Understanding Lymphoma and Chronic Lymphocytic Leukemia (CLL)

T-Cell Lymphoma

Lymphoma Research Foundation

T-cell lymphomas can develop in lymphoid tissues such as the lymph nodes (small bean-shaped structures that help the body fight disease, Figure 1) and spleen, or outside of lymphoid tissues such as the gastrointestinal tract (digestive system which includes esophagus, stomach, and intestines), liver, nasal cavity, skin, bone marrow (the spongy tissue inside the bone) and others.

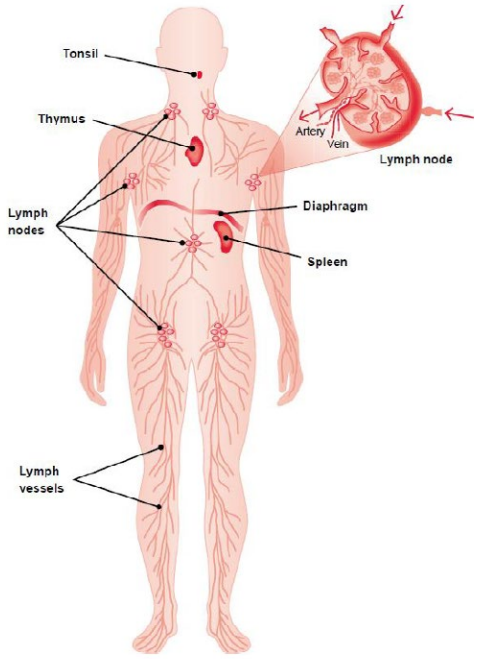

Figure 1: The *lymphatic system* (tissues and organs that produce, store, and carry white blood cells) and lymph nodes.

T-cell lymphomas develop from white blood cells called T lymphocytes (also called T-cells) or natural killer (NK) cells (a type of T-cell), and account for less than 15% of all non-Hodgkin Lymphomas (NHLs) in the United States. T-cells direct the immune response by binding and signaling the cancer cells, while NK cells directly and rapidly kill cancer cells.

Most T-cell lymphomas appear from mature T-cells (T-cells that are fully developed). T-cell lymphomas can be aggressive (fast-growing) or indolent (slow-growing) and are mainly found in the skin (cutaneous T-cell lymphomas, CTCL) or throughout the body (peripheral T-cell lymphomas, PTCL):

- PTCL account for 10-20% of all cases of NHL.
- CTCL account for about 4% of all NHL.

In rare cases (about 1% of all lymphomas), T-cell lymphoma develops from immature (early stages of development) T-cells in the thymus and is called T-lymphoblastic lymphoma. When cancer develops from NK cells (which share many characteristics with T-cells), it is called NK or NK/T-cell lymphoma and is generally grouped with other T-cell lymphomas. Some subtypes of T-cell lymphoma are listed in Figure 2 and described below.

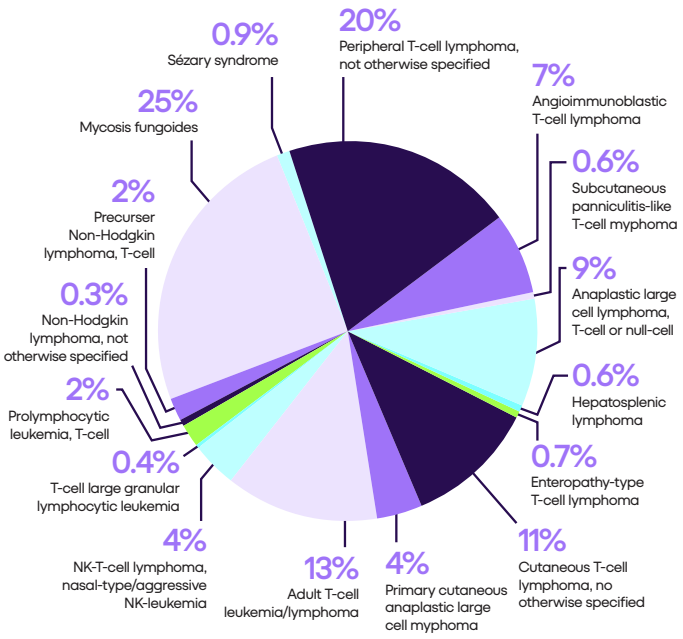

Figure 2: Relative frequencies (probability of T-cell lymphoma happening relative to all lymphomas) of T-cell lymphomas in the United States. Percentages are based on the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER, an official source for cancer statistics) data, 2008-2017. Some very rare types are not shown in the graph. NK, natural killer.

For more information on T-cell Lymphoma diagnosis, please view the *Understanding Lymphoma and CLL* guide on the Foundation's website (visit **lymphoma.org/publications**).

Subtypes of T-Cell Lymphoma

Common Peripheral T-Cell Lymphomas

Peripheral T-Cell Lymphoma, Not Otherwise Specified (PTCL-NOS) refers to a group of diseases that do not fit into any of the other PTCL subtypes. PTCL-NOS accounts for 30% of PTCL and is the most common PTCL subtype. Although most patients with PTCL-NOS are diagnosed when the disease is only in the lymph nodes, extranodal sites (outside of the lymph nodes) such as the liver, bone marrow (the spongy tissue inside the bone), gastrointestinal tract, and skin, may also be involved. This subtype of PTCL is generally aggressive and patients will frequently have symptoms such as fever, night sweats, and unexplained weight loss. For more information, view the *Peripheral T-Cell Lymphoma* fact sheet on the Lymphoma Research Foundation's website (visit **lymphoma.org/publications**).

Anaplastic Large Cell Lymphoma (ALCL) accounts for around 15% of all T-cell lymphomas. There are several different subtypes of ALCLs. Initial symptoms of ALCL can include fever, backache, painless swelling of lymph nodes, loss of appetite, itching, skin rash, and tiredness. All patients with ALCL have a protein called CD30 on the surface of cancer cells, which helps detect and diagnosing ALCL. CD30 is characteristic of some forms of NHLs, while the majority of Hodgkin's lymphoma cells are positive for CD30.

ALCL can be either systemic (occurring throughout the body), cutaneous (limited to the skin), and can rarely be seen around breast implants. Systemic ALCL is typically in an advanced stage (disease has grown in size and/or spread throughout the body) at diagnosis and can progress (grow and/or spread) rapidly. Patients with systemic ALCL are divided into two groups, depending on whether or not the surface of their cells have an abnormal form of a protein called anaplastic lymphoma kinase (ALK):

- *ALK-positive* (ALK protein is present in cancer cells) disease can respond well to treatment and is potentially curable.
- *ALK-negative* (ALK protein is not present in cancer cells) disease may require stronger treatments, and relapse (disease returns after treatment) occurs more frequently than in ALK-positive disease.

Primary cutaneous ALCL appears only on the skin and is often less aggressive (it grows slower). A rare type of ALCL called breast implant-associated (BIA)-ALCL has been observed in some patients who have or had breast implants, especially implants with textured (non-smooth) surfaces. Most patients with BIA-ALCL may be treated with surgery alone. For more information on ALCL, please view the *Anaplastic Large Cell Lymphoma* fact sheet (visit **lymphoma.org/publications**).

Nodal T-follicular helper phenotype lymphomas (nTFHL) including nTFHL angioimmunoblastic-type (nTFHL-AI), nTFHL follicular-type (nTFHL-F) and nTFHL not otherwise specified (nTFHL-NOS), are a rare and aggressive family of T-cell lymphomas, accounting for about 20% of all patients with PTCL in the United States. The most common type is the nTFHL-AI which was previously called angioimmunoblastic T-cell lymphoma (AITL). These lymphomas are more common in older adults (median [average] age at diagnosis of around 65 years) and is usually diagnosed in an advanced stage. Initial symptoms often include fever, night sweats, skin rash, itching, and some autoimmune disorders (the body's own immune system attacks its healthy cells) such as autoimmune hemolytic anemia. For more information, view the *Angioimmunoblastic T-Cell Lymphoma* fact sheet on the Foundation's website (**visit lymphoma.org/publications**).

Uncommon Peripheral T-Cell Lymphomas

Adult T-Cell Leukemia/Lymphoma (ATLL) is a rare and often aggressive form of T-cell lymphoma that can be found in the blood (leukemia), lymph nodes (lymphoma), skin, or other areas of the body. ATLL has been linked to infection with human T-lymphotropic virus type 1 (HTLV-1). However, not all individuals that are positive for HTLV-1 will develop ATLL.

This virus is commonly found in people from the Caribbean, parts of Japan, and some areas of South and Central America, Africa, Middle East, and more rarely in Australia and Asia. The HTLV-1 virus is believed to be passed through sexual contact or contact with blood, but it is most often passed from mother to child through the placenta, at childbirth, or during breastfeeding. Only 5% of those who carry the virus will develop lymphoma. Treatment commonly includes chemotherapy and antivirals to treat the underlying HTLV-1 infection. In some patients, stem cell transplantation (SCT) may be appropriate following remission (disappearance of signs and symptoms). For more information, view the *Adult T-Cell Leukemia/Lymphoma* fact sheet and the *Understanding Cellular Therapy* guide on the Foundation's website (visit **lymphoma.org/lymphoma**).

Enteropathy-Associated T-Cell Lymphoma and Monomorphic Epitheliotrophic Intestinal T-cell Lymphoma are extremely rare and aggressive subtypes of T-cell lymphoma that appear in the intestines. Patients with enteropathy-associated T-cell lymphoma frequently have chronic diarrhea, gluten sensitivity (feeling sick after eating gluten), and celiac disease (autoimmune disease where the ingestion of gluten leads to damage of the small intestine). Monomorphic epitheliotropic intestinal T-cell lymphoma is not generally associated with celiac disease. Other symptoms include abdominal pain and weight loss. Both require aggressive treatment that frequently is followed by SCT in selected patients.

Hepatosplenic Gamma-Delta T-Cell Lymphoma is an extremely rare and aggressive disease that affects the liver and/or spleen. It can spread into the blood and bone marrow. It most often occurs in adolescents and young adults and is more common in males. This lymphoma is associated with immunosuppressive treatments (drugs that lower the activity of the immune system). Patients, especially children, who have been treated with immunosuppressants such as azathioprine and infliximab (Remicade) for Crohn's disease (a type of inflammatory bowel disease), may be more susceptible to this type of lymphoma. SCT are also considered after initial treatment for selected patients.

Extranodal NK/T-Cell Lymphomas develop from natural killer (NK) cells. This aggressive lymphoma is relatively rare in the United States, but common in Asia and parts of Latin America. It typically develops in the interior of the nose or upper airway (nose, nasal cavity, mouth, throat, and larynx) at the back of the throat (in which case it is referred to as *nasal type*) but may appear in the gastrointestinal tract (digestive system which includes mouth, throat, stomach, and intestines), skin, bone marrow, and other organs. The NK/T-cell lymphomas seem to be related to infections with Epstein-Barr virus.

Treatment-Related T-Cell Lymphomas sometimes referred to as post-transplant lymphoproliferative disorder (PTLD), appear in patients who received immunosuppressants (medication that weakens the immune system) after an organ or bone marrow transplant (to prevent rejection of the transplanted organ). These treatments puts patients at risk for this type of lymphoma. While PTLD is more commonly from B cells, it can sometimes come from T cells.

Lymphoblastic Lymphoma can appear from either immature B cells or T cells (B or T cells that are not fully developed), but more commonly comes from T cells, making up to 90% of all lymphoblastic lymphomas. This type of lymphoma is most often diagnosed in adolescents and young adults and is a bit more common in males.

This lymphoma can progress rapidly, if not properly treated, and frequently appears in the middle of the chest, or *mediastinum* (area between the lungs including heart, throat, thymus, and lymph nodes). In this type of lymphoma, immature white blood cells (called lymphoblasts) can appear in the lymph nodes, bone marrow or spleen.

Lymphoblastic lymphomas, like other subtypes of lymphoma, can result in opportunistic infections (infections that happen more often or are more serious in patients with a weaker immune system), and affect the body's ability to make blood cells.

This subtype of T-cell lymphoma spreads to the *central nervous system* (brain and spinal cord) more often than other T-cell lymphomas. It behaves similarly to acute lymphoblastic leukemia (lymphoblasts are found in the bone marrow and blood) and is often treated with intensive (high-dose or over several months) chemotherapy which is associated with a very high rate of complete *remission* (disappearance of signs and symptoms of the disease) and cure.

Common Cutaneous T-Cell Lymphomas

Cutaneous T-Cell Lymphoma (CTCL) describes a group of typically indolent lymphomas that appear on, and most often only affect the skin. Some patients may develop lymphoma in their blood, lymph nodes and, more rarely, other organs.

Mycosis Fungoides is the most common subtype of CTCL (50-65% of all cases). It usually appears as skin patches (flat and often scaly rashes), plaques (thick, raised and often itchy lesions, similar to those found in eczema, psoriasis or dermatitis), or tumors (raised bumps or nodules with a diameter or height ≥ 1cm, which may turn into an open sore). More than one type of lesion may be present at any time.

Sézary Syndrome is a less common and more aggressive form of CTCL that affects both the skin and the blood. Most individuals with Sézary syndrome are adults between the ages of 55 and 60 years. The most common symptoms are swollen lymph nodes and a red, very itchy rash that covers large portions of the body. Cancer T cells, called Sézary cells, can be seen under a microscope and are present in both the skin and blood. There are other rarer forms of CTCL as well. For more information, view the *Cutaneous Lymphoma* fact sheet on the Foundation's website (visit **lymphoma.org/publications**).

Treatment Options

Because there are so many different subtypes of T-cell lymphoma, treatment types vary widely, but initial treatment for the more common types of PTCL typically includes combination chemotherapy regimens usually for curative intent. Standard lymphoma therapies include:

- Chemotherapy (drugs that stop the growth of or kill cancer cells):
  - CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone).
  - CHOEP (CHOP plus etoposide).
  - Dose-adjusted EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone).
- Chemoimmunotherapy: a combination of chemotherapy (drugs that stop the growth of or kill cancer cells) with immunotherapy (drugs that use the body's immune system to fight cancer) such as BV-CHP (brentuximab vedotin, cyclophosphamide, doxorubicin, prednisone).
- Targeted therapies (drugs that target molecules that cancer cells use to grow and spread). This includes inhibitors of proteins involved in cell signaling and growth like histone deacetylase (HDAC) inhibitors, such as belinostat (Beleodaq) and romidepsin (Istodax) for PTCL and vorinostat (Zolinza) for CTCL.
- Immunotherapy such as:
  - Immunomodulatory agents, drugs that work on the immune system directly by regulating(activating or slowing down) the activity of specific proteins.
  - An antibody-drug conjugate (ADC) is a monoclonal antibody (a protein made in the laboratory that binds to cancer cells and helps the immune system destroy them) attached to a chemotherapy drug. The monoclonal antibody in the ADC recognizes and binds to a protein on the cancer cell surface. Once the ADC is inside the cell, the chemotherapy drug separates from the ADC and kills the cancer cell by targeting cell multiplication. The ADC brentuximab vedotin (Adcetris) have been approved for ALCL and CTCL.

- Radiation which uses high-energy radiation to kill cancer cells.
- SCT (the patient is treated with high-dose chemotherapy or radiation to remove their blood-forming cells or stem cells, and then receives healthy stem cells to restore the immune system and the bone marrow's ability to make new blood cells).
  - Allogeneic SCT (patients receive stem cells from a familiar or unrelated donor)
  - Autologous SCT (patient receives own stem cells)

Patients diagnosed with rare forms of lymphoma should consult their medical team to find new promising therapies or to enroll into clinical trials.

In some cases, allogeneic or autologous SCT is recommended for either relapsed disease or to increase the chance of cure from some forms of PTCL. For more information about stem cell transplantation, please view the Understanding Cellular Therapy guide on the Foundation's website (lymphoma.org/publications).

Therapy for CTCL often includes treatments directed at the skin (also called topical therapies which are applied directly to the skin) to improve quality of life, such as:

- Corticosteroids
- Retinoids
- Chemotherapy
- Phototherapy (use of ultraviolet light to kill cancer cells on the skin)
- *Electron beam radiation therapy* (a type of radiation therapy that only affects the skin and does not reach the internal organs).

When skin directed therapies do not provide sufficient disease control or when the disease affects other areas of the body, systemic therapy is considered. For some patients with CTCL that has spread to the bloodstream, a procedure called extracorporeal photopheresis (ECP) is approved. During this procedure, blood is removed from the patient and treated with ultraviolet light, and with drugs that become active when exposed to ultraviolet light. Once the blood has been treated, it is then returned back into the patient's body.

Patients with relapsed or *refractory* (does not respond to treatment) T-cell lymphomas are usually treated with:

- Chemotherapy such as palatrexate (Folotyn), which works as a dihydrofolate reductase inhibitor and blocks the cells' ability to divide and multiply.
- SCT
- Targeted therapies:
  - HDAC inhibitors such as belinostat (Beleodaq) or vorinostat (Zolinza)
  - ALK inhibitors such as crizotinib (Xalkori)
- Immunotherapy, including:
  - Monoclonal antibody such as the anti-CCR4 mogamulizumab (Poteligeo)
  - ADC such as brentuximab vedotin (Adcetris).

In some patients with PTCL, SCT is considered the next step in therapy after combined chemotherapy. However, for some patients, chemotherapy regimens or SCT might not be recommended because of their side effects. Single-agent therapies with less side effects are also available and might cause a long-lasting remission in such patients. These drugs are approved by the FDA for patients who have relapsed or become refractory to first line chemotherapy:

Table 1: FDA-approved treatments for relapsed/refractory T-cell lymphomas.

Agent (drug)	Class (type of treatment)
Belinostat (Beleodaq)	Indicated for PTCL.
Pralatrexate (Folotyn)	Indicated for PTCL.
Mogamulizumab (Poteligeo)	Indicated for CTCL.
Brentuximab vedotin (Adcetris)	Indicated for both PTCL and CTCL.
Crizotinib (Xalkori)	Indicated for relapsed or refractory ALK-positive ALCL.

ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; CTCL, cutaneous T-cell lymphomas; PTCL, peripheral T-cell lymphoma.

Treatments Under Investigation

Treatment options for the different types of newly diagnosed and relapsed/refractory T-cell lymphomas 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.

In addition, a number of promising clinical trials are studying combinations (two or more drugs given at the same time) of these new treatments which in some cases may be more effective than the single agent (one drug) alone. It is critical to remember that 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 the Foundation for any treatment updates that may have recently appeared. It is also very important that all patients with T-cell lymphoma consult a specialist to clear up any questions.

Table 2: Selected agents under investigation for T-cell lymphomas in Phase 2-3 clinical trials

Agent (drug)	Class (type of treatment)
Azacitidine (CC-486)	Chemotherapy
Bendamustine (Treanda)	Chemotherapy
Cemiplimab (Libtayo)	Immunotherapy; immune checkpoint inhibitor, anti-PD-1
Durvalumab (Imfinzi)	Immunotherapy; immune checkpoint inhibitor, anti-PD-1
Duvelisib (Copiktra)	Targeted therapy; PI3K inhibitor
Linperlisib	Targeted therapy; PI3K inhibitor
Golidocitinib (AZD4205)	Targeted therapy; JAK1 inhibitor
Lacutamab (IPH4102)	Immunotherapy; monoclonal antibody, anti-KIR3DL2
Lenalidomide (Revlimid)	Immunotherapy; immunomodulator drug
Magrolimab	Immunotherapy; monoclonal antibody, anti-CD47
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 dual inhibitor
Venetoclax (Venclexta)	Targeted therapy; BCL-2 inhibitor

BCL-2, B-cell lymphoma 2; EZH1/2, enhancer of zeste homologue 1 and 2; JAK1/2, Janus kinase 1/2; PD-1, programmed cell death protein 1; PI3K, phosphoinositide 3-kinase; KIR3DL2, killer cell immunoglobulin like receptor three Ig domains and long cytoplasmic tail 2.

Clinical Trials

Clinical trials are important in finding effective drugs and best treatment doses for patients with T-cell lymphoma. In many of the rare subtypes of T-cell lymphoma, no standard of care is defined. Clinical trial enrollment is critical for establishing more effective, less toxic treatments.

The rarity of the disease also means that the latest treatments are often only available through clinical trials. Patients interested in participating in a clinical trial should view the *Understanding Clinical Trials* fact sheet on the Foundation's website (visit **lymphoma.org/publications**) talk to their physician, or contact the Helpline for an individualized clinical trial search by calling **(800) 500-9976** or emailing **helpline@lymphoma.org**.

Follow-up

Patients with T-cell lymphoma 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 age and gender.
- Patient overall health at the time of treatment.

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

Patients and their care partners are encouraged to keep copies of all medical records. This includes test results as well as information on the types, amounts, and duration of all treatments received. Medical records are important for keeping track of any side effects resulting from treatment or potential disease recurrences. The Foundations award-winning *Focus On Lymphoma* mobile app (**www.FocusOnLymphoma.org**) can help patients manage this documentation.

Lymphoma Care Plan

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. The Foundation'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**.

Patient Education Programs

The Foundation also offers a variety of educational activities, including live meetings and webinars for individuals looking to learn directly from lymphoma experts. These programs provide the lymphoma community with important information about the diagnosis and treatment of lymphoma, as well as information about clinical trials, research advances and how to manage/cope with the disease. These programs are designed to meet the needs of a lymphoma patient from the point of diagnosis through long-term survivorship. To view our schedule of upcoming programs, please visit **lymphoma.org/programs**.

Helpline

The Foundation's 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. The Foundation 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 Helpline at **(800) 500-9976** or **helpline@lymphoma.org**.

Para información en Español, por favor visite **lymphoma.org/es**. (For Information in Spanish please visit **lymphoma.org/es**).

Focus on Lymphoma Mobile App

Focus on Lymphoma is the first app to provide patients and their care partners with tailored content based on lymphoma subtype, and actionable tools to better manage diagnosis and treatment. Comprehensive lymphoma management, conveniently 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 Foundation's Helpline at **(800) 500-9976** or **helpline@lymphoma.org**.

Lymphoma Research Foundation

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