UNDERSTANDING
Anaplastic Large Cell Lymphoma (ALCL)

LYMPHOMA CANADA

Overview

Lymphoma is the most common form of blood cancer. Lymphoma occurs when cells of the immune system called lymphocytes, a type of white blood cell, grow and multiply uncontrollably.

WHAT ARE LYMPHOCYTES?

Lymphocytes are a type of white blood cell and are a major part of the lymphatic system. Together with other cells of the immune system, they work to fight infection and prevent disease. Lymphocytes can be found in the blood and bone marrow; however, most of them are normally circulating in the lymphatic system.

There are two main types of lymphocytes that can develop into lymphomas: B lymphocytes and T lymphocytes. The types of cells that become cancerous in anaplastic large cell lymphoma (ALCL) are T lymphocytes (T cells). T cells are named so because they mature in the thymus gland.

There are over 80 different subtypes of lymphoma. They fall into two main categories:

- Hodgkin lymphoma (HL)
- Non-Hodgkin lymphoma (NHL)

ALCL is a type of NHL. NHLs are approximately eight times more common than HL – 85% of all lymphomas are NHLs. The main difference between HL and NHL is the presence of Reed-Sternberg cells which are large abnormal lymphocytes that can be detected under a microscope. Reed-Sternberg cells are only present in Hodgkin lymphoma and are absent in Non-Hodgkin lymphoma.

NHLs are further sub-categorized by 'grade':

- Low-grade: indolent (or slow-growing) NHLs
- Intermediate or high-grade: aggressive (or fast-growing) NHLs

Indolent lymphomas develop more slowly than aggressive lymphomas. Patients with indolent lymphoma usually do not show symptoms until later, often as the disease progresses, and may therefore not require immediate treatment. Aggressive lymphomas on the other hand develop much more rapidly. Patients will usually experience symptoms from the onset of the disease and may require immediate and more intensive treatment. ALCL may be slow growing (indolent) or fast-growing (aggressive) depending on which subtype of ALCL it is.

Who gets ALCL?

ALCL is a rare type of T-cell lymphoma. It most commonly affects children and young adults, accounting for approximately 15% of all NHLs in this patient population. However, it can still affect those of any age. It is more common in men than in women.

Types of ALCL

There are different subtypes of ALCL:

SYSTEMIC ALCL

Systemic ALCL is an aggressive lymphoma that can affect lymph nodes (nodal sites) as well as organs or tissues other than the lymph nodes (called extranodal sites) including the liver, bone marrow, gastrointestinal tract and skin. Patients with systemic ALCL are divided into two groups depending on if there is a specific genetic change (change to a gene which is a unit of heredity) found within the lymphoma cells. This genetic change causes cells to make an abundance of a type of protein called anaplastic lymphoma kinase (ALK). If the ALK protein is present, this is referred to as ALK-positive ALCL and if the ALK protein is absent, this is called ALK-negative ALCL.

- **ALK-positive ALCL (ALK+ ALCL)** is the most common type of systemic ALCL. ALK-positive ALCL is a fast-growing (aggressive) lymphoma. Patients with this type of lymphoma usually respond well to chemotherapy, resulting in long-term remission or cure for many patients.

- **ALK-negative Systemic ALCL (ALK- ALCL)** is a fast growing (aggressive) lymphoma. The majority of ALK negative patients will relapse within five years following treatment and tend to be treated with more aggressive therapy, often with a stem-cell transplant.

PRIMARY CUTANEOUS ALCL

Primary cutaneous ALCL develops in the skin. This type of ALCL is usually less aggressive than systemic ALCL. It is associated with a rare, non-cancerous condition called lymphomatoid papulosis (LyP). In approximately 10% of cases, primary cutaneous ALCL spreads from the skin to the lymph nodes. If this occurs, it is treated as a systemic ALCL.

BREAST IMPLANT-ASSOCIATED ALCL

Breast implant-associated ALCL is an extremely rare T-cell lymphoma that develops following silicone breast implantation, particularly with textured rather than smooth implants. It is believed to be caused by an inflammatory reaction to the implant. It is usually slow-growing (indolent). Although it develops in the breast, it is not considered a breast cancer.

Symptoms

The first signs and symptoms of ALCL can vary depending on the disease subtype. Generally, the most common symptom of systemic ALCL is a painless swelling in the neck, armpit or groin region, caused by an enlarged lymph node or multiple enlarged lymph nodes. Often, lymph nodes in more than one area of the body are affected.

Since systemic ALCL often affects extranodal sites, patients usually experience different symptoms depending on which part of the body the lymphoma develops in. If the lymphoma is found in the abdomen, symptoms can include nausea, diarrhea, bloating and abdominal pain. If it is in the chest, shortness of breath, coughing and chest pain may occur. If the bone marrow is affected, you may experience anemia (low red blood cell levels) or thrombocytopenia (low platelet levels). Other areas of the body commonly affected can include the skin, liver, and spleen.

Patients may also experience a group of symptoms called **B symptoms**. In the case of lymphoma, B symptoms refer to a specific set of symptoms that may help to predict how your lymphoma will progress.

B SYMPTOMS ARE:

- Fever with temperatures above 38°C (100.4°F), without any sign of an infection;
- Night sweats, enough to drench your pajamas or bedding;
- Weight loss without trying (at least 10% of your body weight over 6 months).

Symptoms of primary cutaneous ALCL may include raised red skin lesions that are usually greater in size than a quarter and may itch. These lesions are actually ALCL tumours. They can appear on any part of the body and they grow slowly.

People with breast implant-associated ALCL usually develop a build-up of fluid or a lump around the implant, which can be uncomfortable. This type of ALCL does not usually spread outside the affected breast.

Diagnosis

A diagnosis of ALCL is typically confirmed by a biopsy of a tumour or abnormal skin tissue. A biopsy involves removing a sample of tissue (cells). The removed tissue is then sent to a lab where it is examined under a microscope by a hematopathologist (a doctor who specializes in diagnosing diseases of the blood and bone marrow). This type of biopsy procedure can usually be performed under local anesthetic.

Other tests may also be performed to confirm your diagnosis. Because ALCL is a blood cancer, it is important to look at the entire body to find all of the lymphoma. This is usually done with blood tests and imaging scans which can include a whole-body computed tomography (CT) scan, positron emission tomography (PET) scan or magnetic resonance imaging (MRI) scan. A bone marrow biopsy may also be used to look for the presence of lymphoma cells in the bone.

Staging

Staging describes a cancer based on how much cancer is in the body and where it is located when first diagnosed. ALCL is staged based on the findings from your clinical examinations. Knowing the stage of your lymphoma helps your doctor determine the extent of your disease and monitor its progression over time.

Your ALCL may be staged using the Ann Arbor Staging System. The stage is determined by the number and location of lymph nodes affected, whether the affected lymph nodes are above, below or on both sides of the diaphragm (the large, dome-shaped muscle under the ribcage that separates the chest from the abdomen), and whether the disease has spread to the bone marrow or to other organs such as the liver.

THERE ARE FOUR MAIN STAGES:

- **Stage I** The lymphoma is in one group of lymph nodes or one extranodal site
- **Stage II** The lymphoma is in two or more groups of lymph nodes on the same side of the diaphragm
- **Stage III** The lymphoma is in nodes both above and below the diaphragm
- **Stage IV** The lymphoma is widespread and found in multiple areas throughout the body including nodal and extranodal sites

Stages I and II are considered early stages. Stages III and IV are considered advanced stages.

YOUR DOCTOR MAY ALSO ADD A SINGLE LETTER TO THE STAGE:

- **A** generally means the patient has not experienced any troublesome symptoms
- **B** means the patient has experienced B symptoms (fever, night sweats, weight loss)
- **X** means the patient has bulky disease (large tumours)
- **E** means the patient has extranodal disease (disease outside of the lymph nodes)

Prognosis

WHAT IS PROGNOSIS?

Prognosis is the medical term used to describe how the disease will progress, how well the patient will respond to treatment, and the likelihood of recovery. It is usually based on information gathered from thousands of other patients who have had the same disease and provides a general idea of what to expect when a patient is diagnosed with ALCL. However, it is important to remember that no two patients are alike and that it is not possible to accurately predict what will happen to a specific patient.

INTERNATIONAL PROGNOSTIC INDEX (IPI)

If you have systemic ALCL, your doctor may give you a prognostic score using the International Prognostic Index (IPI). The IPI is a clinical tool developed by oncologists to aid in predicting the prognosis (outcome and survival) of patients with aggressive NHL.

One point is assigned for each of the following IPI risk factors:

- Age 60 years and over;
- Ann Arbor stage III/IV;
- More than one extranodal site;
- Serum lactate dehydrogenase (LDH) level above normal;
- Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2 (looks at a patient's ability to care for themselves and their daily activity level).

These risk factors help identify if the patient is:

- Low-risk (0-1 factors);
- Low/intermediate-risk (2 factors);
- Intermediate/high-risk (3 factors);
- High-risk (4-5 factors).

There is no prognostic index for primary cutaneous ALCL or breast-implant associated ALCL.

Treatment Options

The type of treatment you will receive for your ALCL depends on the subtype that you have. Some patients with anaplastic large cell lymphoma have a type that grows quite slowly (this is known as the 'indolent form'). In this form, lymphoma cells are often found in the bloodstream but lymph nodes are small or do not grow rapidly. If you have this type of lymphoma, your doctor may suggest the 'watch and wait' approach, where instead of receiving immediate treatment, patients will be regularly monitored by their oncologist or hematologist until symptoms develop and treatment is considered necessary.

SYSTEMIC ALCL

Since both ALK-positive and ALK-negative systemic ALCL are aggressive and grow-rapidly, they are treated as high-grade lymphomas. Many patients with newly diagnosed systemic ALCL respond well to common first-line chemotherapy regimens such as:

- **CHOP** (cyclophosphamide, doxorubicin [Hydroxydaunorubicin], vincristine [Oncovin], prednisone)
- **CHOEP** (cyclophosphamide, doxorubicin [Hydroxydaunorubicin], vincristine [Oncovin], etoposide, prednisone)

These drugs are typically administered intravenously (into a vein). The chemotherapy is usually given in cycles of 2 to 4 weeks. A cycle includes treatment days followed by a period of rest and healing. The number of cycles you receive (called the 'course' or 'regimen') depends on your disease and the recommendation of your medical team based on your test results. Many patients will be able to get their treatment as an out-patient, which means you will not have to stay in the hospital overnight.

Patients with ALK-positive ALCL usually respond well to CHOP or CHOEP. Sometimes ALK-positive patients will also receive radiation therapy to the affected areas. In contrast, patients with ALK-negative disease may have slightly lower survival rates with similar treatments. In some cases, ALK-negative patients may receive higher doses of chemotherapy followed by stem-cell transplantation. For some patients with ALCL, the initial treatment may be effective. However, for patients in whom the disease becomes refractory (does not respond to treatment) or relapses (returns after treatment), further therapies may be required. This may include treatment with **brentuximab vedotin** (Adcentris), a targeted therapy drug. Brentuximab vedotin may be used as monotherapy (by itself) or in combination with chemotherapy, typically **CHP** (cyclophosphamide, doxorubicin [Hydroxydaunorubicin], prednisone). Other options can include salvage chemotherapy and autologous stem-cell transplantation (infusion of a patient's own stem-cells). Newer drugs available through clinical trials may also be effective as second-line or later line treatments. A patient may require multiple lines of therapy if their lymphoma relapses or is refractory to their previous treatment(s).

Patients with relapsed or refractory ALCL are often encouraged to participate in clinical trials so that they can receive newer treatments that are not yet on the market. Clinical trials are crucial for establishing more effective, less toxic treatments for patients. You should consult your medical team for information as to whether a clinical trial is an appropriate treatment option for you.

PRIMARY CUTANEOUS ALCL

Treatment of primary cutaneous ALCL depends on the extent of your skin lesions. If the lymphoma is confined to a single area, surgery to remove the lesions or radiation therapy to the affected area will result in a complete response in most patients. If there are multiple widespread lesions, a systemic treatment such as chemotherapy is usually required along with radiation therapy. Histone deacetylase inhibitors (drugs that inhibit the growth of tumor cells) such as **romidepsin** (Istodax) and **retinoids** (drugs that target skin cell growth) can also be used to treat primary cutaneous ALCL. **Brentuximab vedotin** and newer therapies available through clinical trials may be used in patients whose ALCL has relapsed.

BREAST IMPLANT-ASSOCIATED ALCL (BIA-ALCL)

Surgery to remove the lymphoma and breast implants is usually required to treat BIA-ALCL. Often, surgery is the only treatment that a patient will need. If the lymphoma cannot be removed by surgery or if it has spread outside of the breast, then radiation therapy, chemotherapy or brentuximab vedotin, or newer treatments through a clinical trial may be used.

Treatment Side Effects

Many people may be frightened to learn that there can be side effects associated with the therapies they may take to treat their lymphoma. However, it is important to understand that:

- Not all patients who receive therapy experience side effects;
- Side effects are not always severe, they can be mild;
- Different therapies have different side effects;
- There are many effective treatments that can reduce side effects or prevent them from happening altogether.

Some of the most common side effects of chemotherapy include decreased blood cell production (myelosuppression), fatigue, vomiting, diarrhea, loss of appetite, change in taste, hair loss, “chemo-brain” (cognitive impairment(s) that cause difficulties with concentrating and remembering) and peripheral neuropathy (affects nerve endings causing tingling and numbness).

Most side effects are short-lived, but some can last for a few weeks or months after treatment has finished. Occasionally, side effects can be permanent. Some side effects can also start long after treatment has finished. These are called late side effects. Your doctor will talk to you about any potential side effects before you start treatment.

Depending on the side effects you experience and how strongly you feel them, you might not be able to maintain your usual level of activity during and following treatment. You may need to set aside more time for rest and healing. Additionally, depending on the severity of your side effects related to a drug, your doctor may suggest to stop your treatment, and can change your treatment to one that may not cause as many, or any, side effects.

Follow-Up Care

Once you have completed treatment, you will likely be given a follow-up care plan to monitor your response and recovery, as well as to watch for late effects (side effects that develop months or years after treatment) or a potential recurrence. Follow-up care for your ALCL is often shared between your cancer specialists and your family doctor. Your medical team will work with you to decide on the correct follow-up care plan to meet your needs.

Follow-up care after treatment is an important part of cancer care. It is very important to go to all of your follow-up appointments. Your schedule of visits and the tests and procedures that you will undergo during your follow-up are tailored to your individual lymphoma.

Anaplastic large cell lymphoma will relapse (come back) after treatment in most people. Your doctor will tell you to watch for specific signs or symptoms of relapse or recurrence, such as a swelling of the lymph nodes and "B symptoms". Doctors may perform additional testing including blood tests and imaging scans to check if your lymphoma has relapsed.

Use the time during your follow-up appointments to talk to your medical team about any changes or problems you notice and any questions or concerns that you may have about your health after treatment. If you notice any change in your signs and symptoms between follow-up appointments, be sure to contact your medical team right away.