People Living With Cancer
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Guest Author Series: Part I: Understanding Bone Marrow and Stem Cell Transplantation

This is the first in a four-part series of articles on bone marrow and stem cell transplantation. The series will prepare you to ask your transplant team meaningful questions and help you to understand the answers. This article provides an overview of bone marrow and stem cell transplantation and explains the differences between autologous and allogeneic transplants.

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Occasionally, PLWC asks a member of the American Society of Clinical Oncology (ASCO) to write an article on his or her area of expertise. This four-part series is written by Edward Agura, MD, an advisory panel member for the PLWC Editorial Board. Dr. Agura is Director of the Program in Blood and Marrow Transplant at Baylor University Medical Center in Dallas, TX.

This is the first in a four-part series of articles on bone marrow and stem cell transplantation. The series will prepare you to ask your transplant team meaningful questions and help you to understand the answers. The series will also walk you through the goals of bone marrow transplantation, the types of transplantation donors and what to expect as a donor, side effects, questions to ask your transplant team, and a transplant timeline. This article provides an overview of bone marrow and stem cell transplantation and explains the differences between autologous and allogeneic transplants.

Blood and marrow transplantation is a medical (not a surgical) procedure, lasting weeks to months from start to finish, in which diseased marrow (a spongy, fatty tissue found on the inside of larger bones) or immune system is replaced by a healthier one. For people with cancer, the goal is to destroy every last cancer cell. For people with genetic diseases, the goal is correction of the underlying genetic disease.

To accomplish these goals, the bone marrow must be replaced and/or treated. And in order to accomplish that goal, the doctor will first collect stem cells that will replace the destroyed tissue.

People stay alive by a process of continual self-renewal. Wounds heal, hair grows, and internal organs renew themselves. If this process did not occur, people would not live very long. Rare and highly specialized cells called stem cells distributed throughout the body are responsible for this renewal process.

Every part of the body has its own population of stem cells, which help to renew the organ in which they live. For example, stem cells found in the skin help to renew the skin when it is injured, and liver stem cells help to renew the liver. Blood and bone marrow stem cells help renew the blood and bone marrow.

The natural home of blood and marrow stem cells is inside the bones—in the marrow cavity itself. From this location, they perform their crucial function: to multiply and produce their unique offspring: red cells (also called erythrocytes), white cells (also called leukocytes), and platelets. These are the cellular components of the human bloodstream. Red blood cells are responsible for bringing oxygen to the body's organs and tissues and carrying away waste from the body's organs and tissues. White blood cells are responsible for helping to protect the body from infection. Platelets are responsible for causing blood to clot, which helps to control bleeding. Within this unique "family," blood/marrow stem cells are the parents, and white cells, red blood cells, and platelets are the children.

During the process of bone marrow transplantation, stem cells from the marrow are first removed and then later put into the patient's body. The replacement stem cells may come from the patient, or may come from a donor (another person). The choice of which to use depends on many factors, including the type of illness being treated and the health of the patient's own marrow. When the patient receives his or her own stem cells, it is called an autologous transplant; when donor cells are used, it is called an allogeneic transplant.

Before the patient receives the replacement stem cells, he or she will be treated with chemotherapy and/or radiation therapy, typically for five to seven days, to destroy the diseased bone marrow. Then, the replacement stem cells are transferred into the patient's bloodstream through a simple, intravenous (IV) transfusion. No surgery is involved. The new stem cells float through the bloodstream and gradually find their way back "home" to the bone marrow space. Once in the marrow space, the stem cells "plant" themselves and begin to grow.

It is important to note there is a difference between bone marrow stem cells and embryonic stem cells. Embryonic stem cells are derived from human embryos and are not currently used for bone marrow transplantation.

The goals of blood and marrow transplantation

Patients seek to be cured. Transplantation is a powerful method that has the capability of curing cancers and some genetic diseases which involve the blood. A list of diseases commonly treated this way, along with the preferred transplant method, is below.

Disease	Blood organ/cell type affected	Type of transplants possible	Best result (published to date)
Acute leukemia	white blood cells from bone marrow	autologous allogeneic	cure cure
Myelodysplasia (MDS)	all blood cell types from bone marrow	allogeneic	cure
Non-Hodgkin lymphoma	cells of lymphatic system	autologous allogeneic	cure cure
Hodgkin lymphoma	cells of lymphatic system	autologous allogeneic	cure cure
Chronic leukemia	blood cells from marrow	allogeneic	cure
Damaged marrow syndromes (aplastic anemia, MDS, others)	blood cells from marrow	allogeneic	cure
Multiple myeloma, Waldenström's disease	plasma cells from bone marrow and lymphatics	autologous allogeneic	prolonged remission (the temporary or permanent absence of disease) cure
inherited immunodeficiencies	cells from lymphatic system	allogeneic	cure
inherited anemias (such as thalassemai, Sickle cell anemia)	red blood cells from marrow	allogeneic	cure

The differences between AUTO and ALLO transplants

An autologous transplant, known as an AUTO, uses a patient's own stem cells. The stem cells are removed and stored first (days to weeks ahead), then the patient is given chemotherapy and/or radiation therapy for about one week. At the end of the treatment, the frozen stem cells are thawed and given back to the patient as an intravenous transfusion, often through a vein in the arm.

An allogeneic transplant, known as an ALLO, uses a donor who is genetically matched with the patient for a factor known as "tissue type." The patient's siblings usually have the best chance of being a complete match. Other family members occasionally can match. Or, a volunteer donor may be the best match for the tissue type. During an ALLO transplant, the patient first undergoes treatment very similar to that given during an AUTO transplant (described above). However, the timing of stem cell donation is coordinated, so it occurs at the same time as the end of the chemotherapy and/or radiation therapy the patient receives. Donor stem cells are collected on or near the actual transplant day, and the patient receives these fresh and unfrozen, as an intravenous infusion.
Both AUTO and ALLO transplants kill cancer with dose intensity (high doses of chemotherapy and/or radiation therapy). With AUTO transplants, the cancer-killing effect ends when the chemotherapy/radiation therapy ends. (The remainder of the treatment course is simply to help patients recover from side effects.) In distinction, the ALLO transplant continues to battle cancer even after the chemotherapy/radiation therapy are done.

ALLO transplants have two advantages that make them superior to AUTO transplants for eliminating cancer. The first has to do with giving the patient a cancer-free stem cell product. With an AUTO transplant, there is always the inherent risk that cancer cells will be contained in the frozen stem cell product. The risk does not exist if the stem cells come from a healthy donor. The second reason has to do with the new immune system that develops after an ALLO transplant. This new immune system has an ability to attack cancer cells that may have escaped the chemotherapy/radiation therapy given at the beginning of the transplant process. This enhanced effect is especially strong with certain kinds of cancers and is given the name, graft versus tumor (GVT) effect. On the other hand, a patient receiving an ALLO transplant faces tissue rejection risks that an AUTO transplant patient does not.

Choosing the type of transplant

There are many medical factors involved in the decision regarding which stem cell source to use. Some of the most important ones include whether the bone marrow contains cancerous cells, the extent of bone marrow injury caused by previous chemotherapy, the disease type itself, and the health and age of the patient.

The decision is complex; it cannot be made without the input of a doctor who specializes in transplant medicine and has performed an in-person evaluation of the patient and the potential donor. This means the patient may need to travel to a center where transplantation is routinely practiced to have a consultation.

At the consultation, other nonmedical factors are also considered, such as the patient's support system, their ability to take time away from work or family, insurance coverage, and access to transportation.

When the disease type irreversibly involves the bone marrow, an allogeneic (donor-type) transplant is the only type of transplant that offers a chance to cure. Fortunately, at least one out of three patients turns out to have a suitably matched brother or sister who can donate. The tissue typing is done through a blood test of the potential donor. Transplant can then move forward rapidly.

Unrelated and cord blood donors

If siblings do not match, other family members may be tested, but such matches occur only occasionally. However, people who need a donor can turn to the volunteer and cord blood registries.

Formed in the mid-1980s, volunteer registries are now very large (7 million volunteer donors worldwide). At least two-thirds of patients who need a donor can find one through these registries.

And, for people who cannot find a living matched donor, there is hope with the ever-expanding umbilical cord blood registries. While still a relatively young and emerging source of stem cells, cord blood units are used at cancer centers around the world. The results in children have been excellent. In adults, the technology is still underdeveloped, and patients may face additional risks that should be discussed with the doctor.

Duration of bone marrow transplantation

The duration and timing of bone marrow transplantation is often misunderstood. Many patients think of it as a surgery, which it is not. Many more are surprised when they are told that blood and marrow transplantation does not happen suddenly. Instead, transplantation is a process that takes weeks and months from beginning to end.

Questions to ask your transplant team regarding timing:

* How long will I be away from home?
* When will I feel strong enough to return to full-time work?
* When will I start to feel better than I feel today?

What to expect as the donor

Being a stem cell donor has changed greatly in recent years. Today, most donors undergo a peripheral blood stem cell (PBSC) collection rather than a bone marrow harvest procedure (an operation that involves going to the hospital for a day surgery, undergoing general anesthesia [medication that puts you in a deep sleep], and having one or two transplant surgeons extract marrow from the hip bones using needles). For five days leading up to the PBSC procedure, donors receive injections (lasting 5 minutes a day) of a white blood cell growth hormone called G-CSF (Neupogen). On the fifth day, a needle is placed in each arm and blood is circulated through a machine, which collects the stem cells and returns the unused portion of the blood back to the donor. This takes about three hours and may be repeated on a second donation day. There is very little blood loss. Side effects with this type of procedure may include headaches, bone soreness, and the discomfort of needles during the process.

Occasionally, donor cells do not grow. The chance of this happening depends on many factors, the most important being whether the patient has had previous chemotherapy (prior chemotherapy may indicate success), the intensity (strength) of the transplant treatment to destroy the original bone marrow (stronger may indicate growth), and the amount of donor cells provided (more is better). In most cases, the solution is to obtain more cells from the donor. Most second donations result in the successful growth of donor cells.

Additional resources

National Marrow Donor Program,
Blood and Marrow Transplant Information Network
The Leukemia and Lymphoma Society

Guest Author Series: Part II: Bone Marrow and Stem Cell Transplantation: Special types of transplantation

This is the second article in a four-part series on bone marrow and stem cell transplantation. The series will prepare you to ask your transplant team meaningful questions and help you to understand the answers. This article will discuss special types of transplantation and provide you with a transplant timeline.

The two most common types of transplants are autologous (AUTO), in which the patient's own bone marrow is used, and allogeneic (ALLO), when another person is the donor of the bone marrow. If neither an AUTO nor ALLO transplant is possible, there may be other options available. Special types of transplantation are listed below.

Umbilical cord blood donor. Some patients cannot find a suitable living donor, either due to lack of time or lack of suitable tissue matches. For this reason, an umbilical cord blood transplant is being researched and developed. Cord blood is the cup of blood that remains in the placenta and umbilical cord after a baby is born. It is the baby's own blood, not the blood of the mother. If that blood is saved, tested, and put into a tissue bank, it may be used for a patient who cannot find a donor. Cord blood cells have special properties. They are particularly rich in hematopoietic stem cells and have the property of growing much better and faster than stem cells from a living adult donor. It is also believed, but not fully proven, that such stem cells may cause fewer complications such as graft-versus-host disease (GVHD). But, there are also potential drawbacks. Cord blood can only be used once, the small quantity may not be enough for an adult patient, and the rate of infections may be higher. In general, the use of cord blood remains specialized, even among the community of transplant centers, and not all centers are able to offer this type of transplant to patients. A patient who cannot find a donor should ask his or her transplant team whether a cord blood transplant is an option.

Mini-transplant (nonablative or reduced-intensity transplant). A mini-transplant is a transplant done with mild, rather than strong, treatment prior to the infusion of donor cells. Large transplant centers will offer this approach, if the circumstances fit. The principal advantage of this transplant is fewer side effects early on in the process. For example, there may be no hair loss, fewer blood transfusions, and less time in the hospital. However, the main disadvantage is a less powerful anticancer treatment. Patients in immediate danger from an aggressive cancer are not well-served by this approach. On the other hand, for certain slow-growing cancers, this method may offer the perfect balance of cancer treatment with a lower risk of side effects.

Parent/child and haplotype mismatched stem cell transplant. This is a rare type of transplant, not performed by most centers in the United States because of a high complication rate. Yet, in extreme cases of relapsed leukemia where no matched donors can be easily found, it may be the only option. For this type of transplant, the donor is a family member who is only a 50% match, rather than the 100% match usually sought after. Parents, children, or siblings may be used. The risks are higher due to the lower percentage of tissue match. GVHD, infections, and failure of donor cells to grow happen far more often than with matched-donor transplantation.

Outpatient transplantation. Nowadays, patients are less ill during the transplant process for a variety of reasons. Mini-transplants have reduced the intensity of the treatment and the side effects. Scientific advancements in tissue typing, anti-infective care, and supportive care have reduced illness related to transplants. All of these reasons have helped reduce the need for hospitalization. It is now possible at some centers to perform an entire transplant procedure without any planned overnight stays in the hospital. This is a very good topic to discuss during the time of transplant consultation, to see if this is an option.

A transplant timeline

Every patient has questions about transplant timing, duration, and time of recovery. Some have to do with anticipated family life events (births, graduations, etc.); others relate to economics and return to work.

This section illustrates the timeline of two typical transplants, an AUTO and ALLO. The major steps or phases are described for each. One phase usually leads directly to the next, but some phases (such as stem cell collection) may be done a long time ahead. Phases are consecutive.

AUTO transplant timeline

Phase I: Bone marrow/blood stem cell collection
involves: surgical placement of a transplant catheter (a thin tube temporarily put into a large vein to make injections easier) (1 day); injections of white blood cell growth factor (5 days); bone marrow harvest surgery (1 day) OR blood collections through apheresis (the process of giving only select blood components: platelets, plasma, red cells, granulocytes, or a combination of these) (3 hours/day for 1 to 5 days)
overall duration: 1 to 2 weeks
where: outpatient

Phase II: Transplant treatment (chemotherapy/radiation therapy)

involves: chemotherapy and/or radiation therapy
overall duration: 5 to 7 days
where: outpatient or inpatient

Phase III: Stem cell transfusion/infusion (transplant day)

involves: transfusion of stem cells by intravenous (IV) injection (1 hour)
overall duration: 1 day
where: outpatient or inpatient

Phase IV: Recovery

involves: antibiotics, blood transfusions, growth factors, symptom management
overall duration: 2 weeks
where: outpatient or inpatient

ALLO transplant timeline

Phase I: (Donor) Bone marrow/blood stem cell collection
involves: injections of white blood cell growth factor (5 days); bone marrow harvest surgery (1 day) OR blood collections via apheresis (3 hours/day for 1 to 2 days)
overall duration: 1 week
where: outpatient

Phase II: (Patient) Transplant treatment (chemotherapy/radiation therapy)

involves: chemotherapy and/or radiation therapy
overall duration: 5 to 7 days
where: outpatient or inpatient

Phase III: Stem cell transfusion/infusion (transplant day)

involves: transfusion of stem cells by intravenous (IV) injection (1 hour)
overall duration: 1 day
where: outpatient or inpatient

Phase IV: Recovery

involves: medications (immunosuppressives, antibiotics, growth factors) and for symptom management, blood transfusions and fluids
overall duration: 8 to 12 weeks
where: mostly outpatient, some inpatient

The timelines for special types of transplants, such as those outlined in this article, may be similar or different to the two above. In all cases, patients are encouraged to discuss their treatment timelines with the transplant team as part of their preparation for the process.

Guest Author Series: Part III: Side Effects of Bone Marrow and Stem Cell Transplantation

This is the third in a four-part series of articles on bone marrow and stem cell transplantation. The series will prepare you to ask your transplant team meaningful questions and help you to understand the answers. This article addresses the most common side effects experienced by people having a transplant.

Infection

We live in a world surrounded by living microscopic organisms called bacteria, fungi, and viruses. During transplant treatment, the body's natural defenses against these organisms are lowered, and infection and illness may result.

A common misunderstanding is that the greatest danger from infection during early phases of a transplant comes from the outside world and from other people; this is not true. Most infections occurring during the first four weeks of a transplant are due to organisms that are already in the patient's body. Hiding places, in the lung, sinuses, skin, and the intestines, allow germs to go undetected, and then cause an infection during a period of low immunity. Fortunately, most of these germs are relatively easy to kill with modern antibiotics. The reduced immunity of the early transplant period lasts about two weeks, after which the immune system is back to near full-fighting strength, at which time most common germs are kept at bay by the patient's own immune system.

However, a small danger of infection remains for both autologous (AUTO) and allogeneic (ALLO) transplant recipients beyond this early stage. The danger is greatest if a patient is taking medications to suppress the immune system or if graft-versus-host disease (GVHD, see below) is present. During this time, there is a real danger of getting germs from other people through the air by sneezes and coughs, by handshakes, and from food. There is a further danger from inhaling dust, bacteria from bird droppings, and cigarette smoke. A major lifestyle change is required for many people, so these exposures can be avoided. Those with pets may have to avoid them, smokers will need to quit, and a person may even need to change their workplace, such as avoiding farming.

Patients should talk with their doctors about how long precautions should be taken.

Graft-versus-host disease

The unusual post-transplant illness known as GVHD occurs following an ALLO transplant only, when the donated bone marrow comes from another person. As a general rule, patients who've had an AUTO transplant do not develop this problem.

GVHD is a form of immune system-mediated attack that may occur following solid organ transplantation such as heart, kidney, or liver transplantation. The difference is that following ALLO transplantation, the "target" of the immune attack, is the patient’s entire body rather than any one particular organ. The attacking immune system is derived from the newly infused (transfused) bone marrow from the donor. The illness that may (or may not) result is called GVHD.

Patients who have small amounts of GVHD have a reduced rate of recurrent cancer. They are cured more often. On the other hand, patients with severe GVHD may become seriously ill and may die.

Doctors try to prevent severe GVHD from occurring. This is best accomplished by the choice of donor. Having a perfectly matched donor (either a brother or sister, or a DNA sequence-matched, unrelated donor) results in the lowest chance of severe GVHD. Using other types of donors causes a higher risk of GVHD. However, usually donor choice is dictated by circumstances beyond the patient's control.

In addition, doctors also prescribe medications that suppress the immune system and the GVHD reaction. These medications are taken starting on the day of the transplant and for the first few months following the transplant. All patients having an ALLO transplant will take these medications for a specified time, after which the medications will be gradually cut back and eventually stopped. During this time, small amounts of GVHD may appear and subside several times during the first year. Sometimes, it goes on longer, although it typically "burns itself out."

Chronic graft-versus-host disease

Chronic graft-versus-host disease (CGVHD), a long-lasting autoimmune illness, is a potential problem that can only affect those patients who have had an allogeneic (ALLO) transplant. It does not occur in all patients and has many degrees of severity and can be treated in different ways. Whether it occurs seems most related to whether there was GVHD in the first few months of the transplant process.
First appearing about three months after an ALLO transplant, CGVHD may be clinically "silent," producing no symptoms and requiring no specific therapy. Or, it may become a source of medical problems needing regular medical attention and treatment. Many different body parts can be affected to differing degrees.

CGVHD causes a set of very specific and distinctive symptoms.

* Tightening, stiffening and dryness of the skin
* Dryness, irritation and pain in the eyes
* Dry mouth, mouth sores, cavities
* Difficulty swallowing due to narrowing or contractures (known as strictures) in esophagus
* Weight loss (cachexia)
* Cough, difficulty breathing, lung infections

All of these symptoms can be treated, but CGHVD may persist despite therapy. Regular follow-up care with the transplant physician is strongly suggested, because treatment requires the ongoing use of immunosuppressive drugs, and the danger of infection remains high.

Other common side effects

In addition to infection and GVHD, other side effects may occur during a transplant, often related to destroying the original bone marrow or the treatments given. These include fatigue, mouth sores, sore throat, diarrhea, nausea and vomiting, low blood count, loss of hair, changes in skin pigmentation, and rash. These side effects can usually be managed through medication and do go away over time.

Almost any part of the body has the potential to be affected in some way by the transplant process. Most patients will only experience a few side effects. Furthermore, the same side effect that may be serious or troubling to one person may not occur in another person.

Doctors will monitor a patient's recovery using a variety of tests, including those for the liver, kidneys, lungs, heart, and other organs. The type, quantity, and severity of side effects will depend mainly on a patient's genetics, the amount and quantity of prior treatments (more prior treatments causes more side effects), and the type of transplant regimen received.

There is a risk of some permanent side effects. Infertility (the inability to have children) and cataracts (a clouding of the lens of the eye) are two possible permanent side effects from a bone marrow transplant. Patients are encouraged to discuss with their doctors the possible short-term and long-term effects they may experience prior to having a bone marrow transplant.