LYMPHOMA RESEARCH • FOUNDATION

Understanding Peripheral T-Cell Lymphoma

Peripheral T-cell lymphoma (PTCL) refers to a rare group of different T-cell lymphomas that, together, account for about 5-10% percent of all patients diagnosed with non-Hodgkin Lymphoma (NHL) in the United States, according to the Surveillance, Epidemiology, and End Results (SEER) program.

PTCLs develop in lymphoid tissues outside of the bone marrow such as the lymph nodes, spleen, gastrointestinal tract, and skin. Most PTCLs are *aggressive* (fast-growing) lymphomas, and include PTCL-not otherwise specified (NOS), angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma (ALCL), enteropathy-type T-cell lymphoma, and extranodal NK/T-cell lymphoma. The incidence of PTCL subtypes varies geographically. For more information on PTCL, please visit the Lymphoma Research Foundation's (LRF's) website (click **here**).

COMMON SUBTYPES OF PERIPHERAL T-CELL LYMPHOMA

PTCLs are classified into subtypes, each considered a separate disease based on its distinct clinical features. The three most common subtypes —PTCL-NOS, ALCL and AITL— account for approximately 60 percent of PTCL cases in the United States.

Peripheral T-Cell Lymphoma, Not Otherwise Specified (PTCL-NOS) is the most common subtype of PTCL, accounting for 30 to 40 percent of 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 when the disease is confined to the lymph nodes, extranodal sites 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 stem cell transplant following initial chemotherapy. While PTCL-NOS is potentially curable, the disease tends to *relapse* (disease returns after treatment).

Anaplastic Large Cell Lymphoma (ALCL) accounts for about one percent of all NHLs and about 10 to 20 percent of all TCLs. 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) or *cutaneous* (affects the skin). All patients with ALCL express a protein called CD30 on the surface of tumor cells. Systemic ALCL can respond well to an antibody-drug conjugate targeting the CD30 protein. Brentuximab vedotin (Adcetris) and chemotherapy is potentially curable. Cutaneous ALCL is a less aggressive disease that may be preceded by a rare pre-cancerous condition called lymphomatoid papulosis.

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

Angioimmunoblastic T-Cell Lymphoma (AITL) affects about 10 to 20 percent of all patients with PTCL in the United States. Most patients are middle-aged to elderly and are diagnosed with advanced-stage disease. The disease is aggressive and symptoms are common, including high fever, night sweats, skin rash, and autoimmune disorders 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 and destroys them.

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 (click **here**) and *Understanding the Stem Cell Transplantation Process* publication (click **here**) on LRF's website.

RARE SUBTYPES OF PTCL

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 only occurs in subjects infected with human T-cell lymphotropic virus type 1 (HTLV-1); however, less than five percent 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 transmitted through sexual contact or exposure to contaminated blood, but it is most often passed from mother to child through the placenta, childbirth by Cesarean section, and breastfeeding. For more information, view the *Adult T-Cell Leukemia/Lymphoma* fact sheet on LRF's website (click **here**).

Enteropathy-Type T-Cell Lymphoma is an extremely rare and aggressive subtype that appears in the intestines and was previously recognized in two forms: one that is preceded by celiac disease (Type 1) and one that is not preceded by celiac disease (previously Type 2 but now known as monomorphic epitheliotropic intestinal T-cell lymphoma). Chronic diarrhea and gluten sensitivity frequently precedes type 1 disease. 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, and stem cell transplantation in select patients.

Extranodal NK/T-Cell Lymphoma develops from NK cells, which are closely related to and often have features that overlap with T cells. This aggressive lymphoma is very rare in the United States, but common in Asia and parts of Latin America. This subtype is 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 healthcare team.

TREATMENT 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. Recently, the addition of brentuximab vedotin (Adcetris) to initial chemotherapy significantly improved outcomes for patients with systemic ALCL and other types of PTCL that have the CD30 marker on their surface. Because many patients with PTCL will relapse, some physicians recommend high-dose chemotherapy followed by an *autologous stem cell transplant* (patient's own cells are infused after high-dose chemotherapy) for certain patients. For more information on stem cell transplants, view the *Understanding the Stem Cell Transplantation Process* publication on LRF's website (click **here**).

Patients with relapsed disease may be treated with combination chemotherapy such as ICE (ifosfamide, carboplatin, and etoposide) or other combination regimens, followed by stem cell transplantation. Increasingly, newer U.S. Food and Drug Administration (FDA)-approved therapies such as crizotinib (Xalkori), belinostat (Beleodaq), pralatrexate (Folotyn), and brentuximab vedotin (Adcetris) are used to treat patients whose lymphoma has come back or never responded to initial therapy. Patients should discuss what treatments are most appropriate for them with their physician.

Romidepsin (Istodax) is no longer indicated for treatment of PTCL. Patients who are currently receiving Istodax for PTCL should consult with their treating physician to determine if remaining on treatment is appropriate. Romidepsin (Istodax) it is still available for patients with cutaneous T-cell lymphoma.

TREATMENTS UNDER INVESTIGATION

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

- ALRN-6924Azacitidine (CC-486)
- Bortezomib (Velcade)
- Bendamustine (Treanda)
- Carfilzomib (Kyprolis)
- Devimistat
- Durvalumab (Imfinzi)
- Duvelisib (Copiktra)
- GDP (gemcitabine, dexamethasone, and cisplatin)
- Lenalidomide (Revlimid)
- Panobinostat (Farydak)
- Pembrolizumab (Keytruda)
- Tipifarnib (Zarnestra)
- Tolinapant
- Ruxolitinib (Jakafi)
- Valemetostat
- Umbralisib
- Tenalisib

Other immunotherapy and cellular therapies are also under investigation. 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 view the *Understanding Clinical Trials* fact sheet on LRF's website (click **here**), 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 lymphoma 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, computed tomography [CT] scans, and positron emission tomography [PET] scans) may be required at various times during *remission* (disappearance of signs and symptoms) to evaluate the need for additional treatment.

Some treatments can cause long-term side effects or late side effects, which can vary based on the 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 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 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 side effects resulting from treatment or potential disease recurrences. LRF's award-winning *Focus On Lymphoma* mobile app (www.FocusOnLymphoma.org) can help patients manage this documentation.

LRF'S HELPLINE AND LYMPHOMA SUPPORT NETWORK

A lymphoma diagnosis often triggers a range of feelings and concerns. In addition, cancer treatment can cause physical discomfort. The LRF Helpline staff members are available to answer your general questions about a lymphoma diagnosis 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. A part of the Helpline is LRF's one-to-one peer support programs, Lymphoma Support Network. This program connects patients and caregivers with volunteers who have experience with PTCL, similar treatments, or challenges, for mutual emotional support and encouragement. Patients and loved ones may find this useful whether the patient is newly diagnosed, in treatment, or in remission.

MOBILE APP

Focus On Lymphoma is the first mobile application (app) that provides patients and caregivers comprehensive content based on their lymphoma subtype, including PTCL, and tools to help manage their lymphoma such as, keep track of medications and blood work, track symptoms, and document treatment side effects. The *Focus On Lymphoma* mobile app is available for download for iOS and Android devices in the Apple App Store and Google Play. For additional information on the mobile app, visit FocusOnLymphoma.org. To learn more about any of these resources, visit our website at lymphoma.org, or contact the LRF Helpline at 800-500-9976 or helpline@lymphoma.org.

Resources

LRF offers a wide range of free resources that address treatment options, the latest research advances, and ways to cope with all aspects of lymphoma and PTCL. LRF also provides many educational activities, including our in- person meetings, podcasts, and webinars for people with lymphoma. For more information about any of these resources, visit our websites at lymphoma.org/PTCL or lymphoma.org, or contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org.

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