UNDERSTANDING
Peripheral T-cell Lymphoma (PTCL)

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 peripheral T-cell lymphoma (PTCL) 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)

PTCL is a type of NHL. NHL is approximately eight times more common than HL – 85% of all lymphomas are NHL. One of the main differences between HL and NHL is the presence of Reed-Sternberg cells which are large abnormal lymphocytes that can detected under a microscope. Reed-Sternberg cells are typically present in Hodgkin lymphoma and absent in non-Hodgkin lymphoma.

NHL is 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. Peripheral T-cell lymphoma may be slow growing (indolent), but is usually of the fast-growing (aggressive) type.

"Peripheral" means that the T cells develop in parts of the body outside of the thymus gland, which is their normal place of development. PTCL refers to a number of different T-cell lymphoma subtypes that together affect 5-10% of all patients diagnosed with NHL. PTCL can affect the 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.

Who gets PTCL?

PTCL is relatively uncommon, making up less than 10% of all NHL cases. It most commonly affects people over the age of 60 years and is diagnosed slightly more frequently in men than in women. PTCL can also affect children and younger adults.

Subtypes of PTCL

Peripheral T-cell lymphomas are classified into distinct subtypes based on the clinical presentation of disease. These subtypes include:

PERIPHERAL T-CELL LYMPHOMA NOT OTHERWISE SPECIFIED (PTCL-NOS)

PTCL-NOS refers to an aggressive group of PTCLs not classifiable as a specific subtype. It is the most common PTCL subtype in North America and usually affects those 60 years of age and older. When PTCL-NOS is diagnosed, most patients present with nodal involvement; however, a number of extranodal sites may also be involved. Since this is an aggressive subtype, treatment usually requires combination chemotherapy which may be followed by autologous stem-cell transplantation (patients are infused with their own stem-cells).

ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA (AITL)

AITL is an aggressive PTCL subtype. AITL accounts for about 15% to 20% of all PTCL cases. 'Angio' refers to blood vessels, which often grow in an abnormal pattern in this disease. This subtype is defined by disease in the lymph nodes (lymphadenopathy), enlargement of the liver and spleen, skin rash, and a higher than normal level of antibodies in the blood. The clinical course can be complicated by infection due to suppression of the immune system. These symptoms can be treated with steroids, and steroids can be used in combination with chemotherapy. Autologous stem-cell transplantation (patients are infused with their own stem-cells) may also be considered.

ANAPLASTIC LARGE CELL LYMPOHMA (ALCL)

Please refer to the ALCL subtype fact sheet.

NASAL-TYPE NK/T-CELL LYMPHOMA

Nasal-type NK/T-cell Lymphoma originates from abnormal natural killer (NK) cells. NK cells are lymphocytes that are closely related to T cells that normally help the immune system by killing virus-infected cells and cancer. Genetic mutations (abnormal changes to genes, unit of heredity) can cause these NK cells to not function properly. The development of this subtype is also associated with the Epstein-Barr virus (EBV) and is most commonly found in people living in Asia and parts of South America. This type of lymphoma typically affects the nasal and paranasal sinus areas along with the trachea and gastrointestinal tract. Due to its location in the nose, common symptoms include blockages in your sinuses and strong nose bleeds. Treatment for this lymphoma includes radiation and combination chemotherapy, and may also include a stem-cell transplant.

ADULT T-CELL LYMPHOBLASTIC LYMPHOMA/LEUKAEMIA (ATLL)

ATLL is a subtype caused by the spread of T-cells into the bone marrow and blood. ATLL has been linked to infection with a virus called the human T cell lymphotrophic virus type 1 (HTVL-1). It is rarely seen in patients in North America and is more commonly found in Japan, the Caribbean and some areas of South and Central America and Africa. ATLL causes high levels of calcium in the blood (hypercalcaemia), high white blood cell count, a large mediastinal (chest) mass and abnormal enlargement of organs (organomegaly). ATLL is also likely to affect the central nervous system (the brain and spinal cord), especially if it relapses. ATLL can be further divided into aggressive (acute, lymphomatous) and slow-growing (chronic, smoldering) subtypes which can determine the treatment course for the patient. Treatment usually begins with steroids and combination chemotherapy. Although some patients may initially respond to chemotherapy, the long-term prognosis (outcome and survival) is poor and usually requires other treatments, such as allogenic stem-cell transplantation (patients are infused with stem-cells from a healthy donor).

ENTEROPATHY-TYPE INTESTINAL T-CELL LYMPHOMA (ETL)

ETL is a rare aggressive extranodal lymphoma that is divided into two subtypes: Type I ETL (more common, and develops in patients with celiac disease); and type II ETL (not associated with celiac disease), also called monomorphic epitheliortopic t-cell lymphoma. Celiac disease is an autoimmune disorder that is triggered when you eat gluten (commonly found in wheat, barley, rye). ETL appears to occur more frequently in individuals of Welsh or Irish descent due to genetic changes (changes to a gene which is a unit of heredity) that cause gluten-sensitivity. This lymphoma subtype affects the intestines and can cause abdominal pain, weight loss, gastrointestinal bleeding and bowel perforation. There are a variety of treatment options that may be available depending on the subtype and clinical presentation. These options can include chemotherapy with or without radiation, surgery, autologous stem-cell transplantation, and dietary changes (supplements, gluten-free diet).

HEPATOSPLENIC T-CELL LYMPHOMA (HSTL, OR HSTCL)

HSTL Lymphoma is an extremely rare and aggressive PTCL subtype that commonly affects young adults in their in their twenties and thirties. It can develop in individuals with chronic immune suppression, such as seen with organ transplants. It is a systemic disease, meaning that the cancerous T cells can spread throughout the body such as to the liver, spleen and bone marrow. There is usually no solid tumour(s) present throughout the body. This subtype is typically very aggressive and treatment options may include combination chemotherapies and stem-cell transplant.

SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA (SPTCL)

SPTCL is a rare type of PTCL. It develops primarily in subcutaneous fat tissue (fat located under the skin). SPTCL is often confused with a condition called panniculitis, an inflammation of fatty tissue in the body. Patients may feel bumps under the skin (subcutaneous nodules) which can change to open, inflamed sores. SPTCL is confined to patients that have an alpha-beta T-cell receptor and will usually have an indolent (non-aggressive) clinical course. In Gamma-delta cutaneous T-cell lymphoma, this more rare type will have an aggressive clinical course. Treatment options for SPTCL may include immunomodulatory drugs or combination chemotherapy.

SPCTL is confined to cases with an alpha-beta T-cell receptor and usually have an indolent course. Gamma-delta is combined with a rare cutaneous PTCL called Gamma-delta cutaneous T-cell lymphoma due to similar aggressive course. Treatment options for SPTCL may include immunomodulatory drugs or combination chemotherapy.

Symptoms

The signs and symptoms of PTCL can vary depending on the subtype. Generally, the most common and frequent symptom of PTCL is a painless swelling in the neck, armpit, abdomen or groin region(s) caused by enlarged lymph nodes. Often, lymph nodes in more than one area of the body are affected. Patients may also experience fatigue, loss of appetite, itchy skin and/or rash.

Enlargement of the spleen (splenomegaly) or liver (hepatomegaly) is relatively common for PTCL patients. This may cause the patient to experience bloating or fullness after eating only small amounts of food. It can also cause abdominal pain, diarrhea, and vomiting.

If the bone marrow is affected, some patients may also experience symptoms due to reduced blood cell levels. Low levels of healthy red blood cells can lead to a condition called anemia, causing weakness and fatigue. A low platelet count, called thrombocytopenia, can cause increased bleeding and bruising.

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 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).

Diagnosis

A diagnosis of PTCL is typically confirmed by a lymph node biopsy. This type of biopsy involves removing a sample of tissue (cells) from the lymph node. 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 PTCL 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, and/or magnetic resonance imaging (MRI) scan. A bone marrow biopsy may also be performed 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. PTCL 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 PTCL 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 extra nodal 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)

It is common for patients with PTCL to have advanced-stage disease, and treatment can still be effective in this scenario.

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 which provides a general idea of what to expect when a patient is diagnosed with PTCL. 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.

When diagnosed with PTCL, your doctor may give you a prognostic score using a prognostic scoring system. The following scoring systems are used to help predict the prognosis (outcome and survival) of patients with PTCL. Your doctor may use one or more of these scoring systems.

THE INTERNATIONAL PROGNOSTIC INDEX (IPI)

The IPI is a clinical tool developed by oncologists to aid in predicting the prognosis of patients with aggressive NHL, not just PTCL. This is the most commonly used scoring system for NHLs.

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 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).

THE PROGNOSTIC INDEX FOR PTCL (PIT)

PIT is a prognostic index specifically designed for some subtypes of PTCL, including PTCL-NOS. PIT separates patients into more specific prognostic groups compared to the IPI. PIT is based on four risk factors: age (60+), ECOG performance status (≥ 2), LDH levels above normal, and bone marrow involvement. By using these risk factors instead of the factors associated with the IPI, PIT has a better predictive capacity for determining the prognosis of patients for certain subtypes of PTCL.

THE MODIFIED PROGNOSTIC INDEX FOR PTCL (MPIT)

This is a modified version of PIT using three of the same risk factors (age, ECOG performance status, LDH levels), but substituting a marker for cell growth (Ki-67) (≥ 75%), instead of looking at bone marrow involvement.

THE INTERNATIONAL PTCL PROJECT (IPTCLP) SCORE

IPTCLP is a scoring system used for patients with AITL and PTCL-NOS subtypes. It is based on three risk factors: age (60+), ECOG performance status (≥ 2) and platelet cell count (≥ 150 × 10^9/L).

THE BOLOGNA SCORE

This prognostic scoring system combines clinical and biological factors including tumour proliferation and clinical features such as age, ECOG performance status, and LDH levels.

Treatment Options

Some patients with peripheral T-cell lymphoma have a subtype that can grow quite slowly (this is known as the 'indolent form'). In this form, lymphoma cells are often found in the bloodstream, but the lymph nodes are small or do not grow rapidly. If patients have this type of indolent lymphoma, their doctor may suggest a 'watch and wait' approach, where the patient does not receive immediate treatment and is instead closely monitored.

WHAT IS 'WATCH & WAIT'?

Some people newly diagnosed with indolent PTCL may not need immediate anti-cancer treatment. Indolent PTCL often progresses slowly and do not cause any problems for a period of time. Therefore, instead of immediate treatment, patients will be regularly monitored by their oncologist for months or years until the cancer changes and treatment is considered necessary. This approach is called 'watch and wait', 'watchful waiting' or 'active surveillance'. Watch and wait is a treatment approach for those who have no symptoms, and additionally lets you avoid harmful treatment related side effects when treatment may not be necessary.

Once a patient has been treated, the watch and wait phase will start again, and their oncologist will begin to monitor them for a potential return of their cancer. Throughout the watch and wait period, your doctor will ask you whether you notice any changes in your current symptoms or if you are experiencing any new symptoms. They may also perform a physical examination, blood tests, and imaging scans to assess your response to treatment.

Some patients are concerned about the watch and wait approach and would rather receive immediate treatment following their diagnosis. Clinical trials for early-stage or slow-growing stable cancers have compared the watch and wait approach with immediate treatment. These trials have shown that patients that are monitored through watch and wait do as well or better than those given treatment immediately when treatment is likely to not improve outcomes or survival, and instead cause harmful or toxic side effects.

In most patients, PTCL is diagnosed as an aggressive subtype that grows rapidly, and so it is treated like a high-grade lymphoma. First-line treatment for newly diagnosed PTCLs is usually anthracycline-based chemotherapy regimens including:

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

More recently, chemotherapy regimen **BCHP** (brentuximab vedotin plus cyclophosphamide, doxorubicin [Hydroxydaunorubicin], prednisone) has been approved for CD30+ PTCLs including ALCL, AITL and PTCL-NOS subtypes. For PTCL cases that do not express the CD30+ marker, CHOP or CHOEP are used. A stem-cell transplant may still be considered.

These drugs are typically administered intravenously (into a vein) which is performed in the hospital. A central-line, which is a catheter placed in a large vein, may be used to administer chemotherapy drugs and draw blood for testing. 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 the recommendation of your medical team based on your test results. Many patients will be able to receive their treatment as an out-patient, which means you will not have to stay in the hospital overnight.

After your course of chemotherapy, you may receive radiation therapy to the area affected by the lymphoma. In some cases, radiation therapy without chemotherapy is used, but this is rare. For some patients with PTCL, 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. Therapies may include a combination of chemotherapies and other novel drug therapies such as **brentuximab vedotin (Adcentris)** for ALCL and **romidepsin (Istodax)** or **pralatrexate (Folotyn)** for relapsed PTCLs. Additionally, stem-cell transplantation (autologous or allogeneic), radiation therapy, or newer drugs available through clinical trials may be used. 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 PTCL 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 more information on whether a clinical trial is an appropriate treatment option for you.

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 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 affects you experience and how strongly you feel them, you might not be able to maintain your usual level of activity during treatment. You might 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 may change your treatment to one that does not cause as many, or any, side effects.

Follow-Up Care

Once you have completed active 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 PTCL 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 follow-up are tailored to your individual lymphoma.

Peripheral T-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. These signs and symptoms may include swelling of the lymph nodes and B symptoms (fever, unexplained weight loss, and drenching night sweats). Doctors may perform additional testing including blood tests and imaging scans to confirm 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.

YOU DON'T HAVE TO FACE LYMPHOMA ALONE.

Lymphoma Canada connects patients, their family and friends, medical professionals, researchers, volunteers and donors, to build a strong lymphoma community.

For more information please visit lymphoma.ca or call 1-866-659-5556, or email us at info@lymphoma.ca.

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