

Understanding Anaplastic Large Cell Lymphoma

Anaplastic large cell lymphoma (ALCL) is a rare type of non-Hodgkin lymphoma (NHL) and one of the subtypes of T-cell lymphoma. ALCL comprises about one percent of all NHLs and approximately 10 percent of all T-cell lymphomas. Initial symptoms of ALCL can include fever, backache, painless swelling of lymph nodes, loss of appetite, night sweats, weight loss, and tiredness.

ALCL can initially appear in the skin, in the lymph nodes, or in organs throughout the body. ALCL that appears in the skin is most often called primary cutaneous ALCL, and it typically has a less aggressive disease course than the *systemic* (throughout the body) types. The characteristic features of primary cutaneous ALCL include the appearance of solitary or multiple raised red skin lesions that are usually greater in size than a quarter that do not go away, tend to ulcerate, and may itch. These ALCL lesions are tumors, which can appear on any part of the body, often grow very slowly, and may be present for a long time before being diagnosed. Only about 10 percent of the time does primary cutaneous ALCL extend beyond the skin to lymph nodes or organs. If this occurs, it is usually treated like systemic ALCL.

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). Although both systemic lymphomas are treated as *aggressive* (fast-growing) lymphomas, the disease course may be different in patients who have ALK-positive ALCL compared with those with ALK-negative ALCL. The ALK-positive form of ALCL generally responds better to standard chemotherapy treatments, putting most patients into long-term *remission* (disappearance of signs and symptoms). In contrast, while most patients with ALK-negative ALCL initially respond to treatment as well, the disease is more likely to *relapse* (disease returns after treatment) within five years versus those with ALK-positive ALCL. Sometimes ALK-negative patients (and some ALK-positive patients with certain risk factors) are treated more aggressively, often with a stem cell transplant after remission. While ALK-positive ALCL usually affects children and young adults, ALK-negative ALCL is more common in patients over the age of 55 years. Primary cutaneous ALCL is almost always ALK-negative.

A rare type of ALCL called breast implant-associated (BIA)-ALCL has been observed in some patients who get breast implants, particularly those 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.

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, a computed tomography (CT) scan, a positron emission tomography (PET) scan, a magnetic resonance imaging (MRI) scan, and a bone marrow biopsy.

TREATMENT OPTIONS

Treatment of primary cutaneous ALCL depends on the extent of skin lesions. If the disease is confined to a single lesion or area, radiation therapy or surgical excision will result in complete remission in approximately 95 percent of patients. If there are multiple lesions or relapsed disease in the skin, radiation can eradicate the skin lesions but will not reduce the likelihood of new lesions developing. Those with primary cutaneous ALCL appearing in multiple sites on the body usually need systemic treatment, which travels through the blood and affects many parts of the body. There are very few studies of primary cutaneous ALCL; however, brentuximab vedotin (Adcetris) has been used successfully in such patients in clinical trials and is now FDA approved for this purpose. Although primary cutaneous ALCL tends to relapse in about 40 percent of cases, the long-term prognosis remains excellent if relapses are confined to the skin.

Many patients with newly diagnosed systemic ALCL respond well to common *frontline* (initial) chemotherapy regimens such as CHOEP (cyclophosphamide, doxorubicin, vincristine,

etoposide, and prednisone), although long-term disease outcome varies depending on the subtype and other factors. More recently, the combination of brentuximab vedotin (Adcetris) and cyclophosphamide, doxorubicin, and prednisone (B-CHP) were found to have superior results when compared to CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone). Patients with ALK-positive disease usually respond very well to B-CHP or CHOEP, whereas similar treatments may be slightly less effective for patients with ALK-negative disease. In some circumstances, higher doses of chemotherapy followed by stem cell transplantation may be prescribed.

Brentuximab vedotin (Adcetris) is approved by the FDA for the treatment of patients with *relapsed* (disease returns after treatment) or *refractory* (does not respond to treatment) systemic ALCL after the failure of at least one prior multiagent chemotherapy regimen. Other treatment options for relapsed/refractory disease include romidepsin (Istodax), which is FDA approved for relapsed systemic T-cell lymphomas, including systemic ALCL. Belinostat (Beleodaq) is a newer histone deacetylase inhibitor that is approved for relapsed peripheral T-cell lymphomas,

including systemic ALCL, but not for cutaneous T-cell lymphomas. Finally, pralatrexate (Folotylin) is also approved for the treatment of relapsed/refractory peripheral T-cell lymphomas.

Patients with BIA-ALCL generally undergo surgery to remove the lymphoma, the implant(s), and some surrounding tissue. If the lymphoma cannot be removed by surgery, or if it has spread outside the breast, radiation therapy, chemotherapy, and/or brentuximab vedotin (Adcetris) may be given.

Depending on the subtype, diagnosing ATLL may require removing a small sample of tumor tissue or abnormal skin tissue, called a biopsy, and looking at the cells under a microscope. A blood test may also be necessary to measure the white blood cell count and calcium levels, and to test for exposure to the HTLV-1 virus. Other tests, such as a bone marrow biopsy, a CT scan of the chest, abdomen, liver, and spleen, and/or a PET scan may be used to determine where the cancer is located.

TREATMENTS UNDER INVESTIGATION

There are several drugs showing promising results in clinical trials, including:

- Anti-CD30 chimeric antigen receptor (CAR) T cells
- Ceritinib (Zykadia) for ALK-positive ALCL
- Combination of brentuximab vedotin (Adcetris) and chemotherapy
- Crizotinib (Xalkori) for ALK-positive ALCL
- Entrectinib (Rozlytrek)
- Lenalidomide (Revlimid)
- Onalespib
- Brigatinib (Alunbrig)
- Lorlatinib (Lorbrena)
- Programmed cell death-1 (PD-1) inhibitors

It is critical to remember that today's scientific research is continuously evolving. New treatments for ALCL are being researched all the time. Patients should check with their physician or with the Lymphoma Research Foundation (LRF) for any updates that may have recently emerged.

CLINICAL TRIALS

Clinical trials are crucial in identifying effective drugs and determining optimal doses for patients with lymphoma. Patients interested in participating in a clinical trial should view the *Understanding Clinical Trials* fact sheet on LRF's website at lymphoma.org/publications, and the *Clinical Trials Search*

Contact LRF:

Helpline: (800) 500-9976

Email: helpline@lymphoma.org

www.lymphoma.org

Medical reviewer:

Lauren Pinter-Brown, MD
UCI Chao Comprehensive Cancer Center
UCI School of Medicine

Request Form at lymphoma.org, 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, CT scans, and 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.

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*, connect patients and caregivers with volunteers who have experience with ALCL, similar treatments, or challenges, for mutual emotional support and encouragement. Patients and loved ones may find this information useful whether the patient is newly diagnosed, in treatment, or in remission.

Resources

LRF offers a wide range of resources that address treatment options, the latest research advances, and ways to cope with all aspects of lymphoma, including our award-winning mobile app (lymphoma.org/mobileapp). LRF also provides many educational activities for people living with lymphoma, from in-person meetings to webinars, as well as patient guides and e-Updates that provide the latest disease-specific news and treatment options. To learn about any of these resources, visit our websites at lymphoma.org/ALCL or lymphoma.org, or contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org.

Contact LRF:

Helpline: (800) 500-9976

Email: helpline@lymphoma.org

www.lymphoma.org

Medical reviewer:

Lauren Pinter-Brown, MD
UCI Chao Comprehensive Cancer Center
UCI School of Medicine

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