Understanding Lymphoma and Chronic Lymphocytic Leukemia (CLL)

Anaplastic Large Cell Lymphoma

Lymphoma Research Foundation

Anaplastic large cell lymphoma (ALCL) is a rare type of non-Hodgkin lymphoma (NHL), and one of the subtypes of peripheral T-cell lymphoma (PTCL).

ALCL makes up about 2% of lymphomas and approximately 24% of all PTCL in the US. Initial symptoms of ALCL can include:

- Fever.
- Backache.
- Painless swelling of lymph nodes (bean-shaped structures that help the body fight infections, Figure 1).
- Loss of appetite.
- Night sweats.
- Weight loss.
- Itching.
- Skin rash.
- Tiredness.

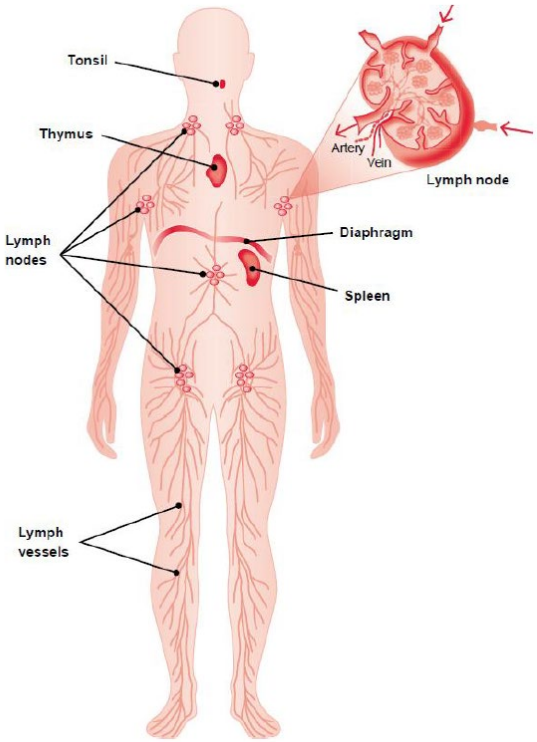

Figure 1: The lymphatic system (tissues and organs that produce, store, and carry white blood cells) and lymph nodes.

Diagnosis and Subtypes

A diagnosis of ALCL requires taking a biopsy (sample of the tumor tissue) and looking at the cells under a microscope. Additional tests may be conducted to give physicians more information about the disease and how far it has spread in the body. These can include:

- Blood tests.
- Computed tomography (CT) scan (a procedure that uses x-rays to make detailed pictures of the inside of the body).
- Positron emission tomography (PET) scan (a procedure that uses a special dye to locate the cancer in the body).
- Magnetic resonance imaging (MRI) scan (a procedure that uses a powerful magnet and radio waves to take detailed pictures of the inside of the body).
- Bone marrow biopsy (a procedure that uses a needle to take samples of the spongy tissue inside the bones).

One characteristic that distinguishes ALCL is that the cancer cells have a marker on their surface called CD30. The disease can present in different forms, which are treated differently:

- *Primary cutaneous* ALCL: disease is limited to the skin.
- *Systemic* ALCL: disease that can affect lymph nodes and other organs, including the skin.
- *Breast implant-associated* (BIA) ALCL: disease is present around breast implants.

Patients with systemic ALCL are divided into two groups, depending on whether their cells produce an abnormal form of a protein called anaplastic lymphoma kinase (ALK):

- ALK-positive ALCL (cancer cells produce ALK) is more common in children and young adults.
- ALK-negative ALCL (cancer cells do not produce ALK) is more common in older adults (over 54 years old).

Both forms of systemic ALCL are treated as aggressive (fast-growing) lymphomas. Patients with ALK-positive ALCL generally respond well to standard chemotherapy and achieve *durable remission* (disappearance of signs and symptoms for a long period of time). While most patients with ALK-negative ALCL initially respond to treatment, the disease is more likely to relapse (return after treatment).

Primary cutaneous ALCL is almost always ALK negative and has a less aggressive disease course than systemic ALCL. This type of ALCL usually appears as persistent red skin lesions (solitary or multiple raised, usually larger than a quarter), which may ulcerate (cause sores of the skin) and itch. These ALCL lesions can become tumors (on any part of the skin) that often grow very slowly and may be present for a long time before being diagnosed. Only about 10% of the time does primary cutaneous ALCL spread to lymph nodes or organs. If this happens, it is usually treated similarly to systemic ALCL. It is important to distinguish primary cutaneous ALCL from another benign blood disease called *lymphomatoid papulosis*.

BIA-ALCL is a rare type of ALCL and is more commonly found in breast implants with textured (non-smooth) surfaces. The U.S. Food and Drug Administration (FDA) recommends that patients with such implants, and their doctors, consider the possibility of BIA-ALCL if they experience any late-onset symptoms such as pain, lumps, or swelling in the breast. In most cases, the cancer occurs years after the implants were placed and is limited to the scar tissue and fluid near the implants. In rare cases, the disease may spread to other parts of the body.

For more information on ALCL diagnosis, please view the *Understanding Lymphoma and CLL Guide* on the Foundation's website (visit **lymphoma.org/publications**).

Treatment Options

Many patients with newly diagnosed systemic ALCL respond well to common *frontline* (initial) chemotherapy. The combination of brentuximab vedotin (Adcetris) and cyclophosphamide, doxorubicin, and prednisone (BV-CHP) was more effective in treating the disease when compared to the prior standard of CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone). BV-CHP is the preferred first line treatment option for systemic ALCL (both ALK-positive and -negative). In some situations, higher doses of chemotherapy followed by stem cell transplantation may be prescribed after having a remission on BV-CHP.

Other treatment options are available for systemic ALCL that has *relapsed* (disease returns after treatment) or become *refractory* (does not respond to treatment):

- Brentuximab vedotin (Adcetris).
- Belinostat (Beleodaq).
- Pralatrexate (Folotyn).
- Crizotinib (Xalkori).

Patients with relapsed or refractory ALCL are often treated similarly to those with other forms of relapsed/refractory PTCL. For more information about treatment of PTCL, view the *Understanding Peripheral T-Cell Lymphoma* fact sheet on the Foundation's website (visit **lymphoma.org/publications**).

Treatment of primary cutaneous ALCL depends on the number and size of skin lesions. Overall, it is treated similarly to a chronic skin disease. If the disease is confined to a single lesion or area, radiation therapy or *surgical excision* (surgery to remove the lesions) will result in remission in approximately 95% of patients and some patients may have recurrent lesions in the future. If there are multiple lesions or recurrent lesions in the skin, radiation can remove individual skin lesions but will not reduce the likelihood of new lesions developing. Those with primary cutaneous ALCL appearing in multiple sites on the body are considered for systemic treatment, which travels through the blood and reaches many parts of the body.

Brentuximab vedotin (Adcetris) is approved to treat adult patients with primary cutaneous ALCL who have received prior systemic therapy. Although primary cutaneous ALCL tends to relapse in about 40% of cases, the long-term *prognosis* (how well the patient will do after treatment) remains excellent if relapses are confined to the skin.

Patients with BIA-ALCL generally undergo surgery to remove the lymphoma, the implant(s), and some surrounding tissue. Most patients have lymphoma limited to the fluid around the breast implant and its capsule, and the majority of patients are cured with complete removal of the implant and the surrounding scar tissue. As this is a rare cancer, there are limited data (information coming from clinical trials) regarding the best treatment. If the lymphoma cannot be removed by surgery, or if it has spread outside the breast, radiation therapy, chemotherapy, and/orbrentuximab vedotin (Adcetris) may be given.

Treatments Under Investigation

Many new treatments (also referred to as investigational drugs) and combination therapies are currently being studied for the treatment of patients with previously untreated or relapsed/refractory ALCL. Results from these clinical trials may improve or change the current standard of care (the proper treatment that is widely used by healthcare professionals and accepted by medical experts). The table below lists some of these investigational drugs that can be accessed through a clinical trial. For more information on clinical trials, view the *Understanding Clinical Trials* publication on the Foundation's website (**lymphoma.org/publications**).

It is important to remember that today's scientific research is always changing. New treatments for ALCL are being researched all the time. Treatment options may change as new treatments are discovered and current treatments are improved. Patients should check with their physician or with the Lymphoma Research Foundation for any updates that may have recently appeared. It is also very important that all patients with ALCL consult with an ALCL specialist to clear up any questions.

Table 1: Investigational drugs for the treatment of ALCL

Agent (drug)	Class (type of treatment)
Duvelisib (Copiktra)	Targeted therapy: PI3K inhibitor
Valemtostat (DS-3201b)	Targeted therapy; EZH1/2 dual inhibitor
Lenalidomide (Revlimid)	Immunotherapy; immunomodulator drug
Brigatinib (Alunbrig)	Targeted therapy; multi-kinase inhibitor
Golidocitinib	Targeted therapy; JAK1 inhibitor
Lorlatinib (Lorbrena)	Targeted therapy; multi-kinase inhibitor
Nivolumab (Opdivo)	Immunotherapy; immune checkpoint inhibitor, anti-PD-1
Pembrolizumab (Keytruda)	Immunotherapy; immune checkpoint inhibitor, anti-PD-1
AUTO4	CAR T cell therapy; anti-TRBC1
Vinorelbine (Navelbine)	Chemotherapy
Lacutamab (IPH4102)	Immunotherapy; monoclonal antibody, anti-KIR3DL2
CD30 biAb-AATC	Immunotherapy; bispecific antibody, anti-CD30 and -CD3.

EZH1/2, enhancer of zeste homologue 1 and 2; JAK, Janus kinase; KIR3DL2, killer cell immunoglobulin like receptor three Ig domains and long cytoplasmic tail 2; PD-1, programmed death receptor-1; PI3K, phosphatidylinositol 3-kinase; TRBC1, T cell receptor beta constant 1.

Clinical Trials

Clinical trials are crucial in identifying effective drugs and optimal treatment doses for patients with lymphoma. 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**), and the *Clinical Trials Search Request Form* at lymphoma.org, talk to their physician, or contact the Foundation's Helpline for an individualized clinical trial search by calling **(800) 500-9976** or emailing **helpline@lymphoma.org**.

Follow-up

Patients with ALCL should have regular visits with their physician. During these visits, medical tests (such as blood tests, CT scans, and 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 side effects can vary depending on the following factors:

- Duration of treatment (how long the treatment lasted).
- Frequency of treatment (how often was the treatment was administered.
- Type of treatment given.
- Age and gender of the patient.
- Patient overall health at the time of their treatment.

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 Foundation's award-winning *Focus On Lymphoma* mobile app 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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