

Understanding The Stem Cell Transplantation Process



A Guide for Patients,
Caregivers, and
Loved Ones



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July 2018

This guide is an educational resource compiled by the Lymphoma Research Foundation to provide general information on stem cell transplantation. Publication of this information is not intended to replace individualized medical care or the advice of a patient's doctor. Patients are strongly encouraged to talk to their doctors for complete information on how their disease should be diagnosed, treated, and followed. Before having a stem cell transplant, patients should discuss the potential benefits and side effects of this treatment with their physician.

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INTRODUCTION

There are many factors for patients and their loved ones to consider when deciding whether or not a stem cell transplant as part of lymphoma treatment is the appropriate treatment decision for them. This booklet is designed to help patients with lymphoma and their caregivers become familiar with the stem cell transplantation process and to become active participants in their healthcare decision-making. **The booklet is divided into several sections, highlighting the pertinent issues that patients need to know before (Part 1), at the time of (Part 2), and after (Part 3) having a transplant, as well as other considerations (Part 4).** Our goal is to provide information and helpful tips that can assist patients on their journey. In addition to this resource, information is available online at the Lymphoma Research Foundation's (LRF's) website at lymphoma.org. The LRF Helpline can also provide additional information and copies of LRF educational and support publications. For Helpline assistance, call (800) 500-9976 or email helpline@lymphoma.org.

GLOSSARY

allogeneic transplant	a type of stem cell transplant in which the stem cells a patient receives come from a donor who is either a closely related family member or a well-matched unrelated person
anemia	a condition marked by low levels of red blood cells; symptoms can include feeling tired, weak, low energy, cold, short of breath, dizzy, and/or confused
antimicrobials	medications that fight infections by various kinds of microorganisms, including bacteria (antibiotics), viruses (antivirals), and fungi (antifungals)
apheresis	a process in which whole blood is removed from a vein, a certain type of cell (such as stem cells) is filtered out and collected, and the rest of the blood is returned to the vein of the patient or donor
autologous transplant	a type of stem cell transplant in which the patient receives his or her own stem cells, collected several weeks before the transplant
bone marrow	the soft, spongy tissue inside bones that contains stem cells and makes blood cells

chimerism	the state of having two different individuals' cells living in a single body; can occur after an allogeneic transplant or a reduced-intensity transplant if some of the patient's stem cells are still alive and mixed in with the donor's stem cells
collection	the process of obtaining stem cells for a transplant, either by harvesting them from bone marrow or by filtering them out of the blood through stem cell apheresis
conditioning (also called preparatory regimen)	cancer treatment (usually high-dose chemotherapy with or without radiation) given just before infusion of stem cells
engraftment	the process in which transplanted stem cells move into the recipient's bone marrow, multiply, and start making new blood cells
fatigue	weariness or tiredness
graft-versus-host disease (GVHD)	a complication of an allogeneic stem cell transplant in which the transplanted stem cells attack the healthy cells in the patient's body such as the skin, gastrointestinal tract, etc.
graft-versus-lymphoma (GVL) effect	a benefit of an allogeneic stem cell transplant in which the donor's stem cells attack and kill any remaining cancerous cells
granulocyte colony-stimulating factors (G-CSF)	medications that can stimulate stem cells to move out of the bone marrow and into the bloodstream (e.g., filgrastim, lenograstim, and pegfilgrastim)
haploidentical	half-matched; used to describe a type of allogeneic stem cell donation in which only half of the cells are matched between the donor and the recipient
harvesting	the process of collecting stem cells from bone marrow that will be used for transplant; cells are harvested from either the patient (in an autologous transplant) or the donor (in an allogeneic transplant)
hematologist-oncologist	a doctor who specializes in the treatment of blood disorders, including blood cancers such as lymphoma
hematopoietic stem cells	immature cells that can develop into any type of blood cell; most live in the bone marrow, but some are found in the bloodstream
high-dose chemotherapy	chemotherapy given in a higher dose than is used in standard chemotherapy; used to kill most or all cancer cells before infusion of stem cells

human leukocyte antigens (HLA)	proteins found on the surface of the blood cells that are used to match a patient with a donor for a stem cell transplant
infertility	the inability to have children
infusion	the process of putting (transplanting) the stem cells into the patient's bloodstream
jaundice	yellowing of the skin or eyes
neutropenia	a condition marked by low levels of neutrophils (a type of white blood cell) that puts an individual at increased risk of infection
peripheral blood stem cells	hematopoietic stem cells that move out of the bone marrow and circulate in the bloodstream
port or portacath	a type of central venous access device that is implanted under the skin in the chest; used to administer stem cells, medications, and blood products and to withdraw blood samples
reduced-intensity transplant (also called non-myeloablative or mini-allogeneic transplant)	a type of allogeneic transplant that uses lower doses of chemotherapy before the transplant; sometimes used in older patients or those whose bodies cannot tolerate high-dose chemotherapy
refractory	lymphoma that does not respond to, or is resistant to, attempted forms of treatment
relapse	the return of cancerous lymphoma cells after a period of improvement
remission	a condition in which the signs and symptoms of lymphoma decrease (partial remission) or disappear (complete remission) after treatment
thrombocytopenia	a condition marked by low levels of platelets (also called thrombocytes) that makes it more difficult for blood to clot and puts an individual at greater risk of bleeding
umbilical cord blood (also called cord blood)	blood that remains in the umbilical cord after a baby is born; contains stem cells that can be used for some allogeneic transplants if an adult donor cannot be found

Part 1 — Concepts and Considerations Before Stem Cell Transplant in Lymphoma

Chapter 1: The Basics of Stem Cell Transplantation in Lymphoma

What Are Stem Cells and What Do They Do?

Hematopoietic (blood-forming) *stem cells* are immature cells that live in the *bone marrow*, a spongy tissue inside bones. They can either divide into more blood-forming stem cells, or they can develop into mature blood cells and move into the bloodstream. These stem cells can turn into different kinds of blood cells, including white blood cells, which fight infection; red blood cells, which transport oxygen; and platelets, which help with blood clotting. All of these types of blood cells live for only a short time, so old and damaged cells are constantly being replaced by newer cells. The body needs an adequate supply of hematopoietic stem cells to create enough new red blood cells, white blood cells, and platelets to stay healthy.

Why Are Stem Cell Transplants Used?

In patients with lymphoma, chemotherapy and radiation are often used to kill the cancerous white blood cells in the body. Unfortunately, these treatments also kill some of the hematopoietic stem cells that the body needs to replace the cancerous cells with new, healthy cells. *High-dose chemotherapy*, which uses stronger than usual doses of chemotherapy medications, often kills most or all of a patient's stem cells. Although high-dose chemotherapy (with or without the addition of radiation therapy) can be very successful at killing cancer cells, it is generally not safe to use as a stand-alone treatment, because the body cannot survive without enough stem cells to make new blood.

This is where stem cell transplantation comes in. A stem cell transplant adds new stem cells back into the body after high-dose chemotherapy with or without radiation, replacing the cells that were destroyed and restoring the bone marrow's ability to make new blood cells. The ability to transplant stem cells allows doctors to use higher doses of chemotherapy than the body would normally tolerate, increasing the probability of treatment success.

Which Patients Can Benefit From a Stem Cell Transplant?

Stem cell transplantation, in combination with high-dose chemotherapy with or without radiation, is used in the treatment of several types of lymphoma. It is used for treatment of both Hodgkin lymphoma and non-Hodgkin lymphoma. High-dose chemotherapy followed by stem cell transplantation is a treatment that can lead to a long-lasting response.

For some patients with lymphoma, a stem cell transplant may be considered for:

- lack of response to a previous treatment (*refractory* disease)
- return of disease after an earlier treatment success (*relapse*)
- achieving a prolonged *remission* (disappearance of signs and symptoms of lymphoma) in patients at high risk of relapse

Stem cell transplantation is most commonly used for patients with relapsed, *aggressive* (fast-growing) lymphoma that is still sensitive to the effects of chemotherapy. *Autologous stem cell transplantation* (patient is his or her own donor) is rarely used for patients with cancers that are not responding to chemotherapy.

Because the combination of high-dose chemotherapy and stem cell transplantation places great strain on a patient's body, this approach may not be an option for every patient. This treatment usually requires a lengthy inpatient or intense outpatient stay and a long recovery process, and there are a number of side effects. Most of these side effects are temporary, such as low blood cell counts, infections, *fatigue* (tiredness), and hair loss, but a few may be permanent, such as *infertility* (inability to have children). For more information about side effects, see Chapters 4 and 5.

In deciding whether a patient is a candidate for a stem cell transplant, the patient's healthcare team considers a patient's age, medical history, current health status, type of lymphoma, and response to previous treatments. They will compare the risks associated with the lymphoma itself versus the potential risks of the transplant procedure, and they will outline these expected risks and benefits with the patient. They may also evaluate other

options such as standard chemotherapy, radiation, or clinical trials to treat the lymphoma (see Chapter 7 for more information on clinical trials). It is important for patients to discuss all potential therapeutic options and their risks and side effects with their healthcare team to determine if a stem cell transplant is the right option for them.

Transplant Centers

Stem cell transplantation is a complex procedure that involves specialized care that is only offered at certain hospitals or specialized transplant centers. If the *hematologist–oncologist* (doctor specializing in treating patients with blood disorders/cancers such as lymphoma) thinks a patient is a good candidate for a transplant, the patient will be referred to a transplant center. The transplant center staff will conduct their own evaluations to confirm whether the patient is eligible for stem cell transplantation. The transplant centers' medical assessment considers the patient's type of lymphoma, overall health, major organ function, and current disease state. This may be followed by a psychosocial assessment to evaluate the patient's support system and other elements that may affect the procedure's success. The transplant team collectively reviews the results of the evaluation and shares them with the patient, family, and referring physician.

Transplantation Stages

- **History and Physical Examination** – assessment of the patient's general level of health to determine the eligibility for the transplant
- **Collection** – the process of obtaining the stem cells to be used in the transplant
- **Conditioning** – treating the patient's lymphoma with high-dose chemotherapy with or without radiation
- **Infusion** – preparation of the stem cells followed by administration (transplant) into the patient
- **Recovery Period** – monitoring the patient for any complications or side effects while the stem cells grow and begin working

The Transplant Team and Considerations Before Transplantation

Transplant centers offer a comprehensive care approach to transplantation, and their group of specialists is referred to as the transplant team. The

team consists of doctors, social workers, dietitians, physical therapists, and a transplant coordinator. The team may also include pharmacists, respiratory therapists, dermatologists, gastroenterologists, pulmonologists, nephrologists, intensive care physicians, psychologists, and other medical/surgical subspecialists who will work together to provide the best outcome for the patient.

The transplant coordinator, who is often a registered nurse, is a key member of the transplant team. The transplant coordinator is in control of timing, tests, stem cell collection, and treatments. The coordinator can help the patient understand the required length of stay in the hospital, required items and those not allowed for the hospital stay, and visitors' regulations. The potential short-term and long-term side effects and coping strategies will also be reviewed with the patient. The transplant coordinator is also the person who can help or find the right transplant team member to answer a patient's questions, including financial assistance and insurance concerns.

Initial discussions with the transplant team should include an overview of the entire transplantation process, as well as the role of a stem cell transplant within the larger plan of lymphoma treatment. For a typical overview of the transplant journey, see pages 48–51. Sample treatment timelines for both autologous and allogeneic transplants begin on page 21.

Patients should inform family and friends about the process and their expectations of its impact on their lives. They should also anticipate and make plans for social and financial support. Finally, it is very important for the patient to choose a caregiver who will help them through the entire process. More information about caregivers can be found in Chapter 6.

For patients of reproductive age, one significant long-term side effect to address prior to treatment is the likelihood that high-dose chemotherapy may cause *infertility*. The treatment can also bring on early menopause in women.

For younger patients who may wish to have children in the future, there are options available to help preserve fertility, including possible protection of the ovaries during treatment, freezing of sperm cells or egg cells before treatment, or in vitro creation and freezing of fertilized embryos. Patients of reproductive age who are concerned about maintaining the ability to have children in the future should discuss their options with the transplant team before beginning treatment. Unfortunately, some lymphomas progress rapidly and any delay in treatment may be life-threatening, so fertility preservation prior to stem cell transplant may not be an option in such cases. This should be discussed with the healthcare team in detail prior to transplantation.

See the Resources in Chapter 9 for information to order the *Transplant Journey Checklist*, which provides an overview of steps to take to prepare for a transplant or to order the *Lymphoma Care Plan* that patients and their healthcare team can complete together to plan their care before, during, and after a transplant.

Part 1 — Concepts and Considerations Before Stem Cell Transplant in Lymphoma

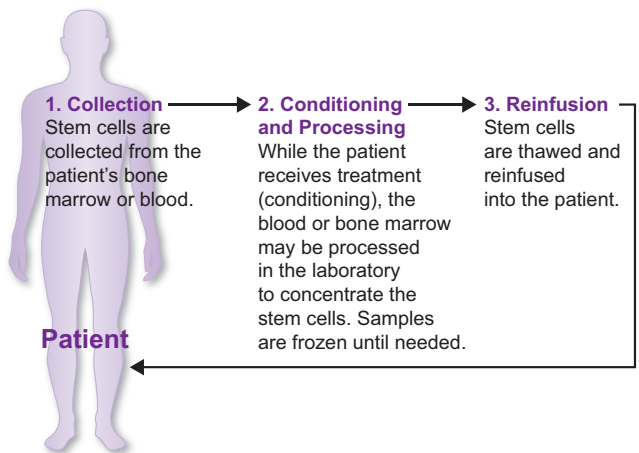
Chapter 2: Treatment Options in Stem Cell Transplantation

As discussed in Chapter 1, a stem cell transplant is used to replace stem cells that have been destroyed by *high-dose chemotherapy* with or without radiation. There are two main types of stem cell transplantation: *autologous* (the patient is his or her own donor) and *allogeneic* (the donor is another person who is genetically similar to the patient). Sources for stem cells include *bone marrow*, *peripheral blood*, and *umbilical cord blood*.

Types of Stem Cell Transplants

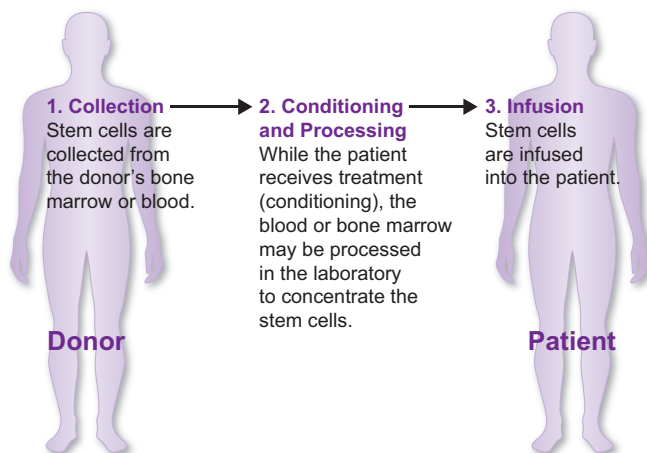
Autologous Stem Cell Transplantation

In *autologous stem cell transplantation*, the patient is his or her own donor. Stem cells are collected from the patient, processed to get them ready, and then frozen. Several days, weeks, or even years later, the patient undergoes *conditioning*, which is another term for the high-dose chemotherapy with or without radiation used to treat the lymphoma. Conditioning may also be called a *preparatory regimen*. After the conditioning treatment is given and most or all of the cancer cells have been killed, the collected stem cells are infused back into the patient to replace the normal stem cells that were destroyed by the treatment. Because a patient is receiving his or her own stem cells, an autologous stem cell transplant ensures a perfect match between the patient and the transplanted cells, which reduces the risk of complications.



Allogeneic Stem Cell Transplantation

In *allogeneic stem cell transplantation*, the stem cell donor is another person who has genetically similar blood cells to the patient. This person is often a brother or sister. For patients who do not have a compatible sibling, the donor can be a person unrelated to the patient who is identified through a registry of possible donors. The donor's stem cells are collected in the same way as a patient's cells are collected in an autologous transplant. Then, once the patient has undergone conditioning, the donor's stem cells are infused into the patient.



One of the benefits of allogeneic transplants is that after the donated cells *engraft* (take hold) in the patient (typically a few months later), they begin to function as part of the patient's immune system and may attack any remaining cancer cells. This benefit is termed *graft-versus-lymphoma (GVL) effect*, and it only occurs in allogeneic stem cell transplants.

One significant risk of allogeneic transplants, however, is that in some cases, the donor's stem cells may start to attack the patient's healthy cells. This is called *graft-versus-host disease (GVHD)*. The more closely matched the donor's cells are to the patient's cells, the less likely this is to occur. See Chapter 4 for more information about GVHD.

Reduced-intensity transplantation (also called non-myeloablative or mini-allogeneic transplantation) is a type of allogeneic transplantation. Compared

with a standard allogeneic transplant, a reduced-intensity transplant uses lower doses of chemotherapy with or without radiation to prepare the patient for the transplant. These types of transplants can be used in patients at a more advanced age or in those with other health conditions that may make it unsafe to completely destroy their bone marrow using a high-dose conditioning treatment.

After a reduced-intensity transplant, the stem cells from both the donor and the patient exist together in the patient's body for some time, but the donor's cells eventually take over the bone marrow and replace the patient's own bone marrow cells over the course of months. The new cells from the donor can then develop an immune response to the cancer cells and exhibit a GVL effect, helping to kill any remaining cancer cells.

The reduced-intensity treatment, however, may be less effective in killing the cancer cells. The conditioning regimen kills as many cancer cells as possible and suppresses the patient's immune system just enough to allow the donor's stem cells to engraft in the bone marrow. The patient's blood cell counts may not fall as low as they would with high-dose chemotherapy, and the reduced-intensity regimen puts less strain on the patient's major organs, making it a more tolerable treatment.

Choosing Which Type of Stem Cell Transplant to Use

The major difference between autologous and allogeneic transplantation is that in autologous transplantation, the main benefit is the high-dose chemotherapy with or without radiation that occurs before the transplant. In allogeneic transplantation, on the other hand, the GVL effect that happens when the donor cells attack the patient's remaining cancer cells may be just as important as—or even more important than—the high-dose conditioning treatment itself. The intensity of the GVL effect varies among patients.

In general, control of the lymphoma is better with allogeneic transplantation, but the toxicity and risk of complications is also higher, because the donor immune cells can sometimes attack the healthy cells of the patient and cause GVHD. On the other hand, an allogeneic transplant is a cleaner stem

cell source, meaning that it avoids the potential contamination of cancer cells that can occur with an autologous transplant.

The decision about which treatment to use is complex, and the factors that have to be considered are different for each individual patient. Therefore, the decision should involve a detailed discussion with the patient's doctor and a referral to a major transplant center.

Sources of Stem Cells for Transplantation

Identifying a Donor

In autologous transplants, there is no need to find another person to donate stem cells, as the patient will be donating to himself or herself. However, for allogeneic transplantation, it is important to find a donor whose blood cells are as similar to the patient's own cells as possible. If the stem cells are too different, the new immune cells from the transplant are more likely to try to destroy healthy cells in the patient's body, leading to GVHD.

Before a transplant, *human leukocyte antigen (HLA) typing* (also called tissue typing) is performed with blood tests or a swab of saliva to check the surface of the blood cells for proteins called HLA markers. The proteins on the outside of the patient's cells are compared to those of a potential donor. Well-matched HLA antigens between recipient and donor result in greater transplant success.

Close family members, particularly siblings, are more likely to have very similar patterns of proteins; however, only 25 to 35 percent of stem cell transplant patients have an HLA-matched sibling. When a patient does not have a matched sibling, the patient's HLA markers can be compared to a database of individuals who have volunteered to donate their stem cells. The likelihood that an unrelated donor can be found who is HLA-matched to a patient ranges from 65 to 99 percent. The best chance for HLA matching occurs when the donor and recipient have the same ethnic background. Although the number of people registered to be donors is increasing overall, people from certain minority ethnic groups may have a lower chance of finding a matching donor. Large volunteer donor registries make it more likely

that an HLA-matched donor not related to the patient can be found. For instance, Be The Match® (bethematch.org), operated by the National Marrow Donor Program® (NMDP), manages the largest and most diverse marrow registry in the world. Be The Match is working to increase the number of available volunteers who have had their tissue typed and are registered to donate, so that they can find a match for all patients in need of a transplant.

Over the past few years, increasing numbers of U.S. transplant centers have begun performing mismatched or *haploidentical* transplants from family members who are not a perfect match. This strategy is most often used when a child, parent, or sibling donates to a patient who is only half-matched. In this case, half or more of the HLA factors will match, while up to half of them don't match. This procedure sometimes requires processing to remove some of the non-matching white blood cells that can cause GVHD. Researchers are also developing promising new techniques to prevent GVHD by using high-dose chemotherapy to eliminate donor white blood cells. This approach may make haploidentical transplants a viable donor option for increasing numbers of patients. Haploidentical transplantation is being used more and more commonly in specialized transplant centers in the United States.

HLA matching does not have anything to do with blood type. For example, if a patient's blood type is A positive, the HLA-matched donor who is identified to provide stem cells for that patient could have a blood type of O negative. In autologous transplants, the patient's blood type does not change after the transplant, because the cells are from his or her own body. However, in allogeneic transplants, the patient's blood type will actually change to the donor's blood type once the stem cells have engrafted and begun making new red blood cells, typically a few months after the transplant.

Whether stem cells for transplantation are collected from the patient or from the donor, they can be obtained from one of three sources: bone marrow, peripheral blood, or umbilical cord blood.

Bone Marrow

Bone marrow is a wet, spongy tissue inside bones where the blood cells are generated. Bone in the pelvis, or hip bone, is a good source of stem cells, and this bone is the most common source of cells for a bone marrow transplant. Bone marrow stem cells can be used for allogeneic or, less commonly, autologous stem cell transplantation. To remove the stem cells, the patient or donor is given general anesthesia. In a process called *harvesting*, a large needle is inserted into the back of the hip bone, and some of the bone marrow is removed and frozen. To collect enough stem cells from the bone marrow for a transplant, more than 100 insertions are made into the bone, usually through a few holes in the skin. The marrow that is harvested is passed through a series of filters to remove bone or tissue fragments and to concentrate the cells. In an allogeneic transplant, if the donor's cells are harvested immediately before the transplant, then the cells are placed in a plastic bag and infused directly into the recipient's vein within a few hours. If the donor is not located near the patient, or if the transplant is autologous and the patient is donating for his or her own use, the marrow can be frozen and stored for years. When it is time for the patient to receive the stem cells, the marrow is administered directly into a vein, just like a blood transfusion.

A hospital stay of about six to 24 hours after the harvesting procedure is needed for the donor to recover from the anesthesia and the pain at the needle insertion sites. Lower back soreness may be experienced for a few days following the procedure. The donor's bone marrow regenerates soon after the procedure. The loss of red blood cells may result in temporary *anemia*, or low levels of iron in the blood, which can make donors feel tired and short of breath, especially when it is severe. Anemia can often be managed with iron supplements.

Peripheral Blood

As discussed in Chapter 1, the stem cells that form blood cells normally live in the bone marrow. However, a small number of these stem cells move into the bloodstream and circulate freely in the blood; these are called peripheral blood stem cells. In many cases, doctors can now use the process called *apheresis* to filter these peripheral stem cells out of the blood, eliminating the need for the surgical removal of bone marrow. In this procedure, blood is removed from a vein, the stem cells are collected, and the rest of the blood is returned to the patient or donor.

The only challenge with this approach is that normally there are very few stem cells circulating in the blood. However, drugs called *granulocyte colony-stimulating factors* (G-CSFs)—such as filgrastim, lenograstim, and pegfilgrastim—can be administered a few days before the apheresis procedure to stimulate more stem cells to move out of the bone marrow and into the bloodstream. Using G-CSFs before the apheresis procedure greatly increases the chances of collecting enough stem cells for the transplant. Some transplant centers also use chemotherapy or other drugs before the administration of G-CSFs to further help release stem cells from the bone marrow. Even so, the apheresis procedure may need to be repeated several times until enough stem cells are collected. The collected stem cells are treated to remove contaminants and then frozen to keep them alive until the patient is ready to receive them.

Collecting stem cells from the blood is easier on the patient or donor than harvesting bone marrow from a bone, because the procedure involves less pain, no anesthesia, and no hospital stay. The entire apheresis procedure also takes just four to six hours, with no recovery time needed. Another benefit of using peripheral blood stem cells is that after they are transplanted, they engraft and begin working more quickly than cells taken from bone marrow.

However, one major disadvantage of using stem cells collected from the blood is that, in allogeneic transplants, this approach is associated with a greater risk of GVHD. Collecting peripheral stem cells from the blood is now the most commonly used method of obtaining cells for autologous stem cell transplants. But in certain situations, especially in allogeneic transplants, stem cells harvested from the bone marrow may be preferred due to the possible lower risk of GVHD.

Umbilical Cord Blood

After the birth of a newborn, some of the baby's blood is left behind in the placenta and umbilical cord; this is known as *umbilical cord blood* or just *cord blood*. Cord blood contains many stem cells, so this blood can be collected and frozen until needed for later use in a stem cell transplant. Stem cell transplantations with cord blood are not as common as those from other sources, for two reasons: 1) there are a smaller number of stem cells present in cord blood, and 2) the cells can take longer to engraft and start working than stem cells from bone marrow or peripheral blood. However, one advantage of this source is that umbilical cord blood stem cells do not need to match entirely with a patient to be acceptable for allogeneic stem cell transplantation. For this reason, umbilical cord blood stem cell transplants may be considered when a well-matched donor cannot be found among family members or volunteers who have signed up to donate.

Questions to Ask Before Deciding to Undergo a Stem Cell Transplant

- What type of transplant is most appropriate for me (autologous or allogeneic) and why?
- If an allogeneic transplant is being considered, how will a donor be found?
- What are the risks associated with this procedure?
- What are the benefits associated with this procedure?
- What complications may arise as a result of having a transplant?
- What are the short-term and long-term side effects I might experience after my transplant?
- What can be done to lessen the side effects?
- Will getting a transplant make me ineligible for other lymphoma treatments?
- How do I identify a hospital or transplant center for the transplant?
- How long will I need to be in the hospital?
- How long will I need someone to care for me after the transplant?
- Will my insurance cover this procedure?
- How sick will this treatment make me?
- How will we know if the treatment is working?
- How and for how long will the treatment affect my normal activities (e.g., work, school, childcare, driving, sexual activity, and exercise)?
- What is my chance of making a full recovery?
- Is the transplant and related treatment part of a clinical trial? (see Chapter 7 for additional details on clinical trials)

Part 2 — The Procedure of Stem Cell Transplantation

Chapter 3: The Stem Cell Transplantation Process

Before Stem Cell Collection

Prior to collecting the stem cells for the transplant, tests will be administered to either the patient (in *autologous transplants*) or the donor (in *allogeneic transplants*) to evaluate their overall health. These may include a complete blood count (CBC); liver and kidney function tests; tests for viral hepatitis and human immunodeficiency virus (HIV); a restaging test (*bone marrow biopsy*, computed tomography [CT], or positron emission tomography [PET]/CT scan) to measure the extent of the lymphoma and response to previous therapy; a bone marrow biopsy (in *autologous transplants*); and lung, heart, and kidney function tests. Stem cell *collection* usually occurs a few weeks prior to *high-dose chemotherapy* with or without radiation.

The Transplantation Process

Once donor stem cells have been obtained, patients undergoing a stem cell transplant will experience a similar procedure whether they are undergoing an autologous transplant or an allogeneic transplant.

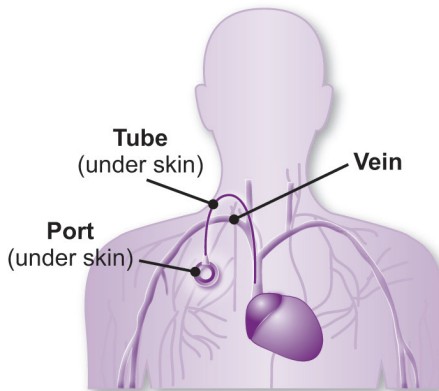
Conditioning

Stem cell transplants are preceded by a high-dose chemotherapy treatment with or without radiation to kill the cancerous cells. The goal of the higher dose of chemotherapy is to kill as many cancer cells as possible before the transplant takes place. These chemotherapeutic treatments typically require seven to 14 days. This process is called *conditioning*, or preparatory therapy. The treatment destroys the patient's stem cells along with the cancerous cells. These conditioning treatments can be relatively toxic.

Most patients will receive high-dose chemotherapy without radiation for conditioning, but the combination of total body radiation with chemotherapy may be used. In certain circumstances, the radiation may be “fractionated,” meaning that the radiation dose is given over several days to decrease the toxicity. Monoclonal antibodies such as rituximab (Rituxan) may also be used.

Central Line or Port Placement

Prior to the transplant, a surgeon or a radiologist will implant some type of central venous access device into the patient's chest near the neck. The device used may either be a long tube called a *central venous catheter* (commonly known as a *central line*) or it may be a round device called a *port* (sometimes called a *portacath*) that is implanted just beneath the skin. The central line or port is inserted surgically after giving local anesthesia to numb the insertion area, and it usually remains in place for the duration of treatment and for several weeks or even months following the transplant. On a central line, the tube coming out of the chest has several openings that can be used to give or take fluids into or out of the body. With a port, fluids can be exchanged by inserting a needle through the skin and into the center of the port, called the septum. The central line or port will be used to infuse the transplanted stem cells, as well as to administer other medications and blood products into the body. It can also be used to draw blood samples for laboratory tests. The figure below shows where the central line or port is typically inserted.



Stem Cell Infusion

Usually a day or two after conditioning treatment is finished, the patient is given the stored stem cells. Donor stem cells are delivered through the central line or port into the patient's veins. Infusing the stem cells usually takes between one and four hours and is typically not painful; however, some patients have reported discomfort or pain, as each patient's pain tolerance is different. Patients are closely monitored throughout the *infusion* process, as they may experience fever, chills, hives, shortness of breath, or a drop in blood pressure during the procedure. To stimulate the growth of infection-fighting white blood cells, *granulocyte colony-stimulating factor* (G-CSF) may also be given at this time. Additionally, blood cell replacement, nutritional support, and drugs to prevent *graft-versus-host disease* (GVHD) may be used.

Recovery

Following a stem cell transplant, inpatient or intense outpatient stays can vary from 12 to 30 days, depending on how quickly the new stem cells *engraft*, or move into the patient's bone marrow and begin making new blood cells. During this engraftment period, the patient's white blood cell levels are very low, making the risk of infection high. These infections can be severe and even life-threatening. To prevent this, the patient receives prophylactic *antimicrobials* (drugs that prevent infections). Infection risk remains high until the stem cells have been able to regenerate the white blood cells, usually in about two to four weeks. Engraftment is faster after transplantation of *peripheral blood stem cells* than after a bone marrow stem cell transplant.

While each patient's transplant is different, the two tables on the following pages show a sample timeline for someone having an autologous stem cell transplant or an allogeneic stem cell transplant. The days leading up to the transplant are given minus numbers, such as Day -3 or Day -2. The day of the transplant is Day 0, and the days that follow are Day +1, Day +2, etc.

Sample Timeline of an Autologous Transplant

	Description	Approximate Time Period
Stem Cell Mobilization	<ul style="list-style-type: none">■ If peripheral blood stem cells will be used, the patient receives daily injections of a <i>G-CSF</i> for five days prior to collection to stimulate the stem cells to move into the bloodstream.	5 Days Prior to Collection
Stem Cell Collection Stem cell apheresis or bone marrow harvesting	<ul style="list-style-type: none">■ For peripheral cell donations, blood is removed from the patient's arm, passed through a machine to collect the stem cells, and then returned into the patient's other arm. This <i>apheresis</i> procedure may need to be repeated one or more times on subsequent days if not enough cells are collected the first time.■ For bone marrow donations, anesthesia is given, and then needles are inserted into the patient's hip bone to withdraw liquid bone marrow. All necessary bone marrow is collected in a single procedure.■ Collected cells are frozen until infusion.	Day -21 to Day -14 A few weeks before high-dose chemotherapy
Conditioning High-dose chemotherapy with or without radiation	<ul style="list-style-type: none">■ High-dose chemotherapy and possibly radiation are given to kill most or all of the remaining cancer cells in the blood.	Day -10 to Day 0 Start date varies depending on particular conditioning treatment
Transplant Infusion of stem cells	<ul style="list-style-type: none">■ Frozen stem cells are thawed prior to transplant.■ Infusion through the central line or port usually takes one to four hours.	Day 0

Sample Timeline of an Autologous Transplant (*continued*)

	Description	Approximate Time Period
Early Recovery Feeling the effects of the chemotherapy	<ul style="list-style-type: none"> White blood cell, red blood cell, and platelet counts are low. Patient may experience diarrhea and/or mouth sores. The risk of developing an infection is high. 	Day 0 to +7
Pre-Engraftment The turning point	<ul style="list-style-type: none"> These days may be the most difficult, as blood counts are still low and the stem cells have not taken hold yet. Rarely, patients develop a fever, rash, and fluid in the lungs, known as "engraftment syndrome." 	Day +7 to Day +10
Engraftment Blood counts return to normal	<ul style="list-style-type: none"> The patient starts feeling better, and the risk of infection decreases. 	Day +12 to +30
Recovery Immune system is still not working properly	<ul style="list-style-type: none"> The patient is sent home to recover with a caregiver. The patient may remain on medications to prevent infections. 	Day +30 to 6 months Continued monitoring by transplant team
Late Recovery Patient returns to normal activities	<ul style="list-style-type: none"> The patient's immune system is almost fully recovered. There is still a risk of late complications, such as organ dysfunction or recurrence of the original disease. Patient receives vaccinations they had during childhood. 	6 months and onward

Sample Timeline of an Allogeneic Transplant

	Description	Approximate Time Period
Donor Identification	<ul style="list-style-type: none"> A potential donor who is <i>HLA</i>-matched to the patient is identified either from within the patient's family or from a database of individuals registered to donate stem cells. Cord blood stem cells may also be used. 	Varies
Donor Screening	<ul style="list-style-type: none"> The potential donor undergoes a physical exam and blood tests to confirm that donation will be safe and effective for both patient and donor. 	Varies
Donor Stem Cell Mobilization	<ul style="list-style-type: none"> If donating peripheral blood stem cells, the donor receives five days of daily injections of a <i>G-CSF</i> to stimulate stem cells to move into the bloodstream. 	5 Days Prior to Collection
Donor Collection Stem cell apheresis or bone marrow harvesting	<ul style="list-style-type: none"> For peripheral cell donations, blood is removed from the donor's arm, passed through a machine to collect the stem cells, and then returned into the donor's other arm. This <i>apheresis</i> procedure may need to be repeated one or more times on subsequent days if not enough cells are collected the first time. For bone marrow donations, anesthesia is given, and then needles are inserted into the donor's hip bone to withdraw liquid bone marrow. All necessary bone marrow is collected in a single procedure. Collected cells are frozen until infusion. 	<p>Varies</p> <p>Can occur while patient is receiving high-dose chemotherapy, but is usually done days, weeks, or months beforehand</p>
Donor Recovery	<ul style="list-style-type: none"> Most donors are able to return to work, school, or other activities within a week of donation. 	1 to 7 Days after Donation

Sample Timeline of an Allogeneic Transplant (*continued*)

	Description	Approximate Time Period
Patient Conditioning High-dose chemotherapy with or without radiation	<ul style="list-style-type: none"> ■ Patient receives high-dose chemotherapy and possibly radiation to kill most or all of the remaining cancer cells in the blood. 	Day -10 to Day 0 Start date varies depending on particular conditioning treatment
Patient Transplant Infusion of stem cells	<ul style="list-style-type: none"> ■ Frozen stem cells are thawed prior to transplant. ■ Infusion of stem cells through the patient's central line or port usually takes one to four hours. 	Day 0
Early Recovery Feeling the effects of the chemotherapy	<ul style="list-style-type: none"> ■ White blood cell, red blood cell, and platelet counts are low. ■ Patient may experience diarrhea and/or mouth sores. ■ The risk of developing an infection is high. 	Day 0 to +7
Pre-Engraftment The turning point	<ul style="list-style-type: none"> ■ These days may be the most difficult, as blood counts are still low and the stem cells have not taken hold yet. 	Day +7 to Day +10
Engraftment Blood counts return to normal	<ul style="list-style-type: none"> ■ The patient starts feeling better, and the risk of infection decreases. ■ Acute <i>GVHD</i> may develop at this point. Typical symptoms are skin rash, diarrhea, and worsening of liver function. ■ Around Day 30, a <i>chimerism</i> study may be performed to make sure that the remaining bone marrow is all from the donor and to further confirm engraftment. 	Day +12 to +30
Recovery Immune system is still not working properly	<ul style="list-style-type: none"> ■ The patient is usually sent home to recover with a caregiver around Day 90. ■ The patient may remain on medications to prevent infections after going home. 	Day +30 to 6 months Continued monitoring by transplant team

Sample Timeline of an Allogeneic Transplant *(continued)*

	Description	Approximate Time Period
Late Recovery Patient returns to normal activities	<ul style="list-style-type: none">■ The patient's immune system is almost fully recovered.■ There is still a risk of late complications, such as organ dysfunction, recurrence of the original disease, and chronic GVHD.	6 months and onward Patient may receive vaccinations they had during childhood

Sharing Knowledge and Experience

Though this process may be new for you, several transplant survivors from the Lymphoma Patient, Caregiver, and Advocacy Advisors have shared the following tips and questions that they thought were helpful to know when going through the transplantation process.

PATIENT TIP

- You may want to ask for a second opinion.
- Several weeks prior to the transplant, you should start completing paperwork such as Family and Medical Leave Act (FMLA) forms, a legal Will, a Living Will, Advanced Directive, Durable Power of Attorney, and a Healthcare Power of Attorney.
- Upon deciding to have the transplant, it is important to get the paperwork started and set up a payment plan or make other financial arrangements with the hospital.
- Find out which member of your transplant team to talk to about working with your insurance company to get coverage for the transplant. In addition, if you will be an outpatient, ask who can help you with lodging arrangements.
- Ask for further explanation from your doctor or healthcare team if you don't understand something.
- Have someone accompany you to all appointments to take notes and to be a second set of ears to help you remember things.
- Assign someone the responsibility of reviewing and paying your bills while you are recovering, and provide them with your accounts, user names, and passwords.

- When preparing for the stem cell transplant, if permitted, consider bringing the following items to the hospital or transplant center:
 - Things to occupy your time during your stay such as books, magazines, music, electronic devices, or knitting. You may find it difficult to concentrate at some times during your stay, so lighter entertainment and reading material may be a good choice.
 - Multiple outfits to wear and socks or slippers.
 - Button-down or V-neck shirts to allow easy access to the central line or port.
 - Your own bedding and towels.
 - Your own toilet paper (it may be comforting to have your favorite brand with you in case you experience diarrhea as a result of the high-dose chemotherapy).
 - Travel-sized toiletries like shampoo, soap, and razors, if the hospital or transplant center does not provide such items.
- The process of receiving the stem cells typically does not hurt, although each person's experience will be different.
- Caregivers should know that their presence in your hospital room after transplantation is important. They don't have to say anything, but just being there is helpful, as you will be going through a lot that is "unexplainable" (see Chapter 6 for more about the caregiver's role).
- Be sure you completely understand and faithfully follow the discharge instructions provided by the hospital/transplant center when you are sent home.
- During the first weeks or months back home, have someone available to clean your house, go to the store for you, and prepare your meals. Not only will you probably be too weak to do these things for yourself, but you also don't want to risk infection by going out in crowded places, handling raw foods, or cleaning contaminated surfaces.
- Try to eat healthy and nutritious foods to help your strength recover.

Questions to Ask Your Medical Team About the Stem Cell Transplantation Process

- For autologous transplants:
 - How will you manage any pain I experience when my stem cells are collected?
 - How will you manage any pain I experience when the stem cells are reinfused into my body?
- For allogeneic transplants:
 - Can donors have their cells collected at a facility near their homes, or do they need to come to my facility for collection?
 - Is it painful for donors to have their cells collected?
 - How long should the donor plan to be away from home/work for the cell collection process?
- Is having the central line or port inserted painful, and will it be uncomfortable once it's in?
- How long will the central line or port remain in my chest?
- What will my insurance cover, and what will I be responsible for paying?
- If there are costs that I need to pay, can I set up a payment plan with the hospital/transplant center?
- Will the FMLA cover the time I will be in the hospital for my transplant in addition to my recovery time?

Questions to Ask Your Medical Team About the Stem Cell Transplantation Process *(continued)*

- What is needed to apply for short-term disability through my employer?
- Once I come home from the hospital after my transplant, what will I require assistance with, and what can I do for myself?
- What types of tests and follow-up care will I need to have after my stem cell transplant?
- How long will it be until I can be near my pet(s) and other people again?
- Will I need to wear a mask when I go out in public or to my doctor's office?
- When will I be able to do my normal activities and go about my normal routine? When will I start to feel like my old self again?

Part 3 — After The Transplant

Chapter 4: Engraftment and Post-Engraftment Periods

During the first month after the transplant, the transplanted cells will start to move into the *bone marrow*, grow and multiply, and produce healthy blood cells that appear in the blood. This process is referred to as *engraftment*. Frequent blood tests may be done to monitor this process. Complete recovery of immune function may take up to several months for *autologous transplant* recipients (a patient is his or her own donor) and one to two years for patients receiving *allogeneic transplants* (the stem cell donor is another person who is genetically similar to the patient). The first sign of recovery is typically a large increase in the white blood cell count. Blood and platelet transfusions are continued as needed. During this period of engraftment, *antimicrobials* (antibiotics and other drugs that kill microorganisms) are continued as needed to prevent infection.

It is strongly suggested that patients discuss all of the potential complications and short-term and long-term side effects of stem cell transplantation with their doctor and healthcare team thoroughly and in detail, so that the patient is informed in their decision making.

Short-Term Side Effects

Because the chemotherapy doses used before a stem cell transplant are usually higher than standard chemotherapy doses, the typical side effects from the chemotherapy—such as nausea, vomiting, *fatigue* (being tired), mouth sores, and loss of appetite—may also be more intense, especially right after transplantation and for a few weeks thereafter. The key to the management of the potential side effects is prevention and early treatment.

Mild kidney issues are common after transplants and will be monitored closely and treated aggressively. To manage fatigue, patients will need to use strategies to minimize their exertion and optimize rest. Issues can also arise related to a patient's limited mobility, such as diminished muscle strength, muscle loss, loss of balance and coordination, a diminished sense of well-being, and risk of chest infections.

It is important to remember that not all patients experience the same side effects or intensity of side effects. Patients and their caregivers should keep a journal of their side effects and discuss them with their healthcare team.

Complications

After treatment with high-dose chemotherapy with or without radiation, all three types of blood counts become very low, which affects the body in several ways.

- A low white blood cell count (*neutropenia*) increases a patient's risk of infection.
- A low red blood cell count (*anemia*) can make a patient feel tired and have low energy.
- A low platelet count (*thrombocytopenia*) reduces the ability of the blood to clot, potentially increasing the risk of bleeding.

All of these are common complications after a stem cell transplant. While waiting for the patient's body to begin making new blood cells, these complications are managed with red blood cell and platelet transfusions and *antimicrobials* to prevent or treat infections.

Veno-Occlusive Disease (VOD)

High-dose chemotherapy also brings the risk of veno-occlusive disease, a complication causing blood vessels that carry blood through the liver to become blocked. Symptoms of VOD include *jaundice* (yellowing of the skin and eyes), fluid retention, and a painfully enlarged liver. While this complication occurs in fewer than two percent of transplant recipients, severe cases can be life-threatening. Because traditional anticlotting medications can cause severe bleeding, doctors had few options for treating VOD until 2016, when the U.S. Food and Drug Administration (FDA) approved defibrotide sodium (Defitelio) for treating confirmed cases of VOD. Ongoing research is now exploring the preventive use of defibrotide to reduce the chances that stem cell transplant recipients will develop VOD.

Graft-Versus-Host Disease (GVHD)

For patients who undergo allogeneic stem cell transplantation, one of the most significant risks is a complication known as *graft-versus-host disease*. This is a common condition that occurs when the donor's stem cells attack the patient's healthy cells, and it can range from a minor problem to a very serious one. When it develops shortly after engraftment of the donated cells, this complication is known as acute GVHD (aGVHD), whereas when it develops or continues months or years after the transplant, it is called chronic GVHD (cGVHD). The two forms were once considered the same disease process occurring at different times, but now some doctors think of cGVHD as a condition more like an autoimmune disease such as lupus or rheumatoid arthritis.

To prevent GVHD, patients undergoing *allogeneic stem cell transplantation* are given corticosteroids such as prednisone to suppress the immune cells and keep them from attacking the patient's healthy cells. Nevertheless, as many as 30 to 70 percent of patients receiving an allogeneic transplant may develop aGVHD, and 20 to 50 percent may experience cGVHD. An individual patient may experience either, both, or neither forms of this condition, but those who develop aGVHD are more likely to subsequently have cGVHD. Both forms can affect many different areas of the body, including the skin, liver, eyes, mouth, and digestive tract.

Treatment with traditional anticlotting medications is not a good option because those drugs can cause severe bleeding. Historically, high doses of corticosteroids and other immunosuppressants have been the primary approach for treating GVHD as well as preventing it. However, long-term immunosuppressant use has many serious potential side effects and risks, including making the body very susceptible to life-threatening infections. In addition, as many as 50 percent of cases of cGVHD do not resolve with corticosteroids alone. For these patients, the only FDA-approved medication for use as a secondline treatment for cGVHD is ibrutinib (Imbruvica), a kinase inhibitor originally approved as a lymphoma treatment. Researchers are now trying to determine whether combining ibrutinib with corticosteroids for frontline treatment of cGVHD is more effective than corticosteroids alone.

As stem cell transplantation has become increasingly common, there has been a tremendous surge in research into new treatments for GVHD. Dozens of clinical trials are currently underway testing numerous promising medications to prevent or treat aGVHD and cGVHD. Like ibrutinib, many of the drugs being studied are targeted therapies already used in the treatment of lymphoma and other blood cancers. For example, the monoclonal antibodies rituximab (Rituxan), ofatumumab (Arzerra), and obinutuzumab (Gazyva)—which are presently approved for the treatment of certain subtypes of B-cell non-Hodgkin lymphoma (NHL)—are now also being studied for preventing and treating GVHD. Other drugs being researched for this purpose include kinase inhibitors such as ruxolitinib (Jakafi), baricitinib (Olumiant), and fostamatinib (Tavalisse), and proteasome inhibitors such as bortezomib (Velcade), carfilzomib (Kyprolis), and ixazomib (Ninlaro).

The Recovery Process

The recovery time needed before returning to work or school is different for each person, but patients receiving an *autologous transplant* may recover sooner than those who undergo an *allogeneic transplant*.

Hair loss is a result of the high-dose chemotherapy. As the hair begins to grow back during the recovery period, it is important to keep the scalp protected from sun, heat, and cold. Patients should be aware that when their hair starts to grow again, it may be a different texture and slightly different in color than it was before the transplant. Often these differences go away in time and hair returns to normal.

Many patients experience a loss of appetite and taste. As a patient's appetite returns, it is better to eat smaller meals more often at first. It is recommended to continue good oral hygiene, but to reduce infection risk, patients should not go to a dentist without permission from the doctor. Patients should alert the doctor in the event of bleeding, ulcers, or cold sores in the mouth. Increased water intake can combat dry mouth.

Some patients may notice that they bruise more easily during this period, and shedding skin is also common. For skin care, baby oil or another non-irritating oil for dry skin is recommended, as is avoiding strong sunlight for approximately six months, then using sunscreen.

Fatigue is common, but it will eventually pass for the majority of people. It is recommended to exercise gently, rest often, and keep a diary to help measure progress. Fatigue may decrease sexual activity and desire at first, but this will likely return to normal over time.

Feeling depressed is also common during this time. Patients should realize that the feeling of depression is normal and many transplant patients experience this. Patients naturally face changes and a certain loss of control after a stem cell transplant. If patients feel that the challenges are too big to conquer, they might feel helpless or hopeless. Some helpful strategies to cope with these struggles are obtaining more information, asking about how other people have coped, and turning to others for support. If these feelings continue, however, the patient should seek help from a counselor or therapist. It is important for the caregiver to take notice if depression lasts for an extended period of time and to mention this to the healthcare team.

Follow-up

Most patients will require a period of three months to one year after transplant to recover. After returning home post-engraftment, patients can do things to continue to prevent infections, such as taking regular showers, washing hands often, keeping their teeth and gums clean, and avoiding contact with sick people. If antibiotics have been prescribed, they should be taken as directed. It will be helpful for patients to take their temperature when feeling hot, chilled or unwell, monitor for blood in urine or stool, and look out for new bruising or persistent nosebleeds. If the central line is still in place, it must be regularly flushed with saline, and the insertion site needs to be cleaned and redressed often. The line will be removed when it is no longer needed. Ports do not require any maintenance care.

Patients with lymphoma should have regular visits with a doctor who is familiar with their medical history and the treatments they have received. Medical tests (such as blood tests, positron emission tomography [PET] scans, and computed tomography [CT] scans) may be required at various times during *remission* (signs of the disease disappear after treatment) to see if the patient needs additional treatment. Some treatments can cause long-term side effects or late side effects. These side effects may depend on the patient's age, gender, and overall health at the time of treatment, as well as on the treatment type, duration, and frequency. A doctor will check for these side effects during follow-up care. Patients and their caregivers are strongly encouraged to keep copies of all medical records and test results as well as information on the types, amounts, and duration of all treatments received using a *Lymphoma Care Plan* document (shown in Chapter 9) or accessing a mobile application such as the Lymphoma Research Foundation's (LRF's) Mobile App (lymphoma.org/mobileapp). These documents will be important for keeping track of the effects of treatment, potential disease *relapse* (disease returns after treatment), or disease that is *refractory* (disease does not respond to treatment).

To learn more about any of these resources, visit LRF's website at lymphoma.org/publication, or contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org.

Post-Transplant Revaccinations

Antibodies to vaccine-preventable diseases decline one to four years after allogeneic or autologous stem cell transplantation, putting transplant recipients at risk of acquiring these infections. Therefore, beginning at six to 12 months after transplant (or as directed by the healthcare team), patients who received an *autologous transplant* should start to be revaccinated for the common childhood preventable infectious diseases. Patients who received an *allogeneic transplant* should wait until their immunosuppressive medications have been discontinued before beginning the revaccination process. After that, they should follow their transplant physician's recommended schedule.

Because every patient is different, physicians will provide guidance on exactly which vaccines a patient should receive and the optimal time to receive them. Vaccines that may be recommended include diphtheria, tetanus, and pertussis (DTaP); measles, mumps, and rubella (MMR); polio; and hepatitis B. Vaccinations against pneumococcus, meningococcus, and *Haemophilus influenzae* type b (Hib) may also be indicated, and most patients will be advised to begin receiving the yearly influenza (flu) vaccine as well. Physicians will provide guidance on a case-by-case basis about whether an individual patient is healthy enough to receive the varicella vaccine against chickenpox.

Patients can use the *Lymphoma Care Plan* (ordering instructions in Chapter 9) to discuss their physician's suggestions for recommended vaccines and the timing of those vaccinations after transplantation.

Part 3 — After The Transplant

Chapter 5: Transplant Survivorship

Many transplant recipients experience ongoing medical symptoms, even two years after transplant. However, at 10 years post-transplant, survivors are nearly as healthy as adults who have never had a transplant.

Long-Term Side Effects

Patients receiving a stem cell transplant may experience significant long-term side effects, including:

- *cataracts* (clouding of the lens of the eye, which causes vision loss)
- early menopause
- organ damage to the liver, kidneys, lungs, heart, and/or bones and joints
- *relapse* (the disease returns)
- secondary or new cancers
- *infertility* (the inability to have children; for information about ways to preserve fertility, see Chapter 1 or refer to the Lymphoma Research Foundation's (LRF's) web page on "Fertility" available at lymphoma.org/fertility)

Survivors are also more likely to experience musculoskeletal complaints (stiffness and cramping), sexual problems, and a higher use of antidepressants and anti-anxiety medications.

While some survivors view their health as worse than an average person their age, many also report positive changes. These can include greater personal growth, an enhanced appreciation for life, greater appreciation of friends and family, different priorities, and a shift in life expectations.

Other issues impacting survivors can include pain management, quality of life, and caregiver burnout. It is important for patients to discuss any problem they experience with their healthcare team, as these issues are very common. Additional resources on these topics are available by visiting LRF's

website at lymphoma.org, or contacting the LRF Helpline at (800) 500-9976.

Relapsed/Refractory Disease

For some transplant recipients, the lymphoma relapses or becomes *refractory* (does not respond to treatment). In this case, other treatment options may be available. In some cases, a second autologous or *allogeneic stem cell transplant* may be an option. Medications may also be used in this situation. Brentuximab vedotin (Adcetris) is approved by the U.S. Food and Drug Administration (FDA) for the treatment of classical Hodgkin lymphoma (cHL) after failure of autologous stem cell transplantation. In addition, it can be used as consolidation or maintenance therapy in patients with cHL who are at high risk of relapse or progression after a stem cell transplant. Another medication called nivolumab (Opdivo) was approved in 2016 for the treatment of patients with cHL that has relapsed or progressed after autologous stem cell transplantation and post-transplantation brentuximab vedotin.

It is critical to remember that today's scientific research is continuously evolving. Treatment options may change as new treatments are discovered and current treatments are improved. Therefore, it is important that patients check with their physician or with the Lymphoma Research Foundation (LRF) for any treatment updates that may have recently emerged.

Support

A lymphoma diagnosis and undergoing transplantation often trigger a range of feelings and concerns. In addition, cancer treatment can cause physical discomfort. One-to-one peer support programs, such as LRF's *Lymphoma Support Network*, connect patients and caregivers with volunteers who have experience with lymphoma or chronic lymphocytic leukemia, similar treatments, or challenges, for mutual emotional support and encouragement. Patients and loved ones may find this useful whether the patient is newly diagnosed, in treatment, or in remission. Contact LRF's Helpline by calling (800) 500-9976 or emailing helpline@lymphoma.org, for more information.

Sharing Knowledge

Below are a few tips about the recovery process shared by other transplant survivors.

PATIENT TIP

- Once the transplant takes place, you should limit visitors other than your caregiver to your hospital room or home to reduce infection risk.
- After discharge from the hospital, you may need to wear a mask when going out in public, including going to doctors' appointments, to reduce infection risk.
- Do not be afraid to ask for help.
- Listen to your body. If you need to rest, you should; if you feel you can move around and walk, you should.
- You will continue to have many follow-up blood tests after returning home from having the transplant. This is one reason why your doctors may decide to leave the central line or port in place after hospital discharge.
- Consider having an oncology massage once you are cleared by your healthcare team to receive one. This is a special type of massage that uses modified massage techniques designed to be safe for patients at any stage of cancer treatment. Be sure the massage therapist you choose is well-trained in oncology massage and designated as a preferred practitioner by the Society for Oncology Massage (s4om.org). An oncology massage can help you relax and sometimes helps to manage any pain you may experience.

Part 4 — Other Considerations and Resources

Chapter 6: The Caregiver's Role

Patients who undergo a stem cell transplant will need to select one or more primary caregivers to help them through the entire transplant process, as the process can be extremely challenging without the support of others. The caregiver role is an active one and includes many important aspects of recovery and care. Three important areas of support and advocacy undertaken by the caregiver are:

- **medical** – gathering information as an active part of the healthcare team, talking to doctors, and helping care for the patient
- **financial** – talking to the insurance company and managing transplant costs and daily household finances
- **emotional and social** – being there to listen to and support the patient, and keeping other family and friends informed and involved

Most transplant centers require a caregiver to be identified, and many transplant centers offer classes to teach caregivers about their important role in assisting the patient. Sometimes a caregiver is one person, but often several people share the responsibilities.

Before the transplant, the caregiver will be a partner with the healthcare team, helping the patient follow the treatment plan and make informed medical decisions. It may be useful for the caregiver to:

- request information and resources from the patient's doctors about stem cell transplantation and other treatment options
- ask the healthcare team to explain what test results mean and how medicines and other treatments will help
- organize information about the patient's treatment in a notebook to help remember the details
- be present when the doctors make their daily rounds to ask questions and hear about any changes to the patient's care during the hospital stay

The caregiver can also help the patient with financial concerns. The first project is planning how to cover the costs of transplant, such as determining what costs will be covered by insurance and what costs will need to be covered by the patient. If major costs will not be paid by the patient's insurance company, the caregiver can help with finding sources of financial assistance and possibly with fundraising. Staff members at the transplant center can assist the patient and caregiver with these tasks. The caregiver and the patient both may need to make plans for taking time away from work, so they may want to look into taking an extended leave under the Family and Medical Leave Act (FMLA) that allows them to keep their health insurance and other benefits. Finally, during the transplant and in the first months of the recovery process, caregivers need to make sure all household bills are paid on time.

Before the transplant, the patient may experience many emotions, including hope, fear, excitement, and anxiety. The caregiver can be present to listen, to talk, or simply to be by the patient's side. If patients feel well enough in the days or weeks before the transplant, it is important for them to spend time doing things they like to do and having fun with friends and family.

After the transplant, the caregiver's role will change. In the transplant center, nurses may have provided the majority of care for the patient, but once the patient returns home, much of that care will transition to the caregiver. The patient's healthcare team will teach the caregiver the necessary skills to care for the patient, and the caregiver should ask for instructions on what to do in case of emergencies or whom to contact with specific questions.

The patient may need to make several clinic visits during the first month at home. Caregivers will need to provide or arrange transportation, accompany the patient to these visits, and discuss with the healthcare team how the patient is doing.

The caregiver's responsibilities at this point include:

- being with the patient all the time, in case a sudden complication develops and help is needed

- watching the patient for new symptoms or problems and reporting them to the doctor or healthcare team right away
- making sure the patient takes the right medications and dosages at the right times
- cleaning and changing dressings on the patient's central line, if applicable
- preparing meals and encouraging the patient to eat
- taking the patient to appointments at the transplant center or clinic, sometimes on short notice
- helping to protect the patient from infections by preparing the home for recovery, making healthy choices, and minimizing visitors
- taking charge of household cleaning
- taking care of pets

For some complications, such as an infection or *graft-versus-host disease* (GVHD), the patient needs to be treated quickly. The caregiver should know what symptoms to look for and have a list of phone numbers to call during office hours, at night, and on the weekends.

The patient and caregiver may need to plan for returning to work and managing ongoing medical bills. Family members, friends, or volunteers may be able to take over at some point so the caregiver can return to work if necessary. During the patient's recovery, there will also be additional costs and ongoing medical bills. The patient's health insurance coverage should remain active during this time.

The patient's return home can involve many emotions, particularly when the patient doesn't feel better as quickly as he or she had hoped or expected. Both the caregiver and patient may feel frustrated if the patient is not able to do activities, help with household tasks, or be as active as he or she was before the illness. It is important to remember that adjustment takes time. Turning to a support group or talking to a professional counselor can help, as well as reaching out to family and friends.

The Caregiver Tips listed below were compiled from caregivers who have helped their loved ones through the transplantation process.

CAREGIVER TIP

- When speaking with the physician or healthcare team, be aware of who is in the room (this may not be a place for children).
- Be mindful that after the transplant, even if everything seems fine, your loved one can still get sick very easily due to their compromised immune system.
- It's okay to ask the patient questions that include:
 - Do you want to see visitors, or do you prefer some time alone?
 - Do you want to talk about what you have been through or do you prefer to talk about other things?
 - Do you want to rest, or can I bring you something to read, watch, or listen to?
- Depression is common for both the patient and you to experience.
- You should also have a person to provide support. You need to remain strong for the patient, but you will still need someone to lean on and talk to. Remember to take care of yourself.

Part 4

Part 4 — Other Considerations and Resources

Chapter 7: Enrolling in a Clinical Trial

Patients who are planning to undergo stem cell transplantation may want to consider enrolling in a clinical trial. A clinical trial is a carefully designed research study that involves people who volunteer to participate. The purpose of a clinical trial is to safely monitor the effects of a new drug, a new combination of drugs, or another type of treatment on patients over time and to identify more effective therapies for specific diseases. By participating in a randomized clinical trial, patients may or may not get access to the newest therapies, but at a minimum they will receive quality care and the standard treatment in a carefully controlled and supportive environment.

Patients who are planning to undergo stem cell transplantation could be eligible for several different types of clinical trials. These trials could include studies comparing different components of the process, such as:

- the *high-dose chemotherapy*, radiation, and other *conditioning* regimens given prior to transplantation
- the source of the stem cells (*bone marrow*, *peripheral blood*, or *umbilical cord blood*)
- medications and strategies used to manage side effects or prevent infection after transplantation
- medications to prevent or treat *graft-versus-host disease* (GVHD)

Clinical trials are described by phase, with each phase designed to find out specific information.

- **Phase I Clinical Trials** – A new research treatment is given to a small number of participants to determine a safe dose and schedule, and to find out what side effects it may cause.
- **Phase II Clinical Trials** – The treatment is given to participants who all have a particular type of lymphoma to learn whether the new treatment has an anticancer effect on that specific type of lymphoma.

- **Phase III Clinical Trials** – Either the new treatment or the standard treatment is given to two larger groups of participants to compare the effectiveness and safety of the two treatments.
- **Phase IV Clinical Trials** – Also called post-marketing studies, the treatment continues to be studied after it has been approved to learn more about the long-term safety and effectiveness.

Clinical trials may offer many benefits and risks. Patients in clinical trials may be able to try new treatments that are not otherwise available to all patients. However, in some trials, patients do not get to choose which treatment they receive, so being part of the trial means that the patient could receive the therapy that turns out to be the less effective of the two treatments being compared. No matter which therapy is received, however, one advantage of all clinical trials is that the health of enrolled patients is monitored very closely. The healthcare team studying the new treatment will explain all of the possible benefits and risks of a specific clinical trial.

Patients interested in learning more about clinical trials should discuss this option with their healthcare teams. Patients interested in participating in a clinical trial should view the *Understanding Clinical Trials* fact sheet on the Lymphoma Research Foundation's (LRF's) website at lymphoma.org/publications, talk to their physician, or contact the LRF Helpline for an individualized clinical trial search by calling (800) 500-9976 or emailing helpline@lymphoma.org.

Questions to Ask About a Clinical Trial

- What is the purpose of this clinical trial?
- Why are you recommending this clinical trial for me?
- Who is sponsoring this trial (the National Cancer Institute [NCI], a cancer center, an international study group, a state or national study group, or a pharmaceutical/biotechnology company)?
- Who has reviewed and approved this clinical trial?
- Does this clinical trial include the additional use of a *placebo* (no active ingredient/no intervention)?
- How long will the study last? Where will it take place?
- What are the risks involved?
- What are the possible benefits? If I benefit from the intervention, will I be allowed to continue receiving it after the trial ends?
- What are my responsibilities during the clinical trial?
- What kinds of additional tests, procedures, or treatments will be performed? How many and how often?
- Will I be in any discomfort or pain?
- Will I be able to see my own doctor during the clinical trial?
- What type of long-term follow-up care is part of this trial?
- Do I have to travel to the site for follow-up care, or is all long-term follow-up done locally?
- What costs will I be responsible for? Who will pay for my participation? Will I be paid for other expenses?
- What happens if my health gets worse during the clinical trial?

Part 4 — Other Considerations and Resources

Chapter 8: Transplant Expenses, Medical Coverage, and Financial Support

Stem cell transplants are very expensive. Over the years, advances in treatment have shortened the length of hospital stays for transplants, somewhat reducing this cost. As soon as stem cell transplant becomes a consideration in treatment, patients are encouraged to discuss these financial issues with their healthcare team. Transplant centers have staff who are available to help navigate patients' financial questions, including insurance and financial assistance.

For certain types of cancers, most health insurance companies cover some of the transplantation costs, and they may also cover some of the costs incurred once the patient has returned home from the hospital after the procedure. Health insurance companies covering transplant costs tend to cover these costs when the transplant meets their criteria of what they consider to be “medically necessary,” and the patient also meets other criteria required for coverage.

Before undergoing a medical procedure, patients should check with their medical insurance provider to see what costs the provider will cover and what costs the patient will be responsible for paying. If there is a dispute about coverage or if coverage is denied, patients should ask the insurance carrier about their appeals process. If a claim is repeatedly denied, the patient should contact their state's insurance agency.

Patients in need of financial assistance should talk with their doctor and social worker about available options and how to enroll in an appropriate program. Cancer organizations like the Lymphoma Research Foundation (LRF) offer limited financial assistance to patients who qualify. Some pharmaceutical companies may have patient assistance programs in place that help to provide drugs to qualifying patients, as well. Federal government

programs such as the National Cancer Institute's Cancer Information Service can provide further information regarding financial assistance at (800) 422-6237.

To learn more about financial aid options, view LRF's *Resources for Financial Assistance* fact sheet at lymphoma.org/publications, or contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org. LRF provides resources for financial assistance through which the patient may qualify for aid related to care for his or her lymphoma.

Part 4 — Other Considerations and Resources

Chapter 9: Resources

The Lymphoma Research Foundation (LRF) is here to help. We have prepared a sample *Transplant Journey Checklist* and *Lymphoma Care Plan* that can be used to help document your journey. These resources are available online at lymphoma.org/publications or by contacting the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org.

A Transplant Journey Checklist

This checklist was developed as a general guideline based upon common experiences. However, patients may need to adapt it during discussions with their transplant team.

8 Weeks Before Transplant

- ☐ Develop and stick to a solid nutritional and physical fitness plan.
- ☐ Have a dental cleaning in preparation for being unable to do so during the recovery period.
- ☐ Secure a legal Will, Living Will, Advanced Directive, Durable Power of Attorney, and Healthcare Power of Attorney.
- ☐ Investigate health insurance coverage of transplant and communicate with the transplant facility coordinator.
- ☐ If needed, develop a transplant payment plan coordinated through health insurance, Medicare, or a related provider.
- ☐ Select, educate, and train the primary transplant caregiver and any secondary caregivers.
- ☐ Ensure that family, friends, associates, and all those affected are aware of the approximate dates during which normal activities will be limited.
- ☐ Share the transplant procedure and recovery schedule with work, school, and other points of contact normally associated with activities of daily living.
- ☐ If preservation of fertility is a concern, make arrangements for appropriate

consultation to discuss freezing of eggs, sperm, or embryos or other fertility-sparing treatments.

- ☐ Contact the Lymphoma Research Foundation (lymphoma.org) and Be The Match (BeTheMatch.org/patient) for free programs and resources to prepare you for transplant and the post-transplant period.

2–3 Weeks Before Transplant

- ☐ Maintain the nutritional and physical fitness plan.
- ☐ Undergo an overall health assessment to ensure fitness for high-dose chemotherapy and stem cell transplantation.
- ☐ Central line or port is placed in chest for use in chemotherapy, stem cell infusion, blood testing, and administering drugs.
- ☐ Growth factors are given to the patient (*autologous*) or the donor (*allogeneic*) to stimulate stem cell growth.
- ☐ Stem cells are collected from the patient or the donor and stored for future infusion.
- ☐ High-dose chemotherapy with or without radiation to kill lymphoma cells begins.

1 Week Before Transplant

- ☐ *High-dose chemotherapy* with or without radiation continues; duration of treatment may vary.
- ☐ Patient is admitted to hospital/transplant center to rest before the procedure.

Transplant Days 0–20

- ☐ Day 0: Infusion of stem cells through the central line or port.
- ☐ Days 0 to 6: The patient feels generally “low” due to the effects of chemotherapy, which may include fatigue, nausea, loss of appetite, and soreness in mouth and throat. Blood counts are low, and the risk of infection is high.
- ☐ Days 7 to 10: These are often the most difficult days. *Engraftment* is beginning to take place, and careful precautions must be taken to prevent infection until blood counts rise. Visitors to the hospital room should be strictly limited.
- ☐ Days 10 to 14: The patient may begin to feel better because white and red blood cell counts are beginning to rise.
 - When white blood cell levels are steady for three days in a row, the transplant is considered engrafted.
 - Another one to two weeks are required for red blood cells and platelets to stabilize.
- ☐ Days 12 to 35: Hospital discharge times vary widely depending on the recovery process. After the stem cell infusion, blood levels slowly return to normal, and other discharge criteria must also be achieved in order to be sent home.

Day 30 (Return Home After Transplant)

- ☐ The primary caregiver and any secondary caregivers are in place. The patient will need a caregiver available around the clock for approximately one to two weeks after discharge.
- ☐ Generalized *lethargy* (low energy levels) is normal as blood counts continue to return to normal.
- ☐ A thermometer should be kept on hand to check temperature if fever is suspected.
- ☐ The caregiver should report blood in urine, stool, or unusual vaginal bleeding as well as bruising and skin rashes.

- ☐ For autologous transplant recipients, the central line or port may be removed at this time. For patients who received an allogeneic transplant, the device may need to be kept in place for another 1–2 months. If a central line is still in place, it should be regularly flushed and cleaned.
- ☐ Exposure to possible infection must be kept to a minimum. Crowded or enclosed spaces should be avoided, and people with infections should not visit the patient. Other infection control practices, including guidelines for contact with pets, will be provided by the treatment team.
- ☐ Maintain a structured nutritional and physical exercise plan.
- ☐ Reintegrate gradually into the normal activities of daily living.
- ☐ Attend follow-up visits to the doctor, transplant center, and/or oncologist.
- ☐ Return to 100% health status may require a few weeks to a few months.

3–4 Months

- ☐ Many patients may be able to return to work in this time frame, but the exact date must be determined in consultation with the healthcare team.
- ☐ Hair may begin to regrow.

Year 1 “The New Normal”

- ☐ Energy levels and stamina may remain low for up to a year, but some patients recover much sooner.

The Lymphoma Research Foundation is pleased to provide this *Lymphoma Care Plan* as a resource and guide to help patients and their physicians discuss and document the cancer experience. Keeping your information in one location can help you feel more in control during and after treatment. Patients should complete this form with their care team. For copies of the *Lymphoma Care Plan*, please visit lymphoma.org/publications or contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org.

Part 4

ABOUT THE LYMPHOMA RESEARCH FOUNDATION

The Lymphoma Research Foundation (LRF) is the largest lymphoma-specific non-profit organization in the United States; the Foundation's mission is to eradicate lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and serve those touched by this disease. Through a national education program, innovative research portfolio and numerous outreach and awareness opportunities, we remain dedicated to serving patients with lymphoma and CLL/SLL and to finding a cure.

Awareness and Outreach

LRF offers numerous advocacy, awareness and fundraising programs—including the signature *Lymphoma Walk* program and *Team LRF*—which allow members of the lymphoma community to become involved with the organization and support the LRF mission. The *LRF Advocacy Program* provides volunteer advocates with the resources necessary to raise attention and support for those public policies most important to the lymphoma and CLL/SLL community. There are currently more than 5,000 LRF advocates in all 50 states and the District of Columbia.

Education Resources and Support Services

LRF provides a comprehensive series of expert programs and services for people with lymphoma and their caregivers, including: Clinical Trials Information Services; Publications focused on each lymphoma subtype and different treatment options; Financial Assistance Resources; In-Person Education Conferences; LRF Lymphoma Helpline; *Lymphoma Support Network*; Mobile App (lymphoma.org/mobileapp); Teleconferences; and Videos, Webcasts, and Podcasts. All programs and materials are offered free of charge. Learn more at lymphoma.org.

Professional Education

LRF is committed to educating healthcare professionals on the latest developments in lymphoma and CLL/SLL diagnosis and treatment. The Foundation offers a wide range of lymphoma-focused continuing education activities for nurses, physicians, and social workers, including workshops, conference symposia, and webcasts.

Research

LRF is focused on finding a cure for lymphoma and CLL/SLL through an aggressively funded research program and by supporting the next generation of lymphoma investigators. LRF supports Clinical Investigator Career Development Awards, Lymphoma Fellowships, and several disease-specific research initiatives. These efforts are led by the Foundation's Scientific Advisory Board (SAB), comprised of 45 world-renowned lymphoma experts. The Foundation has funded nearly \$60 million in lymphoma-specific research.

Contact Information

Helpline: (800) 500-9976
helpline@lymphoma.org
Website: lymphoma.org



FOCUS ON LYMPHOMA MOBILE APP

The Lymphoma Research Foundation's mobile app, *Focus on Lymphoma*, is a great tool and resource for lymphoma patients to manage their disease.

Focus on Lymphoma is the first mobile app that provides patients and caregivers comprehensive content

based on their lymphoma subtype and tools to help manage their diagnosis, including a medication manager, doctor sessions tool and side effects tracker.

The *Focus on Lymphoma* mobile app was recently named Best App by PR News and is available for free download for iOS and Android devices in the Apple App Store and Google Play.

For further information on LRF's award winning mobile app or any of our programs and services, call the **LRF Helpline toll free (800) 500-9976**, email helpline@lymphoma.org or visit us at lymphoma.org.



Understanding The Stem Cell Transplantation Process

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