LEUKEMIA & LYMPHOMA SOCIETY®

Peripheral T-Cell Lymphoma

No. 25 in a series providing the latest information for patients, caregivers and healthcare professionals

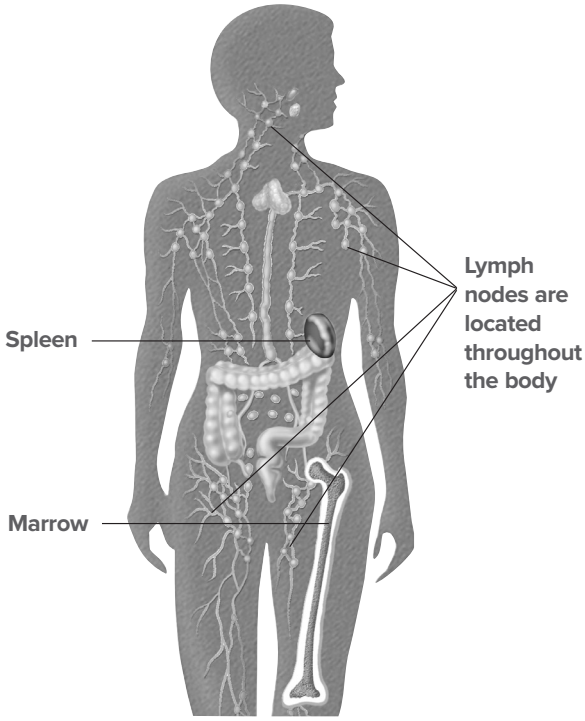
Highlights

- Peripheral T-cell lymphomas (PTCLs) are a diverse group of uncommon and often aggressive subtypes of non-Hodgkin lymphoma that develop in mature T cells and natural killer (NK) cells.
- There are over 27 different types of PTCL.
- PTCLs generally affect people older than 60 years, although they can occur at any time during adulthood. Some types of PTCL can affect children.
- Although the signs and symptoms of PTCLs vary according to the type of PTCL, some common signs and symptoms include enlarged lymph nodes, fatigue, abdominal pain, fever, night sweats, rash and unexplained weight loss.
- For most newly diagnosed cases of PTCL, the initial treatment is usually combination chemotherapy.
- Clinical trials are underway to study the efficacy and safety of potential new drugs and drug combinations to treat PTCL.

Introduction

"Lymphoma" is the name for many different types of cancer that start in the lymphatic system, specifically in a type of white blood cell called a "lymphocyte." The lymphatic system is part of the body's immune system. It is made up of tissues and organs that produce, store and carry lymphocytes throughout the body to fight infections and diseases. The lymphatic system includes the lymph nodes, spleen, thymus, tonsils and bone marrow (see **Figure 1**, below).

Figure 1. The Lymphatic System



The lymphatic system is part of the immune system. The normal immune system helps to protect the body from infection. The marrow, lymph nodes and spleen are some of the parts of the immune system. There are about 600 lymph nodes located throughout the body.

Lymph nodes and other lymphatic tissues that are commonly involved in lymphoma include those around the ears and jaw, in the tonsils and adenoids, in the front and back of the neck, above and below the collar bone, in the armpit, near the elbow, in the chest, in the abdomen, in the pelvis and in the groin. The spleen contains many clusters of lymphocytes that can become malignant and multiply, leading to the enlargement of the spleen. The gut-associated (intestinal) lymph tissue may also be the site of lymphoma development.

Support for this publication provided by Seagen®

Lymphoma is divided into two major categories: Hodgkin lymphoma and non-Hodgkin lymphoma. When lymphoma cells are examined under a microscope, Hodgkin lymphoma cells have a particular appearance and contain Reed-Sternberg cells which are mature, malignant cells that are unusually large and have more than one nucleus. Non-Hodgkin lymphoma cells look different under the microscope and do not contain Reed-Sternberg cells.

There are more than 60 different subtypes of non-Hodgkin lymphoma. Non-Hodgkin lymphomas can start in any one of three types of lymphocytes: B lymphocytes (B cells), T lymphocytes (T cells) and natural killer (NK) cells. B cells make antibodies to fight infection; T cells help fight infections and attack cancer cells; and NK cells attack cancer cells and eliminate viruses. B-cell lymphomas are more common than T-cell and NK-cell lymphomas.

Peripheral T-cell lymphomas (PTCLs) are a diverse group of non-Hodgkin lymphomas. This publication provides information about the most common types of PTCL. It also includes current information about the diagnosis, treatment and new treatments being investigated in clinical trials, along with support resources.

For additional information about non-Hodgkin lymphoma, visit www.LLS.org/booklets to view the free LLS booklets *Non-Hodgkin Lymphoma* and *The Lymphoma Guide – Information for Patients and Caregivers*.

About Peripheral T-Cell Lymphomas

Peripheral T-cell lymphomas (PTCLs) are a group of rare and often fast-growing non-Hodgkin lymphomas that develop from mature T cells and natural killer (NK) cells. They account for approximately 10 percent of non-Hodgkin's lymphoma cases.

A PTCL occurs when a normal, mature T cell or NK cell in the lymphatic system undergoes a change (mutation) to the DNA (deoxyribonucleic acid) that causes it to grow uncontrollably. As the abnormal lymphoma cells begin to multiply, they build up and form a mass (tumor). These masses generally develop in the lymph nodes or in lymphatic tissue found in organs such as the stomach, intestines or skin. In some cases, a PTCL involves the blood and the bone marrow (the spongy tissue in the hollow, central cavity of bones, where blood cell formation occurs). Over time, lymphoma cells can spread to tissue and organs outside the lymphatic system.

PTCLs generally affect people aged 60 years and older, and they are diagnosed slightly more often in men than in women. However, younger adults and children are sometimes diagnosed with a PTCL.

PTCL is a rare disease in the United States. There are some types of PTCL that are more common in Asia, sub-Saharan Africa and the Caribbean. Although the global variation in PTCL cases is not fully understood, studies indicate that exposure to specific viruses such as the Epstein-Barr virus (EBV) and the human T-cell lymphotropic virus-1 (HTLV-1) may play a role in the development of specific types of PTCL.

While there are over 27 different types of PTCL, the information in this publication focuses on the more common types of PTCL. These include:

- Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)
- Anaplastic large cell lymphoma (ALCL)
- Primary cutaneous anaplastic large cell lymphoma (pcALCL)
- Angioimmunoblastic T-cell lymphoma (AITL)
- Extranodal natural killer (NK)/T-cell lymphoma, nasal type (ENK/TCL)
- Adult T-cell leukemia/lymphoma (ATLL)
- Enteropathy-associated T-cell lymphoma (EATL)
- Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)
- Hepatosplenic T-cell lymphoma (HSTCL)
- Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)
- Primary cutaneous gamma/delta T-cell lymphoma (PCGD-TCL)

There is another group of T-cell lymphomas that begin in the skin called "cutaneous T-cell lymphomas." A PTCL that begins in the lymph nodes or another part of the body and then spreads to the skin is not considered a cutaneous lymphoma because it did not start in the skin. Cutaneous T-cell lymphomas consist of a number of different diseases with various signs and symptoms, treatment approaches and outcomes.

For specific information about lymphomas that start in the skin, visit www.LLS.org/booklets to view the free LLS booklet *Cutaneous T-Cell Lymphoma*.

While PTCLs develop from mature T cells, there is a type of cancer that begins in immature T cells called "T-cell lymphoblastic leukemia/lymphoma." It may be diagnosed as either leukemia or lymphoma or both. Patients with lymphoblastic lymphoma generally benefit from treatment with acute lymphoblastic leukemia-like regimens versus traditional lymphoma therapy.

For more information about T-cell acute lymphoblastic leukemia/lymphoma, visit www.LLS.org/booklets to view the free LLS booklets *Acute Lymphoblastic Leukemia (ALL) in Adults* and *Acute Lymphoblastic Leukemia (ALL) in Children and Teens*.

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 in an examination or a lab test result. A symptom is a change that a patient can see or feel.

PTCLs can affect various parts of the body including the lymph nodes, skin, gastrointestinal tract, liver and spleen. Patients' signs and symptoms may vary depending on their type of PTCL. Signs and symptoms may include:

- Painless swelling of one or more lymph nodes that can occur anywhere in the body including the neck, armpit or groin
- Tiredness
- Rash
- Abdominal pain, nausea, vomiting and/or diarrhea
- Enlargement of the liver and spleen
- B symptoms
    - Fever
    - Night sweats
    - Weight loss without dieting

Diagnosis and Pretreatment Testing

A person may have certain signs and symptoms of lymphoma, but laboratory tests are needed to confirm the diagnosis and the specific subtype of lymphoma. An accurate diagnosis helps the doctor to:

- Estimate how the disease will progress
- Determine the appropriate treatment

If your doctor suspects that you may have lymphoma, he or she will ask about your health history and do a physical exam to look for signs of lymphoma. The doctor will examine you and pay special attention to your lymph nodes and other areas of the body that may be affected including the skin, the spleen and the liver.

Biopsy. If you have signs or symptoms of lymphoma, you may undergo a biopsy to determine whether you have lymphoma or another condition. A biopsy is a procedure to remove a sample of cells from the body so that it can be examined under a microscope.

Most PTCLs are diagnosed by removing either all or part of an involved lymph node and examining the tissue under a microscope. The preferred and most common type of biopsy is called an "excisional biopsy." In this type of biopsy the whole lymph node is removed (excised). If the lymph node is just under the skin, the biopsy procedure is usually simple and can sometimes be done with a numbing medication (local anesthetic). If the lymph node is deep inside the chest or abdomen (stomach area), you may be sedated or receive general anesthesia.

PTCLs can develop in parts of the body that do not involve lymph nodes such as the skin and intestines. When lymphoma is suspected in organs or tissues outside of the lymph nodes, the biopsy sample is taken from the tissue that is involved.

The biopsy tissue samples are sent to a hematopathologist (a doctor who has special training in diagnosing blood diseases). The hematopathologist views the samples under a microscope to examine the size and shape of the cells and how they are arranged. If lymphoma is found, additional tests are done on the samples to determine the subtype of lymphoma.

PTCLs are rare, and there are numerous types, so making an accurate diagnosis can be challenging. It requires an experienced hematopathologist. A second opinion from an experienced lymphoma hematopathologist may be needed to confirm a diagnosis.

Flow cytometry. This lab test can detect specific types of cancer cells based on the antigens, or proteins, on the surface of the cells. The findings are used to identify lymphoma cells and help doctors to diagnose specific subtypes of lymphoma. The pattern of the surface proteins is called the "immunophenotype."

Depending on the type of lymphoma, the lymphoma cells can have different antigens on their surfaces. Certain antigens, called "cluster of differentiation (CD) proteins," are helpful in identifying the type of lymphoma cells.

Genetic testing. These tests look closely at the chromosomes and DNA in the lymphoma cells for specific chromosomal abnormalities and genetic mutations. PTCLs are often associated with rearrangements in the *TCR* (T-cell receptor) genes. Also, many people with anaplastic large cell lymphoma have a translocation between chromosomes 2 and 5. A translocation is a genetic change in which a piece of one chromosome breaks off and attaches to another chromosome. As technology advances, additional chromosomal abnormalities and gene mutations may be identified to help better classify PTCLs and develop new treatments.

Other tests used to diagnose and/or stage PTCL include

Imaging tests. These tests, CT (computed tomography), PET (positron emission tomography), and MRI (magnetic resonance imaging) scans can show where the lymphoma is located in the body and provide information that helps the doctor to determine the stage of the PTCL.

Blood tests. In some cases, the findings from blood tests can help doctors determine how advanced the lymphoma is. Blood tests may include a:

- Complete blood count (CBC). This test measures different components of the blood. The results include counts of red blood cells, white blood cells and platelets.
- Comprehensive metabolic panel. This panel often includes tests for up to 14 chemicals in the blood. Chemicals in the blood come from the liver, bones and other organs. Abnormal levels can be caused by cancer or other health problems.
- Lactate dehydrogenase (LDH) test. This test measures the level of LDH in the blood. LDH is a protein found in most cells. When a cell is damaged, LDH is released in the bloodstream. High levels of LDH in the blood can be caused by cancer and can be a sign that the cancer is widespread and treatment is needed soon.
- Human T-cell lymphotropic virus (HTLV)-1. HTLV-1 is a type of virus that infects T cells and can cause leukemia and lymphoma. Testing for the presence of HTLV-1 provides important information for diagnosing a type of T-cell lymphoma. A positive test result for the virus can lead to the diagnosis of adult T-cell leukemia or lymphoma rather than a diagnosis of peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS).

Bone marrow aspiration and biopsy. In some patients with PTCL, the disease has spread to the bone marrow at the time of diagnosis. The findings from a bone marrow aspiration and biopsy can determine whether or not there are lymphoma cells in the bone marrow. This information helps the doctor to evaluate the potential benefit of specific therapies.

Bone marrow aspiration and biopsy are two procedures that remove bone marrow cells and test them for abnormalities. Generally, both procedures are done at the same time. The samples are usually taken from the hip bone after medicine has been given to numb the skin and surface of the bone. Bone marrow has both a solid and a liquid component. For a bone marrow aspiration, a special hollow biopsy needle is inserted through the hip bone into the bone marrow to remove (aspirate) a liquid sample that contains bone marrow cells. For a bone marrow biopsy, a wider gauge needle is used to remove a sample that contains bone and bone marrow. Both samples are sent to the lab where they are examined.

Visit www.LLS.org/booklets to view the free LLS booklets *Understanding Lab and Imaging Tests* and *Understanding Genetics*.

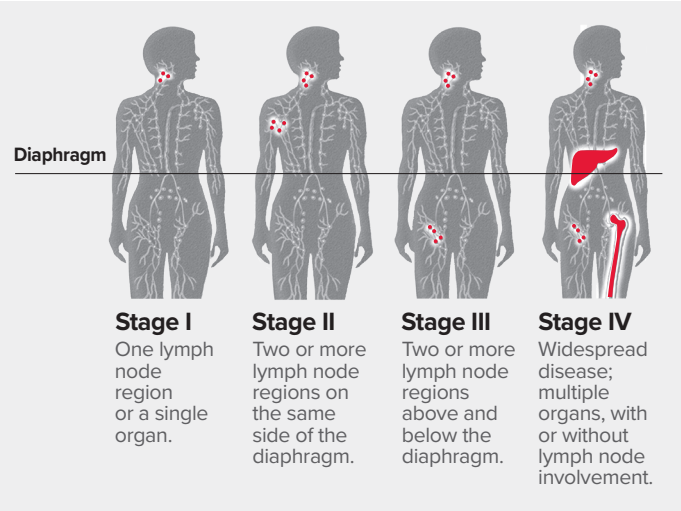
Staging

Staging is the process of determining how much cancer is in the body and where it is located. Tests that are used to stage PTCLs include:

- Blood tests
- Bone marrow aspiration and biopsy. These tests determine whether the disease has spread to the bone marrow
- Imaging tests. These tests are used to determine whether the cancer is present in the deep lymph nodes, liver, spleen or other parts of the body

The Ann Arbor Staging System is the most common system used for staging all subtypes of non-Hodgkin lymphoma. The Ann Arbor system is divided into four stages. Each stage is based on where the disease is located in the body. See **Figure 2**, on page 5 for descriptions of the stages.

Figure 2. Lymphoma Stages



Prognostic Factors

Certain factors can affect a patient's prognosis (chance of recovery or cure). These are called "prognostic factors." Doctors use prognostic factors to help predict how a patient's PTCL is likely to respond to treatment. These factors help doctors plan the most appropriate initial treatment regimen as well as when or whether to consider stem cell transplantation as a treatment option.

The International Prognostic Index (IPI). The IPI is a scoring system that uses known risk factors to predict overall survival and guide treatment decisions. This information helps doctors to determine appropriate care for patients who have been treated for aggressive lymphomas and predict risk of relapse.

One point is assigned for each of the following risk factors:

- Age greater than 60 years
- Stage III or IV disease
- More than one lymph node involved
- An elevated serum lactate dehydrogenase (LDH) level
- Performance status (which uses a scale to evaluate a person's ability to perform daily tasks of living without help) score of 2 or greater.

A person is assigned to an IPI risk group based on his or her IPI score. The IPI risk group predicts the risk of disease relapse. Each point (risk factor) represents some increased risk for disease recurrence. The total number of points identifies the following risk groups: low risk (0-1 point); low-intermediate risk (2 points); high-intermediate risk (3 points); high risk (4-5 points).

The Prognostic Index for PTCL-U (PIT). This prognostic index is used mainly for peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS). It separates PTCL-NOS patients into more specific prognostic groups than the IPI.

The Prognostic Index for PTCL-NOS is based on the following four risk factors:

- Age greater than 60 years
- A performance status score of 2 or greater
- An above-normal serum lactate dehydrogenase (LDH) level
- Bone marrow involvement.

Two points are given for being between the age of 61 and 74 and for having a serum LDH level greater than 3. Three points are given for being age 75 or older. The total number of points assigns patients to one of four risk groups: group 1 (0 points); group 2 (1 point); group 3 (2 points) and group 4 (3 and 4 points).

Patients should discuss risk factors with their doctor in order to understand treatment options, including participation in clinical trials.

Treatment Planning

Once you learn that you have PTCL, you need to decide where to get treatment. A PTCL diagnosis is associated with a wide range of outcomes, so it is essential to seek treatment in a center with doctors experienced in caring for patients who have PTCL.

PTCLs are uncommon, so it is important to choose a doctor who specializes in treating PTCLs and knows about the most up-to-date treatments (a hematologist-oncologist). A hematologist-oncologist is a doctor who specializes in treating blood cancers. It is important for you and your doctor to discuss all treatment options, including treatments being studied in clinical trials.

If you need help locating a treatment center near you, or if you need assistance finding an appropriate clinical trial, contact an LLS Information Specialist by calling (800) 955-4572 or by going to the LLS website at www.LLS.org/InformationSpecialists.

For more information about choosing a doctor and a treatment center, visit www.LLS.org/booklets to view the free LLS booklet *Choosing a Blood Cancer Specialist or Treatment Center*.

Treatment for Newly Diagnosed Patients

New treatments may have been approved since this publication was printed. Check www.LLS.org/DrugUpdates or call (800) 955-4572.

Before you begin treatment, you and your doctor will discuss all your treatment options, their risks and benefits. One option may be a clinical trial. Take an active role in making treatment decisions. Carefully consider all your available options including the possibility of participating in a clinical trial.

Typically, combination chemotherapy is the initial treatment for newly diagnosed cases of PTCL. Although there are specific treatment approaches for different types of PTCL, most nodal (cancer sites in the lymph nodes) PTCLs are treated with:

- New combinations of chemotherapies being studied in clinical trials (preferred)
- **Brentuximab vedotin (Adcetris®)** in combination with **cyclophosphamide**, **doxorubicin**, and **prednisone**. Brentuximab vedotin is approved by the Food and Drug Administration (FDA) for treatment of patients with previously untreated systemic anaplastic large cell lymphoma or other CD30-expressing PTCLs, including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified.
- **CHOP** (cyclophosphamide [Cytoxan®], doxorubicin [hydroxydoxorubicin], vincristine [Oncovin®], prednisone)
- **CHOEP** (cyclophosphamide [Cytoxan®], doxorubicin [hydroxydoxorubicin], vincristine [Oncovin®], etoposide [Etopophos®], prednisone)
- **Dose-adjusted EPOCH** (etoposide [Ethopophos®], prednisone, vincristine [Oncovin®], cyclophosphamide [Cytoxan®], doxorubicin [hydroxydoxorubicin])
- High-dose chemotherapy and autologous stem cell transplantation as part of initial therapy

Some types of PTCL are more often associated with a better prognosis than other types of PTCL. These include

- Anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL)
- ALK-negative anaplastic large cell lymphoma treated with brentuximab vedotin and chemotherapy.
- Localized extranodal natural killer (NK)/T-cell lymphoma, for which localized radiotherapy and anthracycline-based chemotherapy are usually recommended.

See the table *Most Common Types of Peripheral T-cell Lymphomas* on page 8.

Treatment for Patients with Relapsed or Refractory PTCL

New treatments may have been approved since this publication was printed. Check www.LLS.org/DrugUpdates or call (800) 955-4572.

A common standard treatment approach has not been identified for patients who have relapsed or refractory PTCL. Patients who have relapsed or refractory disease should ask their doctors about the possibility of participating in an appropriate clinical trial.

Drugs that are FDA approved for relapsed and refractory PTCL include:

- **Brentuximab vedotin (Adcetris®)**, is a CD30-directed antibody-drug conjugate. It is given intravenously (by IV) and and is FDA approved for treatment of patients with systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multiagent chemotherapy regimen and for patients with primary cutaneous anaplastic large cell lymphoma (pcALCL) who have received prior systemic therapy.
- **Belinostat (Beleodaq®)**, a histone deacetylase (HDAC) inhibitor. It is given by IV and is FDA approved for the treatment of patients who have relapsed/refractory PTCL.
- **Pralatrexate (Folotyn®)**, a metabolic inhibitor that has been shown to reduce tumor size. It is given by IV and is FDA approved for the treatment of patients who have relapsed/refractory PTCL.

- **Romidepsin (Istodax®)** is a histone deacetylase (HDAC) inhibitor. It is given by IV and is approved by the FDA for treatment in patients who have received at least one prior therapy.
- **Crizotinib (Xalkori®)** is a kinase inhibitor approved for the treatment of pediatric patients 1 year of age and older and young adults with relapsed or refractory, systemic anaplastic large cell lymphoma (ALCL) that is ALK-positive.

Some common chemotherapy-based regimens used to treat patients with relapsed or refractory disease are:

- **ICE** (ifosfamide [Ifex®], carboplatin [Paraplatin®], etoposide [Etopophos®])
- **DHAP** (dexamethasone, cisplatin [Platinol®], cytarabine [ara-C])
- **ESHAP** (etoposide [Etopophos®], methylprednisolone, cytarabine [ara-C], cisplatin [Platinol®])
- **GemOx** (gemcitabine [Gemzar®], oxaliplatin [Eloxatin™])
- **GDP** (gemcitabine [Gemzar®], dexamethasone, cisplatin [Platinol®])
- **GVD** (gemcitabine [Gemzar®], vinorelbine [Navelbine®], liposomal doxorubicin [Doxil®])

Stem Cell Transplantation

Some patients with PTCL may benefit from stem cell transplantation. The are two main types of stem cell transplantation:

- Allogeneic. The patient receives stem cells from a matched or a partially matched donor.
- Autologous. The patient's own stem cells are collected before chemotherapy, stored and then given back to the patient after he or she has completed chemotherapy.

The conditioning regimen used to prepare a patient for stem cell transplantation is typically high-dose chemotherapy and/or radiation therapy. Because the high-dose chemotherapy regimens used with stem cell transplantation can cause serious side effects or complications, stem cell transplants are not an appropriate treatment option for everyone with PTCL.

To determine whether or not you are a good candidate for a transplant, your doctor will consider your:

- Medical history
- General health
- Cancer stage
- Response to previous treatment
- Age
- Availability of a stem cell donor (in the case of allogeneic transplantation)

Autologous stem cell transplant is often recommended for patients whose disease is in first remission (no evidence of disease detected with standard tests). Allogeneic transplantation is usually suggested for patients whose disease has relapsed or for those with aggressive types of PTCL that are known to be unlikely to benefit from standard chemotherapy or autologous stem cell transplantation alone.

There is some evidence that the use of reduced-intensity conditioning prior to a stem cell transplant may be a good alternative to high-dose chemotherapy for some PTCL patients who may be at increased risk for developing treatment-related toxicities. This type of transplant may be a treatment option for older patients who cannot tolerate the high doses of chemotherapy used in preparation for a standard allogeneic stem cell transplant. However, larger studies using reduced-intensity conditioning in PTCL patients are needed to determine the effectiveness of the treatment.

For more information visit www.LLS.org/booklets to view the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.

Types of Peripheral T-Cell Lymphoma

The most common types of PTCL are listed in the table on page 8. Each type is considered a separate disease, based on its genetic and clinical features.

Most Common Types of Peripheral T-Cell Lymphoma

Type of PTCL	Characteristics	Treatment Approach
Peripheral T-Cell Lymphoma, Not Otherwise Specified (PTCL-NOS)	• The most common type of PTCL; it accounts for about 30 percent of all PTCL cases. • It usually occurs in adults between 50 and 60 years of age. • It most often appears in the lymph nodes, but it can also affect the liver, bone marrow, gastrointestinal tract and the skin. • It is an aggressive subtype that requires prompt treatment.	• All patients with this diagnosis should be evaluated for CD30 expression. • Brentuximab vedotin is FDA approved for treatment of patients with previously untreated CD30-expressing PTCL-NOS, in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy.
Anaplastic Large Cell Lymphoma (ALCL)	• A rare type of PTCL that constitutes approximately 12 percent of all PTCL cases. • It can appear throughout the body (systemic) or a specific variant called primary cutaneous ALCL that mainly or only affects the skin (see next box below). • Systemic (noncutaneous) ALCL is divided into two major groups based on the presence or absence of the abnormal form of a protein called "anaplastic lymphoma kinase (ALK)." • The overexpression of the ALK protein is caused by a chromosomal translocation that is present in 40 to 60 percent of patients. • ALK-positive ALCL is generally seen in children and younger adults. It is associated with a more favorable prognosis than ALK-negative ALCL.	• Patients with ALK-positive disease usually have a good response to the chemotherapy combination CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or other similar regimens and can achieve long-term remission or cure. • Brentuximab vedotin is FDA approved for the treatment of adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL) in combination with cyclophosphamide, doxorubicin and prednisone. • Brentuximab vedotin is approved for patients with sALCL after failure of at least one prior chemotherapy regimen. • ALK-negative patients more often experience disease relapse and may need more aggressive treatment, including high-dose chemotherapy followed by a stem cell transplant. • Crizotinib (Xalkori®) is approved for the treatment of pediatric patients 1 year of age and older and young adults with relapsed or refractory, systemic anaplastic large cell lymphoma (ALCL) that is ALK-positive.
Primary Cutaneous Anaplastic Large Cell Lymphoma (pcALCL)	• A type of ALCL that primarily affects the skin. • It is an indolent (slow-growing) lymphoma. • It is usually anaplastic lymphoma kinase (ALK) negative, although the prognosis is very good.	• Treatment is directed primarily to the skin and is based on regimens used to treat other cutaneous lymphomas. • Brentuximab vedotin is approved to treat adult patients with pcALCL who have received prior systemic therapy (treatment that reaches and affects the entire body).
Angioimmunoblastic T-Cell Lymphoma (AITL)	• One of the most common types of PTCL in the United States and Europe. • Most patients are middle aged to elderly and are diagnosed with advanced disease. • It is associated with B cells infected with the Epstein-Barr virus. • Common symptoms include enlarged lymph nodes, enlarged liver and spleen, rash, fever, weight loss and autoimmune disorders, such as autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP).	• Brentuximab vedotin is approved for the treatment of previously untreated CD30-expressing AITL in combination with cyclophosphamide, doxorubicin, and prednisone. • Some patients are treated with standard chemotherapy, followed by stem cell transplantation. • New chemotherapy combinations either with or without stem cell transplantation are being evaluated in clinical trials.
Extranodal Natural Killer (NK)/T-cell Lymphoma, Nasal Type (ENK/TCL)	• Most often originates from natural killer (NK) cells but in some cases derives from T cells. • It is a rare and aggressive type of PTCL that accounts for less than 1 to 2 percent of all non-Hodgkin lymphomas. • It has a higher incidence in Asia, Central America and South America. • It affects the nasal area and paranasal areas, including the lining of the nose, the sinus areas behind the nose and cheeks and the upper airway at the back of the throat. • It can also manifest in the skin, adrenal gland, gastrointestinal tract and testes. • It is associated with the Epstein-Barr virus.	• Treatment typically consists of chemotherapy almost always combined with radiation treatment. Occasionally, radiation therapy alone may be recommended. • Chemotherapy regimens used to treat this disease include - VIPD (etoposide, ifosfamide, cisplatin, dexamethasone) - Pegaspargase-containing regimens often with methotrexate and/or gemcitabine - SMILE (dexamethasone, methotrexate, ifosfamide, pegaspargase, etoposide) - DeVIC (dexamethasone, etoposide, ifosfamide, carboplatin). • Clinical trials with checkpoint inhibitors and therapies that target the Epstein-Barr virus are under study.

(Continued)

Most Common Types of Peripheral T-Cell Lymphoma (continued)

Type of PTCL	Characteristics	Treatment Approach
Adult T-Cell Leukemia/ Lymphoma (ATLL)	• Rare and aggressive type of PTCL that is associated with the human T-cell lymphotropic virus-1 (HTLV-1). • HTLV-1 is transmitted through sexual intercourse, childbirth, blood transfusions, shared needles and breast milk. • There is a higher incidence in people from some parts of Japan, the Caribbean, Central and South America, the Middle East and tropical Africa. • It can affect the blood, lymph nodes, skin and other areas. • There are four separate types of ATLL. Two are slower-growing forms (smoldering ATLL, chronic ATLL) and two are more aggressive forms (acute leukemic and acute lymphoma ATLL).	• Smoldering and chronic ATLLs are slow-growing at diagnosis and may occasionally be managed with a "watch-and-wait" approach, interferon or milder therapies. • The acute forms of ATLL are more aggressive and require prompt treatment. Patients may initially respond to chemotherapy, but disease relapses are common and the long-term prognosis is unfavorable. • Clinical trials are underway to evaluate new treatments.
Enteropathy-Associated T-Cell Lymphoma (EATL) and Monomorphic Epitheliotropic Intestinal T-cell Lymphoma (MEITL)	• EATL is a lymphoma of the gastrointestinal tract that is associated with celiac disease, a chronic intestinal disorder caused by a hypersensitivity to gluten proteins found in wheat, rye and barley. • MEITL (formerly called "EATL type II") is a lymphoma of the gastrointestinal tract that is NOT associated with celiac disease. • EATL is typically seen in patients of northern European descent. • MEITL is more common in Asia but can occur in people of any race or ethnicity. • Common signs and symptoms include stomach pain, weight loss, bowel obstruction, gastrointestinal bleeding or bowel perforation.	• Treatment for patients with EATL and MEITL may include chemotherapy regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). Often more intensive regimens are preferred. Other components of treatment may include surgery and stem cell transplantation. • Although not a treatment, a gluten-free diet is advised.
Hepatosplenic T-cell Lymphoma (HSTCL)	• It is an extremely rare and aggressive PTCL. • It starts in the liver and/or spleen and bone marrow. • It usually occurs in young men with a median age of around 35 years. • It is associated with autoimmune disorders and long-term immunosuppression.	• Treatment includes combination chemotherapy and, in most cases, stem cell transplantation. • Allogeneic stem cell transplantation should be considered in patients who achieve remission.
Subcutaneous Panniculitis-like T-cell Lymphoma (SPTCL)	• It is a very rare form of skin lymphoma. • It occurs primarily in the subcutaneous fat tissue, where it causes nodules to form. • Symptoms may include fever, chills, weight loss and oral mucosal ulcers. • It is usually indolent (slow growing).	• Treatment most often includes mild therapies such as low-dose methotrexate or immune suppressive therapy such as cyclosporine. • Other milder therapies may be used as well. • Less often, combination chemotherapy may be used.
Primary Cutaneous gamma/delta T-cell lymphoma (PCGD-TCL)	• It is a very rare type of lymphoma. • It is an aggressive skin lymphoma that has similar signs and symptoms to subcutaneous panniculitis-like lymphoma (SPTCL). See SPTCL above. • An expert hematopathologist or dermatopathologist should assist in distinguishing between PCGD-TCL and SPTCL.	• Often treated like the hepatosplenic T-cell lymphomas (HSTCL). See HSTCL above.

Treatment Complications and Side Effects

Peripheral neuropathy. This is a nerve problem that causes pain, numbness, tingling, swelling or muscle weakness in different parts of the body. It usually begins in the hands or feet and gets worse over time. Peripheral neuropathy can be caused by chemotherapy regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and the medication brentuximab vedotin, both of which are used in the treatment of PTCL. If you notice any symptoms of peripheral neuropathy, contact your doctor right away. Your doctor can use different strategies to manage the problem. These include adjusting the dosage of certain medications and the use of physical therapy, medication and complementary treatments such as acupuncture. Early diagnosis and treatment offer the best opportunity for controlling your symptoms and preventing further nerve damage.

Tumor lysis syndrome (TLS). This syndrome occurs when a large number of cancer cells die within a short period of time. The dead cells release their contents into the bloodstream changing the normal balance of chemicals in the blood. If the body cannot clear the waste released by the cancer cells, serious electrolyte imbalances may cause serious damage to organs, including the kidneys, heart, and liver. TLS is usually observed within 12 to 72 hours after the start of therapy. The treatment team must monitor for signs and symptoms of TLS including nausea, vomiting, shortness of breath and seizures. Patients can be given drugs such as **allopurinol (Zyloprim®)** or **rasburicase (Elitek®)** to prevent or lessen the effects of TLS.

Infection. Cancer and cancer treatments often cause drops in blood counts. When the white blood cell count is low, there is an increased risk of infection. Your doctor will try to prevent and treat any infections that develop. Many precautions are taken to reduce the risk of infection.

Other side effects. Chemotherapy affects tissues that normally have a high rate of cell turnover. The skin, hair follicles and the lining of the mouth and intestines may be affected. Common side effects may include:

- Mouth ulcers
- Diarrhea
- Temporary hair loss
- Rashes
- Nausea and vomiting
- Fatigue

Inform your doctors about any side effects you experience. Your doctor may prescribe medication to prevent or relieve side effects, suggest ways to prevent or minimize side effects, or change dosage or treatment schedules to prevent side effects from getting worse.

Treatments Undergoing Investigation

New approaches to PTCL treatment are being studied in clinical trials that hold the promise of increasing the rate of remission and reducing deaths and treatment-related toxicities. Many clinical trials are being supported by LLS research programs.

Clinical Trials. Every new drug or treatment regimen goes through a series of studies called “clinical trials” before it becomes part of standard therapy. Clinical trials are carefully designed and reviewed by expert clinicians, researchers and patient advocates to ensure safety and scientific accuracy. Participation in a carefully conducted clinical trial may be the best available treatment option and should be considered each time treatment is discussed with the doctor. Patient participation in past clinical trials has resulted in the therapies we have today.

LLS Information Specialists, available at (800) 955-4572, offer guidance on how patients can work with their doctors to determine if a specific clinical trial is an appropriate treatment option. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. When appropriate, patients and caregivers can work with Clinical Trial Nurse Navigators who can help find clinical trials and personally assist them throughout the entire clinical-trial process. Visit www.LLS.org/CTSC for more information.

Research Approaches. Until recently, treatment approaches for patients with PTCL were similar to treatment regimens developed for patients with B-cell lymphomas. However, these treatments have proven to be largely ineffective for PTCL patients. A number of new approaches that use new combinations of drugs or target specific molecular pathways of T-cell lymphomas are being studied in clinical trials.

Numerous approaches are under study in clinical trials for the treatment of patients with PTCLs. Some of the classes of novel therapies and drugs under investigation include:

- **Monoclonal antibodies** (types of protein that can bind to tumor cells) such as:
  - **Mogamulizumab (Poteligeo®)**
  - Monoclonal antibodies and monoclonal antibodies linked to medicines (antibody drug conjugates) to target CD47, CD25, KIR3DL2, ICOS
- **Small molecule inhibitors (targeted therapies)** that target pathways in different lymphomas: there are many of these types of treatments in development including JAK/STAT, SYK and PI3K inhibitors
- **Tyrosine kinase inhibitors** that block the actions of enzymes called tyrosine kinases that can cause lymphoma cells to grow and divide uncontrollably. The FDA has accepted for review a supplemental New Drug Application for **crizotinib (Xalkori®)** for the treatment of pediatric patients with relapsed or refractory systemic anaplastic large cell lymphoma (ALCL) that is ALK-positive.
- **Immunomodulatory drugs** that regulate the function of the immune system and have the capability of slowing the rate at which cancer cells grow and multiply such as **Lenalidomide (Revlimid®)**.
- **Histone deacetylase (HDAC) inhibitors** that cause a chemical change that stops cancer cells from dividing such as:
  - **Romidepsin (Istodax®)**
  - **Belinostat (Beleodaq®)**
- **Chimeric antigen receptor (CAR) T-cell therapy** is a type of immunotherapy that consists of engineering a patient's own immune cells to recognize and then attack cancerous cells. This approach has shown very promising results in patients with some blood cancers. CAR T-cell therapy is being used to treat B-cell lymphoma and leukemia and studies of CAR T-cell therapy to treat T-cell lymphoma are just beginning.

  Visit www.LLS.org/booklets to view the free LLS booklet *Chimeric Antigen Receptor (CAR) T-Cell Therapy* Facts.

Treatment Outcomes

Most types of PTCL are aggressive lymphomas and tend to have poor prognoses, but survival rates can vary depending on a patient's type of PTCL and other prognostic factors. However, for patients with PTCL, the future holds promise. Targeted agents and biomarker-driven therapies are being tested in clinical trials and showing encouraging treatment responses.

Acknowledgement

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 chapters throughout the United States and in Canada. To find the chapter nearest to you, visit our website 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, treatment and support information. Language services (interpreting and translation) are available. Please contact our Information Specialists or visit our website for more information.

- Call: (800) 955-4572 (Monday through Friday, from 9 am to 9 pm ET)
- Email: infocenter@LLS.org
- Live chat: www.LLS.org/InformationSpecialists
- Visit: 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. When appropriate,

patients and caregivers can work with Clinical Trial Nurse Navigators who will help find clinical trials and personally assist them throughout the entire clinical trial process. Visit www.LLS.org/CTSC for more information.

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.

LLS Health Manager™ App. This free mobile app helps you manage your health by tracking side effects, medication, food and hydration, questions for your doctor, and more. Export the information you've tracked in a calendar format and share it with your doctor. You can also set up reminders to take medications, hydrate, and eat. Visit www.LLS.org/HealthManager to download for free.

Financial Assistance. LLS offers financial support including insurance premium and medication co-pay assistance, as well as travel and other needs, to eligible individuals with blood cancer. For more information, please

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

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 provided by a registered dietitian who has experience in oncology nutrition. Dietitians assist callers with information about healthy eating strategies, side effect management and survivorship nutrition. They also provide additional nutrition resources. Please visit www.LLS.org/nutrition to schedule a consultation or 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. *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.

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), local 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

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.

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

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

World Trade Center (WTC) Survivors. People involved in the aftermath of the 9/11 attacks and subsequently diagnosed with a blood cancer may be eligible for 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, lived, worked or were in school in the 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

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