LEUKEMIA & LYMPHOMA SOCIETY®

Graft-Versus-Host Disease

No. 32 in a series providing the latest information for patients, caregivers and healthcare professionals

Highlights

- Graft-versus-host disease (GVHD) is a common and potentially serious complication that may occur after a treatment called "allogeneic stem cell transplantation."
- Allogeneic stem cell transplantation (sometimes called bone marrow transplant) is a procedure in which a patient receives healthy blood-forming stem cells from a donor. Doctors use allogeneic stem cell transplantation to treat people with certain blood cancers such as leukemia and lymphoma.
- GVHD occurs when the donor stem cells ("the graft") attack healthy cells in the patient ("the host"), causing the condition "graft-versus-host disease" or GVHD.
- GVHD can damage a patient's tissues and organs, especially the skin, eyes, mouth, hair, nails, liver, esophagus (the tube through which food passes from the throat to the stomach), intestines, joints, lungs and genitals.
- There are two main types of GVHD: acute GVHD and chronic GVHD.
  - Each type of GVHD has different signs and symptoms.
  - Patients may get one type or both types of GVHD.
  - Some patients may not develop GVHD at all.
- GVHD can range from a mild rash to serious and life-threatening damage to the skin and internal organs.
- There are medicines to help lower the risk of getting GVHD. But even with these treatments, many people still get GVHD.

Introduction

Graft-versus-host disease (GVHD) is a common and potentially serious complication that may occur after allogeneic stem cell transplantation. Allogeneic stem cell transplantation is a treatment for people with certain blood cancers such as leukemia and lymphoma. In this treatment, a patient's own damaged or diseased blood-forming stem cells are destroyed. Then they are replaced with healthy stem cells from a donor.

People need healthy hematopoietic (blood-forming) stem cells to live. These stem cells are special cells in the bone marrow that can develop into all types of blood cells including red blood cells, platelets and white blood cells. Red blood cells carry oxygen throughout the body. Platelets help stop bleeding by clotting (clumping together) at the site of an injury. White blood cells are part of the body's immune system and help fight infection and disease. One type of white blood cell is a lymphocyte. The two main lymphocytes are:

- **B cells.** B cells create a type of protein called an antibody. Antibodies bind to foreign substances such as bacteria and viruses to neutralize them. B cells can also recruit other white blood cells to help destroy an infected cell.
- **T cells.** T cells can destroy infected and cancerous cells. They also help B cells to eliminate foreign invaders.

Before an allogenic stem cell transplant, the patient and the potential donor are tested to see if the donor's stem cells are a good match for the patient. Human leukocyte antigen (HLA) typing, also called "tissue typing," is a test done to identify proteins called HLAs found on the surface of most cells in the body. There are many HLA markers, and different people have different patterns of markers. Except for identical twins, everyone has different HLA markers.

HLA markers play an important role in the body's immune response to foreign substances such as bacteria and viruses. They tell white blood cells in the immune system which cells belong in the body and which ones do not.

These white blood cells know which pattern of HLA markers is normal for a person's body. If they find cells with a different pattern of markers, they will attack and kill those cells. That is why it is important for the donor's stem cells to have HLA markers that are as similar to the patient's as possible—to prevent the donor's cells from attacking the patient's cells.

Once a donor is found, a patient receives a "conditioning regimen" to prepare for the transplant. This consists of high-dose chemotherapy and sometimes radiation therapy. The conditioning regimen is designed to:

- Kill cancer cells
- Destroy blood-forming stem cells in the patient's bone marrow to create space for the new, healthy donor stem cells
- Suppress the patient's immune system to prevent rejection of the new donor stem cells

After the conditioning regimen, donor stem cells are infused into the patient's body. The stem cells travel to the patient's bone marrow, where they begin to produce new red blood cells, white blood cells and platelets. This process is known as "engraftment." The white blood cells that develop from the donor stem cells create a new immune system for the patient.

The new white blood cells, including B cells and T cells, have the HLA markers of the donor, not the patient. If the HLA markers of the donor are too different from the HLA markers of the patient, the new white blood cells will see the cells in the patient's body as foreign and attack them. This may potentially cause organ damage and organ failure. When donor cells (the graft) attack the tissue and the cells of the patient (the host), this condition is called "graft-versus-host disease" (GVHD).

There are two main categories of GVHD: acute GVHD and chronic GVHD.

- Acute GVHD usually develops within the first 100 days after transplantation, but it can occur later. It can affect the skin, the liver and the gastrointestinal (GI) tract (stomach, intestines and colon).
- Chronic GVHD may occur at any time after transplantation, but it typically develops at least 100 days after the day of transplant. Chronic GVHD may involve a single organ or possibly many organs.

Acute GVHD and chronic GVHD have different signs and symptoms. Patients may develop one or both types, or may not develop either type. Both types of GVHD can be mild, moderate or severe.

There are medicines to help lower the risk of getting GVHD. Even with medication, many patients still get GVHD. For patients who develop GVHD, there are successful treatments, but for some, GVHD may not respond to treatment. In addition, treatment for GVHD often weakens the immune system, leaving patients more vulnerable to infections or other complications.

Acute GVHD

Acute GVHD is a significant cause of medical problems and death following an allogeneic stem cell transplantation. Somewhere between 30 percent and 70 percent of transplant recipients develop acute GVHD. Acute GVHD primarily affects the skin, the liver and the gastrointestinal (GI) tract.

Risk Factors. The following risk factors are usually associated with an increased chance of moderate to severe acute GVHD:

- HLA mismatch—receiving stem cells from a related donor who is not a perfect HLA match
- Unrelated donor—receiving stem cells from an unrelated donor even if the donor is a perfect HLA match
- Older age of the donor or recipient
- Female donor for male recipient
- Intensity of the transplant conditioning regimen
- Receiving total body irradiation as part of the conditioning regimen

Signs and Symptoms. Signs and symptoms are changes in the body that may indicate the presence of disease. A "sign" is a change that the doctor sees during an examination or in a laboratory test result. A "symptom" is a change that a patient can notice and/or feel.

Signs and symptoms of acute GVHD most often affect the skin, gastrointestinal (GI) tract or liver. Some may be mild, and some can be severe and even life-threatening. See **Table 1** on page 3 for a list of common symptoms of acute GVHD.

Patients must be aware of the symptoms of acute GVHD. Call your transplant team immediately if you have any of these symptoms. Early detection and treatment may help limit the severity of GVHD.

Table 1. Symptoms of Acute GVHD

Skin	• Rash is the most common symptom of GVHD of the skin. • Rash often starts as a faint redness that may appear anywhere, including the palms of the hands and the soles of the feet. • Rash may spread to cover the entire body. • Mild rash may be slightly sore or itchy and look like a minor sunburn. • More severe rash may include blistering or peeling skin.

Gastrointestinal (GI) tract	• The most classic symptom of GVHD of the GI tract is diarrhea, caused by inflammation of the colon. Diarrhea can be as severe as several liters of stool each day.
	• Other symptoms include:
	  ◦ Blood in the stool
	  ◦ Nausea
	  ◦ Loss of appetite
	  ◦ Vomiting

Liver	• Acute GVHD of the liver most commonly has no symptoms. It can only be identified by blood tests that show higher than normal liver enzymes, indicating damage to the liver. • Acute liver GVHD can appear as jaundice (yellowing of the skin or eyes) from liver damage and inability to excrete a substance called bilirubin (bilirubin is produced when the liver breaks down old red blood cells). • Some patients develop liver failure, with symptoms of bleeding, confusion or ascites (excess fluid in the abdomen).

Low blood counts are not necessarily classic signs of acute GVHD, but it is extremely common for patients with GVHD to develop low blood counts. This is the body's response to the immune system's attack on organs.

Diagnosis and Staging. Patients with signs and symptoms of acute GVHD may need to have tests to confirm the diagnosis and rule out other conditions that may mimic acute GVHD, such as drug reactions and infections.

Acute GVHD may be mild, moderate or severe. Doctors classify the severity of acute GVHD according to the number of organs involved and the degree to which they are affected.

Each organ is staged individually, with each stage ranging between 1 (mildest) to 4 (most severe). The skin is given a stage based on the amount of body surface area involved. The gastrointestinal (GI) tract is staged based on the amount of diarrhea or bowel movements a patient has per day. The liver is given a stage based on the rise in bilirubin level in the blood. Bilirubin is a yellowish substance found in bile, a fluid made by the liver. If the liver is not working as well as it should, there may be too much bilirubin in the blood. This can cause jaundice, a condition that causes the skin and eyes to turn yellow.

Once each organ is given a stage, the doctor is able to group these organs into an overall grade. Acute GVHD is also graded from 1 (mildest) to 4 (most severe). Patients with grade 3/4 acute GVHD tend to have poorer outcomes and decreased survival. For staging and grading of acute GVHD see **Table 2** on page 4.

Table 2. Staging and Grading of Acute GVHD*

Extent of Organ Involvement			
	Skin	**Liver**	**Gut**
Stage			
1	Rash on <25% of skin	Bilirubin 2-3 milligrams per deciliter (mg/dl)	Diarrhea >500 milliliters per day (ml/day)[a] or persistent nausea
2	Rash on 25%-50% of skin	Bilirubin 3-6 mg/dl	Diarrhea >1000 ml/day
3	Rash on >50% of skin	Bilirubin 6-15 mg/dl	Diarrhea >1500 ml/day
4	Generalized erythroderma (severe inflammation of most of the body's skin surface) with bullous formation (blisters)	Bilirubin >15 mg/dl	Severe abdominal pain with or without ileus (a condition in which the muscle contractions that move food through the intestines do not work correctly)
Grade			
I	Stage 1-2	None	None
II	Stage 3	Stage 1	Stage 1
III	—	Stage 2-3	Stage 2-4
IV	Stage 4	Stage 4	—

* Modified Glucksberg Criteria. Source: Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus conference on acute GVHD grading. *Bone Marrow Transplant*. 1995;15:825-828.

[a] Volume of diarrhea applies to adults.

Chronic GVHD

Chronic GVHD is a syndrome that may involve a single organ or several organs. It is one of the leading causes of medical problems and death after allogeneic stem cell transplantation. It affects approximately 40 percent to 50 percent of patients receiving an allogeneic stem cell transplantation. Since GVHD is a chronic condition, it can last for years or even a lifetime. Symptoms range from mild to life-threatening.

Risk Factors. The following risk factors are associated with higher rates of chronic GVHD:

- HLA mismatch or unrelated donor
- Older patient age
- Older donor age
- Female donor for male recipient (the risk increases if the female donor has ever been pregnant)
- Stem cell source
  - Stem cells retrieved from peripheral blood have a higher risk of causing chronic GVHD than stem cells retrieved from bone marrow
  - Stem cells retrieved from cord blood have the lowest risk of causing chronic GVHD
- Prior acute GVHD

Symptoms. Symptoms of chronic GVHD may be restricted to a single organ or site in the body, or they may be widespread. The most common organs involved are the skin, eyes and mouth. See **Table 3** on page 5 for symptoms of chronic GVHD.

Table 3. Symptoms of Chronic GVHD

Eyes

- Dry, painful, itchy eyes
- Difficulty tolerating bright lights
- Blurred vision
- Blindness

Mouth

- Very dry mouth
- Sensitivity to hot, cold, spicy and acidic foods, mint (often in toothpaste), and carbonated drinks
- Painful mouth sores that may extend down the throat
- Difficulty eating
- Gum disease and tooth decay
- Trouble swallowing

Skin

- Rash
- Dry, tight, itchy skin
- Thickening of the skin which may result in restriction of joint movement
- Change in skin color
- Intolerance to temperature changes caused by damaged sweat glands
- Ulcers (sores) that do not heal

Nails

- Changes in nail texture
- Hard, brittle nails
- Nail loss

Scalp and body hair

- Loss of hair on the head
- Premature gray hair
- Loss of body hair

Gastrointestinal (GI) tract

- Loss of appetite
- Unexplained weight loss
- Feeling like food is stuck after swallowing
- Nausea
- Vomiting
- Diarrhea
- Stomach pain

Lungs

- Shortness of breath and difficulty breathing
- Persistent cough that does not go away
- Wheezing

Liver

- Abdominal swelling
- Jaundice (yellow discoloration of the skin and/or eyes)

Muscles and joints

- Muscle weakness and cramps
- Joint stiffness or difficulty fully extending fingers, wrists, elbows, knees and ankles

Genitals and sex organs

- Female
  - Vaginal dryness, itching and pain
  - Vaginal ulcerations and scarring
  - Narrowing of the vagina
  - Difficult or painful intercourse
- Male
  - Narrowing or scarring of the urethra
  - Itching or scarring on the penis and scrotum
  - Irritation of the penis

In rare cases, symptoms of chronic GVHD may also affect the kidneys or nervous system, or cause fluid around the heart or lungs.

Chronic GVHD usually develops more than 100 days after transplant, but it can also occur months to years later. By that time, you may no longer have weekly appointments with your transplant team. It is important to examine your body, in particular your mouth, eyes, skin, genitals and joints, for symptoms of chronic GVHD. If you have any symptoms, contact your doctor immediately. Although a symptom may be caused by something other than chronic GVHD, a doctor needs to evaluate it. Early detection and treatment may help limit the severity of the disease.

Preventing GVHD

People who develop moderate to severe GVHD are at increased risk of significant illness and discomfort, and a shortened life expectancy. Once it is established, GVHD is difficult to treat. Because of this, doctors try to take every precaution to prevent GVHD before and after the transplant.

Finding the Best Donor Match. GVHD can develop when the donor and the recipient have different tissue types. The patient's transplant team will try to find a donor who closely matches the patient. A close match between a patient's and donor's HLA markers is essential to reduce the risk of GVHD. There are many HLA markers. HLA matching, however, is usually based on either eight or ten HLA markers. The more markers the donor and patient share, the greater the chance that the new immune system established by the donor cells will not attack the patient's healthy cells.

Siblings. Often the ideal donor is a patient's sibling who has inherited the same HLA markers. Every person inherits half their HLA markers from their mother and half from their father. Each biological child of a set of the same parents has four possible combinations of HLA types, which are inherited randomly. Therefore, each full biological sibling has a 25 percent chance of being a perfectly matched donor.

Haploidentical donors. To increase the number of potential donors for patients who cannot find a closely matched HLA donor, some transplant centers have begun to perform half-matched (called "haploidentical") transplant. In many cases a healthy, first-degree relative (a parent, sibling or child) can donate stem cells, even if they are only a half match. Since children receive half of their HLA markers from a parent, biological children and their parents will always be a half match, while there is a 50 percent chance of a sibling being a half match. Consequently, most individuals will have a suitable related haploidentical donor.

Since the patient and the donor are only half matched, the patient is at greater risk for GVHD. To prevent GVHD, the doctor will remove some of the T cells from the donor stem cells. Additionally, the drug cyclophosphamide (Cytoxan®) is administered shortly after the infusion of the stem cells to try to eliminate some of the donor T cells.

Matching registered donors. Patients who do not have a donor in their family may be able to find a perfectly matched stem cell donor on a volunteer donor registry. The likelihood of finding a match on a donor registry has increased for patients from all racial and ethnic groups. Even with millions of potential donors, however, some patients are unable to find a match because their tissue types are uncommon. Thus, there is a continued need for more potential donors.

Cord blood donors. For patients without perfectly matched donors, cord blood stored in public banks can be used as an alternative source of stem cells. In a cord blood transplantation, the stem cells have been collected from the umbilical cord of a healthy newborn. The cord blood, which is usually thrown away after a baby is born, contains a large number of blood stem cells. One advantage of using cord blood is that it does not have to match as closely as a stem cell donation from an adult donor. Cord blood also has fewer T cells, so there is a lower chance of severe GVHD.

Medication. GVHD occurs when donor cells attack the tissue and the organs of the patient. Donor T cells may regard HLA or other markers on the patient's cells as foreign and attack the patient's healthy cells. Doctors try to prevent GVHD by treating patients with immunosuppressive drugs to suppress donor T-cell function. The drugs are given before and after the stem cell infusion.

There is no standard regimen for preventing GVHD, and different combinations of medications are given at different institutions.

Some of the medications used to prevent GVHD may also be used to treat it. These include:

- **Chemotherapy drugs** that eliminate certain donor T cells:
  - Cyclophosphamide (Cytoxan®)–IV infusion
  - Methotrexate (Trexall®)–IV infusion, oral administration
- **Calcineurin inhibitors** that suppress enzymes that activate the immune system:
  - Cyclosporine (Neoral®)–IV infusion, oral administration
  - Tacrolimus (Prograf®)–IV infusion, oral administration
- **Immunosuppressants** that lower the body's immune response:
  - Mycophenolate mofetil (CellCept®)–IV infusion, oral administration
  - Sirolimus (Rapamune®)–oral administration
- **Corticosteroids** that weaken the body's immune response and reduce inflammation:
  - Methylprednisolone or prednisone–IV infusion or oral administration
- **Biologics** that stop or slow inflammation:
  - Abatacept (Orencia®) was approved by the US Food and Drug Administration (FDA) in 2021 to prevent GVHD–IV infusion
    - Abatacept is indicated for the prophylaxis of acute GVHD in combination with a calcineurin inhibitor and methotrexate, in adults and pediatric patients 2 years of age and older undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated donor.
  - Antithymocyte globulin (ATG)–IV infusion
  - Alemtuzumab (Campath®)–IV infusion
  - Tocilizumab (Actemra®)–IV infusion

T-Cell Depletion. Often transplanted stem cells from a donor also contains T cells from the donor. T cells can increase a patient's risk of developing GVHD. To prevent GVHD in some patients, the transplant team will remove some of the T cells from the donor stem cells before they are infused into the patient. This procedure is called a "T-cell depleted allogeneic stem cell transplant." Eliminating T cells from the donor cells may reduce the risk of GVHD. There are two methods:

- *In vivo* (within the body) T-cell depletion consists of giving medications like ATG or alemtuzumab to the recipient just before or just after transplant. *In vivo* T-cell depletion is typically added to another immune suppressant regimen to reduce the risk of GVHD.
- *Ex vivo* (outside the body) T-cell depletion uses a machine to remove T cells from the stem cells before the stem cells are given to the patient. This procedure removes more of the T cells than the *in vivo* method.

Treatment

The goals of treatment for GVHD are to manage symptoms and to prevent further damage to the body's organs. Immunosuppression (suppression of the body's immune system and its ability to fight infections and other diseases) with corticosteroids forms the basis of therapy in both acute and chronic GVHD. Other medications that lower the immune response are also used. Treatment may be either outpatient or inpatient. Treatment decisions are determined by the severity of the patient's symptoms and concerns about complications.

Treatment for Acute GVHD. After transplantation, patients usually continue to take drugs to suppress the immune system (such as cyclosporine, tacrolimus, sirolimus and methotrexate) that they were given before transplantation. Patients who develop stage 1 mild skin-only acute GVHD are usually treated with non-systemic therapy including topical steroid creams (topical means applied directly to the skin).

Patients with more severe symptoms typically require systemic or "whole-system" treatment, which travels in the bloodstream and reaches cells throughout the entire body. Treatment for patients with grade 2-4 acute GVHD usually consists of continuing the original immunosuppressive prevention and adding a corticosteroid such as methylprednisolone or prednisone taken orally (by mouth). For patients who respond to the corticosteroids, the dose is gradually tapered over time. Patients not responding to the corticosteroids, are considered "steroid refractory," and second-line treatments are needed. See *Options for Steroid-Refractory GVHD* on page 8.

There is no clear best treatment to use in patients with acute GVHD who do not respond to steroids. New drugs and strategies to treat acute GVHD are currently being tested in clinical trials. Patients with steroid-refractory acute GVHD are encouraged to explore clinical trials as a treatment option. See *Clinical Trials for Blood Cancers* on page 10.

Treatment for Chronic GVHD. Patients with mild symptoms limited to a single organ or site can often be managed with close observation or with local therapies. For example, patients with mild chronic GVHD of the skin may be treated with topical steroid ointments, and others with chronic GVHD of the eye (ocular GVHD) may be treated with steroid eye drops.

Patients with more severe symptoms or multi-organ involvement typically require systemic or "whole-system" treatment, which travels in the bloodstream and reaches cells throughout the entire body. Prednisone is the standard first-line systemic therapy for chronic GVHD. For patients who do not respond to steroid treatment, second-line treatments are available. Please see the section *Options for Steroid-Refractory GVHD* below for information on second-line treatments.

It is important for patients to continue taking their medication, even if they start to feel better. Stopping medication too soon may cause chronic GVHD to flare up or worsen, which may result in permanent damage. Once chronic GVHD begins to stabilize and improve, doctors may consider tapering the medications over time, and eventually the drugs may be discontinued.

Options for Steroid-Refractory GVHD. Patients whose acute or chronic GVHD does not improve with corticosteroids are considered to have "steroid-refractory" GVHD. Doctors will try second-line therapies. Patients with steroid-refractory GVHD are encouraged to participate in clinical trials, which may offer access to new drugs or better administration of current drugs.

Systemic therapy. Systemic therapy is treatment that affects the whole body. It is usually given orally (by mouth) or infused through an IV to reach cells thoroughout the body.

The US Food and Drug Administration (FDA) approves drugs to treat certain health conditions. The FDA has currently approved five drugs for the treatment of steroid-refractory GVHD.

- Ruxolitinib (Jakafi®) is indicated for the treatment of:
  - Steroid-refractory acute GVHD disease in adult and pediatric patients age 12 years and older
  - Chronic GVHD after failure of one or two lines of systemic therapy in adult and pediatric patients age 12 years and older
- Remestemcel-L-rknd (Ryoncil®) is indicated for the treatment of steroid-refractoryacute graft versus host disease (SR-aGvHD) in pediatric patients 2 months of age and older.
- Ibrutinib (Imbruvica®) is indicated for the treatment of adult and pediatric patients age 1 year and older with chronic GVHD after failure of one or more lines of systemic therapy
- Belumosudil (Rezurock®) is indicated for the treatment of adult and pediatric patients age 12 years and older with chronic GVHD after failure of at least two prior lines of systemic therapy
- Axatilimab-csfr (Niktimvo™) is indicated for the treatment of chronic graft-versus-host disease (cGVHD) after failure of at least two prior lines of systemic therapy in adult and pediatric patients weighing at least 40 kg (about 88 pounds).

Drugs that are not FDA-approved to treat GVHD can be used as "off-label" treatments. "Off-label" prescribing is when a doctor gives a drug that is FDA-approved to treat one condition for another condition, if the doctor feels it will benefit the patient. This is a common practice. **Table 4** on page 9 lists drugs recommended by the National Comprehensive Cancer Network (NCCN) for the treatment of steroid-refractory GVHD. Some are FDA approved for the treatment of GVHD, and some are used as off-label treatments.

Extracorporeal photopheresis (ECP). Extracorporeal photopheresis treatment uses light to treat acute and chronic GVHD that has not improved after steroid treatment. This procedure requires central venous access through a special port and biweekly visits when starting. In this procedure, blood is removed from the patient's body and enters a machine that separates the lymphocytes from the blood. The blood is returned to the patient without the lymphocytes. The lymphocytes are exposed to a photosensitizing agent, 8-methoxypsoralen, and then treated with ultraviolet light. The treatment of lymphocytes alters their function, and the altered lymphocytes are returned to the body. Researchers do not know exactly how extracorporeal photopheresis works. One theory suggests that it decreases swelling and inflammation in the body.

Supportive Treatments for GVHD. In addition to medications, it is critically important that patients receive appropriate supportive therapies. These depend on the patient's type of GVHD and organs involved. Common supportive therapies include:

- TPN (total parenteral nutrition), also called intravenous feeding, for acute GVHD of the bowel, to prevent malnutrition and keep patients from getting weaker
- Antimicrobials (medicines against bacteria, viruses and fungi) to prevent additional risks of infection from the added immunosuppressants used to prevent and treat GVHD
- Bone-strengthening agents to prevent bone loss from steroids

Taking these medications as prescribed may be as important for patient health as the medicines for GVHD.

Table 4. Suggested Systemic Agents for Steroid-Refractory GVHD

Acute GVHD	Chronic GVHD
The following agents are often used with the original immunosuppressive agent. (listed in alphabetical order except category 1) • Ruxolitinib (category 1) • Alemtuzumab • Alpha-1 antitrypsin • ATG • Basiliximab • CNIs (eg, tacrolimus, cyclosporine) • Etanercept • Extracorporeal photopheresis (ECP) • Infliximab • mTOR inhibitors (eg, sirlolimus) • Mycophenolate mofetil • Pentostatin • Remestemcel-L-rknd • Tocilizumab	*The following systemic agents may be used in any site in the body; however, some agents are more commonly given when a particular organ is affected.* (listed in alphabetical order except category 1) • Ruxolitinib (category 1) • Abatacept • Alemtuzumab • Belumosudil • CNIs (eg, tacrolimus, cyclosporine) • Etanercept • Extracorporeal photopheresis (ECP) • Hydroxychloroquine • Ibrutinib • Imatinib • Interleukin-2 • Low-dose methotrexate • mTOR inhibitors (eg, sirlolimus) • Mycophenolate mofetil • Pentostatin • Rituximab

Source: NCCN (National Comprehensive Cancer Network) Clinical Practice Guidelines in Oncology. Hematopoietic Cell Transplantation (HCT). 2023.

Side Effects of Treatment

Many medications used to treat GVHD are immunosuppressants. They work by weakening the immune system, so all of these drugs can increase a patient's risk of getting an infection. In addition to infection, each of them can also cause other side effects:

- Corticosteroids (prednisone, methylprednisolone, dexamethasone, beclomethasone, clobetasol)—prolonged systemic use may cause weight gain, insomnia, osteoporosis (bone loss), high blood sugar, high blood pressure, cataract formation, mood swings, depression
- Cyclosporine/Tacrolimus—these drugs may cause kidney problems, increased hair growth on the body, and rarely neurologic problems such as seizures, tremors, confusion, anxiety
- Methotrexate—may cause liver problems, nausea, vomiting, abdominal pain, mouth sores
- Sirolimus—may cause mouth sores, liver function abnormalities, very high fat levels in the blood, lung toxicity, diarrhea; may affect levels of other drugs in the body, requiring dose adjustments

Patients should discuss any side effects they experience with their doctors. Doctors will try to find the lowest dose of medicine needed to control GVHD while limiting side effects. Most medication side effects improve or go away once treatment is completed.

Clinical Trials for Blood Cancers

Every new drug for cancer, and for cancer complications such as GVHD, goes through a series of carefully controlled research studies before it can become part of standard care. These research studies are called "clinical trials" and they are used to find better ways to care for and treat people who have cancer. In the United States, the FDA requires that all new drugs and other treatments be tested in clinical trials before they can be used. At any given time, there are thousands of cancer clinical trials taking place. Doctors and researchers are always looking for new and better ways to treat cancer.

Researchers use cancer clinical trials to study new ways to:

- Treat cancer using
  - A new drug
  - A drug that has been approved, but to treat a different kind of cancer
  - A new combination of drugs
  - A new way of giving a drug—by mouth, intravenously (IV), etc.
- Prevent and/or manage treatment complications such as GVHD
- Manage cancer signs and/or symptoms and ease treatment side effects
- Find and diagnose cancer
- Keep cancer from coming back (recurring) after treatment
- Manage long-term side effects

By taking part in a clinical trial, patients can see doctors who are experts in their disease, gain access to new, cutting-edge therapies, and provide helpful information for future patients. The treatments and information we have today are due in large part to patients being willing to join clinical trials. Anyone interested in being part of a clinical trial should talk to their hematologist-oncologist about whether a clinical trial might be right for them. During this conversation it may help to:

- Have a list of questions to ask about the risks and benefits of each trial (visit www.LLS.org/WhatToAsk for lists of suggested questions)
- Ask a family member or friend to go with you when you see your doctor—both for support and to take notes

Clinical trials can be difficult to understand and to navigate, but The Leukemia & Lymphoma Society is here to help. Patients and caregivers can work with **Clinical Trial Nurse Navigators** who will help find potential clinical trials, overcome barriers to enrollment and provide support throughout the entire clinical-trial process. Our Clinical Trial Nurse Navigators are registered nurses who are experts in adult and pediatric blood cancers and clinical trials. Your Clinical Trial Nurse Navigator will:

- Talk with you about your treatment goals
- Help you understand the clinical-trial process, including your rights as a patient
- Ask you for details about your diagnosis (such as past treatments, treatment responses, and your cancer genetic profile), your current health and your medical history, because these might impact whether you can take part in certain clinical trials
- Help you understand how your finances, insurance coverage, support network, and ability and willingness to travel might impact your choice of clinical trials
- Guide and help you in your efforts to find and enroll in a clinical trial, including connecting you with trial sites
- Help deal with any problems you might have as you enroll in a trial
- Support you throughout the clinical-trial process

Please call an LLS Information Specialist at (800) 955-4572 or visit www.LLS.org/CTSC for more information about clinical trials and the Clinical Trial Support Center at LLS.

Also, visit www.LLS.org/booklets to view *Understanding Clinical Trials for Blood Cancers.*

Take Care of Yourself

There are some steps patients can take to help minimize the risk of developing GVHD. In some cases, however, GVHD will occur despite all efforts to prevent it. Here are some suggestions to help limit the occurrence and complications of GVHD:

- If a doctor prescribes medications to help prevent GVHD, it is important to take these medications, even when you are feeling healthy. **If you are unable to take medications for any reason, or if you notice any symptoms of GVHD, you should call your doctor immediately.** Early detection and treatment may help limit the severity of the disease.

- Many drugs used to treat GVHD can weaken the immune system and increase your risk of developing a serious infection. It is important for you to try to prevent infections. You should wash your hands often and ask family members and friends who are sick not to visit until they are healthy.
- Exposure to the sun's ultraviolet rays may increase your risk of developing GVHD. It is important to avoid the sun as much as possible. When outside, wear a hat, long sleeves and pants. Some companies offer sun-protective clothing that can help shield skin from the sun's harmful ultraviolet rays. Apply sunscreen with SPF 30 or higher on any exposed skin.
- Keeping skin moist will help prevent it from becoming overly dry and flaky. Avoid long showers, and use a gentle, mild soap and a good moisturizing lotion every day. Try to avoid scratching. Your doctor may prescribe steroid creams to ease itching and burning and to treat GVHD of the skin.
- If chronic GVHD is affecting your eyes, be sure to wear sunglasses with UV protection when outside to protect eyes from further damage. You may also want to find an ophthalmologist who specializes in the management of dry eyes and diseases of the cornea.
- Patients with chronic GVHD of the mouth may have a very dry mouth, which can lead to cavities. You should maintain good oral (dental) hygiene. It is important to see a dentist for routine dental cleanings and checkups. More frequent dental check-ups may be needed—four times per year rather than twice—for good prevention and maintenance.
- Patients with diarrhea should follow the diet prescribed by the doctor and dietitian to prevent worsening diarrhea. Avoid spicy foods. It is also important to avoid skin problems caused by diarrhea, such as irritation around the rectal area. Clean this area well after each occurrence of diarrhea. Tell the doctor if this area gets red, cracked, painful or infected.
- Consider regular exercise and stretching. These activities can help preserve bone health, increase muscle strength, decrease pain and fatigue, and improve mobility. Physical therapy to maintain strength and joint mobility can prevent disability that may occur from chronic GVHD and the side effects of immunosuppressive treatments.
- You should receive vaccinations offered by your transplant team. The immunities to disease that patients acquired prior to their transplantation are generally lost after stem cell transplantation. Most transplant centers will start vaccinations 6 to 12 months after transplantation. These often include the inactivated flu vaccine, pneumococcal vaccine, and "childhood" vaccines such as DTaP and hepatitis B. COVID-19 vaccines are also recommended. Patients with chronic GVHD or T-cell depleted transplants are usually advised to avoid vaccinations with live viruses such as varicella (chicken pox) until the GVHD is resolved and the use of immunosuppressive drugs has ended.
- Living with GVHD can be emotionally difficult. It is normal to feel depressed or anxious while coping with GVHD. Let your doctor know if you feel anxious, sad or depressed and your mood does not improve over time. Speaking with a mental health professional can often help patients deal with their emotions. Treatment for anxiety and depression has benefits for people living with GVHD.

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The Leukemia & Lymphoma Society appreciates the review of this material by:

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We're Here to Help

LLS is the world's largest voluntary health organization dedicated to funding blood cancer research, education and patient services. LLS has regions throughout the United States and in Canada. To find the region nearest to you, visit our website at www.LLS.org/LocalPrograms or contact an Information Specialist at (800) 955-4572.

LLS offers free information and services for patients and families affected by blood cancers. This section lists various resources you may find helpful.

For Help and Information

Consult with an Information Specialist. Information Specialists can assist you through cancer treatment and financial and social challenges, and provide accurate,

up-to-date disease, treatment and support information. Our Information Specialists are highly trained oncology social workers and nurses. Language services are available. For more information, please:

- Call: (800) 955-4572 (Monday through Friday, 9 a.m. to 9 p.m. ET)
- Email and Live chat: www.LLS.org/InformationSpecialists

Clinical Trials (Research Studies). Research is ongoing to develop new treatment options for patients. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. Pediatric and adult patients and caregivers can work with our Clinical Trial Nurse Navigators who will help find clinical trials and provide personalized support throughout the entire clinical trial process. Visit www.LLS.org/CTSC for more information.

Nutrition Consultations. Schedule a free one-on-one nutrition consultation with one of our registered dietitians who have expertise in oncology nutrition. Consultations are available to patients of all cancer types and their caregivers. Dietitians can assist with information about healthy eating strategies, side effect management and more. Please visit www.LLS.org/nutrition for more information.

Free Information Booklets. LLS offers free education and support booklets for patients, caregivers and healthcare professionals that can either be read online or ordered. Please visit www.LLS.org/booklets for more information.

Telephone/Web Education Programs. LLS offers free telephone/web and video education programs for patients, caregivers and healthcare professionals. Please visit www.LLS.org/programs for more information.

Financial Assistance. LLS offers financial support to eligible individuals with blood cancer for insurance premiums, co-pays, and non-medical expenses like travel, food, utilities, housing, etc. For more information, please:

- Call: (877) 557-2672
- Visit: www.LLS.org/finances

Resources for Families. Blood cancer occurs in a small number of children. Families face new challenges, and the child, parents and siblings may all need support. LLS has many materials for families including a caregiver workbook, children's book series, an emotion flipbook, dry erase calendar, coloring books and a coloring app, a school re-entry program, and other resources. For more information, please:

- Call: (800) 955-4572
- Visit: www.LLS.org/FamilyWorkbook

Podcast. *The Bloodline with LLS* is here to remind you that after a diagnosis comes hope. Listen in as patients, caregivers, advocates, doctors and other healthcare professionals discuss diagnosis, treatment options, quality-of-life concerns, treatment side effects, doctor-patient communication and other important survivorship topics. Visit www.LLS.org/TheBloodline for more information and to subscribe to access exclusive content, submit ideas and topics, and connect with other listeners.

3D Models. LLS offers interactive 3D images to help visualize and better understand blood cell development, intrathecal therapy, leukemia, lymphoma, myeloma, MDS, MPNs and lab and imaging tests. Visit www.LLS.org/3D for more information.

Free Mobile Apps.

- LLS Coloring For Kids™ – Allows children (and adults) to express their creativity and offers activities to help them learn about blood cancer and its treatment. Visit www.LLS.org/ColoringApp to download for free.
- LLS Health Manager™ – Helps you track side effects, medication, food and hydration, questions for your doctor, and more. Visit www.LLS.org/HealthManager to download for free.

Suggested Reading. LLS provides a list of selected books recommended for patients, caregivers, children and teens. Visit www.LLS.org/SuggestedReading to find out more.

Connecting with Patients, Caregivers and Community Resources

LLS Community. The one-stop virtual meeting place for talking with other patients and receiving the latest blood cancer resources and information. Share your experiences with other patients and caregivers and get personalized support from trained LLS staff. Visit www.LLS.org/community to join.

Weekly Online Chats. Moderated online chats can provide support and help cancer patients and caregivers reach out and share information. Please visit www.LLS.org/chat for more information.

Local Programs. LLS offers community support and services in the United States and Canada including the *Patti Robinson Kaufmann First Connection® Program* (a peer-to-peer support program), local support groups and other great resources. For more information about these programs or to contact your region, please:

- Call: (800) 955-4572
- Visit: www.LLS.org/LocalPrograms

Advocacy and Public Policy. Working closely with dedicated volunteer advocates, LLS's Office of Public Policy elevates the voices of patients to state and federal elected officials, the White House, governors and even courts. Together, we advocate for safe and effective treatments. We pursue policies that would make care more accessible to all patients. And, most of all, we advocate for the hope for a cure. Want to join our work? Visit www.LLS.org/advocacy for more information.

Other Helpful Organizations. LLS offers an extensive list of resources for patients and families. There are resources that provide help with financial assistance, counseling, transportation, patient care and other needs. For more information, please visit www.LLS.org/ResourceDirectory to view the directory.

Additional Help for Specific Populations

Información en Español (LLS information in Spanish). Please visit www.LLS.org/espanol for more information.

Language Services. Let members of your healthcare team know if you need translation or interpreting services because English is not your native language, or if you need other assistance, such as a sign language interpreter. Often these services are free.

Information for Veterans. Veterans who were exposed to Agent Orange while serving in Vietnam may be able to get help from the United States Department of Veterans Affairs. For more information, please

- Call: the VA (800) 749-8387
- Visit: www.publichealth.va.gov/exposures/AgentOrange

Information for Firefighters. Firefighters are at an increased risk of developing cancer. There are steps that firefighters can take to reduce the risk. Please visit www.LLS.org/FireFighters for resources and information.

World Trade Center Health Program. People involved in the aftermath of the 9/11 attacks and subsequently diagnosed with a blood cancer may be able to get help from the World Trade Center (WTC) Health Program.

People eligible for help include:

- Responders
- Workers and volunteers who helped with rescue, recovery and cleanup at the WTC-related sites in New York City (NYC)
- Survivors who were in the NYC disaster area and those who lived, worked or were in school in that area
- Responders to the Pentagon and the Shanksville, PA, crashes

For more information, please

- Call: WTC Health Program at (888) 982-4748
- Visit: www.cdc.gov/wtc/faq.html

People Suffering from Depression. Treating depression has benefits for cancer patients. Seek medical advice if your mood does not improve over time, for example, if you feel depressed every day for a two-week period. For more information, please:

- Call: The National Institute of Mental Health (NIMH) at (866) 615-6464
- Visit: NIMH at www.nimh.nih.gov and enter "depression" in the search box.

Other Resources

Be The Match®
(888) 999-6743
www.BeTheMatch.org

Be The Match® is a global leader in bone marrow transplantation. Be The Match,® operated by the National Marrow Donor Program,® manages the largest and most diverse marrow registry in the world. Be The Match® also conducts research to improve transplant outcomes and provides support and resources for patients.

Blood & Marrow Transplant Information Network (BMT InfoNet)
(888) 597-7674
www.bmtinfonet.org

The Blood & Marrow Transplant Information Network (BMT InfoNet) is dedicated to providing patients and their loved ones with emotional support and high quality, easy-to-understand information about blood stem cell transplants (bone marrow, peripheral blood and cord blood) and other cellular therapies.

National Bone Marrow Transplant Link (nbmtLINK)
(800) 546-5268
www.nbmtlink.org

The mission of the National Bone Marrow Transplant Link (nbmtLINK) is to help patients as well as their caregivers and families cope with the social and emotional challenges of bone marrow/stem cell transplant, from diagnosis through survivorship, by providing vital information and personalized support services.

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