

No. 33 in a series providing the latest information for patients, caregivers and healthcare professionals

Highlights

- A lymphoproliferative disorder is a disease in which cells of the lymphatic system grow uncontrollably.
- Post-transplant lymphoproliferative disorders (PTLDs) are rare, but can develop in people whose immune system has been suppressed.
- The most common time that a patient's immune system is suppressed on purpose is before a transplant from a donor—either a blood (allogeneic stem cell) transplant or a solid organ transplant.
- PTLDs are most often caused by the Epstein-Barr Virus (EBV). Most people have been infected with EBV, but their immune system keeps it under control.
- When a person has a transplant and they receive medicine to suppress their immune system, the EBV can reactivate and cause a PTLD by making B cells grow uncontrollably.
- There are currently no therapies approved by The Food and Drug Administration (FDA) for PTLD. Commonly used treatment for PTLDs includes rituximab (Rituxan®). When rituximab fails, other options include chemotherapy and T-cell immunotherapy.

Introduction

The lymphatic system is part of the body's immune system. It consists of the tissues and organs that produce, store and carry white blood cells (lymphocytes) that fight infections and other diseases. The lymphatic system includes the bone marrow, spleen, lymph nodes and lymphatic vessels (a network of thin tubes that carry lymphatic fluid and white blood cells).

The bone marrow produces three main types of lymphocytes (types of white blood cells): B lymphocytes, T lymphocytes, and natural killer (NK) cells:

- B lymphocytes (B cells) make antibodies in response to foreign substances (antigens) in the body. Foreign substances are bacteria, viruses and fungi. B-cell antibodies attach to the intruder, making it possible for another type of white blood cell to recognize the invading cell and destroy it.
- T lymphocytes (T cells) have several functions including assisting B lymphocytes in making antibodies against invading bacteria, viruses or other microbes. T lymphocytes also recognize and kill virus-infected cells and early cancer cells.
- Natural killer (NK) cells have granules with enzymes, which can kill tumor cells or cells infected with a virus.

Most lymphocytes are found in the lymph nodes. There are 500 to 700 lymph nodes throughout the body. When a person has an infection, the number of lymphocytes in the body increases to provide more cells to fight the invading organism.

While an increase in lymphocytes is a natural immune response, there are some diseases that result in excessive growth of lymphocytes that is not beneficial. In fact, this excessive growth becomes a disease known as a lymphoproliferative disorder. It results from a problem with the immune system that would normally regulate the growth and expansion of lymphocytes. A lymphoproliferative disorder is a disease in which cells of the lymphatic system grow uncontrollably. Lymphoproliferative disorders are often treated like cancer, and many (but not all of these disorders) meet the definition of cancer.

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About Post-Transplant Lymphoproliferative Disorders

Post-transplant lymphoproliferative disorders (PTLDs) are potentially fatal diseases that result from an uncontrolled growth of lymphocytes after a solid organ transplant (SOT) or an allogeneic hematopoietic stem cell transplant (HSCT).

A solid organ transplant is an operation in which a surgeon removes a patient's solid organ (such as the heart, liver, or kidney) that is failing and replaces it with another solid organ from a healthy donor. An allogeneic transplant is a stem cell blood transplant that uses healthy stem cells from a donor to restore a patient's marrow and blood cells. Allogeneic stem cell transplant is used for blood cancer patients whose own blood is cancerous and has not responded to other treatments. (There is a type of stem cell transplant in which the patient's own blood can be used—this is called autologous transplant.) In this booklet, only stem cell transplant that uses donor blood, called “allogeneic” transplant, is discussed.

As part of the procedure for both solid organ and stem cell transplants, patients receive medications that suppress their immune systems. This treatment is called “immunosuppression.” This is important because without this procedure, the patient's own immune system might attack and reject the transplanted organ or donor blood. PTLDs are linked to this suppression of the immune system and the resulting rapid reproduction of the Epstein-Barr virus (EBV).

PTLDs are most often caused by the Epstein-Barr Virus (EBV). See *Causes* on page 2. EBV is the virus that causes infectious mononucleosis (called “mono”). Most people get some form of EBV when they are young and carry EBV throughout their lives once they are infected. But most do not get sick from it because the immune system keeps it under control. In rare cases, when a patient's immune system has been suppressed after a transplant, EBV can cause B lymphocytes to grow uncontrollably. These growths of B lymphocytes can range from benign (noncancerous) tumors to potentially fatal malignant lymphomas.

PTLDs can result in someone who has already had the Epstein-Barr virus if

- They receive a transplant and their own EBV is reactivated
- The EBV from the transplant donor is reactivated in the patient

PTLDs can also result if

- The transplant recipient gets infected with EBV for the first time from someone they come in contact with after receiving a transplant

Causes

Epstein-Barr Virus. The great majority of PTLDs are caused by the Epstein-Barr Virus, a type of herpes virus. It is the same virus that causes mononucleosis. It is most commonly transmitted by contact with saliva through kissing, coughing, or by sharing drinking glasses or eating utensils. Primary infection usually occurs in childhood. Children infected before the age of ten usually have mild respiratory tract symptoms or no symptoms at all. In adolescents and adults, primary EBV infection often presents as mononucleosis with symptoms that may include fever, enlarged lymph nodes and sore throat. More than 90 percent of people are infected with EBV at some time during their lives, but most people have no symptoms after the first few weeks. Once people are infected with EBV, they carry the virus for life—in a dormant state—in their B lymphocytes. In a healthy immune system, specific T lymphocytes keep the virus from multiplying and from causing any further illness.

Epstein-Barr Virus in Transplant. Allogeneic stem cell transplant and solid organ transplant use immunosuppressive treatment to destroy remaining cancer cells.

- **Allogeneic Stem Cell Transplant.** Before an allogeneic stem cell transplant, patients receive a “conditioning regimen,” which consists of chemotherapy with or without radiation therapy. This regimen is called immunosuppressive, and is given to a patient having a transplant for a blood cancer to destroy any remaining cancer cells in their body and to suppress their immune system so it will not reject the new blood cells from the donor. Weakening the immune system helps prevent the patient's own immune system from attacking the donated cells after the transplant. This allows the donor cells to

move through the patient's bloodstream to the bone marrow, where the donor cells begin to produce a new immune system in the patient by making new red blood cells, platelets and white blood cells. This is called engraftment.

After stem cell transplant, patients are very susceptible to infection because:

- o It takes time for the new immune system to mature
- o Immunosuppressive medications are given to patients to prevent donor cells from attacking their own cells and causing graft-versus-host disease (GVHD). See *page 3*.
- **Solid Organ Transplant.** Patients transplanted with solid organs start taking immunosuppressive medications when they have the transplant, and they stay on them for their entire lives to prevent their own immune system from rejecting the new organ. This puts them at risk for PTLN throughout their entire post-transplant life span.

In both types of transplant—stem cells infused or a new organ placed in the body—the transplanted donor cells also contain other blood cells. These “other blood cells” may include B lymphocytes infected with Epstein-Barr Virus. In a normal healthy body with a healthy immune system, the immune system would keep the virus in check. But patients receiving a transplant have also been given drugs to suppress their immune system so the body will not reject the transplant. Without a healthy immune system to control the virus, the EBV-infected B lymphocytes can grow and divide out of control in the patient's lymph nodes, spleen, liver, lungs and brain. Although PTLNs are rare, they are more likely to occur if a donor is less well matched, because stronger suppression of the immune system must be used. The more immunosuppression used, the greater the risk of PTLN.

Tissue Matching. Tissue matching means testing to determine how closely the tissue type of one person matches the tissue type of another person. This is done by doing a test called human leukocyte antigen (HLA) typing on both the patient's and the donor's blood. The donated stem cells may come from a blood relative, an unrelated donor or cord blood (stem cells that have been collected from the umbilical cord of healthy newborn babies).

Tissue Matching and GVHD. When a matched relative is not available as a donor, the patient may use stem cells from a mismatched family member or a matched unrelated donor. But this substantially increases the risk for graft-versus-host disease (GVHD). GVHD is caused when T lymphocytes from a donated stem cell graft attack the normal tissue of the transplant patient. The donor's T lymphocytes recognize the patient's cells as a foreign entity and unleash an attack on the patient's tissues and organs. This can impair the ability of the patient's normal organs to function properly or cause them to fail altogether.

For patients with mismatched donors, doctors may use stronger methods to suppress the immune system to prevent GVHD. One method is to remove all the patient's T lymphocytes. Other techniques include anti-T-cell therapy that kills T lymphocytes after the transplant. Reducing the number of donor T lymphocytes in the patient's body does decrease the rate of GVHD. On the other hand, this suppression of the immune system also causes an increase in the rate of PTLNs.

PTLNs can sometimes occur from a cause other than Epstein-Barr Virus. This is called EBV-negative PTLN. This type of PTLN is not as well understood as EBV PTLN.

See the free LLS booklet *Graft-Versus-Host Disease* at www.LLS.org/booklets.

Risk Factors

In patients undergoing stem cell transplant, factors associated with increased risk for PTLNs include

- Unrelated or mismatched stem cell donors, including cord blood
- Removal of T lymphocytes from a donor stem cell graft (T-cell depletion)
- Anti-T-cell therapy (called ATG or anti-CD2 monoclonal antibody) for prevention or treatment of GVHD or solid organ graft rejection
- Age of recipient—higher risk for children younger than 10 years and adults older than 60 years

Incidence

Most stem cell transplant recipients are infected (or eventually will become infected) with EBV. But only a small fraction of them will develop a PTLD. The incidence of PTLD following stem cell transplantation depends on the donor type, with an overall incidence of about 3 percent. The vast majority of PTLDs in stem cell transplant patients occur early, within 6 to 12 months of transplant when the immune system is still very weak.

The incidence of PTLDs following solid organ transplant depends on the transplanted organ. In the adult population, recipients of kidney transplants have the lowest incidence of PTLDs (0.8 to 2.5 percent), followed by recipients of pancreatic transplants (0.5 to 5.0 percent), liver transplants (1.0 to 5.5 percent), heart transplants (2.0 to 8.0 percent), lung transplants (3.0 to 10.0 percent), and multi-organ and intestinal transplants (about 20 percent). Following solid organ transplant, if PTLDs are going to happen, they usually occur in 2 “peaks.” An initial spike (most involving EBV-positive transplant recipients) occurs during the first year. A second, later spike (often involving EBV-negative recipients), typically occurs 5 to 15 years after transplantation. A growing number of very late cases develop more than 20 years after transplantation.

Signs and Symptoms

Symptoms of PTLDs can vary from patient to patient. Common symptoms include:

- General feeling of discomfort, illness, uneasiness; “not feeling good”
- Fatigue
- Fever
- Decreased appetite
- Unintentional weight loss
- Night sweats
- Infectious mononucleosis symptoms: sore throat, swollen glands in the neck
- Swelling of the lymph nodes (called “lymphadenopathy”)

A patient may feel a swollen lump in the neck, armpit or groin. These lumps are swollen lymph nodes where abnormal B lymphocytes have collected. Lymph nodes can become enlarged in parts deeper inside the body that a patient may not be able to feel. These swollen

lymph nodes can only be detected through imaging tests such as computed tomography (CT) scans or magnetic resonance imaging (MRI) scans. Occasionally, PTLDs start in a site other than the lymph nodes, such as a bone, a lung, the gastrointestinal (GI) tract or the skin. In these circumstances, patients may experience symptoms associated with that specific site.

It is important for patients to report any symptoms to their transplant team as soon as possible. An early diagnosis gives patients the best chance for successful treatment.

Diagnosis

A biopsy of an involved lymph node or other tumor site is needed to confirm the diagnosis of a PTLD. Generally, either the lymph node or part of the lymph node is surgically removed so that a doctor who specializes in the diagnosis of blood disorders and blood cancers (a hematopathologist) may study the tissue under a microscope or perform other tests on the cells.

In addition to microscope studies, the hematopathologist examines the cells using “immunophenotyping.” Immunophenotyping is a process that uses antibodies to identify cancer cells based on the types of proteins expressed on the surface of cells. Immunophenotyping should include testing for B-cell, T-cell and NK-cell–associated markers. The hematopathologist may also look for specific markers to help diagnose the PTLD and its subtype. Doctors may perform additional diagnostic tests and procedures to determine the extent of the disease and where it is located in the body. This enables doctors to predict the future course of disease and the chance of survival (prognosis) and tailor treatment to individual patients. Additional tests may include:

- **Physical Examination.** The exam may include taking the patient’s temperature to see if there is a fever. The doctor will examine the patient’s lymph nodes in the chest, neck, throat, armpit, groin, and abdomen to see whether they are enlarged. The doctor may also assess the size of the patient’s liver and spleen.
- **Blood Tests**
 - **CBC with differential.** This test measures the number of blood cells in a sample that includes red blood cells, white blood cells and platelets. There are several types of white blood cells. The “differential” counts the number of each type of white blood cell in the sample. These tests give a picture of a patient’s overall health.

- **Metabolic panel.** A group of blood tests that measure the levels of certain substances released into the blood by organs and tissues in the body. These substances include electrolytes (such as sodium, potassium and chloride), fats, proteins, glucose (sugar) and enzymes. Blood chemistry tests give important information about how well a person's kidneys, liver and other organs are working. These tests are not used to diagnose PTLDs, but an abnormal amount of a particular substance in the blood may be a sign of a PTLD infiltration into an organ, or may indicate other health problems.
- **Lactate dehydrogenase (LDH) levels.** LDH is a chemical that is found in most cells. It enters the blood when a cell is damaged. A high level of LDH is a sign of cell damage. High levels of LDH can be caused by cancer or, for example, a heart attack. In cases of lymphoma, high levels of LDH may be a sign that the cancer is more widespread, or that it will prove less responsive to treatment.
- **EBV viral load.** A test to measure the amount of Epstein-Barr Virus in the body. This is called quantitative polymerase chain reaction (Q-PCR). Assessment of EBV viral load is important for early identification and appropriate monitoring of high-risk transplant recipients.
- **Imaging Tests.** CT scans of the chest, abdomen and pelvis should be performed. In some cases, positron-emission tomography/computed tomography (PET-CT) scan of the whole body and/or MRI of the brain may be useful. These imaging tests will be used to understand whether the disease is present in the lymph nodes, the liver, the spleen or in other parts of the body.
- **Bone Marrow Aspiration and Biopsy.** In select cases, patients undergo a bone marrow aspiration and biopsy to determine whether the disease has spread to the bone marrow.

For additional information about laboratory and imaging tests, see the free LLS booklet *Understanding Lab and Imaging Tests*.

Classification/Types

Post-transplant lymphoproliferative disorders (PTLDs) are classified by the World Health Organization into the following categories:

- Plasmacytic hyperplasia
- Infectious mononucleosis-like PTLD
- Florid follicular hyperplasia
- Polymorphic PTLD
- Monomorphic PTLD (B-cell, T-cell/NK-cell types)
- Classical Hodgkin lymphoma-type PTLD

The different categories and subtypes of PTLD will help the doctor determine the best treatment plan.

Prevention

Before transplant, stem cell donors and recipients should be tested to see if there are EBV antibodies in their blood. This is particularly important in pediatric patients (children) who may have never been exposed to the EBV virus. For prevention of PTLDs, it is important to monitor patients who are at high risk for developing the disorder. High-risk situations include

- Use of stem cells from unrelated or mismatched donors
- T-cell depletion
- Anti-T-cell antibodies

High-risk patients need to be monitored frequently through blood testing. Screening of EBV levels may begin on the day of transplantation and may continue weekly, then every 2 weeks for the first three months, and then monthly. Because there is no accepted standard schedule for this testing, speak to your doctor and ask how often screening should be done. There are currently no FDA approved treatments for preventing PTLD. For patients with high levels (or viral loads) of EBV, treatments to prevent PTLDs include: reducing the amount of immunosuppressive medication, infusing the drug **rituximab (Rituxan®)** or infusing donor T cells.

Treatment

Treatment for a PTLD depends on the subtype of the disease. In any case, the first treatment approach is often reducing the immunosuppression medication. The reduction of immunosuppression drugs may allow the patient's immune system to fight the EBV-infected cells. Reduction in immunosuppression should be managed in coordination with the patient's transplant team in order to minimize the risk of GVHD or solid organ graft rejection.

Although there are no therapies approved by the FDA to treat PTLD, there are other treatment options that are commonly used. Other treatment options include using the drug **rituximab (Rituxan®)** to kill the EBV-infected B lymphocytes. For PTLD that is localized in one area of the body, surgical removal of the site of the PTLD (usually a lymph node or tumor) may be a treatment option. For patients with aggressive disease in which rituximab fails, combination chemotherapy is usually recommended.

T-cell immunotherapy with cytotoxic T lymphocytes is a treatment in which T lymphocytes are collected from the blood of another person—not the donor of the blood or organ transplant. These collected T cells are exposed to certain proteins expressed by the EBV. When these T lymphocytes are infused into the patient's body, they are able to identify the EBV-positive lymphoma cells and kill them, leaving other normal tissues in the body unharmed. Only a few cancer centers in the United States have this treatment available, and all patients receiving this therapy must be on research protocols.

Treatments Under Investigation

Every new drug or treatment regimen available today has gone through a series of studies called clinical trials before it became a part of standard therapy. Clinical trials are carefully designed and reviewed by expert clinicians and researchers to ensure safety and scientific accuracy. Participation in a carefully conducted clinical trial may be the best available therapy. Patient participation in past clinical trials has resulted in the therapies we have today.

LLS Information Specialists, at (800) 955-4572, can offer guidance on how patients can work with their doctors to determine if a specific clinical trial is an appropriate treatment option. Information Specialists can offer guidance and conduct individualized clinical-trial

searches for patients, family members and healthcare professionals. When appropriate, Information Specialists can refer patients for personalized clinical-trial navigation by trained nurses, which is available through the LLS Clinical Trial Support Center.

Research Approaches. Scientific research is being done to learn more about PTLDs: how best to treat them and how to provide patients the best care. The following treatments are under study in clinical trials for the treatment of patients with PTLD.

Tabelecleucel (tab-cel™) is a T-lymphocyte product targeted against antigens expressed by EBV. Tabelecleucel is in Phase 3 clinical trials for EBV-PTLD following allogeneic stem cell transplant and solid organ transplant. (Rituximab-refractory means that the patient's disease has not responded to the drug rituximab.)

Brentuximab vedotin (Adcetris®) is currently approved for the treatment of patients who have Hodgkin lymphoma and anaplastic large cell lymphoma. The CD30 antigen is not commonly found on healthy cells, but approximately 70 to 80 percent of PTLD cells express CD30. The brentuximab portion of the drug is a monoclonal antibody that targets the CD30 antigen on the surface of cancer cells. When it attaches to the cancer cell, it allows the antibody drug to enter the cell and ultimately leads to death of the cancer cell. Brentuximab vendotin is being studied in many CD30-positive lymphoid malignancies and may have a role in CD30-positive PTLDs.

Patient Outcomes

Reported rates of survival in PTLDs vary, depending on the subtype of PTLD. All patients should discuss survival information with their doctors. It is important to remember that outcome data can only show how other people with PTLDs respond to treatment; it cannot predict how any one person will respond.

PTLDs are some of the most severe diseases that occur following allogeneic stem cell transplant or solid organ transplant. Although outcomes after allogeneic stem cell transplantation have traditionally been quite poor, over the past twenty years, survival rates have improved with the introduction of new approaches to treating PTLD. It is important to speak to your doctor about your specific diagnosis and how it may be successfully treated.

Acknowledgment

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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 chapters throughout the United States and in Canada. To find the chapter nearest to you, visit our Web site at www.LLS.org/chapterfind or contact:

The Leukemia & Lymphoma Society
3 International Drive, Suite 200
Rye Brook, NY 10573
Contact an Information Specialist at (800) 955-4572
Email: infocenter@LLS.org

LLS offers free information and services for patients and families touched by blood cancers. The following entries list various resources available to you. Use this information to learn more, to ask questions, and to make the most of your healthcare team.

Consult with an Information Specialist. Information Specialists are master's level oncology social workers, nurses and health educators. They offer up-to-date disease and treatment information. Language services are available. For more information, please

- Call: (800) 955-4572 (M-F, from 9 am to 9 pm EST)
- Email: infocenter@LLS.org
- Live chat: www.LLS.org/information specialists
- Visit: www.LLS.org/information specialists

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

Co-Pay Assistance Program. LLS offers insurance premium and medication co-pay assistance for eligible patients. For more information, please

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

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

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.

One-on-One Nutrition Consultations. Access free one-on-one nutrition consultations by a registered dietitian with experience in oncology nutrition. Consultants assist callers about healthy eating strategies, side effect management and survivorship nutrition. They also provide additional nutrition resources. Please visit www.LLS.org/nutrition for more information.

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

Podcast. Listen in as experts and patients guide listeners in understanding diagnosis and treatment, and suggest resources available to blood cancer patients. *The Bloodline with LLS* is here to remind you that after a diagnosis comes hope. Visit www.LLS.org/TheBloodline for more information and to subscribe.

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

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

Clinical Trials (Research Studies). New treatments for patients are ongoing. Patients can learn about clinical trials and how to access them. For more information, please call (800) 955-4572 to speak with our LLS Information Specialist who can help conduct clinical-trial searches. When appropriate, personalized clinical trial navigation by trained nurses is also available.

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. Please visit www.LLS.org/resourcedirectory for more information.

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 2-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. Enter “depression” in the search box

Advocacy. The LLS Office of Public Policy (OPP) engages volunteers in advocating for policies and laws that encourage the development of new treatments and improve access to quality medical care. For more information, please

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

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