ANALYZING FACTORS INFLUENCING GRAFT SUCCESS AND COMPLICATIONS IN TRANSPLANTATION: FOCUS ON GRAFT-VERSUS-HOST DISEASE

Neha, Vikash shah

Galgotias university

ABSTRACT

Allogeneic stem cell transplantation and reduced-intensity allogeneic stem cell transplantation are associated with the increased risk of graft-versus-host disease (GVHD). A patient's own defective or sick stem cells that produce blood are killed off in this procedure. Afterwards, donor stem cells are used to replace them. Organs such as the skin, intestines, liver, and lungs,eyes,mouth,nails,scalp and body hear,gastrointestinal(GI) track,lungs,muscles and goints,gentitals and sex organs are susceptible to harm in the first hundred days after a transplant because to this onslaught. There are several clinical manifestations and approaches to treatment for acute and chronic types of GVHD. Learn all you need to know about GVHD—its causes, symptoms, diagnosis, and treatment—in this comprehensive activity. Through this course, participants will learn more about the signs and symptoms of GVHD, how to assess them, and how the interdisciplinary team can help with their care. Timely interventions are crucial for improving outcomes, and this activity also emphasizes the need of multidisciplinary teamwork in optimizing treatment programs and providing complete care for GVHD patients.

Keywords: Graft, Transplantation, Donor, Acute, Chronic.

Introduction

Graft-versus-host disease (GVHD) is a serious complication that may occur after allogeneic stem cell transplantation. An allogeneic stem cell transplantation is a treatment for many genetic diseases and blood cancers such as leukemia and lymphoma. During allogeneic stem cell transplantation, a person receives stem cells from a donor or from donated umbilical cord blood. These "new" stem cells replace the patient's stem cells that have been damaged by disease or by treatments for the disease. These are the stages of an allogeneic stem cell transplant: l Before an allogeneic stem cell transplantation, patients receive a conditioning regimen, consisting of chemotherapy and sometimes radiation therapy. The conditioning regimen is given to destroy cancer cells in the body (in patients having transplants for cancer). The conditioning regimen also suppresses the recipient's immune system, which allows the new stem cells from the donor to start making new blood cells and ultimately generate a new immune system in the recipient's body. There is a lag between when the previous (the patient's) immune system stops functioning and the new (the donor's) immune system takes over. During this period without healthy bone marrow, patients' bodies are unable to make blood cells, including white blood cells. Without adequate white blood cells, patients are unable to fight infections properly, leading to a period of increased risk of infection.

l After the conditioning regimen, patients receive an infusion of donor stem cells to replace the patient's blood-making system and immune system. The transplanted stem cells travel to the bone marrow where they begin to produce new white blood cells, red blood cells and platelets in a process known as "engraftment." l Donated stem cells that are transplanted also contain some T-cells from the donor. T-cells are a type of white blood cell that help protect the body from infection. They recognize what belongs in the body and what is foreign and potentially dangerous. T-cells know that bacteria, viruses and fungi are harmful. To defend itself from infection, the body must be able to distinguish between what belongs in the body ("self") and what is foreign to it ("non-self")

One of the benefits of an allogeneic transplant is that the donor T-cells may recognize as foreign any of the patient's cancer cells that survived the conditioning regimen. The donor T-cells are much more likely than the patient's own T-cells to identify the cancer cells as "non-self," and they coordinate an attack to eliminate them. This helps prevent the cancer from relapsing. T his is called the "graft-versus-tumor effect." But the same ability of T-cells to recognize self from non self can create a severe complication. T-cells recognize "self" from "non-self" by a system of proteins called human leukocyte antigen (HLA) that marks many cells. Human leukocyte-associated antigens are proteins found on the surface of most cells in the body. They make up a unique person's tissue type. – The donor's T-cells may regard HLA or other markers on the patient's cells as "non-self" and may attack the patient's healthy cells in organs, impairing their ability to function and potentially causing 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). At first, the donor cells (the graft) are partially weakened and controlled by the patient's own immune system. Graft-versus tumor and graft-versus-host effects do not tend to reach full strength until the patient's immune system has been fully suppressed. This tends to happen early within the first 30 days with a myeloablative (full strength) transplant but may occur later with a reduced intensity or a non-myeloablative (mini) transplant. GVHD can be mild, moderate or severe. Successful treatments for GVHD have been developed, but in some patients, GVHD may not respond. In addition, treating GVHD often weakens T-cells and can leave patients more vulnerable to infections or other complications

Classification/Types of GVHD

T here are two main categories of GVHD: acute graft-versus host disease and chronic graft-versus-host disease. Each type affects different organs and tissues and has different signs and symptoms. Patients may develop one type or both types, or may not develop either type. T he National Institutes of Health consensus criteria has classified GVHD based on the timing of presentation and the signs present: l l Classic Acute GVHD

– Signs of the disease occur within 100 days of stem cell transplantation and display features of acute GVHD. Diagnostic and distinctive features of chronic GVHD are absent. Persistent, recurrent or late-onset Acute GVHD – Cases present more than 100 days after transplantation, with features of acute GVHD. Diagnostic and distinctive features of chronic GVHD are absent

l l Classic Chronic GVHD

– Cases may present at any time after transplantation. Diagnostic and distinctive features of chronic GVHD are present. There are no features of acute GVHD. Overlap syndrome – Cases may present at any time after transplantation with features of both chronic GVHD and acute GVHD.

Acute GVHD -

GVHD is a significant cause of medical problems and death following an allogeneic stem cell transplantation. T he frequency of acute GVHD varies significantly among populations, making it impossible to specify how common it is. Somewhere between 30 and 70 percent of transplant recipients develop acute GVHD, depending on donor type, transplant technique, and other features. Acute GVHD primarily affects the skin, the liver and the gastrointestinal tract (stomach, intestines and colon).

Risk Factors.

The following risk factors are usually associated with an increased risk of moderate to severe acute GVHD: l l l l l HLA "mismatch," or unrelated donor Older patient age Female donor to male recipient Intensity of the conditioning regimen or total body irradiation during conditioning regimen Donor lymphocyte infusion: a procedure after a stem cell transplantation that infuses more lymphocytes, including T-cells, from the stem cell donor

Symptoms-

. The following are some symptoms of acute GVHD. l l l

Skin rash

Rash is the most common symptom of acute GVHD Often starts as a faint rash that may appear anywhere, including the palms of the hands and soles of the feet Rash may spread to cover the entire body Mild forms may be minimally uncomfortable and look like a mild sunburn More severe rash features blistering and peeling skin

Gastrointestinal (GI) tract disorders

T he most classic sign of GI GVHD is diarrhea, caused by an inflammation of the colon, and it can be as severe as several liters of stool each day. Other symptoms include abdominal pain, bleeding and/or nausea with vomiting.

Liver: acute GVHD of the liver

Acute GVHD of the liver is most commonly asymptomatic and can only be identified by blood tests Can appear as jaundice (yellowing of skin or eyes) from liver toxicity and inability to excrete a substance called FS32 Graft-Versus-Host Disease I

bilirubin (bilirubin is produced when the liver breaks down old red blood cells) Sometimes patients develop bleeding, confusion, or ascites (excess fluid in the abdomen) due to liver failure 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 Grading.

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. Acute GVHD is staged and graded from I (mildest) to IV (most severe). Patients with grade III/IV acute GVHD tend to have poorer outcomes and decreased survival. Patients must be aware of the warning signs of acute GVHD and should call their doctors immediately if they have any symptoms. Early detection and treatment may help limit the severity of the disease.

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. Approximately 30-70 percent of patients receiving an allogeneic stem cell transplantation develop chronic GVHD. Since it is a chronic condition, it can last for years or even a lifetime. Chronic GVHD symptoms range from mild to life-threatening. Today, doctors are making every effort to prevent GVHD.

Risk Factors.

The following risk factors are associated with chronic GVHD: l HLA mismatch or unrelated donor l Older patient age l Older donor age l Female donor for male recipient and number of children the female donor has had l 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. l 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. Among the most commonly affected parts of the body are the skin, mouth, eyes, liver, gastrointestinal (GI) tract, lungs and joints. Symptoms of chronic GVHD may include any of the following: l Eyes

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

Mouth

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

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 l

Nails

Changes in nail texture Hard, brittle nails Nail loss l

Scalp and body hair

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

Gastrointestinal (GI) tract

Loss of appetite Unexplained weight loss Nausea Vomiting Diarrhea Stomach pain l

Lungs

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

l Liver

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

Muscles and joints

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

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

Patients should contact their doctors immediately if any of these symptoms occur. While a symptom may be caused by something other than chronic GVHD, it needs to be evaluated by the doctor. Early detection and treatment may help limit the severity of the disease

Preventing GVHD

The development of moderate and severe GVHD is associated with significant illness and a decrease in survival. Once it is established, it is difficult to treat. Because of this, doctors try to reduce the occurrence and severity of GVHD before and after transplantation and take every precaution to prevent GVHD.

HLA Typing and Finding a 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. This helps reduce the risk of GVHD in a transplant using standard techniques. Human leukocyte antigen (HLA) typing is a blood test used to determine how closely the tissue type of one person matches the tissue type of another. There are many HLA markers. HLA matching, however, is usually based on either eight or ten HLA markers. The more markers two people share, the greater the chance that their immune systems will not view each other as foreign and are less likely to attack each other. Identical twins match exactly because they have the same genes. But for most people, possible matches include

Siblings

l People inherit half their HLA markers from their mothers and half from their fathers l Often the ideal donor is a patient's sibling who has inherited the same HLA markers l Each child of a set of the same parents has four possible combinations of HLA types which are inherited randomly. Therefore, each full sibling has a 25 percent chance of being a perfectly matched donor l Smaller families mean only about 30 percent of patients have a matched sibling

Matching registered donors

l Finding a perfectly matched donor may depend on volunteer donor registries l Finding a perfectly matched unrelated donor may depend on a patient's ethnic origin l People of white European origin have a 75 percent chance of finding a perfectly matched related donor based on a narrow range of HLA types in populations that settled in Europe and prevalence of these populations in countries with large unrelated donor registries l People of African origin have a very poor chance of having a perfectly matched unrelated donor

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 cord blood transplantation, the stem cells have been collected from the umbilical cord of healthy newborns. l Cord blood units have fewer T-cells and they are less mature, so there is a lower chance of severe GVHD l Cord blood units do not have to match as closely as stem cell donations from adult donors l Cord blood may be a viable alternative source of stem cells for patients without a well-matched related or unrelated donor l But because cord blood units contain fewer stem cells It may be difficult to use in people with larger body sizes Smaller cell dose and a more immature immune system tends to be linked to longer times to engraftment and higher risks of infection, which may make these transplants more dangerous for some patients

Haploidentical Transplant. Over the last several years, investigators around the world have discovered methods to transplant from family members who are only half matched. This is called a haploidentical transplant. When

comparing haploidentical transplants using post-transplant cyclophosphamide to typical matched transplants, the risk of acute GVHD does not seem to be any worse and the rate of chronic GVHD appears to be lower related to the use of post-transplant cyclophosphamide. Cord blood and haploidentical transplants have a major advantage over matched unrelated donors because they are available much more quickly (potentially in 2-4 weeks), while matched unrelated donor cells may take a month or more to obtain. This is extremely important in high-risk blood cancers for patients who may relapse while waiting for a transplant. The donor type (matched

unrelated, cord blood, or half-matched) that ultimately leads to the best outcomes is unclear, and is under active investigation.

Medication.

Doctors try to prevent GVHD by treating patients with immunosuppressive drugs to suppress donor T-cell function. These drugs are given before and after the stem cell infusion. T here is no standard regimen for the prevention of GVHD, and different combinations of medications are given in different institutions. Some common medications that are given to prevent GVHD include: l l l l l l l l l Methotrexate (Trexall®) Cyclosporine Tacrolimus (Prograf®) Mycophenolate mofetil (CellCept®) Sirolimus (Rapamune®) Corticosteroids (methylprednisolone or prednisone) Antithymocyte globulin (ATG) Alemtuzumab (Campath®) Cyclophosphamide (Cytoxan®) In the United States, two main drug regimens are used for preventing GVHD

l l Calcineurin inhibitor-based immunosuppression. This is currently the most commonly used regimen in the United States and Europe. It combines a calcineurin inhibitor (tacrolimus or cyclosporine) with another medicine (usually methotrexate, mycophenolate mofetil, or sirolimus). Typically, both medications are started right around the time of stem cell infusion. The second drug is usually tapered within the first month or so after the transplant while the calcineurin inhibitor is continued for 60-120 days after the transplant. High dose post-transplant cyclophosphamide. This type of regimen involves a high dose of the chemotherapy drug cyclophosphamide in the first few days after the transplant. This drug selectively targets a population of recovering cells that may be particularly inclined to cause GVHD. Patients who receive matched stem cells may only be prescribed cyclophosphamide, while those whohave haploidentical donors usually receive additional oral medicines such as calcineurin inhibitors, sirolimus and/or mycophenolate mofetil.

Graft-versus-host disease (GVHD) is a life-threatening complication that can occur after certain stem cell or bone marrow transplants.

Alternative Names

GVHD; Bone marrow transplant - graft-versus-host disease; Stem cell transplant - graft-versus-host disease; Allogeneic transplant - GVHD

Causes

GVHD may occur after a bone marrow, or stem cell, transplant in which someone receives bone marrow tissue or cells from a donor. This type of transplant is called allogeneic. The new, transplanted cells regard the recipient's body as foreign. When this happens, the cells attack the recipient's body.

GVHD does not occur when people receive their own cells. This type of transplant is called autologous.

Before a transplant, tissue and cells from possible donors are checked to see how closely they match the recipient. GVHD is less likely to occur, or symptoms will be milder, when the match is close. The chance of GVHD is:

Around 35% to 45% when the donor and recipient are related

Around 60% to 80% when the donor and recipient are not related

Symptoms

There are two types of GVHD: acute and chronic. Symptoms in both acute and chronic GVHD range from mild to severe.

Acute GVHD usually happens within days or as late as 6 months after a transplant. The immune system, skin, liver, and intestines are mainly affected. Common acute symptoms include:

Abdominal pain or cramps, nausea, vomiting, and diarrhea

Jaundice (yellow coloring of the skin or eyes) or other liver problems

Skin rash, itching, redness on areas of the skin

Increased risk for infections

Chronic GVHD usually starts more than 3 months after a transplant, and can last a lifetime. Chronic symptoms may include:

Dry eyes, burning sensation, or vision changes

Dry mouth, white patches inside the mouth, and sensitivity to spicy foods

Fatigue, muscle weakness, and chronic pain

Joint pain or stiffness

Skin rash with raised, discolored areas, as well as skin tightening or thickening

Shortness of breath due to lung damage

Vaginal dryness

Weight loss

Reduced bile flow from the liver

Brittle hair and premature graying

Damage to sweat glands

Cytopenia (decrease in number of mature blood cells)

Pericarditis (inflammation in the membrane surrounding the heart; causes chest pain)

Exams and Tests

Several lab and imaging tests can be done to diagnose and monitor problems caused by GVHD. These may include:

X-ray abdomen

CT scan abdomen and CT chest

Liver function tests

PET scan

MRI

Capsule endoscopy

Liver biopsy

A biopsy of the skin, mucous membranes in the mouth, may also help to confirm the diagnosis.

Treatment

After a transplant, the recipient usually takes medicines, such as prednisone (a steroid), which suppress the immune system. This helps reduce the chances (or severity) of GVHD.

You'll continue taking the medicines until your health care provider thinks the risk for GVHD is low. Many of these medicines have side effects, including kidney and liver damage. You'll have regular tests to watch for these problems.

Outlook (Prognosis)

Outlook depends on the severity of GVHD. People who receive closely matched bone marrow tissue and cells usually do better.

Some cases of GVHD can damage the liver, lungs, digestive tract, or other body organs. There is also a risk for severe infections.

Many cases of acute or chronic GVHD can be treated successfully. But this doesn't guarantee that the transplant itself will succeed in treating the original disease.

When to Contact a Medical Professional

If you have had a bone marrow transplant, call your provider right away if you develop any symptoms of GVHD or other unusual symptoms.

Bishop MR, Keating A. Hematopoietic stem cell transplantation. In: Goldman L, Schafer AI, eds. Goldman-Cecil Medicine. 26th ed. Philadelphia, PA: Elsevier; 2020:chap 168.

Im A, Pavletic SZ. Hematopoietic stem cell transplantation. In: Niederhuber JE, Armitage JO, Kastan MB, Doroshow JH, Tepper JE, eds. Abeloff's Clinical Oncology. 6th ed. Philadelphia, PA: Elsevier; 2020:chap 28.

Reddy P, Ferrara JLM. Graft-versus-host disease and graft-versus-leukemia responses. In: Hoffman R, Benz EJ, Silberstein LE, et al, eds. Hematology: Basic Principles and Practice. 7th ed. Philadelphia

Acute GVHD usually happens within days or as late as 6 months after a transplant. The immune system, skin, liver, and intestines are mainly affected. Common acute symptoms include:

Abdominal pain or cramps, nausea, vomiting, and diarrhea

Jaundice (yellow coloring of the skin or eyes) or other liver problems

Skin rash, itching, redness on areas of the skin

Increased risk for infections

Chronic GVHD usually starts more than 3 months after a transplant, and can last a lifetime. Chronic symptoms may include:

Dry eyes, burning sensation, or vision changes

Dry mouth, white patches inside the mouth, and sensitivity to spicy foods

Fatigue, muscle weakness, and chronic pain

Joint pain or stiffness

Skin rash with raised, discolored areas, as well as skin tightening or thickening

Shortness of breath due to lung damage

Vaginal dryness

Weight loss

Reduced bile flow from the liver

Brittle hair and premature graying

Damage to sweat glands

Cytopenia (decrease in number of mature blood cells)

Pericarditis (inflammation in the membrane surrounding the heart; causes chest pain)

Exams and Tests

Several lab and imaging tests can be done to diagnose and monitor problems caused by GVHD. These may include:

X-ray abdomen

CT scan abdomen and CT chest

Liver function tests

PET scan

MRI

Capsule endoscopy

Liver biopsy

A biopsy of the skin, mucous membranes in the mouth, may also help to confirm the diagnosis.

Treatment

After a transplant, the recipient usually takes medicines, such as prednisone (a steroid), which suppress the immune system. This helps reduce the chances (or severity) of GVHD.

You'll continue taking the medicines until your health care provider thinks the risk for GVHD is low. Many of these medicines have side effects, including kidney and liver damage. You'll have regular tests to watch for these problems.

Outlook (Prognosis)

Outlook depends on the severity of GVHD. People who receive closely matched bone marrow tissue and cells usually do better.

Some cases of GVHD can damage the liver, lungs, digestive tract, or other body organs. There is also a risk for severe infections.

Many cases of acute or chronic GVHD can be treated successfully. But this doesn't guarantee that the transplant itself will succeed in treating the original disease.

When to Contact a Medical Professional

If you have had a bone marrow transplant, call your provider right away if you develop any symptoms of GVHD or other unusual symptoms.

What is graft versus host disease (GvHD)?

GvHD is a common complication that can occur after a blood stem cell (also known as bone marrow) transplant using donor cells. These are called allogeneic transplants. An allogeneic transplant is a lifesaving treatment for people with leukemia, lymphoma, and other cancers.

The donor cells form the person's new immune system. There are small differences between the new immune system and the cells in the body after an allogeneic transplant.

GvHD occurs when the donated cells (the graft) see your body cells (the host) as unfamiliar cells that need to be destroyed. This is different to a solid organ transplant when the host can reject/attack the donated organ.

The treatment team will assess for GvHD as part of follow up care for an allogeneic transplant.

Who develops graft versus host disease?

It is difficult to predict who will be affected by GvHD and who won't.

Between half to a third of all people who have an allogeneic transplant develop some symptoms of GvHD.

People are more likely to develop GvHD if:

they are older

they have had a splenectomy

the pre-transplant treatment is reduced intensity

Their donor

was not a perfect match or not related to them

was older

has been pregnant

is a different sex

is positive for a common virus called cytomegalovirus (CMV)

Types of graft versus host disease?

GvHD can range from mild to severe and can affect quality of life. It can develop early (acute) or late (chronic) post-transplant, it can be one type or both types at the same time.

Acute GvHD: typically happens within the first 100 days post-transplant. There is also late acute GvHD which starts after day 100.

Chronic GvHD: happens more than 100 days post-transplant.

Overlap syndrome: occurs when both acute and chronic GvHD are present.

GvHD is given a staging and grading by your treatment team, this is used to guide treatment and monitor improvement. The stage and/or grade of GvHD is determined by if it is acute and/or chronic GvHD, symptoms, test results and the number of organs involved.

Preventing graft versus host disease

The transplant team make sure the donor is as closely matched as possible. This is called tissue typing and helps reduce the risk of developing GvHD.

Your treatment team for allogeneic transplant, will prescribe anti-rejection drugs called immunosuppressants. These suppress the 'new' (donor) immune system. You will take these drugs before, during and for some time after the transplant.

It is important that you continue to take the immunosuppressant medications as instructed by the treatment team to reduce the likelihood of developing GvHD.

When is graft versus host disease likely to occur?

When medication that suppresses the immune system is reduced, usually a few months after the transplant. This enables the new immune cells to become more active and they may identify a difference in the host cells. The new immune system then attacks the unfamiliar host cells.

If you have a donor lymphocyte infusion (DLI), using white blood cells from the donor, this may be required if your disease comes back after a donor transplant.

Treatment for graft versus host disease

Treatment for GvHD may include additional medications to further suppress the new immune system.

The treatment for GvHD depends on several factors:

the organs of the body involved,

severity of symptoms, grade/stage of GvHD

preventative treatment used

how the body responds to the different lines of therapy

balance between treating GvHD and the importance of the graft-versus-tumour effect.

Medications commonly used:

1. Steroids:

This is the most common treatment for GvHD. Steroids suppress your immune response and reduce inflammation.

prednisolone, which you take as a tablet

methylprednisolone, which you usually have as an injection into a vein

steroid creams to reduce skin GvHD

steroid eye drops for GvHD affecting the eye

2. Calcineurin inhibitors:

such as Tacrolimus and Cyclosporin

These medications are used during and post stem cell transplant to suppress your immune system, they are also used to treat GvHD.

3. Purine analogs:

such as Mycophenolate mofetil

These medications work by reducing the activity of the immune system to treat GvHD.

Extracorporeal photopheresis (ECP) also known as light therapy:

you may have ECP after other treatment has not worked or has stopped working.

ECP is a complicated process, and it may take up to 6 months before you see any real improvement in symptoms.

From March 1, 2022, ECP using the drug methoxalen will be available for patients with chronic GvHD following an allogeneic stem cell transplant in Australia at limited treatment centres.

Clinical trials and research:

There are ongoing studies focusing on the best ways to prevent and treat GvHD. Your treatment team can help determine which clinical trials may be an option.

For information on clinical trials see Clinical Trial Refer and Australian Clinical Trials.

Your treatment team will decide on the best treatment for you. More information can be found here.

Options for Steroid-Refractory GVHD.

For patients whose acute or chronic GVHD does not improve with corticosteroids, doctors will try second-line therapies. Patients are encouraged to participate in clinical trials, which may offer access to new drugs or better administration of current drugs. Widely used drugs include: l l l l l l Ruxolitinib (Jakafi®). This drug is FDA-approved for the treatment of adult and pediatric patients 12 years and older with steroid-refractory acute graft-versus-host disease. Ibrutinib (Imbruvica®). This drug is FDA-approved for the treatment of adult patients with chronic graft-versus host disease (cGVHD) after failure of one or more lines of systemic therapy Mycophenolate mofetil Sirolimus Tacrolimus or cyclosporine Monoclonal antibodies such as infliximab (Remicade®), tocilizumab (Actemra®), alemtuzumab (Campath®),

basiliximab (Simulect®), daclizumab (Zinbryta®), and denileukin diftitox (Ontak®) l l Antithymocyte globulin (ATG) Pentostatin (Nipent®) Photopheresis: doctors may also recommend this extracorporeal (outside the body) treatment that uses light to treat acute GVHD. 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. One theory suggests that when these altered lymphocytes go back into the body, they die or are killed by residual portions of the patient's immune system. T his may help slow or stop the progression of

GVHD. New drugs and strategies to treat acute GVHD are currently being tested in clinical trials. Patients are encouraged to explore clinical trials as a treatment option

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: l l l TPN (total parenteral nutrition), also called intravenous feeding, for acute GVHD of the bowel, to prevent malnutrition and keep people 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 as the medicines for GVHD in assuring function and survival.

Side Effects of Treatment

Many medications used to treat GVHD are immunosuppressants. They work by weakening the immune system, so these drugs can all increase a patient's risk of getting an infection. In addition to infection, each of them can cause other side effects: l l Corticosteroids (prednisone, methylprednisolone, dexamethasone, beclomethasone, clobetasol)—prolonged systemic use may cause weight gain, insomnia, bone loss (osteoporosis), high blood sugar, high blood pressure, cataract formation, mood swings, depression Cyclosporine/Tacrolimus—kidney problems, increased hair growth on the body, and rarely neurologic problems

Take Care of Yourself

T here 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. The following are some suggestions to help limit the occurrence and complications of GVHD: l l l l l l l l l If a doctor prescribes medications to help prevent GVHD, it is important to take these medications, even when patients are feeling healthy. If the patient is unable to take medications for any reason, or if any symptoms of GVHD are noticed, the doctor should be called immediately. Early detection and treatment may help limit the severity of the disease. It is important for patients to try to prevent infections. Patients should wash their 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 a patient's 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 SPF30 sunscreen 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. The doctor will prescribe steroid creams to ease itching and burning and to treat GVHD of the skin. If chronic GVHD is affecting the eyes, be sure to wear sunglasses with UV protection when outside to protect eyes from further damage. Patients 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. Patients should maintain good oral (dental) hygiene. It is important to see a dentist for routine dental cleanings and checkups. Dental check-ups may need to increase from the usual twice per year to four or more times per year 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. Unless they have allergies or severe contraindications, patients should receive vaccinations offered by their transplant team. The immunities to disease that patients acquired prior to their transplantation are generally FS32 Graft-Versus-Host Disease

CONCLUSION

In the success of transplantation is intricately linked to the balance between graft acceptance and the management of complications such as Graft-Versus-Host Disease (GVHD). Despite advances in immunosuppressive therapies and donor selection, GVHD continues to pose significant challenges, particularly in allogeneic transplants. A deeper understanding of the factors influencing graft success, coupled with innovative strategies to prevent and treat GVHD, is essential for improving patient outcomes. Continued research and clinical advancements are crucial to overcoming these obstacles and enhancing the long-term viability of transplants.

References

Couriel D, Carpenter PA, Cutler C, et al. Ancillary therapy and supportive care of chronic graft-versus-host disease: national institutes of health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: V. Ancillary Therapy and Supportive Care Working Group Report. Biology of Blood and Marrow Transplantation. 2006;12(4):375-396. Devergie A. Graft versus host disease. In: Apperley J, Carreras E, Gluckman E, et al, eds. ESH-EBMT Handbook on Haematopoietic Stem Cell Transplantation. 5th ed. 2008:219-234. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus Host Disease: I. Diagnosis and Staging Working Group Report. Biology of Blood and Marrow Transplantation. 2005;11(12):945-956. Flowers ME, Inamoto Y, Carpenter PA, et al. Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graft-versus-host disease according to National Institutes of Health consensus criteria. Blood. 2011;117:3214-3219. Flowers ME, Martin PJ. How we treat chronic graft-versus host disease. Blood. 2015;125(4):606-615. Gragert L, Eapen M, Williams E, et al. HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry. N Engl J Med. 2014;371(4):339-348. doi: 10.1056/NEJMsa1311707. Jacobsohn DA, Vogelsang GB. Acute graft versus host disease. Orphanet Journal of Rare Diseases. 2007;2:35. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-Versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. Biology of Blood and Marrow Transplantation. 2015;21(3):389-401. Kollman C, Spellman SR, Zhang MJ, et al. The effect of donor characteristics on survival after unrelated donor transplantation for hematologic malignancy. Blood. 2016;127(2):260-267. doi: 10.1182/blood-2015-08-663823. Im A, Hakim FT, Pavletic SZ. Novel targets in the treatment of chronic graft-versus-host disease. Leukemia. 2017;31(3):543-554. NCI Staff. Ibrutinib relieves chronic graft-versus-host disease symptoms. National Cancer Institute Web site. Published January 11, 2017. https://www.cancer.gov/news-events/ cancer-currents-blog/2017/ibrutinib-stem-cell-transplant gvhd. Accessed April 14, 2017. Ruutu T, Gratwohl A, de Witte T, et al. Prophylaxis and treatment of GVHD: EBMT-ELN working group recommendations for a standardized practice. Bone Marrow Transplantation. 2014;49(2):168-173. Sung AD, Chao NJ. Concise review: acute graft-versus-host disease: immunobiology, prevention, and treatment. Stem Cell Translational Medicine. 2013;2(1):25-32

Bishop MR, Keating A. Hematopoietic stem cell transplantation. In: Goldman L, Schafer AI, eds. Goldman-Cecil Medicine. 26th ed. Philadelphia, PA: Elsevier; 2020:chap 168.

Im A, Pavletic SZ. Hematopoietic stem cell transplantation. In: Niederhuber JE, Armitage JO, Kastan MB, Doroshow JH, Tepper JE, eds. Abeloff's Clinical Oncology. 6th ed. Philadelphia, PA: Elsevier; 2020:chap 28.

Reddy P, Ferrara JLM. Graft-versus-host disease and graft-versus-leukemia responses. In: Hoffman R, Benz EJ, Silberstein LE, et al, eds. Hematology: Basic Principles and Practice. 7th ed. Philadelphia