

Understanding Lymphoma: Peripheral T-Cell Lymphoma

Peripheral T-cell lymphoma (PTCL) refers to a rare group of different T-cell lymphomas that account for about 5%-10% of all patients diagnosed with non-Hodgkin Lymphoma (NHL) in the United States. The incidence (number of new cases) of PTCL subtypes varies across different parts of the world.

PTCLs develop in lymphoid tissues (tissues that produce, store, and carry white blood cells) outside of the bone marrow (the spongy tissue inside the bones) such as the lymph nodes (small bean-shaped structures that help the body fight infection), spleen, gastrointestinal tract (digestive system which includes esophagus, stomach, and intestines), and skin. Most PTCLs are aggressive (fast-growing) lymphomas, and include:

- PTCL-not otherwise specified (NOS)
- Angioimmunoblastic T-cell lymphoma (AITL)
- Anaplastic [a]rge cell lymphoma (ALCL)
- Enteropathy-associated T-cell lymphoma (EATL)
- Extranodal natural killer (NK)/T-cell lymphoma (ENKTL)
- Subcutaneous panniculitis-like T-cell lymphoma (SPTL)
- Hepatosplenic T-cell lymphoma (HSTCL)

There are also other types of T-cell lymphoma that are present mainly in the skin (called cutaneous T-cell lymphoma [CTCL]), which are not discussed below. For more information on CTCL, view the *Cutaneous T-Cell Lymphoma* fact sheet on the Lymphoma Research Foundation (LRF)'s website (visit lymphoma.org/publications).



COMMON SUBTYPES OF PERIPHERAL T-CELL LYMPHOMA

PTCLs are classified into subtypes – each considered a separate disease based on its distinct characteristics. The three most common subtypes — PTCL-NOS, AITL, and ALCL — account for approximately 60% of PTCL cases in the United States. Patients are usually treated with combination chemotherapy. Some patients may be considered for a stem cell transplant (SCT) after initial treatment. In this procedure, the patient is treated with high-dose chemotherapy or radiation and then receives healthy stem cells (blood-forming cells). For more information, view the *Understanding Cellular Therapy* fact sheet on LRF's website (visit lymphoma.org/publications).

Peripheral T-Cell Lymphoma-Not Otherwise Specified (PTCL-NOS) is the most common subtype of PTCL (around 30% of PTCLs in the United States) and refers to a group of lymphomas that do not fit into any of the other PTCL subtypes. PTCL-NOS usually occurs in adults in their 60s. Although most patients with PTCL-NOS are diagnosed when the disease is only located in the lymph nodes, extranodal sites (sites in the body outside the lymph nodes), such as the liver, bone marrow, gastrointestinal tract, and skin, are frequently involved. This group of PTCLs is generally aggressive and requires urgent treatment. Patients are most often treated with chemotherapy

and may be considered for a SCT following initial chemotherapy. While PTCL-NOS is potentially curable in some patients, the disease tends to relapse (returns after treatment).

Anaplastic Large Cell Lymphoma (ALCL) accounts for about 2% of lymphomas and about 15% of all PTCLs. Initial symptoms of ALCL can include fever, backache, painless swelling of lymph nodes, loss of appetite, and tiredness. ALCL can be systemic (throughout the body), cutaneous (limited to the skin), and, rarely, around breast implants (breast implant-associated [BIA-ALCL]). All patients with ALCL have a protein called CD30 on the surface of their cancer cells.

Cutaneous ALCL is less aggressive than systemic ALCL. Patients with systemic ALCL are divided into two groups that depend, depending on whether or not the surface of their cells has an abnormal form of a protein called anaplastic lymphoma kinase (ALK). ALK-positive disease (ALK protein is present) can respond well to treatment and is potentially curable. ALK-negative disease (ALK protein is not present) may require stronger treatments (often with SCT) and relapses more frequently. Most patients with BIA-ALCL may be treated with surgery alone. For more information on ALCL, please visit LRF's website (visit lymphoma.org/publications).

Angioimmunoblastic T-Cell Lymphoma (AITL) is a rare lymphoma that affects about 20% of all patients with PTCL in the United States. Most patients are older adults (half of the cases

are detected in patients over 65 years old) and are diagnosed with advanced-stage disease (cancer has grown and spread in the body). The disease is aggressive, and symptoms are common and including high fever, night sweats, skin rash, joint inflammation (reddening, pain, and/or swelling), and autoimmune disorders (the body's own immune system attacks its own healthy tissues), such as autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP). As a result of these autoimmune disorders, the body's immune system recognizes its own red blood cells (in AIHA) or platelets (in ITP) as foreign (not a part of the patient's body) and destroys them. For more information, view the *Angioimmunoblastic T-Cell Lymphoma* fact sheet on LRF's website (visit lymphoma.org/publications).



RARE SUBTYPES OF PTCL

Adult T-Cell Leukemia/Lymphoma (ATLL) is a rare and often aggressive PTCL that can be found in the blood (leukemia), lymph nodes (lymphoma), skin, or other areas of the body. ATLL only occurs in subjects infected with human T-cell lymphotropic virus type 1 (HTLV-1); however, less than 5% of individuals with HTLV-1 infection will ever 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 may be passed through sexual contact or exposure to contaminated blood, but it is most often passed from mother to child through the placenta, at childbirth, and during breastfeeding. For more information, view the *Adult T-Cell Leukemia/Lymphoma* fact sheet on LRF's website (visit lymphoma.org/publications).

Enteropathy-Associated T-Cell Lymphoma (EATL) and **Monomorphic Epitheliotropic Intestinal T-Cell Lymphoma (MEIL)** are extremely rare and aggressive subtypes of PTCL that appear in the intestine. Patients with EATL frequently have chronic diarrhea and feel sick after eating foods with gluten. This condition is associated with celiac disease (an autoimmune disease where eating gluten leads to damage of the small intestine). In contrast, MEIL is not associated with celiac disease. Other symptoms include abdominal (stomach) pain and weight loss. Both diseases require aggressive treatment, which may include surgery, combination chemotherapy such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), and SCT, in select patients.

Extranodal Natural Killer (NK)/T-Cell Lymphoma (ENKTL) develops from NK cells (a type of white blood cell that kills tumor cells or cells infected with a virus). This aggressive lymphoma is very rare in the United States, but common in Asia and parts of Latin America, and is associated with the Epstein-Barr virus. It usually starts in the interior (the inner tissues) of the nose or at the back of the throat (in which case it is referred to as nasal type), but may appear in the gastrointestinal tract, skin, and other organs. Treatment of nasal NK/T-cell lymphoma usually involves radiation treatments combined with chemotherapy.

Hepatosplenic Gamma-Delta T-Cell Lymphoma (HSGDTCL) is an extremely rare and aggressive disease that affects the liver and/or spleen. It can also involve blood and bone marrow. It most often occurs in adolescents and young adults and is more common in males. Approximately 20% of cases occur in patients who are receiving immunosuppressive treatments (drugs that

lower the activity of the immune system). Patients, especially children, treated with immune suppression agents such as azathioprine and infliximab (Remicade) for *Crohn's disease* (a type of inflammatory bowel disease), may be more susceptible to this type of PTCL.

As with other rare cancers, patients with EATL, nasal NK/T-cell, or hepatosplenic gamma-delta T-cell lymphomas should discuss whether clinical trials offer potential treatment options with their healthcare team. To learn more about clinical trials, view the *Understanding Clinical Trials* fact sheet on LRF's website (lymphoma.org/publications).

Subcutaneous Panniculitis-Like T-Cell Lymphoma (SPTL) is a rare and aggressive form of PTCL that develops from T-cells in subcutaneous adipose tissues (fatty tissues under the skin). The disease appears as skin lesions or plaques in the legs, arms, trunk, and rarely, the face. In some cases, the patients may also have other symptoms like fever, chills, night sweats, and weight loss. Half the patients who are diagnosed with SPTL are under 36 years old. Most patients with SPTL respond well to chemotherapy regimens that include doxorubicin. In rare cases, treatment options may include surgery, radiotherapy, and a SCT.

Hepatosplenic T-Cell Lymphoma (HSTCL) is a highly aggressive and rare disease that develops from mature (fully developed) T-cells in the liver and spleen. It is more common in male adolescents and young adults, and approximately 20% of cases occur in patients with a lowered or dysregulated (inappropriate and uncontrolled) immune response. Symptoms include fever, weight loss, fatigue, swollen lymph nodes, an enlarged belly, and low blood cell counts. HSTCL requires intensive treatment, usually with chemotherapy followed by a SCT.

For more information on PTCL by subtype, please visit the LRF website (visit lymphoma.org/publications).



TREATMENT OPTIONS

For most subtypes of PTCL, the first-line (initial) treatment is typically a combination chemotherapy regimen (the patients receive cycles of treatment with chemotherapy drugs over a set period of time), such as CHOP, CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone), or other multidrug regimens. Recently, the addition of brentuximab vedotin (Adcetris) to initial chemotherapy (BV-CHP [brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone]) significantly improved outcomes for patients with systemic or primary cutaneous ALCL and other types of PTCL that have the CD30 marker on the surface of lymphoma cells. In very specific cases, radiation therapy is given after chemotherapy as a part of first-line treatment. Because many patients with PTCL will relapse, some physicians recommend high-dose chemotherapy followed by an autologous SCT (patient's own cells are infused after high-dose chemotherapy) for certain patients. For more information on stem cell transplants, view the *Understanding Cellular Therapy* guide on LRF's website (visit lymphoma.org/publications).

Patients with relapsed disease may be treated with combination chemotherapy, such as ICE (ifosfamide, carboplatin, and etoposide) or other combination regimens, followed by SCT. Increasingly, newer U.S. Food and Drug Administration (FDA)-approved therapies such as crizotinib (Xalkori), belinostat (Beleodaq), pralatrexate (Folotylin), and brentuximab vedotin

(Adecetris) are used to treat patients whose lymphoma has come back or never responded to initial therapy. Romidepsin (Istodax) was previously FDA approved for PTCL, but approval was voluntarily withdrawn by the manufacturer in 2021. It may remain available to these patients. Patients should discuss what treatments are most appropriate for them with their physician.

TREATMENTS UNDER INVESTIGATION

Treatment options for the different types of newly diagnosed and relapsed/refractory PTCL are expanding as new treatments are discovered and current treatments are improved. Treatments currently being investigated alone or in combination are described in the table below.

Table 1. elected Agents Under Investigation for PTCL in Phase 2-3 Clinical Trials

Agent (Medicine)	Class (Type of Medicine)
Azacitidine (CC-486)	Chemotherapy
Bendamustine (Treanda)	Chemotherapy
Bortezomib (Velcade)	Targeted therapy; proteasome inhibitor
Cemiplimab (Libtayo)	Immunotherapy; immune checkpoint inhibitor, anti-PD-1
Devimistat (CPI-613)	Targeted therapy; lipoic-acid antagonist
Durvalumab (Imfinzi)	Immunotherapy; immune checkpoint inhibitor, anti-PD-1
Duvelisib (Copiktra)	Targeted therapy; PI3K inhibitor
GDP	Chemotherapy
Lacutamab (IPH4102)	Immunotherapy; monoclonal antibody, anti-KIR3DL2
Lenalidomide (Revlimid)	Immunotherapy; immunomodulator drug
MEDI-570	Immunotherapy; anti-ICOS
Nivolumab (Opdivo)	Immunotherapy; immune checkpoint inhibitor, anti-PD-1
Pembrolizumab (Keytruda)	Immunotherapy; immune checkpoint inhibitor, anti-PD-1
Ruxolitinib (Jakafi)	Targeted therapy; JAK1/2 inhibitor
Valemetostat (DS-3201B)	Targeted therapy; EZH1/2 inhibitor
Venetoclax (Venclexta)	Targeted therapy; BCL-2 inhibitor

BCL-2, B-cell lymphoma 2; EZH1/2, enhancer of zeste homolog 1/2; GDP, gemcitabine, dexamethasone, cisplatin; ICOS, inducible T-cell co-stimulator; JAK1/2, Janus kinase 1/2; KIR3DL2, killer cell immunoglobulin like receptor three Ig domains and long cytoplasmic tail 2; PD-1, programmed cell death protein 1; PI3K, phosphoinositide 3-kinase; PTCL, peripheral T-cell lymphoma.

Several other clinical trials are exploring combinations of these new treatments, which in some cases may be more effective than the single agent alone. It is important to remember that today's scientific research is always 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 appeared. It is also important that patients with PTCL consult with a specialist to clear up any questions.

CLINICAL TRIALS

Clinical trials are important in finding effective drugs and the best treatment doses for patients with PTCL. Because PTCL is a rare disease and no standard of care (treatment that is accepted as proper by medical experts and widely used by health care professionals) is defined, clinical trial enrollment is critical for establishing more-effective less-toxic treatments. This type of lymphoma is rare, and the most novel (newer) treatments are available only through clinical trials. Patients interested in participating in a clinical trial should view the *Understanding Clinical Trials* fact sheet on LRF's website (visit lymphoma.org/publications), 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.

FOLLOW-UP

Patients with PTCL should have regular visits with their physician. During these visits, medical tests (such as blood tests, computed tomography [CT] scans, and positron emission tomography [PET] scans) may be required to evaluate the need for additional treatment.

Some treatments can cause long-term side effects (occur **during** treatment and continue for months or years) or late side effects (appear only months, years, or decades **after** treatment has ended). These can vary depending on the following factors:

- Duration of treatment (how long the treatment lasted)
- Frequency of treatment (how often the treatment was administered)
- Type of treatment given
- Patient's age and gender
- Patient's overall health at the time of treatment

A physician will check for these side effects during follow-up care. Visits may become less frequent the longer the disease remains in remission.

Patients and their caregivers are encouraged to keep copies of all medical records. This includes test results as well as information on the type, amount, and duration of all treatments received. Medical records are important for keeping track of any side effects resulting from treatment or potential disease recurrences. LRF's award-winning *Focus on Lymphoma* mobile app (www.focusonlylymphoma.org) can help patients manage this documentation.



LYMPHOMA CARE PLAN AND PATIENT EDUCATION PROGRAMS

Keeping your information in one location can help you feel more organized and in control. This also makes it easier to find information pertaining to your care and saves valuable time. LRF's *Lymphoma Care Plan* document organizes information on your health care team, treatment regimen, and follow-up care. You can also keep track of health screenings and any symptoms you experience to discuss with your health care provider during future appointments. The *Lymphoma Care Plan* document can be accessed by visiting lymphoma.org/publications. LRF also offers a variety of educational activities, including live meetings and webinars, for individuals looking to learn directly from lymphoma experts. To view our schedule of upcoming programs, please visit lymphoma.org/programs.



LRF FOCUS ON LYMPHOMA MOBILE APP

Focus on Lymphoma is the first app to provide patients and their caregivers with tailored content based on lymphoma subtype and actionable tools to better manage diagnosis and treatment. It provides convenient and comprehensive lymphoma management in one secure and easy-to-navigate app, no matter where you are on the care continuum. Get the right information first, with resources from the entire Lymphoma Research Foundation content library, use unique tracking and reminder tools, and connect with a community of specialists and patients. To learn more about this resource, visit our website at lymphoma.org/mobileapp, or contact the LRF Helpline at **800-500-9976** or helpline@lymphoma.org.

LRF Helpline

The LRF Helpline staff are available to answer your general questions about lymphoma and treatment information, as well as provide individual support and referrals to you and your loved ones. Callers may request the services of a language interpreter. LRF also offers a one-to-one peer support program called the Lymphoma Support Network and clinical trials information through our Clinical Trials Information Service. For more information about any of these resources, visit our website at lymphoma.org, or contact the LRF Helpline at **(800) 500-9976** or helpline@lymphoma.org.

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Contact LRF:

Helpline: (800) 500-9976

Email: helpline@lymphoma.org

www.lymphoma.org

Supported through grants from:



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