donor cells are transplanted, immunosuppressant drugs are given to help prevent complications. More information begins on page 29.

History of Transplantation. In the mid-19th century, Italian scientists proposed that the marrow was the source of blood cells. The idea that a factor in the blood-forming tissues from one individual might restore the injured marrow of another individual was considered a century ago. Some thought this factor was a chemical that could be transferred by eating the marrow. At the turn of the 20th century, scientists began to formulate the idea that a small number of cells in the marrow might be responsible for the development of all blood cells. They began to refer to them as "stem cells." Attempts to use the marrow cells of a healthy individual to restore the lost marrow function of another person are more than 60 years old. Early attempts at human marrow transplantation were largely unsuccessful because the scientific basis for achieving successful outcomes was not yet known.

The scientific exploration of marrow transplantation as a form of treatment began at the end of World War II. Stem cells are very sensitive to irradiation injury. Thus, marrow injury was an important and potentially lethal side effect of exposure to the atomic bomb or to industrial accidents in the atomic weapons industry. In the late 1940s, studies of marrow transplantation as a means of treating radiation-exposed combatants or civilians were spurred by the Atomic Energy Commission's concern about the spread of nuclear technology and weapons.

The basis for stem cell transplantation is that all blood cells and immune cells arise from stem cells in marrow. The idea that medical disorders that affect blood cell or immune cell formation could be cured by marrow transplantation encouraged research by civilian scientists as well. These research efforts led to the current success of stem cell transplantation as medical treatment. Estimates from the data reported to the Center for International Blood and Marrow Transplantation Research (CIBMTR) indicate that about 7,880 patients received allogeneic stem cell transplants in 2005 (the most current data available.) CIBMTR estimates that about 10,840 patients received autologous stem cell infusions (autotransplants) in 2005.

Immune Deficiency Diseases. Children who are born with severe immune cell deficiencies are unable to make lymphocytes. In the absence of normal lymphocytes and immune function, these children may experience repeated and often life-threatening infections. Lymphocytes can be restored by stem cell transplantation. The body's acceptance of the transplanted cells is actually aided by the recipient's deficiency of immune cells, which makes it unlikely that the recipient will reject donor stem cells. Therefore, a recipient of transplantation for immune cell deficiency does not require intensive pretreatment (conditioning) with radiation or chemotherapy to suppress the immune system. Also, in these diseases, the patient with immune deficiency may accept a graft that is not a complete HLA or immunologic match.

Inherited Severe Blood Cell Diseases. Marrow transplantation is used to treat inherited blood disorders, including thalassemia and sickle cell diseases. With these disorders, a mutant gene is inherited. This gene is expressed only in the blood-forming cells. For patients with inherited blood cell disease, transplantation is a form of genetic therapy—the genetically abnormal blood-forming stem cells are replaced with normally functioning cells. A sibling with a matching tissue type is the stem cell donor. For example, the patient may have sickle cell disease (having received the mutant gene from both mother and father), and the sibling donor may be a carrier of the gene, with sickle cell trait (having received the mutant gene from either the mother or father). Yet, it is possible for stem cells from the donor to cure the recipient by replacing sickle cell disease, a very severe disorder, with sickle cell trait, a condition that usually does not cause any symptoms.

Which patients with inherited blood cell disorders should take the risk of transplantation and when to undertake the procedure are issues still being studied.

Other Inherited Disorders. There is a group of inherited disorders in which there is a gene defect in the monocytes. Soon after birth very disabling abnormalities, including blindness, mental retardation and severe neurological dysfunction, may develop in the affected infant. Abnormal monocytes can be replaced by normal cells through the transplantation of stem cells from a healthy compatible donor.

Aplastic Anemia. Stem cell transplantation has been used successfully to restore the function of marrow that has been injured. This type of marrow failure, referred to as “aplastic anemia,” can be drug induced, autoimmune, or, more rarely, inherited (Fanconi anemia). In many cases, the cause of the marrow failure is not known. Patients with severe aplastic anemia who have a compatible donor can be treated by stem cell transplantation. In this situation, pretreatment of the patient with chemotherapy and/or radiation therapy is required to suppress the immune system of the patient and enhance the likelihood of success of the transplant.

Information about stem cell transplantation for cancers of the blood and marrow begins on page 9.

Normal Blood and Marrow

A brief description of normal blood and marrow is provided for background.

Blood is composed of plasma and cells suspended in plasma. The plasma is largely made up of water in which many chemicals are dissolved. These chemicals include

- Proteins such as: albumin; antibodies, including those developed by the body after vaccination (such as poliovirus antibodies); and clotting factors
- Hormones, such as thyroid hormones
- Minerals, such as iron, calcium, magnesium, sodium, and potassium
- Vitamins, such as folate and B₁₂.

The cells suspended in plasma include red cells, platelets and white cells (neutrophils, eosinophils, basophils, monocytes and lymphocytes).

- The red cells make up 40 to 45 percent of the blood volume. They are filled with hemoglobin, the protein that picks up oxygen in the lungs and delivers oxygen to the cells all around the body.
- The platelets are small cell fragments (one-tenth the size of red cells) that help stop bleeding at the site of an injury in the body. For example, when an individual has a cut, the vessels that carry blood are torn open. Platelets stick to the torn surface of the vessel, clump together and plug up the bleeding site. Later, a firm clot forms. The vessel wall then heals at the site of the clot and returns to its normal state.
- The neutrophils and monocytes are white cells. They are called “phagocytes” (or eating cells) because they can ingest bacteria or fungi and kill them. Unlike red cells and platelets, white cells leave the blood and enter the tissues, where they can ingest invading bacteria or fungi and help combat infection. Eosinophils and basophils are two additional types of white cells that respond to allergens.
- Most lymphocytes, another type of white cell, are in the lymph nodes, the spleen and lymphatic channels, but some enter the blood. There are three major types of lymphocytes: T cells, B cells and natural killer (NK) cells. These cells are key parts of the immune system.

Marrow is a spongy tissue where blood cell development takes place. It occupies the central cavity of bones. In newborns, all bones have active marrow but by young adulthood, the bones of the hands, feet, arms, and legs no longer have functioning marrow. The backbones (vertebrae), hip and shoulder bones, ribs, breastbone, and

skull contain marrow that makes blood cells in adults. Blood passing through the marrow picks up formed red and white cells, and platelets for circulation.

The process of blood cell formation is called “hematopoiesis.” A small group of cells, the stem cells, develop into all the blood cells in the marrow by the process of differentiation (see Figure 1). When the fully developed and functional cells are formed, they leave the marrow and enter the blood. In healthy individuals there are enough stem cells to keep producing new blood cells continuously.

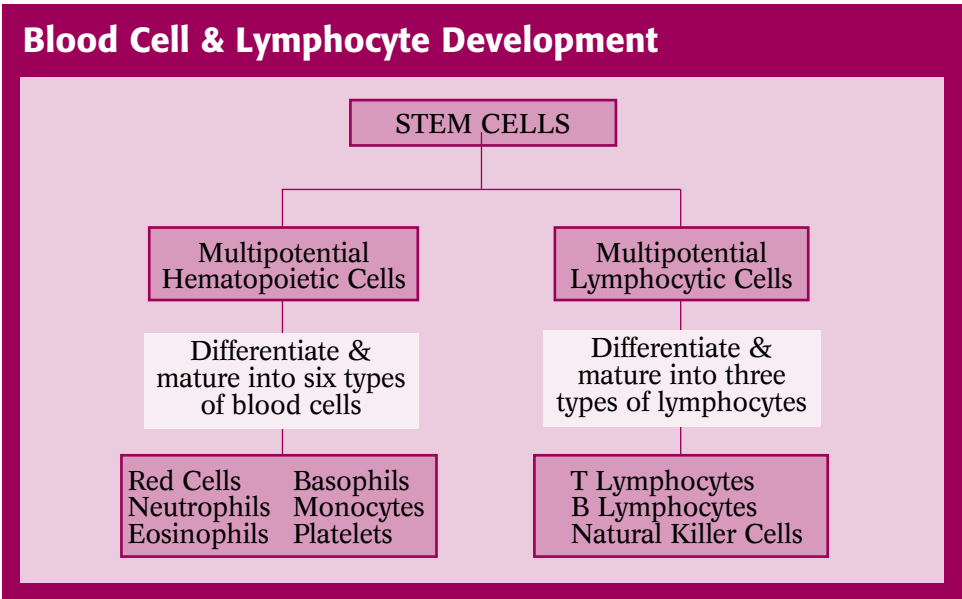


Figure 1. This simplified diagram depicts the process of stem cells developing into functional blood cells (hematopoiesis) and lymphatic cells.

Some stem cells enter the blood and circulate. They are present in such small numbers that they cannot be counted or identified in the usual type of blood counts. Their presence in the blood is important because they can be collected by a special technique and if enough stem cells are harvested from a compatible donor, they can be transplanted into a recipient.

Stem cell circulation, from marrow to blood and back, also occurs in the fetus. After birth, placental and umbilical cord blood can be collected, stored and used as a source of stem cells for transplantation.

Stem Cell Transplantation and Cancers of the Blood and Marrow

Acute leukemia, lymphoma, myeloma and myelodysplastic syndromes have remission and cure rates that increase in relationship to the amount of chemotherapy given to the patient. Large doses of chemotherapy and/or radiation are required to destroy the diseased cells. These intensive therapies can destroy normal cells in the marrow as well. The capability of the marrow to make healthy blood cells is so severely impaired after the very-high-dose chemotherapy and/or radiation therapy required to treat refractory or relapsed disease that few patients would survive such treatment without replacement of the blood-forming cells. They would succumb as a result of infections (because of the absence of white cells) or hemorrhage (because of the absence of platelets).

Transplant physicians employ stem cell transplantation so that they can administer large doses of chemotherapy or radiation therapy and then restore normal blood cell production. The infusion of a sufficient number of stem cells from a closely matched donor, such as a sibling, can rapidly begin to restore marrow function and blood cell production and allow recovery from the intensive treatment. After several decades of research, discovery and clinical trials, allogeneic stem cell transplantation can now be used successfully to cure some patients who are at high risk of relapse, who do not respond fully to treatment, or who relapse after prior successful treatment (see Table 1, page 10). Autologous stem cells (obtained from the blood or marrow of the patient) can also be used in some circumstances.

A critical component of allogeneic transplantation is the generation of a graft versus tumor (GVT) effect that may be even more important than the very intensive therapy administered to destroy cancer cells. This effect is a result of the donor lymphocytes “recognizing” the patient’s cancer cells and eliminating them. Unfortunately, despite appropriate tissue matching, similar donor cells may also react against the patient’s normal cells and generate a serious condition called graft versus host disease (GVHD). The use of autologous stem cells has neither the drawbacks of GVHD nor the advantages of a potent donor cell-derived anti-tumor effect.

A patient with leukemia, lymphoma or myeloma, myelodysplastic syndrome or idiopathic myelofibrosis whose disease is poorly responsive to standard therapy, or has biological features that are known to predict a poor response to chemotherapy,

may be treated with very intensive chemotherapy and/or radiotherapy, which requires complementary allogeneic transplant or autologous stem cell infusion (autotransplant). The decision to use this treatment approach takes into account

- The patient’s age, general health and medical condition
- The likelihood that the disease will respond to the conditioning regimen
- The availability of an HLA-matched donor or the ability to use the patient’s own stem cells.

Table 1. Cancers of the Blood and Marrow for Which Allogeneic Stem Cell Transplantation Has Been Used

Acute myelogenous (myeloid) leukemia
(all subtypes)

Adult acute lymphocytic leukemia

Childhood acute lymphocytic leukemia
(if very-high-risk type or does not enter
remission or relapses)

Chronic lymphocytic leukemia
(all subtypes)

Chronic myelogenous (myeloid)
leukemia

Hodgkin lymphoma
(if refractory to treatment
or recurrent)

Idiopathic myelofibrosis
(agnogenic myeloid metaplasia)

Non-Hodgkin lymphoma
(all subtypes, if refractory to treatment
or recurrent)

Myelodysplastic syndromes
Myeloma

When considering a transplant for a patient in remission, there are two central questions that should be answered. They are

- Does the current medical evidence indicate that stem cell transplantation will be more likely to cure the disease than other forms of therapy?
- Is there an appropriate donor available as a source of stem cells?

Other important factors that influence the decision include the patient’s age, the specific disease being treated, biologic features at the time of diagnosis that indicate a poor prognosis, and the presence of complicating medical conditions (see Figure 2, page 11).

The age of the patient is a compelling factor in the decision to do a transplant. About three-quarters of individuals who develop a cancer of the blood and marrow are more than 50 years old. However, older individuals are more susceptible to GVHD

and more likely to have complicating medical problems. Older persons are also more likely to have decreased tolerance for the cumulative effects of the intensive chemotherapy and the conditioning treatments that they will have to undergo before a transplantation procedure.

These are generalizations, and allogeneic transplantation can be used in older individuals when medically appropriate. Nonmyeloablative or reduced-intensity transplant is a modified form of allogeneic transplant in which the dose of intensive therapy is reduced but sufficient to suppress the patient's immune system and enable the donor cells to engraft. This approach is under active study in clinical trials but appears to be particularly useful in older patients or those with additional medical conditions who are unlikely to be able to tolerate a standard allogeneic transplant (see *Reduced-intensity Allogeneic Stem Cell Transplantation*, page 29). Autologous stem cell infusions (autotransplants) with high-dose chemotherapy can be performed in certain instances in patients up to their mid-70s.

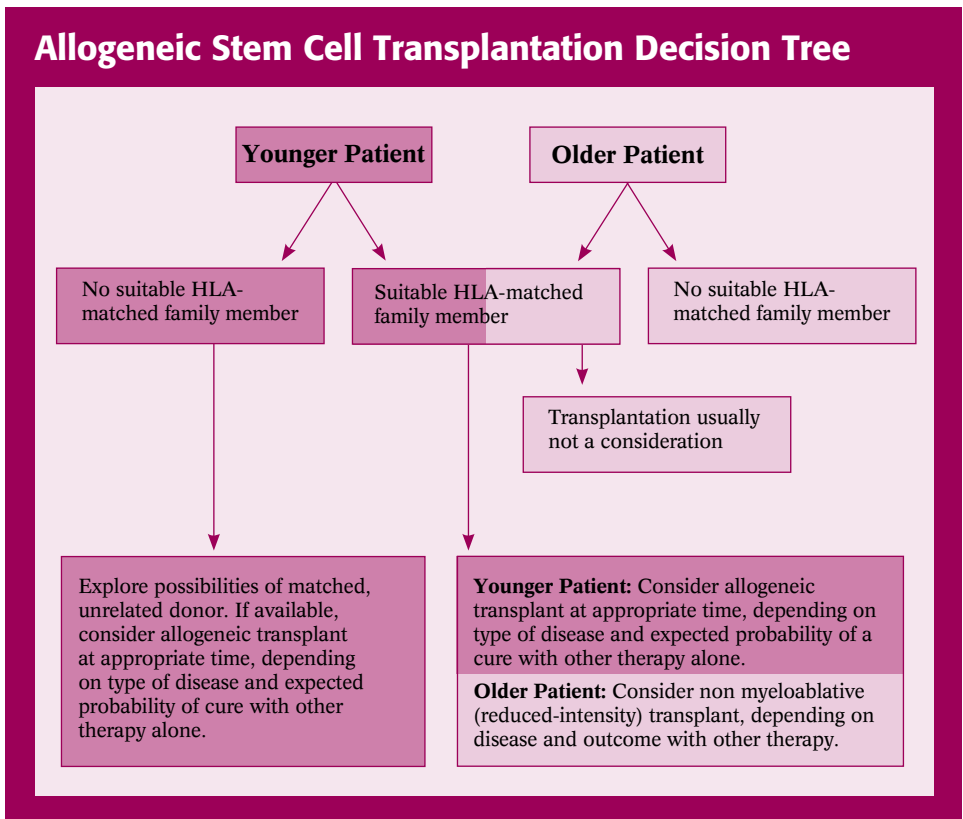


Figure 2. The option for stem cell transplantation depends on several factors.

The risks of stem cell transplantation have decreased with each succeeding decade of use. Continued research may further improve the risk-versus-benefit in favor of transplantation. However, effective new drugs and new therapeutic modalities may lessen the potential benefits (as compared to the risk) of transplantation.

Testing to Identify Donors

When a transplant is under consideration, the patient and his or her siblings will be tested to determine their tissue (HLA) type. The HLA system produces a tissue type that is distinct from the red blood cell type that determines transfusion compatibility.

The tissue type of an individual is determined by proteins on the surface of cells. Like other tissue cells, the leukocytes (white cells) contain these surface proteins. By testing the leukocytes obtained from a blood sample, transplant physicians can identify the HLA type of the patient and potential donors. The immune reactions that occur when nonidentical individuals receive a transplant are governed largely by these cell surface proteins. The lymphocytes of the recipient can sense that the donor's cells are "foreign" and attempt to kill (reject) them. The donor's immune cells can sense that the patient's cells are foreign and attack them.

The degree of difference in tissue type between donor and recipient is the main determinant of the intensity of

- Host versus graft effect (the patient's cells reject the transplanted donor stem cells)
- Graft versus host disease (GVHD), (the transplanted donor immune cells attack the patient's body).

These two reactions do not happen if the recipient and donor are identical twins. However, these reactions do happen when the recipient and donor are nonidentical siblings, even if they are matched by tissue typing. Such cases show that HLA testing does not examine all relevant tissue type factors. Consequently, two processes are necessary to permit a successful transplant: suppression of the recipient's immune system before transplant and suppression of the donor's immune cells in the recipient after transplant.

A person's HLA type is governed by genes on chromosome 6 in tissue cells. All human somatic cell-types have 46 chromosomes: a pair of each chromosome numbered from 1 to 22 plus the two sex chromosomes (either XX in a female or

XY in a male). The genes on the pair of chromosomes that determine HLA type are transmitted to a child as shown in Figure 3. One of each pair is inherited from one's mother (AB) and the other of the pair from one's father (CD). Each parent's contribution is referred to as a "haplotype." The term "haploidentical" indicates that the potential donor who is being HLA-typed shares half the HLA type of the potential recipient. In the example shown in Figure 3, siblings AC and AD are haploidentical, sharing their mother's chromosome A, but each receiving different chromosomes from their father.

Even though, on average, a person has one chance in four of having the same HLA antigens as his or her sibling, many patients will not have a sibling of the same tissue type.

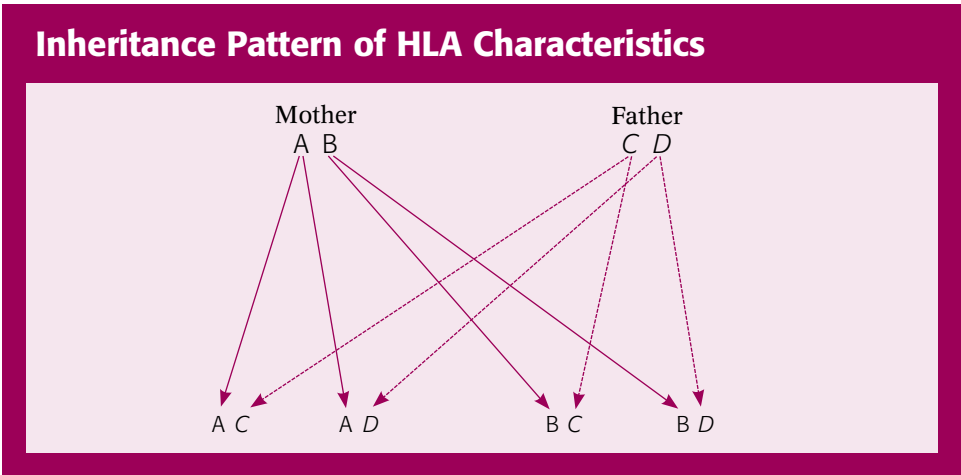


Figure 3. A and B depict the two chromosomes 6 of mother and C and D depict the two chromosomes 6 of father. Among four children, each will inherit a chromosome pair as shown, either A or B from mother and either C or D from father. Based on these outcomes, it is estimated that a match will occur on average one in four times. In other words, on average, if a child with AC chromosomes requires a transplant, a match should occur in one of four siblings. Of course, this probability holds true in large sample sizes; in an individual family, there might be no match or more than one match among siblings.

The HLA system is broken down into two groups of cell surface antigens: class I and class II. Class I antigens are determined by genes referred to as "A," "B" and "C." Class II antigens are determined by genes referred to as "D." In populations, these genetic loci, A through D, have many variations called "alleles" that make each individual unique. For example, one person may have A1, another A2, and another A3, and so on. In families, these variations are minimized, making it more likely to find a match among siblings.

HLA types are determined by a method called “molecular typing.” In this technique, the DNA of the recipient and prospective donor are characterized to identify specific genes that direct the formation of the HLA antigens on the surface of cells.

Since the probability of finding a match among siblings is only one in four, efforts are being made to develop methods to permit transplantation between individuals who are only partially matched. For example, the ability to transplant from parent to child would make the availability of transplantation nearly universal for childhood disorders. Children’s bodies are more tolerant of deviations from ideal matching, and hope exists that with better control of the immune reactions involved, moderately mismatched transplants may be feasible. Studies are under way to improve the delay in immune system recovery for recipients of partially matched (haploidentical) donor cells.

Collecting Stem Cells for Transplantation or Infusion

Blood. Peripheral blood (also called “circulating blood”) is currently the most common source of stem cells for transplant. Peripheral blood stem cells (PBSCs) are blood-forming stem cells that are released from the marrow into the blood. Normally, the marrow releases only a small number of these stem cells into the blood. To obtain enough stem cells from the peripheral blood for a transplant, a donor is given stem-cell releasing cytokines, such as granulocyte-colony stimulating factor (G-CSF), which encourages more blood-forming stem cells to move from the marrow to the blood. When a patient’s own stem cells are used, in most cases the stem cells are mobilized by a combination of chemotherapy used to treat the underlying disease and G-CSF.

Before the stem cells are collected the blood is tested for hepatitis viruses, human immunodeficiency virus (HIV) and other infectious diseases. A test result that is positive for cytomegalovirus (CMV) or certain other viruses does not necessarily disqualify a person from being a donor.

The cells are collected from the blood using a process called “apheresis,” also called “hemapheresis.” For apheresis, a needle is placed in the donor’s vein, usually in the arm. The blood of the donor (or the patient, in the case of an autologous infusion [autotransplant]) is pumped through an apheresis machine, which separates the blood into four components: red cells, plasma, white cells and platelets. The latter

two fractions are collected because they contain the stem cells. The red cells and plasma are returned to the donor (or patient).

If there is not an adequate collection of stem cells after three to four pheresis procedures, many physicians will halt the process and attempt other means of obtaining stem cells. The use of PBSCs, however, avoids the need for general or spinal anesthesia that is required to collect stem cells from the donor's marrow and the few days of discomfort from the sites where needles are inserted into the pelvic bone in order to recover marrow stem cells.

Marrow. Obtaining marrow stem cells for transplantation requires that an appropriate donor receives a thorough health examination, including an electrocardiogram, chest x-ray, blood chemistry evaluation, and confirmation that blood cell counts are within normal limits. The donor is tested to insure that hepatitis viruses and HIV are not present in the blood. The presence of a positive CMV test result does not necessarily prevent a person from being a donor. Tests are run to identify other viruses as well; however, positive test results do not necessarily disqualify a donor.

Marrow donation is a surgical procedure and is performed in an operating room suite. The donor is given anesthesia. The transplant physician then uses a special hollow needle attached to a syringe and withdraws samples of marrow from the top edge of the pelvic bones. This area can be easily felt under the skin of the sides and back just below the waist. The insertion of the needle through the skin and into the rim of the pelvic bone is repeated until several pints of marrow are removed. The donor usually remains in the hospital for about six to eight hours before going home. During this time, the donor recovers from both the anesthesia and the pain at the needle insertion sites. The donor can expect to feel some soreness in the lower back for a few days or longer. Most donors are back to their normal routine in a few days. The donor's body replaces the donated bone marrow in four to six weeks.

The amount of marrow removed from the donor is related to the size of the recipient. A large adult requires more marrow cells than a small child does for the transplanted stem cells to engraft. The harvested marrow is passed through a series of filters to remove fragments of bone or tissue and then placed in a plastic bag from which it can be infused into the recipient's vein. It is usually administered to the recipient within a few hours and, in most cases, within less than 24 hours. If necessary, the harvested marrow cells can be frozen and stored for later use. The marrow can be frozen for years and remain suitable for stem cell transplantation.

For example, freezing is commonplace in anticipation of autologous marrow infusion (autotransplant). In this circumstance, the patient's own stem cells are collected during a period of disease remission following treatment. The stem cells are thawed and then returned to the patient after the intensive treatment has been given.

Placental and Umbilical Cord Blood. The stored cord blood collected from the umbilical cord and placenta after a baby is born is called a “cord blood unit.” Cord blood stem cells are collected from the umbilical cord and placenta after a baby is born. During delivery, the focus is on the mother and baby. After the baby is delivered, the umbilical cord is clamped. The blood from the umbilical cord and placenta is then collected before or after the placenta is delivered, depending upon the procedure at the hospital. Blood is collected into a sterile bag; this bag of blood is the cord blood unit. The collected blood is given an identification number and stored temporarily. The cord blood unit is transported to a cord blood bank for testing, freezing and long-term storage. Testing procedures include HLA typing to determine the level of matching to potential recipients, cell counts and testing for infectious agents such as the human immunodeficiency virus (HIV), cytomegalovirus (CMV) and hepatitis viruses. The cord blood unit is also checked to make sure it has enough blood-forming cells for a transplant. If there are too few cells, the cord blood unit may be used for research to improve the transplantation process for future patients or it may be discarded. Next, the blood is frozen and held at a very low temperature, usually in liquid nitrogen, for future use. When needed for a transplant, the cord blood unit can be shipped, often within a few days, to the transplant center where it is thawed and infused into the patient.

The number of cells required to give a transplant patient the best chance for engraftment and for surviving the transplant is based on his or her weight, age and disease status. A cord blood unit might contain too few stem cells for the recipient's size. Due to the smaller number of stem cells in the cord blood unit, cord blood stem cell transplants engraft more slowly than stem cells from marrow or peripheral blood. Until engraftment occurs, patients are at risk of developing life-threatening infections. Thus, cord blood transplant recipients may be vulnerable to infections for an average of up to one to two months longer than marrow and peripheral blood stem cell recipients. On the other hand, cord blood transplants may result in less GVHD than other types of transplants and because of decreased risk of GVHD, a lower level of matching between the donor cord and recipient HLA system may be allowed. There are other important considerations in using cord stem cells. Research is under way to improve the yield of cord blood stem cells and to examine whether use of more than one cord blood unit for a transplant will be beneficial

in speeding the time to engraftment. See the LLS fact sheet *Cord Blood Stem Cell Transplantation* for more information.

Administration. The infusion of a suspension of cells containing the stem cells into the recipient's vein is similar to a blood transfusion but must be given through a large central vessel via an indwelling catheter (central line). This type of administration is used regardless of whether marrow or blood is the source of the stem cells.

Most indwelling catheters are positioned on the chest wall. Placement is usually done with local anesthesia. To place the central line, a small incision is made where the catheter enters the vein and the distal end of the catheter is passed under the skin and exits at a second small incision at a distance from the first. This distance helps prevent infection. There may be a few stitches at one or both sites until the areas have healed. Small, clear dressings are changed frequently to prevent infection.

Many patients will be discharged from the hospital with a central line in place. This allows for transfusions, blood administration, and other infusions the patient may still require after discharge. Hospital or clinic staff will show patients or family how to clean and care for the central line. Also, home care agencies can provide help with catheter care at home to help prevent infection.

T-lymphocyte Depletion

T lymphocytes in a donor's marrow or blood can cause GVHD. In order to minimize this harmful reaction, the marrow or blood cell collection to be used for transplant can be treated with agents that can decrease the number of T lymphocytes that will be infused with the stem cells. This technique reduces the incidence and severity of GVHD. The procedure is known as "T-lymphocyte depletion."

Transplant physicians must be careful about how many T lymphocytes are removed during this procedure. T lymphocytes are depleted only in certain circumstances because T lymphocytes are also beneficial. They help the donated stem cells take hold (engraft) and grow in the recipient's marrow. In some cases, T lymphocytes attack blood cancer cells, enhancing the results of other treatment. This "graft versus tumor (GVT) effect" can be seen mostly in the myelogenous (myeloid) leukemias. The attack on the remaining blood cancer cells makes it less likely that the disease will return after transplant.

Stem Cell Selection. In some cases, the stem cell suspension may be depleted of most T lymphocytes, as described in the previous section. Alternatively, stem cell selection, which also results in a marked decrease in the number of T lymphocytes, may be employed before the stem cells are administered to the recipient. There are specific features on the outer coat of stem cells that permit them to be removed selectively from a mixture of cells and then recovered. This selection procedure results in a cell population that is enriched in stem cells and has many fewer other cells, including T lymphocytes. By reducing the number of T lymphocytes, the frequency or severity of the graft versus host immune reaction can be decreased.

Types of Stem Cell Transplantation

Syngeneic Transplantation. This is the term used when the donor and recipient are identical twins, with identical genetic make-up and the same tissue type. With this type of transplant, donor cells are not rejected and the recipient's tissues are not attacked by the donor's immune cells (lymphocytes). No treatments are needed to prevent graft rejection or GVHD.

Autologous Stem Cell Infusion (Autotransplant). Autologous stem cell infusion after very intensive chemotherapy is an important treatment option. Strictly speaking, it is not transplantation; it is a technique that obtains stem cells from an individual's blood or marrow and then infuses them back into the same individual. There are no known immune-related transplantation issues with this procedure. It is usually conducted in a transplant facility, supervised by transplant specialists, and is mainly referred to as "autologous stem cell transplantation" or "autotransplant." To be a feasible option, the procedure requires that an individual have sufficient numbers of healthy stem cells in the marrow or blood despite the disease for which he or she is being treated. For example, in patients with acute leukemia, remission must be achieved before the patient's marrow or blood is harvested and frozen for later use (see Figure 4, page 20).

Allogeneic Transplantation. This is the term that describes a transplant with donor cells. The term also implies that the donor's tissue type closely matches the recipient's. The donor who has the potential to match the prospective recipient most closely is the sibling of the patient, since both received their genetic composition from the same parents. Siblings do not always have closely matched tissue types, but the probability for a close match between siblings is much greater than it is among unrelated individuals.

Transplant physicians can test to determine the degree of compatibility before a decision is made to use the donor. Compatibility is assessed by laboratory tests that identify the tissue type of donor and recipient. (See *Testing to Identify Donors*, page 12).

There are two types of allogeneic donors. They are

- Related allogeneic donors, usually sibling donors
- Unrelated allogeneic donors, usually found within very large pools of volunteers, and matched to a tissue type that is the same as the patient's. This is called transplantation from a matched unrelated donor (MUD).

Both related and unrelated allogeneic transplantation differ from either syngeneic or autologous stem cell infusion because of possible

- Immune rejection of the donated stem cells by the recipient (host versus graft effect)
- Immune reaction by the donor's cells against the tissues of the recipient (GVHD).

The immune rejection or host versus graft effect is usually prevented by intensive treatment of the recipient before the transplant (conditioning) to suppress the immune system. The immune reaction or GVHD is treated by giving drugs to the recipient after the transplant to reduce the ability of the donated immune cells to attack and injure the patient's tissues (see *Graft Versus Host Disease*, page 26).

The Autologous Stem Cell Infusion (Autotransplant) Process

The principal concerns are that

- The number of stem cells harvested is adequate to obtain full engraftment when returned to the patient
- There are insufficient contaminating tumor cells in the autograft to reestablish the tumor in the patient.

Autologous stem cells are used to restore blood cell production after intensive radiation and/or chemotherapy for the treatment of pediatric and adult patients—mainly those with cancers of the blood and marrow but also in cases involving some other malignancies.

Autologous Stem Cell Infusion for Cancers of the Blood and Marrow

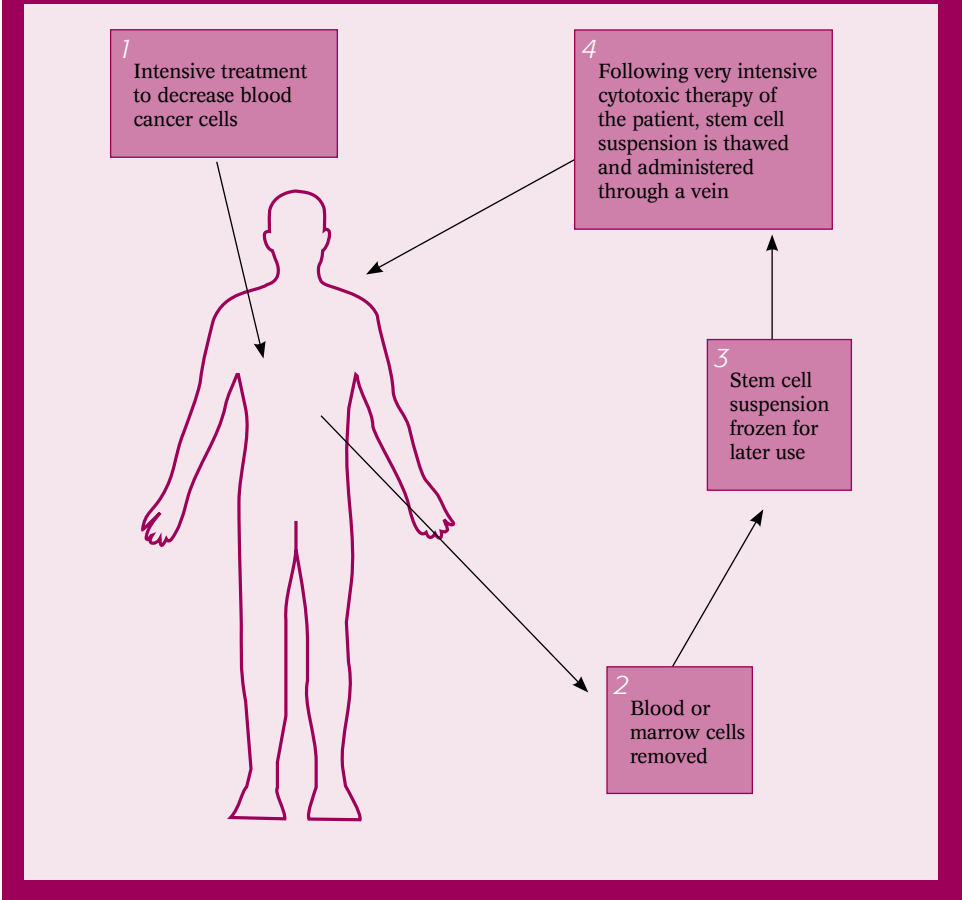


Figure 4. This diagram explains the steps involved in autologous stem cell infusion (autotransplant). Stem cells are obtained from the patient who is treated intensively (1) to control the disease and to markedly decrease the number of cancer cells in marrow and blood. If the marrow is the source of stem cells, the patient is taken to the operating room, anesthetized, and the marrow is removed under sterile conditions. If blood is used as the source of stem cells, the patient is treated usually with granulocyte-colony stimulating factor (G-CSF; Neupogen®) after chemotherapy, which draws stem cells out of the marrow and into the blood. The stem cells from blood or marrow are then harvested (2). The cells are mixed with a cryoprotective agent so that they can be frozen and later thawed without injury (3). At a later time, when the patient is treated intensively again, the frozen stem cell suspension is thawed and infused into the patient so that blood cell production can be restored (4). The infusion of autologous blood or marrow does not carry the risk of either graft rejection or GVHD and thus does not require immunosuppressive treatment. However, the patient does receive very intensive cytotoxic therapy to kill residual leukemia, lymphoma or myeloma cells. The autologous stem cells are used to restore blood cell production, thereby making chemotherapy and radiation therapy tolerable. There is a possibility that the patient's blood cancer cells may contaminate an autograft (from blood or marrow) even when obtained from a patient in remission. However, purging techniques used in an attempt to eliminate any remaining malignant cells have not improved outcomes and are no longer performed, except in the context of clinical trials.

LEUKEMIA

LYMPHOMA

MYELOMA

Adverse Effects of Autologous Stem Cell Infusion. The main adverse effects of this procedure are the result of the high-dose chemotherapy and/or radiotherapy that is used to further destroy remaining cancer cells. Markedly decreased blood counts may lead to infection. Patients may need transfusions of red cells (for anemia) or platelets (to prevent or treat hemorrhage). Certain drugs can result in specific organ injury, such as lung complications, especially interstitial pneumonia, which may be the result of infection or damage from intensive therapy. Painful oral ulcers, called oral “mucositis,” may develop and can, rarely, prevent fluids or solids from being taken by mouth. When appropriate, agents such as the skin-cell growth factor, palifermin (Kepivance®), given intravenously, can be used to prevent or minimize the effects of intensive therapy on the lining of the mouth. GVHD and graft rejection are not side effects since there is no donor/recipient incompatibility.

The Allogeneic Stem Cell Transplantation Process

Conditioning. A patient with cancer of the blood and marrow who is going to receive an allogeneic transplant is first treated with conditioning therapy, which

- Treats the remaining cancer cells intensively to make a recurrence of the cancer less likely
- Inactivates the patient’s immune system to minimize the chance of stem cell graft rejection
- Enables donor immune cells to engraft and exert their potent anti-tumor effect.

There are a number of different conditioning regimens that can be used, depending on the disease being treated and other factors. These may consist of chemotherapy drugs alone (for example, busulfan [Myleran®] and cyclophosphamide [Cytosan®]) or chemotherapy given with total body irradiation. Certain conditioning regimens may have unique side effects, and members of the transplant team will discuss these with the patient before beginning the conditioning therapy.

Radiation therapy is administered in several smaller daily doses. This technique is referred to as “fractionation of the dose.” Fractionation minimizes side effects such as lung injury, nausea and vomiting (see Table 2, page 24). The drugs and radiation therapy are given during the week before transplant. The number of days of treatment and sequence of administration depends on the specific conditioning

regimen. The days prior to the transplant are labeled day minus 6, minus 5, and so on; transplant (donor stem cell infusion) is day zero; the day after the transplant starts with plus 1, plus 2, and so forth.

Stem Cell Transfusion. The transfusion process consists of the following measures:

- The donor stem cell suspension (derived from blood or marrow) is collected in a plastic blood transfusion bag. If the donor and recipient do not share the same red blood cell type, either the red cells or the plasma (the fluid surrounding the cells) may need to be removed. If stem cells from marrow are infused, special filters are used to remove bone fragments, fatty particles, and large clusters of cells from the cell suspension before the product is placed into the transfusion bag.
- The cell suspension is infused through the patient's vein; the procedure is similar to a blood transfusion. Infusing the suspension usually takes several hours. Patients are checked frequently for signs of fever, chills, hives, a drop in blood pressure or shortness of breath. Side effects occasionally occur; these are treated and the infusion is completed. Often, patients experience no side effects from the transfusion.

Reactions from the cryopreservative in frozen-thawed stem cell suspensions may also occur in patients receiving this treatment. Side effects may include headache, nausea, flushing, shortness of breath and others. These problems can usually be managed and the infusion completed.

The Immediate Post-transplant Period. By the second or third day after the transplant, the intensive conditioning regimen and the decrease in marrow function begin to have their effects. The allogeneic transplant patient is kept in a protected environment to minimize contact with infectious agents (see *Infections*, page 25).

Usually within two to five weeks after the transplant, the engraftment of donated cells becomes apparent by the appearance of normal white cells in the blood of the patient. Red cells and platelets are transfused periodically until marrow function is restored by the transplanted stem cells. The patient is monitored carefully by physical examinations, blood chemistries, imaging studies and other tests to be sure that major organs such as the heart, lung, kidneys and liver are functioning normally.

Allogeneic Stem Cell Transplantation for Cancers of the Blood and Marrow

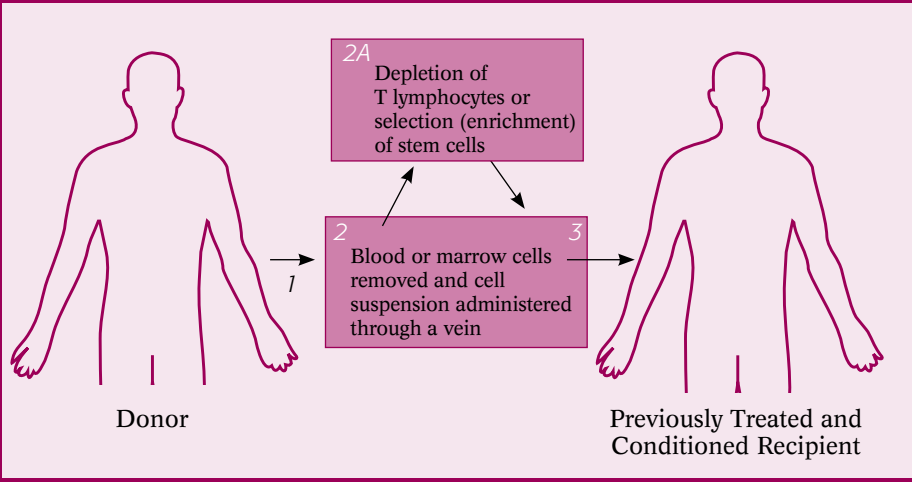


Figure 5. A matched-donor is identified, usually among the patient's siblings (see *Testing to Identify Donors*, page 12). When blood is used as the source of stem cells, the donor is treated with granulocyte-colony stimulating factor (G-CSF; Neupogen®), which draws stem cells out of the marrow and into the blood. When marrow is the source of stem cells, the patient is anesthetized and the cells are harvested in an operating room. The stem cells from blood are recovered by apheresis (1). The marrow stem cell suspension is filtered and placed in a plastic bag; the cell suspension is administered through a vein to the recipient, who has been treated intensively with total body irradiation and/or chemotherapy (2 and 3). In some cases, the stem cell suspension may be depleted of most T lymphocytes. Alternatively, stem cell selection may be employed, which also results in a marked decrease in the number of T lymphocytes (2A), then the stem cells are administered to the recipient.

Most patients undergoing allogeneic transplantation for a cancer of the blood and marrow require blood cell replacement, nutritional support, and special drugs to treat GVHD. Periods of intravenous feeding, called “hyperalimentation,” may be needed for some patients to ensure adequate nutritional intake in the presence of poor appetite and diarrhea.

Side Effects of the Conditioning Regimen

Cytotoxic Effects. The conditioning treatment prior to allogeneic stem cell transplant or autologous stem cell infusion (autotransplant) can impair any system that is dependent on replacement by stem cells. In particular, the following areas of the body are very sensitive to cytotoxic drugs and radiation therapy:

Gastrointestinal tract. Ulcers and dysfunction of the gastrointestinal tract occur frequently. Mouth sores (oral mucositis), nausea, diarrhea, intestinal cramps, and rectal or anal ulceration may occur. Several strategies, including treatment with a skin-cell growth factor, palifermin (Kepivance®), may be used to minimize the severity of oral mucositis. Palifermin stimulates the cells that line the mouth and gastrointestinal tract to grow and develop. Other topical and intravenous agents, are being evaluated for their ability to prevent or treat mucositis.

Skin. Rashes may develop. Skin effects are evaluated and treated to help make patients more comfortable and prevent serious complications.

Hair follicles. Hair loss occurs with many conditioning regimens. It is generally temporary and hair growth resumes when drug dosages are decreased or the drugs are discontinued.

Lungs. This part of the body is sensitive to the conditioning regimen, especially with total body irradiation following chemotherapy. A reaction called “interstitial pneumonitis” (pneumonia) can occur. This side effect is caused by a tissue reaction and does not mean that an infection is present. However, it can be very severe and

Table 2. Some Side Effects of Conditioning Treatment

Nausea and vomiting	Occlusion (blockage) of veins in liver
Diarrhea	Congestive heart failure
Mucositis	Premature menopause*
Hair loss	Infertility*
Loss of blood cell formation	Growth retardation*
Pneumonitis (pneumonia)	Cataracts*

**These effects are more likely to occur if total body irradiation is required for conditioning.*

prevent the efficient exchange of oxygen in the lungs. This complication is treated with drugs. It may occur at any time—from a few days after high-dose chemotherapy to several months after treatment—and may even occur after a patient has returned home from a transplant center. It is important for a patient who experiences shortness of breath or a new cough after allogeneic transplant to bring this to the immediate attention of his or her physician.

Blood vessels. Leaky blood vessels can result from the accumulated injury caused by chemotherapy and radiotherapy. Chemicals released from the immune reactions that occur after transplant also contribute to this effect by damaging vessel walls. Fluid escapes from the circulation and causes edema, or waterlogging of tissues. In the lungs, fluid accumulation can cause congestion, poor exchange of oxygen and shortness of breath. Agents such as corticosteroids, which decrease inflammation, are sometimes used to manage this complication.

Liver. The blood vessels that lead into and pass through the liver are prone to blockage after transplantation. This serious side effect is called veno-occlusive disease or VOD because the veins are plugged. This effect is brought about by toxic changes in the liver that were caused by chemotherapy and radiotherapy. These changes cause injury to the liver, and manifest as jaundice (yellowing of the skin and eyes), and accumulation of fluid in the abdomen and elsewhere. Sometimes toxins normally removed by the liver can accumulate, leading to mental confusion and sleepiness. Treatment of VOD may include red blood cell transfusions, diuretics, and drug therapy, such as the investigational agent defibrotide, which is being examined for its potential benefit in this setting.

Infections. Intensive treatment is usually required to suppress immune function (when donor cells are transplanted) and kill tumor cells prior to transplant. The resulting suppression of white cells that normally prevent or combat infections leads to a high risk of infection. Infections by bacteria, fungi, viruses, or other parasites are likely. These organisms are present most often on the skin and in the mouth or the lower bowel. They are also found in uncooked food (for example, leafy green salads) and in the air.

When blood cell and immune cell levels are normal and when the skin and lining of the mouth and bowel are intact, the body easily fends off such microbes. These normal defenses are lost in transplant patients. For this reason, antibiotics and other antimicrobial drugs are sometimes administered to patients in anticipation of the development of infection. The drugs are usually continued until the white cells reappear in the blood in sufficient numbers to make infections unlikely. The term

“opportunistic infection” applies to infections caused by bacterial, fungal and viral agents that rarely cause disease in healthy persons but cause infection in persons with severe immunodeficiency. Infectious agents include varieties of *Candida*, *Aspergillus*, *Pneumocystis* or *Toxoplasma* organisms.

Many precautions are taken to minimize the risk of infection. Measures to combat infection include the use of a single room with filtered air, controlling contact with visitors, use of masks, and meticulous hand washing by staff and visitors who enter the patient’s room. Central line sites must be kept clean. Patients are usually advised to eliminate certain foods that may carry surface bacteria or fungi from their diets, including uncooked fruits, vegetables and other raw foods.

Sometimes, implementing several of these measures can isolate the patient for the month or more that it takes for the donor stem cells to begin forming enough blood and immune cells to replenish the body’s immune system.

Graft Versus Host Disease

Graft versus host disease (GVHD) is a condition in which the transplanted donor stem cells attack the patient’s body (see Table 3, page 27). GVHD is not a side effect of autologous stem cell infusion (autotransplant) because donor stem cells are not used. In all allogeneic stem cell transplant settings, medications are given to prevent GVHD. These are usually started one to two days before the stem cell transfusion. Multiple agents have been used to prevent GVHD. Common regimens include: cyclosporine and methotrexate; tacrolimus (Prograf®) and methotrexate; tacrolimus and mycophenolate mofetil (CellCept®), among others. Recently, a combination of tacrolimus and sirolimus (Rapamune®) has been reported to be effective for the prevention of GVHD. All of these regimens suppress the immune system and patients may need to continue to take them for many months after transplantation.

GVHD occurs in many transplant patients. GVHD may be acute or chronic. It ranges from a barely perceptible condition to one that is life-threatening. With each advancing decade of age, the reaction occurs more frequently and severely. The severity of GVHD depends on the differences in tissue type between patient and donor.

Table 3. Graft Versus Host Disease

Skin changes
•
Gastrointestinal tract malfunction
•
Liver injury
•
Other organ system impairment

Table 3. Immune cells recognize other cells that are not genetically identical. The graft versus host reaction results when the donor's immune cells, especially the T lymphocytes, sense that the host cells are different from themselves. In the case of stem cell transplantation, the donor cells monitor the recipient's cells for differences and attack them if they find significant variations. The differences may involve cell surface proteins that are not measured by HLA typing, or there may be subtle differences in HLA type that permit transplantation but cause the reaction. With the exception of identical twins, some incompatibility will exist even though HLA testing indicates enough similarity to permit a successful transplant.

Acute GVHD. Acute GVHD can occur soon after the transplanted cells begin to appear in the recipient and, by definition, starts in the first 90 days after transplantation. The first signs are usually

- A rash, with burning and redness of the skin that occur on the patient's palms or soles; the rash, along with the burning and redness, may spread to the patient's trunk and eventually develop over the entire body.
- Blistering; the exposed surface of the skin may flake off.
- Nausea, vomiting, abdominal cramps and loss of appetite are signs of GVHD in the gastrointestinal tract. Diarrhea is common.
- Jaundice, which may indicate that GVHD has injured the liver; the liver may be enlarged. Abnormalities of liver function would be noticed on blood test results.

Acute GVHD may be mild, moderate, or severe. It may be a life-threatening condition if its manifestations are difficult to control.

Chronic GVHD. Chronic GVHD usually occurs after the third month post-transplant or may not develop for a year or more after the transplant. As is the case with the acute reaction, older patients are more likely to develop chronic GVHD. It is more likely to occur in patients who previously have had acute GVHD, but it may appear without prior acute GVHD.

Most patients experience skin problems. A rash and itching may occur first. The skin may become scaly. If the reaction is severe, patches of skin may be lost. Patients'

skin color may deepen and the texture becomes very hard. The skin may heal by scarring, and the motion of nearby joints, such as the fingers, may be restricted. Hair loss may accompany the skin injury.

The drying and scarring effects of the attack by the donor immune cells can affect the inside of the mouth and the esophagus (a tube that extends from the mouth to the stomach). It may become excessively dry and damaged and ulcers can result. The tendency to drying may lead to loss of tear formation; dryness of the vagina and other surfaces may also occur. The lungs also may show effects of drying and scarring. Liver injury may result in failure of liver function and the diminished flow of bile. In severe cases, the bile may back up into the blood and cause jaundice. In other cases, these problems may not be overt, but they can be detected by blood chemical measurements. The chronic graft versus host reaction can be mild (with later improvement), or more severe, persistent, and incapacitating.

Treatment for GVHD. Several drugs are used to prevent or minimize GVHD. The development of new drugs to treat GVHD, combined with early detection and advances in understanding the disease, have resulted in significant reductions in serious or fatal outcomes from GVHD. Successful treatments for both acute and chronic GVHD have been developed, but GVHD does not always respond to these treatments.

Advances in transplantation techniques, such as more precise HLA-matching, treating patients with immunosuppressive drugs, depletion of T lymphocytes from the donor graft and, when possible, using umbilical cord blood as the source of donor cells have helped to reduce patients' risk of developing acute GVHD.

If acute GVHD does develop after transplantation, glucocorticoids such as methylprednisolone or prednisone in combination with cyclosporine are administered. New drugs and strategies that are available now or in clinical trials can supplement standard treatment. They include but are not limited to

- Antithymocyte globulin (rabbit ATG; Thymoglobulin®)
- Denileukin diftitox (Ontak®)
- Monoclonal antibodies, such as: daclizumab (Zenapax®); infliximab (Remicade®); or more rarely, alemtuzumab (Campath®)
- Mycophenolate mofetil (CellCept®)
- Sirolimus (Rapamune®)
- Tacrolimus (Prograf®)

Primary therapy for chronic GVHD is administration of corticosteroids. Cyclosporine and prednisone may be used on alternating days. Clinical trials investigating steroid-refractory GVHD have reported some success for the following treatments among others:

- Daclizumab (Zenapax®)
- Etanercept (Enbrel®)
- Extracorporeal photopheresis (procedure)
- Infliximab (Remicade®)
- Mycophenolate mofetil (CellCept®)
- Pentostatin (Nipent®)
- Rituximab (Rituxan®; role still being investigated)
- Tacrolimus (Prograf®)
- Thalidomide (Thalomid®)

Drug dosages depend on the severity of the graft versus host reaction and whether the donor is related or unrelated. Supportive care measures for skin, eyes, oral cavity, vaginal mucosa, and lungs are also important as is attention to nutrition. One of the most important aspects of chronic GVHD treatment is surveillance for and treatment of any infections which may develop in this condition where the immune system is suppressed by both the disease itself and its treatments. If GVHD stabilizes or improves, the dosages of medications for GVHD may sometimes be tapered and then, eventually, the drugs may be discontinued. A state of tolerance between the donor immune cells and the host presumably occurs with time.

Reduced-intensity Allogeneic Stem Cell Transplantation

A reduced-intensity allogeneic stem cell transplant uses less intense conditioning treatment to prepare for the transplant than does a standard transplant. The term “reduced-intensity transplant” is sometimes used interchangeably with the terms “nonmyeloablative transplant” or “mini-transplant.” The treatment for a reduced-intensity transplant may be mild enough for patients to receive it in an outpatient setting. However, the treatment varies among transplant centers and treatment ranges from very low intensity (a nonmyeloablative regimen) to treatments only somewhat milder than the standard regimen. Some reduced-intensity transplants are of intermediate intensity and may be used in certain disease states when a full

transplant would not be tolerated and a nonmyeloablative transplant would not be sufficient for control of the disease.

A standard transplant involves very high doses of chemotherapy drugs and/or radiation. Transplant physicians have been developing reduced-intensity pretransplant conditioning regimens that may be suitable for a wider range of patients.

A reduced-intensity transplant may be an option for an older patient. Allogeneic stem cell transplants for patients ages 55 or older have been relatively uncommon because the pretransplant conditioning required is generally not well tolerated by older patients or patients with poor overall health, especially those with poorly functioning internal organs.

A reduced-intensity or nonmyeloablative transplant does not completely destroy the patient's diseased marrow. Patients being prepared for a nonmyeloablative transplant receive much lower doses of conditioning therapy. While a standard transplant uses the pretransplant treatment to destroy most of the patient's disease cells, a reduced-intensity transplant relies on the donor-immune-cells to fight disease (GVT).

The effectiveness of reduced-intensity transplants depends on the GVT effect in which the recipient's new immune system (originating from the donated stem cells) may destroy the bulk of remaining cancer cells. The procedure uses low rather than very high doses of either radiation or chemotherapy to condition the patient. Potent immune therapy is given to suppress the recipient's T lymphocytes to avoid rejection of the donor stem cells. The goal is to have the donor stem cells take up residence in the recipient's marrow and produce lymphocytes (immune cells) that attack the patient's blood cancer cells. If successful, the immune cells made from the donor's stem cells attack and suppress the remaining cancer cells in the recipient.

Reduced-intensity transplantation may also be advantageous for

- Patients with less rapidly progressive blood cancers
- Patients with certain infections where prolonged marrow suppression would be detrimental
- Older patients
- Patients with additional serious medical conditions.

Sufficient numbers of reduced-intensity transplants have been performed to conclude that this may be an appropriate treatment for patients who are otherwise unsuitable for myeloablative stem cell transplant due to their advanced age or poor health. The GVT effect underlying the allogeneic transplant procedure, including nonmyeloablative allogeneic transplants, is strongest in patients being treated for chronic myelogenous (myeloid) leukemia (CML). Patients with other malignancies also benefit from GVT but to lesser degrees.

Because reduced-intensity transplant is relatively new, its risks and benefits have not yet been clearly established. However, one definite advantage is that a transplant may now be an appropriate option for individuals in their 60s and 70s. One disadvantage is that physicians have limited long-term survival data on reduced-intensity transplant recipients. Survival rates for these patients cannot be compared with survival rates for those receiving fully myeloablative stem cell transplants or for those receiving chemotherapy or other nontransplant treatments until more data are available. Also, as is the case with allogeneic stem cell transplant, GVHD is an important and potentially disabling side effect of reduced-intensity stem cell transplant.

Patients interested in exploring the possibilities of a reduced-intensity transplant must locate a transplant center performing these procedures. Many centers are working to answer unknown questions about the risks and benefits of these types of transplants. To locate transplant centers performing nonmyeloablative transplants, you can

- Speak to your physician
- Contact the LLS Information Resource Center at (800) 955-4572 or access the LLS Web site at www.LLS.org.
- Contact the National Cancer Institute at 800-4-CANCER ([800] 422 6237).
- Search for the locations of clinical trials at the National Cancer Institute's Web site at www.cancer.gov/clinical_trials.

Leaving the Hospital

Some transplant centers perform autologous stem cell infusions (autotransplants) on an outpatient basis. Patients at some transplant centers may have a portion of either an autologous infusion or allogeneic transplant performed on an outpatient basis.

Most patients treated on an inpatient basis have recovered sufficiently to leave the hospital by three to five weeks post-transplant. Before discharge, both the physician and patient should feel comfortable that there are no remaining needs that require very close surveillance or hospital-based resources. The recovery rate of blood cell counts and the severity of other associated complications, especially GVHD vary from patient to patient. A patient is ready for discharge when

- The patient's marrow is producing a sufficient number of healthy red cells, white cells and platelets
- There are no severe treatment complications
- The patient has a sense of well-being (as a result of restored blood cell counts)
- Mouth sores and diarrhea lessen or disappear
- Appetite improves; it is important that patients are able to eat and drink to get sufficient fluid and nourishment before they are discharged from the hospital
- The patient does not have fever and is not vomiting.

Many patients will be discharged from the hospital with a central line in place. Hospital or clinic staff will show patients or family how to clean and care for the central line. Also, home care agencies can provide help with catheter care at home to help prevent infection.

After discharge, for a variety of reasons, some allogeneic transplant patients require rehospitalization. Less often, rehospitalization may also be necessary after autologous infusion. A return to the hospital may be for a problem such as infection, management of dehydration, or management of GVHD.

Aftercare

In general, there is a shorter recovery period after autologous stem cell infusion (autotransplant). Some of the complications and restrictions described in this section are identified as applying mainly to allogeneic transplant patients.

After discharge from the hospital, the patient continues to recover at home. Before leaving the hospital, patients and families are instructed in the continuing care needed at home. They learn what signs, such as fever, pain or diarrhea, should prompt a call to their healthcare provider. Home visits by nurses or physicians and patient visits to the outpatient clinic are important for follow-up and adjustment of activities and medications. Visits may be frequent at first. Allogeneic transplant patients may need to return to the transplant center for follow-up visits several times per week at first. After several months, if all is going as anticipated, central lines (indwelling catheters) can be removed and the frequency of follow-up visits decreased. Many patients who receive autologous stem cell infusion (autotransplant) will be followed by their referring oncologist within a short time of discharge.

It often takes at least six to 12 months to recover nearly normal blood cell levels and immune cell function in a patient who receives an allogeneic transplant. During this time

- Patients should discuss their risk of infection and any recommended precautions and prophylactic antibiotics with their physicians.
- Patients may be advised to avoid contact with children who have had recent immunization with live viruses.
- The lenses of the eyes of patients treated with total body radiation during conditioning would have become irradiated and there is the possibility that cataracts may develop.
- Irradiation of the gonads may lead to infertility in men and women. Hormone replacement is usually not necessary for men. For women, estrogen and progesterone replacement therapy may be needed.
- Children may have a slowed growth rate and may require growth hormone treatment and replacement of other hormones. In young patients, puberty may be delayed and hormonal therapy required.
- Radiation may decrease thyroid function so thyroid hormone may need to be administered orally.
- The severity of chronic GVHD is the major determinant of the patient's quality of life. This immune reaction can result in serious complications, including troublesome infections. Treatment for severe GVHD can also cause complications.

Long term follow-up care is important after both autologous stem cell infusion (autotransplant) and allogeneic transplantation. If a patient is unable to return to the transplant center for yearly follow-up visits, it is important that his or her local oncologist be aware of all the recommendations for follow-up of various organ systems. In addition to the items mentioned in this section, attention to bone health for those patients who require corticosteroid therapy is important. New vaccinations to boost immunity to various infectious agents are usually administered after one year, and your transplant physician can provide a schedule for these. Observation for secondary malignancies, dental caries, and dry eyes or cataracts is also important.

See the LLS free fact sheets *Fertility, Long-term and Late Effects of Treatment in Childhood Leukemia or Lymphoma* and *Long-term and Late Effects of Treatment in Adults* for more information about treatment effects and follow-up care.

Research and Clinical Trials

A patient may have the opportunity to participate in a clinical trial during various phases of stem cell transplantation. A cancer clinical trial is a carefully controlled research study conducted by doctors to improve the care and treatment of cancer patients. The purpose of clinical trials for cancers of the blood and marrow is to improve treatment options, increase survival and improve quality of life. Advances in treatment depend on clinical trials of new therapies or new combinations of therapies.

Many studies are attempting to address critical questions about how to improve stem cell transplantation. For example, some trials are examining ways to improve management of symptoms or complications during the transplant process; others are looking at new approaches to the transplant procedure such as using a unique combination of chemotherapeutic agents or a novel way to process stem cells. Studies are under way to determine overall patient survival or risk of complications that are related to the source of the stem cells for transplant (marrow, PBSCs or cord blood units).

A clinical trial may be sponsored by a transplant center, a cooperative group of transplant centers (for example, the Blood and Marrow Transplant Clinical Trials Network), a pharmaceutical company, or by the National Cancer Institute. Some studies will have the potential to benefit the individual undergoing the transplant but others will only have the potential to benefit future transplant recipients.

Participation in clinical trials involves a detailed consent process and a careful weighing of risks and benefits of participation in each individual's case. These trials are of great importance in improving understanding of how transplantation can be most effective. Patients are encouraged to ask members of their transplant teams for more information.

The LLS Information Resource Center, (800) 955-4572, offers guidance to help patients work with their physicians to find out if a specific clinical trial is an appropriate treatment option. Information specialists will conduct individualized clinical trial searches for patients, family members and healthcare professionals. This service is also available at www.LLS.org. Information about clinical trials that is maintained by the National Institutes of Health can be accessed at clinicaltrials.gov.

LLS invests research funds in both basic and applied research programs to improve the cure rate for patients with cancers of the blood and marrow, including funding to develop a new stem cell transplant procedure to more rapidly rebuild the transplant patient's immune system.

Social and Emotional Effects

Patients and families who consider a stem cell transplant face both physical and emotional challenges. With the help of their oncology teams, patients and families will weigh the grave issues of risk of disease recurrence or progression and death if transplantation is not chosen against the possibility of an earlier death or severe side effects if transplantation is chosen. This challenge is balanced by the hope of recovery and cure and the likelihood that new and better methods may make a successful transplant more likely and side effects more manageable.

The patient's oncology team and a number of support organizations are there to help with understanding new medical information, dealing with the uncertainty about finding a donor, making arrangements for patients who will be treated at a transplant center that is not in the community and other issues. Emotional support is available to help patients cope with the temporary loss of autonomy, sense of isolation, and separation from work, school, friends, colleagues, as well as other problems, that may arise.

Help is available for family members too. Children may worry about the outcome of a parent's illness and the separation from a parent, grandparent or sibling. Parents

must cope with the uncertain outcome of a child’s treatment. Most established transplant centers have a team including social workers, counselors, chaplains, and medical financial counselors, to aid in support throughout the transplant process.

Finances. Cancer treatment can be financially difficult for many families due to loss of income and the high cost of many medications and procedures. The cost of the transplant and possible relocation of family is usually in the range of several hundred thousand dollars. Although much of this cost may be recovered from insurance, some will not. The LLS *Patient Financial Aid Program* offers financial reimbursement for some medications, transportation and procedures for those in need. The LLS *Co-Pay Assistance Program* offers assistance to patients toward private health insurance premiums, private insurance co-pay obligations, Medicare Part B, Medicare Plan D, Medicare Supplementary Health Insurance and Medicare Advantage premium or co-pay obligations. Prescription drugs covered under this program include those supplied to the patient by a pharmacy or administered in an office or hospital by a healthcare provider. Public or private prescription drug coverage is required to qualify for this program.

Depression. The transplant experience is psychologically challenging for patients and families. Many patients have a successful outcome and a return to vitality and to school, job and other roles and relationships. It is important to seek medical advice if a patient or family member’s mood does not improve over time—for example, if a person is feeling depressed every day for a two-week period. Depression is an illness that should be treated even when a person is undergoing treatment for cancer. There are many sources of help available to patients and caregivers. Aspects of care such as making treatment choices, finding the time and money for medical care and communicating with family members and friends can be stressful. Contact LLS or ask the healthcare team for guidance and referrals to other sources of help such as support groups, counseling services or community programs. The National Institute of Mental Health (NIMH) has several publications about depression that may be helpful. For more information go to www.nimh.nih.gov and enter “depression” in the search box at the top of the Web page or call NIMH at (866) 615-6464.

We Can Help. LLS also offers programs through its local chapters to help ease the emotional and economic pressures that come with a blood cancer diagnosis. Visit www.LLS.org or contact the Information Resource Center at (800) 955-4572 to locate a chapter in your area, order free publications or speak directly to an Information Specialist.

Glossary

Absolute Neutrophil Count

The number of neutrophils (a type of white cell) that a person has to fight infection. The absolute neutrophil count (ANC) is calculated by multiplying the total number of white blood cells by the percentage of neutrophils.

Allogeneic Stem Cell Transplantation

A treatment that uses donor stem cells to restore a patient's marrow and blood cells. First, the patient is given "conditioning therapy" (high-dose chemotherapy or high-dose chemotherapy with total body radiation) to treat the disease and to "turn off" the patient's immune system so that the donor stem cells will not be rejected. A type of transplant called a "nonmyeloablative" transplant (also called a "mini-transplant" or a "reduced-intensity transplant") is under study. It uses lower doses of conditioning therapy and may be safer, especially for older patients.

Anemia

A decrease in the number of red cells and, therefore, the hemoglobin concentration of the blood. This results in diminished ability of the blood to carry oxygen. If severe, anemia can cause a pale complexion, weakness, fatigue, and shortness of breath on exertion.

Antibodies

Proteins released by plasma cells (derived from B lymphocytes) that recognize and bind to the specific foreign substances called antigens. Antibodies coat, mark for destruction or inactivate foreign particles like bacteria and viruses or harmful toxins. Antibodies can also be made in the laboratory in two ways. If one injects material from one species into another, the latter will recognize it as foreign and make antibodies to it. These antibodies are usually polyclonal antibodies, that is, they react to multiple targets (antigens). A laboratory technique is used to produce a specific antibody known as a monoclonal antibody. Monoclonal antibodies react to only one target (antigen) and can be used in several important ways. They can be used to identify and classify human leukemias and lymphomas or can be altered to make them useful in antibody-mediated immunotherapy.

Antigen

A foreign substance that enters the body and stimulates the production of complementary antibodies by B lymphocytes. A foreign substance may stimulate the response of T lymphocytes as well. When bacteria infect a tissue, the immune system recognizes them as foreign and causes the B lymphocytes to create antibodies against them. These antibodies attach to the antigen. This attachment of antibodies to their antigen facilitates the ingestion of bacteria by bacteria-eating neutrophils (phagocytes). Transplanted cells can act to stimulate an immune response of a different type in which T lymphocytes of the recipient attack the cells perceived as foreign from the donor, or T lymphocytes in the cell suspension from the donor can attack the tissue cells perceived as foreign in the recipient (see Graft Versus Host Disease).

Apheresis

The process of removing components of a donor's blood and returning the unneeded parts to the donor. Apheresis uses continuous circulation of blood from a donor through a machine and back to the donor. It makes it possible to remove desired elements from large volumes of blood. Platelets, red cells, white cells, or plasma can be removed separately. For example, this technique permits the harvest of enough platelets for transfusion from one donor (rather than six to eight separate donors). In so doing, the recipient of the platelets is exposed to fewer donors or can be given HLA-matched platelets from a single related donor. Apheresis is also used to remove circulating blood stem cells, which can be frozen, stored, and later used, instead of marrow stem cells, for transplantation.

Autologous Stem Cell Infusion (Autotransplant)

A technique that involves autologous stem cell infusion after intensive therapy has the following components 1) harvesting the patient's stem cells from blood or marrow, 2) freezing them for later use and 3) thawing and infusing them via an indwelling catheter after the patient has been given intensive chemotherapy or radiation therapy. The blood or marrow may be obtained from a patient with a disease of the marrow, such as acute myelogenous (myeloid) leukemia, when in remission or when the marrow and blood are not overtly abnormal (for example, in lymphoma). Technically, this procedure is not transplantation, which implies taking tissue from one person (donor) and giving it to another person (recipient). The purpose of this procedure is to restore blood cell production from the preserved and reinfused stem cells after intensive therapy has severely damaged the patient's remaining marrow. This procedure can be performed using marrow or blood stem cells. The latter can be harvested by apheresis.

Autotransplant (see Autologous Stem Cell Infusion)

Basophil

A type of white cell that participates in certain allergic reactions.

B Lymphocyte

One of three specialized lymphocyte types. They produce antibodies in response to any foreign substance, but to bacteria, viruses, and fungi in particular. These lymphocytes are a vital part of the immune system and are important to our defense against infection. Some B lymphocytes mature into plasma cells, which are the principal antibody-producing cells.

Bone Marrow

The bones are hollow and their central cavity is occupied by marrow, a spongy tissue that plays the major role in the development of blood cells. By puberty, the marrow in the spine, ribs, breastbone, hip, shoulders, and skull is most active in blood cell formation. In the adult, the bones of the hands, feet, legs and arms do not contain marrow in which blood cells are made. In these sites the marrow is filled with fat cells. When marrow cells have matured into blood cells, they enter the blood that passes through the marrow and are carried throughout the body.

Cellular Immunity

That portion of the immune system that protects the individual from infection by the action of T lymphocytes, monocytes, macrophages and other specialized lymphocytes called NK cells. Deficiency in this portion of the immune system can permit infection by microbes such as the bacillus of tuberculosis, cytomegalovirus, and many other organisms that might be fended off more easily in a healthy individual. T lymphocytes also cooperate with B lymphocytes to increase the effectiveness of antibody formation.

Central Line (see Indwelling Catheter)

Chemokines

These are small molecules which may stimulate inflammation and which may play a role in stem cell mobilization

Chemotherapy

The use of chemicals (drugs or medications) to kill malignant cells. Numerous chemicals have been developed for this purpose, and most act to injure the DNA of the cells. When the DNA is injured, the cells cannot grow or survive. Successful chemotherapy depends on the fact that malignant cells are somewhat more sensitive to the chemicals than normal cells. Because the cells of the marrow, the gastrointestinal tract, the skin, and hair follicles are most sensitive to these chemicals, injury to these organs cause the common side effects of chemotherapy, such as mouth sores and hair loss.

Chromosome

One of 46 structures in all human cells, made up principally of genes, which are specific stretches of DNA. "Genome" is the term for an organism's complete set of DNA. It is estimated that the human genome has about 30,000 genes. The genes on the X and Y chromosomes, the sex chromosomes, are the determinants of our gender: two X chromosomes in females and an X and a Y chromosome in males. The number or size of chromosomes may be altered in cancer cells, as a result of chromosome breakage and rearrangement (translocation).

Clonal (Monoclonal)

A population of cells derived from a single primitive cell. Virtually all neoplasms, benign and malignant (cancers), are derived from a single cell with an injury to DNA (mutation) and, thus, are clonal. The mutated cell has an alteration in its DNA, which forms an oncogene. This leads to its transformation into a cancer-causing cell. The cancer is the total accumulation of cells that grow from the single mutated cell. Leukemia, lymphoma and myeloma are examples of cancers that are clonal, that is, derived from a single abnormal cell.

Conditioning Treatment

Intensive therapy with cytotoxic drugs or drugs and total body radiation before autologous stem cell infusion or allogeneic transplantation. The therapy serves several purposes. First, if the person is being treated for a blood cancer, this intensive therapy serves to greatly reduce any remaining tumor cells. Second, it markedly decreases the number of marrow cells. This may be important in order to open up the special niches that transplanted stem cells lodge in to engraft. Third, if donor stem cells are used (allogeneic transplant) it severely depresses the lymphocytes that are the key cells in the immune system. This action helps to prevent the rejection of the stem cell graft.

Cord Blood Stem Cells

Stem cells that are present in blood drained from the placenta and umbilical cord. These stem cells can repopulate the marrow of a compatible recipient and produce blood cells. Frozen cord blood is a source of donor stem cells for transplantation to HLA-matched recipients. Most cord blood transplants are done using matched or nearly matched unrelated donors.

Cryopreservation

A technique used to keep frozen cells intact and functional for many years. Blood or marrow cells, including stem cells, can be stored for very long periods and remain functional if they are suspended in a fluid that contains a chemical that prevents cellular injury during freezing or thawing. This chemical is referred to as a “cryoprotective” agent. Dimethyl sulfoxide (DMSO) is one of the most commonly used agents. The freezing temperature is much lower (colder) than that of a household freezer.

Culture

A sample of bodily fluid, such as sputum, blood, and urine and swabs of the inside of the nose, throat, and rectum, which are used to determine the principal site and the type of bacterium, fungus, or other microorganism involved so that the most specific antibiotic can be selected as treatment. When an infection is suspected, samples are placed on culture medium in special sterile containers and incubated at body temperature (37°C, [98.6°F]) for one to several days. These cultures are examined to see if bacteria, fungi, or other organisms are present in significant numbers. If present, the organisms can be tested with several antibiotics to learn which of them kill the organism. This is called determining the “antibiotic sensitivity” of the organism.

Cycle of Treatment

This is the term for an intensive, clustered period of chemotherapy (and/or radiotherapy). The treatment may be given for several days or weeks and represents one cycle of treatment. The treatment plan may call for two, three, or more cycles of treatment.

Cytokines

These are cell- (cyto-) derived chemicals that are secreted by various types of cells and act on other cells to stimulate or inhibit their function. Chemicals derived from lymphocytes are called “lymphokines.” Chemicals derived from lymphocytes that act on other white cells are called “interleukins,” that is, they interact between two types of leukocytes. Some cytokines can be made commercially and used in treatment. Granulocyte-colony stimulating factor (G-CSF) is one such cytokine. It stimulates the production of neutrophils and shortens the period of low neutrophil counts in the blood after chemotherapy. Cytokines that stimulate cell growth are sometimes referred to as “growth factors.” Cytokines such as G-CSF are used to mobilize stem cells from marrow to blood.

DNA

The abbreviation for deoxyribonucleic acid, the material inside the nucleus of cells that carries genetic information. Genes tell the cell how to make the proteins that enable the cell to carry out its functions. DNA can become highly abnormal in cancer cells.

Engraftment

The process of transplanted stem cells homing to the recipient’s marrow and producing blood cells of all types. This occurrence is first evident when new white cells, red cells, and platelets begin to appear in the recipient’s blood following transplantation.

Eosinophil

A type of white cell that participates in allergic reactions and helps to fight certain parasitic infections.

Erythrocyte

A synonym for red cell (see Red Cell).

Extracorporeal Photopheresis

A procedure being studied to treat steroid-refractory graft versus host disease (GVHD). The procedure involves a series of treatments. Blood is removed through a vein, then white cells are isolated and treated with methoxsalen (UVADEX®), a drug that sensitizes the cells to ultraviolet light. UVA rays are used to irradiate the cells, which are then reinfused into the patient.

Fractionation of the Dose

In order to minimize the significant side effects of total body irradiation conditioning therapy, the dose of radiation required is given in several daily smaller doses rather than one larger dose. This approach has decreased the adverse effects of this treatment.

Graft Versus Tumor (GVT) Effect

The potential immune reaction of transplanted T lymphocytes to recognize and attack the malignant cells of the recipient. This effect was noted when: 1) leukemia recurrence after transplant was seen to be more likely if the donor and recipient were identical twins than if they were nonidentical siblings; 2) the more prominent the graft versus host disease the less likely was leukemia recurrence; and 3) the removal of donor T lymphocytes decreased the incidence of graft versus host disease but also resulted in a higher frequency of leukemia relapse. Each of these observations could be explained best by an immune attack by donor lymphocytes against recipient leukemia cells that collaborated with the intensive conditioning treatment to keep the leukemia in check. This effect seems to be most active in myelogenous (myeloid) leukemia, although it may also occur in patients with myeloma.

Graft Versus Host Disease (GVHD)

The immune attack by lymphocytes in the donor's marrow or blood cell suspension (the graft) against the tissues of the recipient (the host). The immune cells most engaged in this reaction are donor T lymphocytes, which are present in the donor's blood or marrow, the source of stem cells. The principal sites of injury are the skin, the liver and the gastrointestinal tract. The reaction does not occur in identical twin transplants. The reaction may be minimal in closely matched individuals or severe in less well-matched individuals. These reactions are mediated in part by antigens that are not in the major HLA system and cannot be matched prior to transplant. For example, in the case of a female stem cell donor and a male recipient, factors that are produced by genes on the Y chromosome may be seen as foreign by the female donor's cells, which do not share the genes on the Y chromosome. This fact does not prohibit female donors and male recipients, but it makes the risk of immune reaction higher.

Granulocyte

A type of white cell that has a large number of prominent granules in the cell body. Neutrophils, eosinophils and basophils are types of granulocytes.

Granulocyte-Colony Stimulating Factor (see Cytokines)

LEUKEMIA

LYMPHOMA

MYELOMA

Growth Factors (see Cytokines)

Haplotype

The tissue type contributed by either the mother or father to his or her offspring. It is implied that it represents the genes on one parental chromosome. When a transplant procedure is between a donor and recipient that are haplotype identical, it means that the tissue type or HLA type of each is identical in respect to mother or father but not identical to the other. In some situations, if the discrepancy is not too great, the transplant may still be possible if the underlying disease makes the risk of partial compatibility warranted. Conditioning of the recipient and lymphocyte depletion of the donor stem cell suspension are steps taken to mitigate the risk of immune cell activation by the tissue type differences.

Hemapheresis (see Apheresis)

Hematologist

A physician who specializes in the treatment of blood cell diseases. This person is either an internist, who treats adults, or a pediatrician, who treats children.

Hematopathologist

A pathologist who specializes in the diagnosis of blood cell diseases and who performs the specialized laboratory tests often required to make a conclusive diagnosis.

Hematopoiesis

This term describes the process of blood cell development in the marrow. The most undeveloped cells in the marrow are stem cells. They start the process of blood cell development. The stem cells begin to develop into young or immature blood cells like red cells or white cells of various types. This process is called “differentiation.” The young or immature blood cells then further develop into fully functional blood cells. This process is called “maturation.” The cells then leave the marrow and enter the blood and circulate throughout the body. (See Figure 1, page 8.) Hematopoiesis is a continuous process that is active normally throughout life. The reason for this activity is because most blood cells live for short periods and must be continuously replaced. Red cells die in four months, platelets in 10 days and most neutrophils in two or three days. About five hundred billion blood cells are made each day. This requirement for very rapid replacement explains the severe deficiency in blood cell counts when the marrow is injured by replacement with leukemia, lymphoma, or myeloma cells.

HLA

The acronym for human leukocyte antigen(s). These proteins are on the surface of most tissue cells and give each individual his or her unique tissue type. Hence, the testing for HLA antigens is referred to as “tissue typing.” There are four major groups of HLA antigens: A, B, C, and D. These proteins act as antigens when donated (transplanted) to another individual, such as a bone marrow or stem cell recipient. If the antigens on the donor cells are identical (those from identical twins, for example) or very similar (such as those from HLA-matched siblings), the transplant (comprising donated marrow or cells) is more likely to survive in the recipient (engraft). In addition, the recipient’s body cells are less likely to be attacked by the donated cells (graft versus host disease).

Host

The recipient of the transplant who acts as “host” to the transplanted stem cells.

Immunophenotyping

A method that uses the reaction of antibodies with cell antigens to determine the specific types of cells in a sample of blood cells, marrow cells or lymph node cells. A tag is attached to antibodies that react with specific antigens in the cells. The tag can be identified by the laboratory detector used for the test. As cells carrying their array of antigens are tagged with specific antibodies, they can be identified; for example, myelogenous (myeloid) leukemia cells can be distinguished from lymphocytic leukemia cells. This method helps to subclassify cell types, information that may help physicians to decide on the best treatment to apply in a particular type of blood cancer.

Immunosuppression

A state in which the immune system does not function properly and its protective functions are inadequate. The patient is more susceptible to infections, including those from microbes that are usually not highly infectious (see Opportunistic Infection). This can occur as a result of intensive chemotherapy and radiation therapy, especially when used in high doses to condition a patient for transplantation. It also can occur because of disease states. Human immunodeficiency virus infection is one such disease. Graft versus host disease (GVHD) creates an immunosuppressive state in which immune protection against infection is inadequate. In the transplant patient the conditioning regimen and severe GVHD can result in overwhelming infection.

Indwelling Catheter

Several types of catheters (such as the Groshong[®], Hickman[®], Broviac[®] and others) can be used for patients receiving intensive chemotherapy or nutritional support. An indwelling catheter is a special tubing inserted into a large vein in the upper chest. The catheter is tunneled under the skin of the chest to keep it firmly in place. The external end of the catheter can be used to administer medications, fluids, or blood products or to withdraw blood samples. With meticulous care, catheters can remain in place for long periods of time (many months), if necessary. They can be capped and remain in place in patients after they leave the hospital and used for outpatient chemotherapy or blood product administration. Another type of long-term catheter incorporates an implanted port. The port is surgically inserted under the skin's surface on the upper chest wall. After the site heals, no dressings are needed and no special home care is required. When medicines are needed, a physician, physician assistant or nurse inserts a needle through the skin to access the port. The patient can choose to have a local numbing cream applied to the injection site before the port is used. Blood can be drawn, and blood products can be received through this device.

Interstitial Pneumonitis

A severe inflammation in the lungs that can occur as a toxic effect of total body irradiation in the conditioning regimen. The small airways and intervening spaces between air sacs get congested, swollen, and exchange of oxygen can be compromised. Typically, no infection is present although a similar reaction can occur as a result of infection.

Intrathecal

The space between the covering or lining of the central nervous system and the brain or spinal cord. The lining is called the “meninges.” In some situations drugs have to be administered directly into the spinal canal when cancer cells are in the meninges. This is called “intrathecal” therapy.

Leukocyte

A synonym for white cell (see White Cell).

Leukopenia

A decrease below normal in the number of blood leukocytes (white cells).

Lymph Nodes

Small structures, the size of beans, which contain large numbers of lymphocytes and are connected with each other by small channels called “lymphatics.” These nodes are distributed throughout the body. In patients with lymphoma, Hodgkin lymphoma, and some types of lymphocytic leukemia, the malignant lymphocytes grow and expand the lymph nodes so that they may be enlarged. This enlargement of lymph nodes can be seen, felt, or measured by computed tomography (CT) scan or magnetic resonance imaging (MRI), depending on the degree of enlargement and location.

Lymphocyte

A type of white cell that participates in the body’s immune system. There are three major types of lymphocytes: B lymphocytes that produce antibodies to help combat infectious agents such as bacteria, viruses, and fungi; T lymphocytes that have several functions, including assisting B lymphocytes to make antibodies and attack virus infected cells; and natural killer (NK) cells that can attack tumor cells.

Lymphokine (see Cytokines)

Monoclonal Antibodies

Antibodies made by cells belonging to a single clone. These highly specific antibodies can be produced in the laboratory. They are very important reagents for identifying and classifying disease by immunophenotyping cells. They also have clinical applications for targeted delivery of drugs to leukemia or lymphoma cells and can be used to purify cells used for stem cell transplants.

Monocyte (macrophage)

A type of white cell that assists in fighting infection. The monocyte and the neutrophil are the two major microbe-eating and killing cells in the blood. When monocytes leave the blood and enter the tissue, they are converted to macrophages. The macrophage is the monocyte in action and can combat infection in the tissues or can serve other functions, such as ingesting dead cells (scavenging).

Mucous Membranes

The inner lining of cavities such as the mouth, nose, and sinuses. These linings require new cells to be made to replace those that drop off. This replacement is a normal process and keeps the lining intact and moist. Radiation therapy or chemotherapy drugs that block cells from dividing prevent the replacement of lost

cells. The linings become dry, defective, and may ulcerate in patients who receive such treatment. This change can be painful, such as when ulcers develop in the mouth. These painful, ulcerating lesions are referred to as oral “mucositis.” Anal ulcers can also develop. The loss of what is referred to as the barrier function of mucous membranes permits microbes to enter the tissue or blood and often leads to infection.

Multidrug Resistance (MDR)

A characteristic of cells that makes them resistant to the effects of several different classes of drugs. There are several forms of drug resistance. Each of these are determined by genes that govern how the cell will respond to the chemical agents. One type of MDR involves the ability to eject several drugs out of cells. The cell outer wall or membrane of the cell contains a pump that ejects chemicals, preventing them from reaching a toxic concentration. The resistance to drugs can be traced to the expression of genes that direct the formation of high amounts of the protein that prevents the drugs from having their effects on the malignant cells. If the gene or genes involved are not expressed or are weakly expressed, the cells are more sensitive to the drug’s effect. If the genes are highly expressed, the cells are less sensitive to the drug’s effect.

Mutation

An alteration in a gene that results from a change to a part of the stretch of DNA that represents a gene. A “germ cell mutation” is present in the egg or the sperm and can be transmitted from parent(s) to offspring. A “somatic cell mutation” occurs in a specific tissue cell and can result in the growth of the specific tissue cell into a tumor. Most cancers start after a somatic mutation. In leukemia, lymphoma, myeloma or myelodysplastic syndromes, a primitive marrow or lymph node cell undergoes a somatic mutation(s) that leads to the formation of malignant cells. In these cases, the cells are usually widely distributed when detected; they usually involve the marrow of many bones or involve lymph nodes in several sites.

Neutropenia

A decrease below normal in the number of blood neutrophils, a type of white cell.

Neutrophil

The principal phagocyte (microbe-eating cell) in the blood. This blood cell is the main cell that combats infection. Often, it is not present in sufficient quantities in patients with acute leukemia or after chemotherapy, which increases their susceptibility to infection. A neutrophil may be called a “poly” (for polymorphonuclear) or “seg” (for segmented nucleus).

Nonmyeloablative Allogeneic Stem Cell Transplant

Also referred to as a “mini-transplant” and as a “reduced-intensity transplant,” a type of stem cell transplant that uses less induction chemotherapy and radiation. The theory being tested with a nonmyeloablative allogeneic transplant is that by undergoing less-toxic methods prior to the transplant, the body is better able to withstand the transplant but donor full engraftment still takes place and the GVT effect still occurs.

Oncologist

A physician who diagnoses and treats patients with cancer. This person is usually an internist, who treats adults, or a pediatrician, who treats children. Radiation oncologists specialize in the use of radiation to treat cancer, and surgical oncologists specialize in the use of surgical procedures to treat cancer. These physicians cooperate and collaborate to provide the best treatment plan (surgery, radiation therapy or chemotherapy) for patients.

Opportunistic Infection

A bacterial, viral, fungal or protozoan infection that usually does not cause disease in a healthy individual but can produce serious infections in persons with immune deficiency, such as those undergoing allogeneic stem cell transplantation.

Pancytopenia

A decrease below normal levels in the concentration of the three major blood cell types: red cells, white cells and platelets.

Pathologist

A physician who identifies disease by studying tissues under a microscope. A hematopathologist is a type of pathologist who studies diseases of blood cells by looking at peripheral blood smears, bone marrow aspirates and biopsies, lymph nodes and other tissues, and uses his/her expertise to identify diseases such as acute myelogenous (myeloid) leukemia. In addition to using a microscope,

a hematopathologist also uses laboratory values, flow cytometry, and molecular diagnostic tests to make the most accurate diagnosis. The hematopathologist works closely with the hematologist/oncologist who sees the patient and decides on the best treatment based upon the diagnosis.

Phagocyte

A cell that readily eats (ingests) microorganisms such as bacteria or fungi and can kill them as a means of protecting the body against infection. The two principal phagocytes in the blood are neutrophils and monocytes. A decrease in the number of these blood cells is the principal cause of susceptibility to infection in patients with leukemia or those treated with intensive radiation therapy and/or chemotherapy, which suppresses blood cell production in the bone marrow.

Platelet

A cell fragment (about one-tenth the volume of red cells) that stick to the site of a blood vessel injury, aggregate, and seal off the injured blood vessel to stop bleeding. Thrombocyte is a synonym for platelet and is often used as the prefix in terms describing disorders of platelets, such as thrombocytopenia or thrombocythemia.

Platelet Transfusion

The transfusion of donor platelets is frequently needed to support patients treated for leukemia or lymphoma. The platelets can be pooled from several unrelated donors and given as “pooled random-donor platelets.” Platelets from about six one-unit blood donors are needed to significantly raise the platelet count in a recipient. Sufficient platelets can be obtained from one donor if his or her platelets are obtained by apheresis. The advantage of single-donor platelets is that the patient is not exposed to the different antigens on platelets from many different people and is less likely to develop antibodies against donor platelets. HLA-matched platelet transfusion can be given from a related donor with an identical or very similar HLA tissue type.

Red Cell

A blood cell that carries hemoglobin, which binds oxygen and transports it to the tissues of the body. The red cells make up about 40 to 45 percent of the volume of the blood in healthy individuals.

Reduced-intensity Allogeneic Stem Cell Transplantation

Stem cell transplantation that involves preconditioning with administration of chemotherapy plus or minus radiation that is not given in full doses administered in a standard allogeneic stem cell transplant. This term is sometimes used as a synonym for nonmyeloablative or mini-transplant.

Refractory Disease

This is the term that describes disease that does not go into remission or improve substantially after initial treatment with standard therapy for the disease.

Relapse (Recurrence)

A return of the disease after it has been in remission following treatment.

Remission

A disappearance of evidence of a disease, usually as a result of treatment. The terms “complete” or “partial” are used to modify the term “remission.” Complete remission means all evidence of the disease is currently gone. Partial remission means the disease is markedly improved by treatment, but residual evidence of the disease is present. Long-term benefit usually requires a complete remission, especially in acute leukemia or progressive lymphomas and certain other cancers of the blood and marrow.

Resistance to Treatment

The ability of cells to live and divide despite their exposure to a drug that ordinarily kills cells or inhibits their growth. Refractory disease is the circumstance in which a proportion of malignant cells resist the damaging effects of a drug or drugs. Cells have several ways to develop drug resistance. (See Multidrug Resistance.)

Spleen

An organ of the body that is in the left upper portion of the abdomen just under the left side of the diaphragm. It contains clusters of lymphocytes and also filters the blood of old or worn out cells. It is often affected in lymphocytic leukemias and lymphomas. Enlargement of the spleen is referred to as “splenomegaly.” Removal of the spleen by surgery is referred to as splenectomy. Removal of the spleen is used to treat certain diseases. Most of the functions of the spleen can be performed by other organs, such as the lymph nodes and liver, but a person whose spleen has been removed has a greater risk for infection. He or she is given antibiotic therapy immediately at the first sign of infection, such as a fever.

Stem Cells

The multipotential cells in marrow that are required to make red cells, white cells and platelets. Generally, the stem cells are largely found in the marrow but some leave the marrow and circulate in the blood. Using special techniques, the stem cells in blood can be collected, preserved by freezing and, later, thawed and used for stem cell therapy. (See Hematopoiesis.)

T-lymphocyte Depletion

A process to decrease the number of immune cells that cause GVHD (graft versus host disease). Typically antibodies against T lymphocytes are used to draw them out of the stem cell sample to be used for transplant. The decreased presence of T lymphocytes in the transplant minimizes the intensity of GVHD. T lymphocytes are depleted only in certain circumstances because T lymphocytes are also beneficial. They help the donated stem cells take hold (engraft) and grow in the recipient's marrow. In some cases, T lymphocytes attack blood cancer cells, enhancing the results of other treatment. This "graft versus tumor effect" can be seen mostly in the myelogenous (myeloid) leukemias. The attack on the remaining blood cancer cells makes it less likely that the disease will return after transplant.

Thrombocytopenia

A decrease below normal in the number of blood platelets (thrombocytes).

Tolerance

A very important event in the long-term success of transplantation. After a time, usually a year or so, the prior host and donor T lymphocytes die off and new lymphocytes are formed from the donor's engrafted stem cells. These "adapt" to the new host and stop attacking the recipient's cells. If tolerance is present, the immune system is no longer distracted and can serve the patient by working efficiently to protect against microbes. Risk of infection diminishes and approaches that of a healthy person. Immunosuppressive therapy can be stopped.

Veno-occlusive disease (VOD)

A disease that may be a complication following high-dose chemotherapy and/or radiation, in which the blood vessels that carry blood through the liver swell and become clogged.

White Cell

A synonym for leukocyte. There are five major types of white cells: neutrophils, eosinophils, basophils, monocytes and lymphocytes.

Resources

The Leukemia & Lymphoma Society (LLS) Patient Materials

To order publications or obtain information about LLS programs and services for patients, call your local chapter or call the Information Resource Center at (800) 955-4572. You may also visit our Web site at www.LLS.org.

LLS free publications include:

Blood Transfusion; 2006.

Co-Pay Assistance Program; 2007

Coping With Childhood Leukemia and Lymphoma; 2007.

Coping: Support for People Living with Leukemia, Lymphoma or Myeloma; 2005.

Cord Blood Stem Cell Transplantation (fact sheet); 2007.

Each New Day: Ideas for Coping with Leukemia, Lymphoma or Myeloma; 2006.

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Financial Health Matters; 2007.

Long-Term and Late Effects of Treatment for Childhood Leukemia or Lymphoma (fact sheet); 2007.

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Pictures of My Journey: Activities for kids with cancer; 2007.

The Stem Cell Transplant Coloring Book; 2007.

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