Introduction

Peripheral T-cell lymphomas (PTCLs) are uncommon and aggressive types of non-Hodgkin lymphoma (NHL) that develop in mature white blood cells called “T cells” and “natural killer (NK) cells.”

NHL is the name for many different types of cancer that start in cells called “lymphocytes,” a type of white blood cell that helps the body fight infection. There are three types of lymphocytes: B lymphocytes (B cells), T lymphocytes (T cells) and natural killer cells (NK cells). NHL may arise in B cells or T cells. B-cell lymphomas are more common than T-cell lymphomas. NHLs may be indolent (slow growing) or aggressive (fast growing). For more information about NHL, please see the free Leukemia & Lymphoma Society (LLS) booklets Non-Hodgkin Lymphoma and The Lymphoma Guide – Information for Patients and Caregivers.

This publication provides descriptions of the various subtypes of PTCL. It also includes specific information on the diagnosis, stages and treatment of PTCLs; new drugs being studied in clinical trials; and support resources.

About Peripheral T-Cell Lymphoma

Between 10 percent and 15 percent of all patients with NHL have a T-cell lymphoma subtype. PTCLs generally affect people aged 60 years and older and are diagnosed slightly more often in men than in women. However, younger adults and children are also diagnosed with PTCLs. PTCL is an uncommon disease in the United States. Some forms of PTCL are more common in Asia, Africa and the Caribbean, possibly as a result of exposure to specific viruses, such as the Epstein-Barr virus (EBV) and the human T-cell leukemia virus-1 (HTLV-1).

The World Health Organization (WHO) classification system recognizes subtypes of PTCL and has grouped the diseases into three categories: nodal, extranodal and leukemic. WHO has also divided T-cell lymphomas into two groups: aggressive (fast growing) and indolent (slow growing).

PTCLs are a varied group of diseases that differ from B-cell lymphomas. Because PTCLs are less common than B-cell

Highlights

- Peripheral T-cell lymphomas (PTCLs) comprise a diverse group of uncommon and aggressive diseases in which the patient’s T cells become cancerous. T-cell lymphomas account for between 10 percent and 15 percent of all non-Hodgkin lymphomas (NHLs).
- The World Health Organization (WHO) divides PTCLs into three categories (nodal, extranodal and leukemic) and classified subtypes within these categories of PTCLs. Getting an accurate diagnosis and knowing your PTCL subtype is important.
- PTCLs are rare in the United States and are more common in Asia, Africa and the Caribbean, possibly due to exposure to specific viruses, such as the Epstein-Barr virus (EBV) and the human T-cell leukemia virus-1 (HTLV-1).
- PTCLs generally affect people older than 60 years, although they can occur anytime during adulthood.
- Although the signs and symptoms of PTCLs vary according to the subtype, some common signs and symptoms of the diseases include fatigue, a painless swelling in the neck, armpit or groin (due to an enlarged lymph node), night sweats, rash and weight loss.
- New therapies are showing some effectiveness in treating patients who have certain subtypes of PTCL, and other potential therapies are being studied in clinical trials. However, standards of care have not been established for newly diagnosed PTCL patients or for patients who have disease that has relapsed (recurred) or is refractory (resistant to treatment).
- More research and clinical trials focusing specifically on the various subtypes of PTCL are needed to define the best management of patients who have these diseases.
Peripheral T-Cell Lymphoma

lymphomas, they are not as well understood. Techniques to distinguish and study the various subtypes of PTCL have only recently been developed. As a result, standards of care for how best to treat PTCLs have not been established for newly diagnosed patients or for patients whose disease has relapsed (recurred) or is refractory (resistant to treatment). In general, treatment outcomes have been poor with conventional chemotherapy regimens. However, a greater understanding of PTCLs and new genetic and molecular testing techniques have led to the development of new targeted drugs (see Treatment Under Study on page 4). Other therapies are being explored and tested in research laboratories and in human clinical trials designed specifically for T-cell lymphomas (see Peripheral T-Cell Lymphoma Subtypes on pages 5 and 6).

Because PTCLs are so uncommon, it is best to seek treatment at a medical center specializing in the diagnosis and treatment of NHL (see the free LLS fact sheet Choosing a Blood Cancer Specialist or Treatment Center for more information).

Another group of T-cell lymphomas is called “cutaneous T-cell lymphomas (CTCLs),” or skin lymphomas. CTCLs consist of a number of different diseases with various signs and symptoms, treatment approaches and outcomes. While there may be skin involvement with some PTCLs, CTCLs originate in the skin. CTCLs are primarily slow growing. This group of diseases is described in detail in the free LLS fact sheet Cutaneous T-Cell Lymphoma Facts.

Signs and Symptoms

The first signs of PTCL vary depending on the disease subtype. Because lymph nodes in several different areas of the body are frequently involved, the most common sign of PTCL is an enlarged, painless lymph node in the neck, armpit or groin. Enlarged lymph nodes can also appear near the ears or elbows. These lymphomas also affect various organs in the body, including the bone marrow, liver, spleen, stomach and skin. Other symptoms may include:

- Night sweats
- Fever
- Weight loss
- Rash.

Diagnosis

Most PTCLs are diagnosed by taking a small sample (a “biopsy”) of an enlarged lymph node and then examining the cells under a microscope. Generally, either the lymph node, or a part of the lymph node, is surgically removed so that the hematopathologist (a doctor who specializes in interpreting and diagnosing the physical changes caused by diseases of the blood and marrow) has enough tissue to make a firm diagnosis. Lymph node biopsy tissue can often be removed after the administration of a local anesthetic.

The cells in many subtypes of PTCLs look alike; therefore, making an accurate diagnosis may require the use of additional diagnostic tests, including blood tests, CT (computerized axial tomography), PET (positron emission tomography) scans, MRI (magnetic resonance imaging), and bone marrow biopsy.

An accurate diagnosis is the start for planning the treatment approach. An experienced hematopathologist is needed to analyze the biopsy slides. A second opinion by another hematopathologist may be necessary if there is any doubt about the diagnosis.

Treatment Planning

Every patient’s medical situation is different and should be evaluated individually by an oncologist who specializes in treating NHL. It is important for you and members of your oncology team to discuss all treatment options, including treatments being studied in clinical trials.

Staging

Knowing the stage of your disease helps members of your health care team determine the most effective course of treatment for you. The Ann Arbor Staging System is the most common system used for classifying all subtypes of NHL.

The system is divided into four stages and is based on where the disease is located in the body:

- Stage I—The cancer is in a single lymph node or lymph node region or, the cancer is in an organ or site other than a lymph node (extranodal) but has not spread to other organs or lymph nodes.
- Stage II—The cancer is in two or more lymph node regions on the same side of the diaphragm.
- Stage III—The cancer is in lymph node regions on both sides of the diaphragm, with or without partial involvement of an extranodal organ or site above or below the diaphragm.
- Stage IV—The cancer is widespread, including multiple involvements in one or more extranodal sites, such as the bone marrow.
Treatment for Newly Diagnosed Patients

Currently, newly diagnosed PTCL patients are usually treated with anthracycline-based chemotherapy regimens. Most subtypes of PTCL are treated as follows:

- CHOP (cyclophosphamide, hydroxydoxorubicin [doxorubicin], Oncovin* [vincristine], prednisone)
- CHOEP (cyclophosphamide, hydroxydoxorubicin [doxorubicin], Oncovin* [vincristine], etoposide, prednisone)
- EPOCH (etoposide, prednisone, Oncovin* [vincristine], cyclophosphamide, hydroxydoxorubicin [doxorubicin])
- Hyper-CVAD (cyclophosphamide, Oncovin* [vincristine], Adriamycin® [doxorubicin], dexamethasone); “hyper” refers to “hyperfractionation of the dose,” meaning that the chemotherapy is given in small, frequent doses to minimize side effects.
- Clinical trials with new combinations of chemotherapies (preferred).

Unfortunately, cure rates for PTCL remain low with the exception of the cure rates for:

- ALK-positive anaplastic large cell lymphoma (see Peripheral T-Cell Lymphoma Subtypes on pages 5 and 6)
- Localized extranodal NK/T-cell lymphoma, for which localized radiotherapy and anthracycline-based chemotherapy are usually recommended.

Patients with PTCL should consult with the members of their medical team about the availability of appropriate clinical trials for initial treatment (see Treatment Under Study on page 4).

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
- Elevated serum lactate dehydrogenase (LDH)
- Performance status, which uses a scale to evaluate a person’s ability to perform daily tasks of living without help.

The number of IPI ‘risk factors’ a person has defines the IPI risk group to help predict the risk of relapse. Each point represents some increased risk for disease recurrence. The total number of points identifies the following risk groups: low risk (0-1 points); low-intermediate risk (2 points); high-intermediate risk (3 points); high risk (4-5 points). For patients younger than 60 years, the risk categories are slightly different; low risk (0 points); low-intermediate risk (1 point); high-intermediate risk (2 points); high risk (3 points).

The Prognostic Index for PTCL (PIT). PIT is a prognostic index used mainly for peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS). PIT separates PTCL-NOS patients into more specific prognostic groups than the IPI. PIT is based on four risk factors: age, performance status, serum lactate dehydrogenase (LDH) and bone marrow involvement. By using these risk factors instead of the risk factors associated with the IPI, PIT has a better predictive capacity for PTCL-NOS.

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

Treatment for Patients With Relapsed or Refractory PTCL

A common standard of care has not been identified for patients with relapsed or refractory PTCL. Patients with relapsed or refractory disease should consult with the members of their medical team for information about participating in an appropriate clinical trial.

Drugs that are currently FDA approved to treat relapsed or refractory PTCL include:

- Belinostat (Beleodaq™), a histone deacetylase (HDAC) inhibitor, given intravenously (IV)
- Pralatrexate (Folotyn®), a metabolic inhibitor that has been shown to reduce tumor size and is given by IV
- Romidepsin (Istodax®), a histone deacetylase (HDAC) inhibitor, given by IV. Istodax is approved for treatment in patients who have received at least one prior therapy.

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

- ICE (ifosfamide, carboplatin, etoposide)
- DHAP (high-dose cytarabine [ara-C], dexamethasone, cisplatin [Platinol®-AQ])
- ESHAP (etoposide, methylprednisolone, cytarabine [ara-C], cisplatin [Platinol®-AQ])
- GND (gemcitabine, navelbine, dexamethasone) or other gemcitabine containing regimens.
Stem Cell Transplantation

Consolidation therapy, which consists of high-dose chemotherapy followed by a stem cell transplant, is often recommended for patients in first-time remission (no evidence of disease detected with standard tests). The exceptions are specific PTCL patients who are considered to be at low risk for relapse and patients with ALK-positive anaplastic large cell lymphoma, who usually have a good prognosis.

There are two types of stem cell transplants: autologous, in which patients receive their own stem cells, and allogeneic, in which patients receive stem cells from a matched donor. Both types of transplants are used to treat PTCLs. The use of autologous versus allogeneic transplant is being studied to know what the best option is for individual patients.

Because the high-dose chemotherapy regimens used with stem cell transplantation can cause serious side effects or complications, including bone marrow suppression and infections, stem cell transplants are not a treatment option for everyone with PTCL. To determine whether you are a good candidate for a transplant, members of your medical team will consider your

- Medical history
- General health
- Cancer stage
- Response to previous treatment
- Age.

There is some evidence that the use of reduced-intensity conditioning (RIC) 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. However, larger studies using RIC in PTCL patients are needed to determine the effectiveness of the treatment. See the free LLS booklet Blood and Marrow Stem Cell Transplantation for more information.

Treatment Under Study

Until recently, treatment approaches for patients with any type of 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. New classes of therapies that target specific molecular pathways of T-cell lymphomas are being studied in clinical trials. Some of the classes of novel therapies and drugs under investigation include

- Histone deacetylase (HDAC) inhibitors, which target “epigenetic” changes (changes that affect certain cell processes without changing the genetic makeup of the cell). Therapies include vorinostat (Zolinza®), already approved for the treatment of patients who have cutaneous T-cell lymphoma, belinostat (Beleodaq™) and panobinostat (LBH-589).
- Proteasome inhibitors, which block the action of proteasomes. A proteasome is a large cell protein that helps destroy other cell proteins when they are no longer needed. Bortezomib (Velcade®), an agent that is approved to treat patients with myeloma or mantle cell lymphoma, is currently being evaluated in clinical trials both as a single agent and in combination with conventional chemotherapy.
- Immunomodulatory drugs, a novel class of small-molecule anticancer and anti-inflammatory drugs with broad biologic activities. Lenalidomide (Revlimid®), FDA approved to treat patients with myeloma or myelodysplastic syndromes, is currently being studied to treat PTCL patients.
- Monoclonal antibodies, types of protein that can bind to tumor cells. Therapies being investigated for PTCL include alemtuzumab (Campath®), which is already approved in the treatment of chronic lymphocytic leukemia.
- Nucleoside analogs, which activate pathways that prevent cell cycle progression and repair DNA. Two examples of nucleoside analogs being studied in the treatment of PTCL are gemcitabine (Gemzar®), approved in the treatment of several solid tumor cancers including ovarian and breast cancer, and nelarabine (Arranon®). Arranon* is approved by the FDA for the treatment of relapsed or refractory PTCL subtype precursor T-cell acute lymphoblastic leukemia and precursor T-cell acute lymphoblastic lymphoma in adults and children.

Treatment Outcomes

Peripheral T-cell lymphomas comprise a group of rare and diverse diseases that are difficult to cure. As a result, standard of care for how best to treat PTCLs in newly diagnosed patients or in patients whose disease has relapsed (recurred) or become refractory (does not respond to treatment) has not been established. However, many new agents currently being tested in clinical trials (see Treatment Under Study on this page) are showing encouraging responses in the treatment of PTCLs.

Because PTCLs are so rare and may be difficult to treat, it is best to seek treatment at a medical center specializing in the diagnosis and treatment of NHL. Your medical team will then discuss what your treatment options are and whether
Peripheral T-Cell Lymphoma Subtypes

Peripheral T-Cell Lymphoma, Not Otherwise Specified (NOS)—Peripheral T-cell lymphoma, NOS is the most common type of PTCL and comprises a group of mixed T-cell diseases that do not fit into any of the other subtypes of PTCL. Most patients with PTCL-NOS will have nodal involvement, but extranodal sites, such as the liver, bone marrow, gastrointestinal tract and skin, may also be involved. This group of PTCLs is considered aggressive and in the past has usually been treated with standard CHOP (cyclophosphamide, hydroxydoxorubicin [doxorubicin], Oncovin® [vincristine], prednisone) chemotherapy at initial diagnosis. However, since the chemotherapy combination CHOP has not produced very good outcomes, doctors are currently evaluating other chemotherapy combinations for initial therapy. Other drugs that may be effective in treating patients who have PTCL-NOS include gemcitabine (Gemzar®) and bortezomib (Velcade®), which are showing response rates of about 60 percent and 30 percent, respectively. A number of small studies have demonstrated disease-free survival rates of between 35 percent and 45 percent in some patients who received high-dose chemotherapy followed by autologous stem cell transplantation. However, larger studies need to be conducted to more accurately assess the long-term effectiveness of this type of treatment. Clinical trials evaluating newer combinations of therapies are ongoing.

Anaplastic Large Cell Lymphoma—This rare T-cell lymphoma constitutes about 3 percent of all cases of lymphomas in adults and between 10 and 30 percent of all lymphomas in children. It usually affects nodal sites, although extranodal sites can also be involved. Anaplastic large cell lymphoma (ALCL) is divided into two major subtypes based on the presence or absence of a protein called “anaplastic lymphoma kinase (ALK).” Patients with ALK-positive disease usually have a good response to the chemotherapy combination CHOP (cyclophosphamide, hydroxydoxorubicin [doxorubicin], Oncovin® [vincristine], prednisone) and other similar chemotherapy combinations and can achieve long-term remission or cure. Brentuximab vedotin, (Adcetris®) also known as SGN-35, is FDA approved for the treatment of patients with systemic anaplastic large cell lymphoma (ALCL) after failure of at least one prior multi-agent chemotherapy regimen. Brentuximab vedotin is administered by injection. ALK-negative patients usually relapse and may need more aggressive treatment, including high-dose chemotherapy and a stem cell transplant.

Anaplastic Large Cell Lymphoma (Primary Cutaneous)—Primary cutaneous ALCL is thought to be a more indolent (slow-growing) lymphoma and typically affects the skin. This lymphoma is usually ALK negative, although the prognosis is fairly good.

Angioimmunoblastic T-Cell Lymphoma—Angioimmunoblastic T-cell lymphoma (AITL) accounts for between 1 percent and 2 percent of all cases of NHL and typically follows an aggressive course, although spontaneous disease regression sometimes occurs. AITL usually occurs in the lymph nodes and may affect the spleen or liver. Some symptoms may include fever, weight loss and rashes. The chemotherapy combination CHOP (cyclophosphamide, hydroxydoxorubicin [doxorubicin], Oncovin® [vincristine], prednisone) has also been commonly used for this subtype of lymphoma, but the results do not produce many long-term disease-free survivors. For this subtype of lymphoma, new chemotherapy combinations either with or without stem cell transplantation are being evaluated. For patients with relapsed disease, therapies such as immunosuppressive agents or targeted agents are being evaluated in clinical trials.

Nasal, Natural Killer (NK)/T-cell Lymphoma—Extranodal nasal, NK/T-cell lymphoma typically affects the nasal area and the paranasal sinus areas behind the nose and cheeks, although the...
Peripheral T-Cell Lymphoma can also occur at extranodal sites such as the skin, gastrointestinal tract and testes. The disease is rare in the United States, accounting for less than 1.5 percent of all NHLs. Extranodal, nasal NK/T-cell lymphoma is more commonly found in Asia and Latin America and is associated with the Epstein-Barr virus (EBV). Radiation and chemotherapy treatments are usually recommended for localized nasal NK/T-cell disease.

**Adult T-Cell Acute Lymphoblastic Lymphoma or Leukemia**—Adult T-cell acute lymphoblastic lymphoma or leukemia (ATLL), which is more commonly found in Japan and the Caribbean than in the United States, is associated with the human T-cell leukemia virus-1 (HTLV-1). The HTLV-1 virus is transmitted through sexual intercourse, childbirth, blood transfusions, shared needles and breast milk. Although people who have ATLL may initially respond to chemotherapy, the long-term prognosis is poor. Clinical trials are under way to investigate adding agents such as arsenic trioxide and bortezomib (Velcade®) as well as treatments ranging from stem cell transplantation to conventional chemotherapy regimens.

**Enteropathy-Associated Lymphoma**—This T-cell lymphoma is associated with celiac disease, a chronic intestinal disorder caused by a hypersensitivity to gluten proteins found in wheat, rye and barley. Symptoms usually include stomach pain, weight loss, gastrointestinal bleeding or bowel perforation. Treatment for patients with enteropathy-associated T-cell lymphoma includes an anthracycline-based chemotherapy regimen, nutritional supplements and, if appropriate, a gluten-free diet.

**Hepatosplenic Lymphoma**—This type of T-cell lymphoma is an extremely rare and aggressive disease that starts in the liver or spleen and usually affects young adults in their 20s and 30s. Treatment for patients with hepatosplenic T-cell lymphoma includes anthracycline-based chemotherapy and, in some cases, stem cell transplantation.

**Subcutaneous Panniculitis-Like Lymphoma**—Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is the rarest and least well-defined of the T-cell lymphomas. This lymphoma occurs primarily in the subcutaneous fat tissue, where it causes nodules to form. Symptoms include fever, chills, weight loss and oral mucosal ulcers. SPTCL may be either rapidly aggressive or indolent (slow growing). Treatment includes combination anthracycline-based chemotherapy or localized radiation.

**Precursor T-Cell Acute Lymphoblastic Lymphoma or Leukemia**—This subtype of PTCL may be diagnosed as leukemia or lymphoma or both. This cancer is found in both children and adults and is most commonly diagnosed in adolescent and adult males. Treatment for newly diagnosed patients with precursor T-cell acute lymphoblastic lymphoma or leukemia is aggressive chemotherapy and radiation. Nelarabine (Arranon®) is approved for the treatment of relapsed or refractory precursor T-cell acute lymphoblastic lymphoma or leukemia in adults and children.

**Blastic NK-Cell Lymphoma**—This T-cell lymphoma is very rare, very fast growing and difficult to treat. Patients with blastic NK-cell lymphoma should talk to their medical team about participating in promising clinical trials.

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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 or contact

**The Leukemia & Lymphoma Society**
1311 Mamaroneck Avenue
Suite 310
White Plains, NY 10605
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 lists 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 can answer general questions about diagnosis and treatment options, offer guidance and support and assist with clinical-trials searches. Language services are available.

For more information, please
- Call: (800) 955-4572 (M-F, 9 a.m. to 9 p.m. EST)
- Email: infocenter@LLS.org
- Live chat: www.LLS.org
- Visit: www.LLS.org/informationspecialists.

**Free Materials.** LLS offers free education and support publications that can either be read online or downloaded. Free print versions can be ordered.

For more information, please visit www.LLS.org/publications.

**Telephone/Web Education Programs.** LLS offers free telephone/Web education programs for patients, caregivers and healthcare professionals.

For more information, please visit www.LLS.org/programs.

**Co-Pay Assistance Program.** LLS offers insurance premium and medication co-pay assistance for certain eligible patients.

For more information, please
- Call: (877) 557-2672
- Visit: www.LLS.org/copay.

**Online Blood Cancer Discussion Boards and Chats.** Online discussion boards and moderated online chats can help cancer patients to reach out, share information and provide support.

For more information, please visit www.LLS.org/getinfo.

**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 with PTCL are under way. Many are part of clinical trials. 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 Specialists who can help conduct clinical trial searches
- Visit: www.LLS.org/clinicaltrials.

**Advocacy.** The LLS Office of Public Policy (OPP) enlists volunteers to advocate for policies and laws to speed new treatments and improve access to quality medical care.

For more information, please
- Call: (800) 955-4572
- Visit: www.LLS.org/advocacy.

**Other Resources**

**The National Cancer Institute**
(800) 422-6237
www.cancer.gov
The National Cancer Institute is part of the National Institutes of Health and is a national resource center for information and education about all forms of cancer, including peripheral T-cell lymphomas (PTCLs). The NCI also provides a clinical-trials search feature, the PDQ®Cancer Clinical Trials Registry, at the website www.cancer.gov/clinicaltrials/search-form-help, where PTCL patients can look for clinical trials for their specific subtype.

**FocusonPTCL.org**
FocusonPTCL.org (focusonptcl.org) offers comprehensive information on PTCLs, including treatment options.

**References**


Peripheral T-Cell Lymphoma


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