

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).

T-cell lymphomas can develop in lymphoid tissues such as the lymph nodes and spleen, or outside of lymphoid tissues (i.e., gastrointestinal tract, liver, nasal cavity, skin, and others). A similar lymphocyte called a natural killer (NK) cell shares many features with T cells. When NK cells become cancerous, the cancer is called NK or NK/T-cell lymphoma and is generally grouped with other T-cell lymphomas. T-cell lymphomas account for about seven percent of all NHLs in the United States according to the Surveillance, Epidemiology, and End Results (SEER) program. Each particular subtype of T-cell lymphoma tends to be uncommon. They can be *aggressive* (fast-growing) or *indolent* (slow-growing).

Lymphomas are often, but not always, named from a description of the normal cell that leads to cancer. Lymphomas that arise from mature T cells are sometimes categorized together under the general term peripheral T-cell lymphoma (PTCL), which distinguishes them from the lymphoma that arise from immature T cells or lymphoblastic lymphoma. Under this broad meaning, almost all types of T-cell lymphoma fall under the category of PTCL. More specific subtypes of T-cell lymphoma are listed here.

Common Subtypes of T-Cell Lymphoma

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 about 20 percent of T-cell lymphomas and is the most common PTCL subtype. 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. Patients with this subtype of PTCL will frequently have constitutional symptoms (i.e., fevers, serious night sweats, and unexplained weight loss). For more information, view the *Peripheral T-Cell Lymphoma* fact sheet on the Lymphoma Research Foundation's (LRF's) website at www.lymphoma.org/publications.

Anaplastic Large Cell Lymphoma (ALCL) describes several types of T-cell lymphomas and accounts for approximately one percent of all NHLs and 10 percent of all T-cell lymphomas. Initial symptoms of ALCL can include fever, backache, painless swelling of lymph nodes, loss of appetite, itching, skin rash, and tiredness.

ALCL can be either *systemic* (occurring throughout the body) or *cutaneous* (limited to the skin). Systemic ALCL is typically in an advanced stage at diagnosis and can progress rapidly. 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 anaplastic lymphoma kinase (ALK). Systemic ALCL, especially *ALK-positive* (expresses the protein) disease, can respond well to treatment and is potentially curable. Patients with *ALK-negative* (does not express the protein) disease, may require more aggressive treatments, and *relapse* (disease returns after treatment) occurs more frequently than in ALK-positive disease.

The non-systemic type is called primary cutaneous ALCL, appears only on the skin, and has a good prognosis. A rare type of ALCL called breast implant-associated (BIA)-ALCL has been observed in some patients who get breast implants, particularly those with those implants with textured (non-smooth) surfaces; the *prognosis* (outlook) for this type of lymphoma is usually very good. For more information on ALCL, please visit LRF's *Focus On Anaplastic Large Cell Lymphoma* website at www.FocusOnALCL.org or view the Anaplastic Large Cell Lymphoma fact sheet at www.lymphoma.org/publications.

Angioimmunoblastic T-Cell Lymphoma (AITL) is a rare, aggressive type accounting for about seven percent of all patients with T-cell lymphomas in the United States. Most patients are middle-aged to elderly and are diagnosed with advanced-stage disease. There is some evidence that AITL develops from an ongoing immune response potentially due to a latent viral infection (like Epstein-Barr virus), but not all latent viral infections develop into lymphoma. Initial symptoms often include fever, night sweats, skin rash, itching, and some autoimmune disorders such as autoimmune hemolytic anemia (AIHA; where the immune system attacks red blood cells) and immune thrombocytopenia (ITP; where the immune system attacks platelets). For more information, view the *Angioimmunoblastic T-Cell Lymphoma* fact sheet on LRF's website at www.lymphoma.org/publications.

Cutaneous T-Cell Lymphoma (CTCL) accounts for about 11 percent of all T-cell lymphomas and usually affects adults. The term cutaneous T-cell lymphoma describes a group of typically indolent lymphomas that appear on, and are most often confined to, the skin.

Mycosis fungoides, which appears as skin patches, plaques, or tumors, is the most common type of CTCL. 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* (develop into an ulcer). More than one type of lesion may be present at any time.

Sézary syndrome is a less common form of CTCL that affects both the skin and 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 both the skin and blood.

Other, rare forms of CTCL include primary cutaneous anaplastic large cell lymphoma and lymphomatoid papulosis. For more information, view the *Cutaneous T-Cell Lymphoma* fact sheet on LRF's website at www.lymphoma.org/publications.

Uncommon Subtypes of T-Cell Lymphoma

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 multiple areas of the body. ATLL has been linked to infection by the human T-lymphotropic virus type 1 (HTLV-1). This virus is commonly found in people from the Caribbean, parts of Japan, 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 the placenta, childbirth by Cesarean section, and breastfeeding. Less than five percent of those who carry the virus will develop lymphoma. This lymphoma requires urgent treatment in most patients and stem cell transplantation is frequently needed for cure. For more information, view the *Adult T-Cell Leukemia/Lymphoma* fact sheet on LRF's website at www.lymphoma.org/publications.

Enteropathy-Type T-Cell Lymphoma is an extremely rare and aggressive subtype of T-cell lymphoma that appears in the intestines. One form of this disease is frequently preceded by chronic diarrhea and gluten sensitivity and is associated with celiac disease. Another form of this disease is not generally associated with celiac

disease. Other symptoms include abdominal pain and weight loss. It requires aggressive treatment that frequently is followed by stem cell transplantation in select patients.

Hepatosplenic Gamma-Delta T-Cell Lymphoma is an extremely rare and aggressive disease that starts in and involves the liver and/or spleen. It can spread into the blood and bone marrow. It most often occurs in teenagers and young adults and is more common in males. This lymphoma is associated with immunosuppressive treatments. Patients, especially children, who have been treated with azathioprine and infliximab (Remicade) for Crohn disease, may be more susceptible to this type of lymphoma.

Lymphoblastic Lymphoma can arise from either immature B cells or T cells, but more commonly comes from T cells, comprising more than 80 percent of all lymphoblastic lymphomas. This type of lymphoma is most often diagnosed in adolescents and young adults and is a bit more common in men than women. Tumors frequently arise in the middle of the chest, or mediastinum, though lymphoma cells may appear in the lymph nodes as well as in the bone marrow or spleen. Central nervous system involvement is more common than in other T-cell lymphomas. This lymphoma, like other subtypes, can result in impaired immunity and opportunistic infections, and interfere with the body's ability to make blood cells. When red blood cells are low, it can result in fatigue, and when platelets are low, people bruise or bleed more easily. This lymphoma is aggressive and can progress rapidly, if not properly treated. With intensive chemotherapy, the complete *remission* (disappearance of signs and symptoms of the disease) rate can be very high and many patients can be cured.

Nasal NK/T-Cell Lymphomas develop from natural killer (NK) cells, which are closely related to and often have features that overlap with T cells. Although this aggressive lymphoma is relatively rare in the United States, it is more common in Asia and parts of Latin America. It typically originates in the lining of the nose or upper airway 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. 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 are intentionally immunosuppressed after solid organ or bone marrow transplantation. While this subtype is more commonly a proliferation of B cells, it can occasionally arise from T cells. The immune system suppression that is required to prevent rejection of the transplanted organ puts patients at risk for this type of lymphoma.

Treatment Options

Because there are so many different subtypes of T-cell lymphoma, treatment varies widely. Standard lymphoma therapies may include chemotherapy, targeted therapy, immunotherapy (like antibody-drug conjugates) immunomodulatory agents, radiation, stem cell transplantation, and surgery. Patients diagnosed with rare forms of lymphoma should consult their medical team to find new promising therapies or to enroll into clinical trials.

Treatments aimed at the skin, such as topical corticosteroids, topical retinoids, topical chemotherapy, ultraviolet light therapy, or *electron beam therapy* (a type of radiation that does not penetrate to internal organs), are effective for many of the slow-growing T-cell lymphomas that appear in the skin (CTCL).

In addition, a procedure called extracorporeal photopheresis (ECP) is approved to treat people with CTCL. For 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.

When systemic chemotherapy treatments are appropriate, initial treatment is typically a combination chemotherapy regimen, such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CHOEP (CHOP plus etoposide) or EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone), or other multidrug regimens. Treatments might vary widely depending on the subtype of lymphoma that you have.

Three histone deacetylase inhibitors—a type of targeted therapy—have been approved by the U.S. Food and Drug Administration (FDA) in the past decade: belinostat (Beleodaq) for peripheral T-cell lymphoma and romidepsin (Istodax) and vorinostat (Zolinza) for cutaneous T-cell lymphoma.

In some cases, it may be determined that transplantation is the most appropriate approach to treatment. For more information on transplants, view the *Understanding the Stem Cell Transplantation Process* publication on LRF's website at www.lymphoma.org/publications.

Patients with relapsed disease are usually treated with combination chemotherapy such as ICE (ifosfamide, carboplatin, and etoposide) if stem cell transplantation is contemplated as the next step in therapy. However, some regimens or transplant might not be suited for everyone because of their high toxicity levels. Less toxic single-agent therapies are also available and might induce a long-lasting remission in such patients. These therapies include belinostat (Beleodaq), brentuximab vedotin (Adcetris), pralatrexate (Foloty),

and romidepsin (Istodax). These drugs are approved by the FDA for patients who have relapsed or those who have not responded to their first line of chemotherapy.

Treatments Under Investigation

Treatment options for the different types of T-cell lymphomas are expanding as new treatments are discovered and current treatments are improved. Treatments currently being investigated singly or in combination include:

- Alisertib (MLN8237)
- ALRN-6942
- Anti-CD30 CAR T cells
- Bendamustine (Treanda)
- Bortezomib (Velcade)
- Brentuximab vedotin (Adcetris) (approved for relapsed or refractory ALCL only)
- CPI-613
- Crizotinib (Xalkori)
- Durvalumab (Imfinzi)
- Duvelisib
- EDO-S101
- Entrectinib (RXDX-101)
- GDP (gemcitabine, dexamethasone, and cisplatin)-based regimens
- Lenalidomide (Revlimid)
- MEDI-570
- Nivolumab (Opdivo)
- Onalespib (AT13387)
- Pembrolizumab (Keytruda)
- Plitidepsin (Aplidin)
- Rituximab (Rituxan)
- RP6530
- Ruxolitinib (Jakafi)

In addition, a number of promising clinical trials are exploring combinations of these new agents which in some cases may be more active than the single agent alone. 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 for identifying effective drugs and determining optimal doses for patients with lymphoma. In many of the rare subtypes of T-cell lymphoma, 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 also often only available through clinical trials. Patients interested in participating in a clinical trial should view the *Understanding Clinical Trials* fact sheet on LRF's website at www.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 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 to evaluate the need for additional treatment.

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.

Patient and Caregiver Support Services

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 who have experience with lymphoma, 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.

Patient Education

LRF offers a wide range of opportunities to learn about lymphoma.

Ask the Doctor About Lymphoma is a national series of two-hour, topic-specific, community-based programs that combine a presentation by a medical doctor with an extensive question-and-answer session.

Lymphoma Workshops are regional, full-day educational programs that provide the latest information about lymphoma, current treatment options, and patient support issues.

The North American Educational Forum on Lymphoma is held annually and provides critical information on treatment options, patient support issues, and the latest in lymphoma research.

Webcasts are available on specific types of lymphoma, treatment options, and support topics.

Teleconferences are hour-long, interactive telephone programs that provide an opportunity to learn more about lymphoma, treatments, and promising research from leading lymphoma experts.

Patient Services and Support

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.

Patient Publications

LRF offers a series of print and digital patient education publications. LRF offers comprehensive guides on non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), and the transplantation process in lymphoma, along with a variety of disease- and topic-specific fact sheets. Contact the LRF Helpline at (800) 500-9976 or visit our website at www.lymphoma.org/publications.

Mobile App

Focus On Lymphoma is the first mobile application (app) that provides patients and caregivers comprehensive content based on their lymphoma subtype and tools to help manage their disease 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 www.FocusOnLymphoma.org.

To learn more about any of these resources, visit our website at www.lymphoma.org, or contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org.

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Supported
through
grants from:



Genentech
A Member of the Roche Group

Biogen

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