

Peripheral T-Cell Lymphoma

Overview

Lymphoma is the most common blood cancer. The two main forms of lymphoma are Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Lymphoma occurs when cells of the immune system called lymphocytes, a type of white blood cell, grow and multiply uncontrollably. Cancerous lymphocytes can travel to many parts of the body, including the lymph nodes, spleen, bone marrow, blood, or other organs, and form a mass called a tumor. The body has two main types of lymphocytes that can develop into lymphomas: B lymphocytes (B cells) and T lymphocytes (T cells).

Peripheral T-cell lymphoma (PTCL) refers to more than 10 different T-cell lymphomas (TCLs) that, together, account for about four percent of all patients diagnosed with NHL in the United States according to the Surveillance, Epidemiology, and End Results (SEER) program. Each particular subtype of PTCL is very rare. The most common NHL subtypes include PTCL, not otherwise specified (PTCL-NOS), anaplastic large cell lymphoma (ALCL), angioimmunoblastic T-cell lymphoma (AITL), adult T cell leukemia/lymphoma (ATLL), and cutaneous T-cell lymphoma (CTCL).

T-cell lymphomas develop in lymphoid tissues outside of the bone marrow such as the lymph nodes, spleen, gastrointestinal tract, and skin. Most are *aggressive* (fast-growing) lymphomas, with the exception of some forms of CTCL. Aggressive PTCL subtypes include PTCL-NOS, AITL, ALCL, the CTCL Sézary syndrome, enteropathy-type natural killer (NK)/T-cell lymphoma, and extranodal NK/T-cell lymphoma. The incidence of PTCL subtypes varies geographically. PTCL-NOS is more common in North America, while AITL is more common in Europe. Anaplastic lymphoma kinase (ALK)-negative ALCL is somewhat more common in Europe, while ALK-positive ALCL is more common in North America. The NK/T-cell lymphomas and ATLL are more common in Asia and seem to be related to infections with human T-lymphotropic virus type 1 (HTLV-1) and Epstein-Barr virus, respectively. For more information on PTCL, please visit the Lymphoma Research Foundation's (LRF's) *Focus On Peripheral T-Cell Lymphoma* website at www.FocusOnPTCL.org.

Subtypes of Peripheral T-Cell Lymphoma

PTCLs are classified into various subtypes, each of which is typically considered to be a separate disease based on its distinct clinical features. The four most common subtypes of PTCL—PTCL-NOS, ALCL, AITL, and CTCL—account for approximately 88 percent of all PTCL cases in the United States.

Peripheral T-Cell Lymphoma, Not Otherwise Specified (PTCL-NOS) is the most common subtype of PTCL, accounting for about 36 percent of all PTCLs, and refers to a group of diseases that do not fit into any of the other PTCL subtypes. PTCL-NOS usually occurs in adults in their 50s and 60s. Although most patients with PTCL-NOS are diagnosed with their disease confined to the lymph nodes, sites outside the lymph nodes such as the liver, bone marrow, gastrointestinal tract, and skin may also be involved. This group of PTCLs is very aggressive, requires urgent treatment, and tends to *relapse* (disease returns after treatment).

Anaplastic Large Cell Lymphoma (ALCL) is rare, accounting for about one percent of all NHLs and about 11 percent of all TCLs. Initial symptoms of ALCL can include fever, backache, painless swelling of lymph nodes, loss of appetite, and tiredness. ALCL occurs either *systemically* (throughout the body) or *cutaneously* (affects the skin). Systemic ALCL can respond well to chemotherapy and is potentially curable. *Cutaneous* (skin) ALCL is a less aggressive disease that is often preceded by a rare condition called lymphomatoid papulosis.

Patients with systemic ALCL are divided into two groups, depending on whether or not the surface of their cells express an abnormal form of a protein called ALK. The outcome for ALCL depends on whether a patient is *ALK positive* (expresses the protein) or *ALK negative* (does not express the protein). ALK-positive disease responds well to standard chemotherapy, putting most patients in long-term remission. Although a majority of ALK-negative patients initially respond to treatment, they tend to relapse within five years and are sometimes treated more aggressively, often with stem cell transplantation. For more information on ALCL, please visit LRF's *Focus On Anaplastic Large Cell Lymphoma* website at www.FocusOnALCL.org.

Angioimmunoblastic T-Cell Lymphoma (AITL) is a rare, aggressive PTCL that affects about seven percent of all patients with PTCL in the United States. Most patients are middle-aged to elderly and are diagnosed with advanced stage disease. Symptoms include high fever, night sweats, skin rash, and some types of autoimmune disorders such as autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP). As a result of these autoimmune disorders, the body's immune system does not recognize, and consequently destroys, its own cells or tissues, such as red blood cells (in the case of AIHA) or platelets (in the case of ITP).

Initially, AITL may be treated with steroids to relieve symptoms such as joint inflammation/pain and skin rash. Most patients are treated with combination chemotherapy and sometimes stem cell transplantation. For more information, view the *Angioimmunoblastic T-Cell Lymphoma* fact sheet and *Understanding the Stem Cell Transplantation Process* booklet on LRF's website at www.lymphoma.org.

Cutaneous T-Cell Lymphomas (CTCLs) are a group of T-cell lymphomas that originate in the skin. These lymphomas are generally less aggressive, have a different prognosis, and have different treatment approaches than other types of PTCLs.

The most common subtype of CTCL is mycosis fungoides, which is generally an *indolent* (slow-growing) cancer that starts in the skin and can appear as patches, plaques, or tumors. Patches are usually flat, possibly scaly, and look like a rash; plaques are thicker, raised, usually itchy lesions that are often mistaken for eczema, psoriasis, or dermatitis; and tumors are raised bumps, which may or may not ulcerate. It is possible to have more than one type of lesion. The rash can sometimes become thicker or more extensive to involve significant areas of the body.

Sézary Syndrome is a rare, aggressive form of CTCL that affects both the skin and the peripheral blood. Most cases occur in adults over the age of 60 years. The most common symptoms are swollen lymph nodes and a red, very itchy rash that covers large portions of the body. Abnormal T cells, called Sézary cells, can be seen under a microscope and are present in the blood. For more information on CTCLs, see the *Cutaneous T-Cell Lymphoma* fact sheet on LRF's website at www.lymphoma.org.

Rare Types

Adult T-Cell Leukemia/Lymphoma (ATLL) is a rare and often aggressive T-cell lymphoma that can be found in the blood (leukemia), lymph nodes (lymphoma), skin, or multiple areas of the body. ATLL has been linked to infection by HTLV-1; however, less than five percent of individuals with HTLV-1 will develop ATLL. Currently, physicians have no way of predicting which infected patients will develop ATLL.

The HTLV-1 virus is most common in parts of Japan, the Caribbean, and some areas of South and Central America and Africa. The HTLV-1 virus is believed to be transmitted through sexual contact or exposure to contaminated blood, but it is most often passed from mother to child through breastfeeding. For more information, see the *Adult T-Cell Leukemia/Lymphoma* fact sheet on LRF's website at www.lymphoma.org.

Enteropathy-Type T-Cell Lymphoma is an extremely rare and aggressive subtype that appears in the intestines and is recognized in two forms: one that is preceded by celiac disease and one that is rarely preceded by celiac disease. Chronic diarrhea and gluten sensitivity frequently precedes the former type. Other symptoms include abdominal pain and weight loss. Very specialized treatments are usually necessary to treat this unique subtype and may include surgery, combination chemotherapy such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), and stem cell transplantation in select patients.

Nasal NK/T-Cell Lymphoma develops from NK cells, which are closely related to and often have features that overlap with T cells. Although this aggressive lymphoma is very rare in the United States, it is more common in Asia and parts of Latin America. This subtype has been associated with the Epstein-Barr virus. It typically originates in the lining of the nose or upper airway at the back of the throat but may appear in the gastrointestinal tract, skin, and other organs (in which case it is referred to as *nasal type*). Treatment of nasal NK/T-cell lymphoma usually consists of radiation treatments combined with chemotherapy. Chemotherapies for this rare disease include VIPD (etoposide, ifosfamide, cisplatin, and dexamethasone), peg-asparaginase (Oncaspar) or L-asparaginase alone or combined with methotrexate and dexamethasone (AspaMetDex), DeVIC (dexamethasone, etoposide, ifosfamide, and carboplatin), or SMILE (dexamethasone, methotrexate, ifosfamide, peg-asparaginase, and etoposide).

Hepatosplenic Gamma-Delta T-Cell Lymphoma is an extremely rare and aggressive disease that involves the liver and/or spleen. It can also involve blood and bone marrow. It most often occurs in young adults and is more common in males. This subtype of PTCL can be associated with immunosuppressive treatments. Patients, especially children, treated with azathioprine and infliximab (Remicade) for Crohn's disease may be more susceptible to this type of PTCL.

As with other rare cancers, patients with enteropathy-type, nasal NK/T-cell, or hepatosplenic gamma-delta T-cell lymphomas should discuss whether clinical trials offer potential treatment options with their health care team.

Treatments Options

For most subtypes of PTCL, the initial treatment is typically a combination chemotherapy regimen, such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone), or other multidrug regimens. Because most patients with PTCL will relapse, some physicians recommend high-dose chemotherapy followed by an *autologous stem cell transplant* (in which patients receive their own stem cells that are preemptively collected). While promising, there is no firm clinical data to prove that undergoing a transplant in this setting is more beneficial than not undergoing a transplant. For more information on stem cell transplants, view the *Understanding the Stem Cell Transplantation Process* booklet on the LRF's website at www.lymphoma.org.

Patients with relapsed disease are usually treated with combination chemotherapy such as ICE (ifosfamide, carboplatin, and etoposide), followed by stem cell transplantation. However, some regimens might not be suited for everyone because of their high toxicity levels. Other therapies are also available including belinostat (Beleodaq), pralatrexate (Folotyn), romidepsin (Istodax), and brentuximab vedotin (Adcetris); the first three agents are approved by the U.S. Food and Drug Administration (FDA) for the treatment of PTCL, while brentuximab vedotin is approved for ALCL only. Patients should discuss what treatments are most appropriate for them with their physician.

Treatments Under Investigation

Many new drugs are being studied in clinical trials for the treatment of PTCL, including:

- Alisertib
- Bendamustine (Treanda)
- Bortezomib (Velcade)
- GDP (gemcitabine, dexamethasone, and cisplatin)
- Lenalidomide (Revlimid)
- Nivolumab (Opdivo)
- Panobinostat (Farydak)
- Pembrolizumab (Keytruda)
- PI3K inhibitors

It is critical to remember that today's scientific research is continuously evolving. Treatment options may change as new treatments are discovered and current treatments are improved. Therefore, it is important that patients check with their physician or with LRF for any treatment updates that may have recently emerged.

Clinical Trials

Clinical trials are crucial in identifying effective drugs and determining optimal doses for patients with lymphoma. Because PTCL is a rare disease and no standard of care is established, clinical trial enrollment is critical for establishing more effective, less toxic treatments. The rarity of the disease also means that the most novel treatments are often available only through clinical trials. Patients interested in participating in a clinical trial should talk to their physician or contact the LRF Helpline for an individualized clinical trial search by calling (800) 500-9976 or emailing helpline@lymphoma.org. For more information on clinical trials, view the *Understanding Clinical Trials* fact sheet on LRF's website at www.lymphoma.org.

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Follow-up

PTCL is generally characterized by multiple disease relapses after responses to a variety of treatments. Patients in remission should have regular visits with a physician who is familiar with their medical history and the treatments they have received. Medical tests (such as blood tests and computed tomography [CT] scans) may be required at various times during remission to evaluate the need for additional treatment.

Some treatments can cause long-term effects or late effects, which can vary based on duration and frequency of treatments, age, gender, and the overall health of each patient at the time of treatment. A physician will check for these effects during follow-up care.

Patients and their caregivers are encouraged to keep copies of all medical records and test results as well as information on the types, amounts, and duration of all treatments received. This documentation will be important for keeping track of any effects resulting from treatment or potential disease recurrences.

Support

A lymphoma diagnosis often triggers a range of feelings and concerns. In addition, cancer treatment can cause physical discomfort. One-to-one peer support programs, such as LRF's Lymphoma Support Network, connects patients and caregivers with volunteers that have experience with PTCL, similar treatments, or challenges, for mutual emotional support and encouragement. You may find this useful whether you or a loved one is newly diagnosed, in treatment, or in remission.

Resources

LRF offers a wide range of resources that address treatment options, the latest research advances, and ways to cope with all aspects of lymphoma and PTCL, including our award-winning mobile app. LRF also provides many educational activities, from in-person meetings to teleconferences and webcasts for people with PTCL, as well as disease-specific websites, videos, and e-Updates for current lymphoma information and treatment options. To learn more about any of these resources or LRF's T-Cell Lymphoma Transportation Assistance Fund, visit our websites at www.FocusOnPTCL.org, www.FocusOnALCL.org, or www.lymphoma.org, or contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org.