UNDERSTANDING
Cutaneous T-cell Lymphoma (CTCL)

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 cutaneous T-cell lymphoma (CTCL) 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)

CTCL 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.

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. CTCLs are considered to be an indolent (slow-growing) Non-Hodgkin lymphoma. Most CTCLs are treatable and non-life-threatening, however they are not curable. Cutaneous T-cell lymphomas develop from malignant T cells that are in the skin. CTCL normally remains within the skin, however sometimes it can spread outside of the skin. This is still considered a cutaneous lymphoma. However, if a lymphoma did not originate in the skin but has spread to the skin, it is not considered a cutaneous lymphoma.

Who gets CTCL?

CTCLs are a rare group of Non-Hodgkin lymphomas. They most commonly affect adults who are 50-60 years of age or older. Rarely, they can affect children and young adults. CTCLs are more common in men than in women.

Types of CTCL

CTCL is not one disease. It is a group of T-cell lymphomas that affect the skin. Some common subtypes of CTCL include:

MYCOSIS FUNGOIDES (MF)

MF is the most common subtype of CTCL, making up more than half of all CTCL cases. It is an indolent (slow-growing) lymphoma. MF can cause different types of skin lesions (see the Symptoms section). Symptoms of MF often resemble those of other skin conditions such as psoriasis and eczema, and thus can be difficult to diagnose as MF. MF can spread from the skin to other areas in the body including the lymph nodes, but rarely to other parts of the body such as the liver, spleen and lungs. MF is rarely life-threatening. There are many different subtypes of MF, with the most common including:

- **Classical Mycosis Fungoides** is the most common subtype of MF. It usually starts off as irregularly shaped or oval scaly patches which are often found on the chest, back or buttocks. Plaques and skin tumours may develop and can turn into ulcers. Some people may also develop erythroderma (total body redness).
- **Folliculotropic Mycosis Fungoides** causes different types of lesions to form on the skin including comedones (small skin coloured bumps), acneiform lesions (raised red pustules), cysts, plaques and tumors, that are often accompanied by itching. You may experience only one, or many of these types of lesions. Folliculotropic MF targets hair follicles in particular, which can lead to hair loss. It most commonly affects the head, neck, and face.
- **Pagetoid Reticulosis (Woringer-Kolopp Disease)** usually presents as a single scaly plaque on the hands and feet, and/or ears and nose. This type never spreads outside of the skin.

- **Granulomatous Slack Skin** is a rare subtype that is most common amongst people with lighter skin tones. It is characterized by the development of loose folds of skin that usually appear in the armpits or groin regions. Patches and plaques may develop in these skin folds.
- **Hypopigmented Mycosis Fungoides** causes hypopigmentation (patches of skin that are lighter than your overall skin tone) to occur instead of classic MF lesions (i.e. patches, plaques, tumours). It predominately affects those with darker complexions. Unlike other types of MF, hypopigmented MF most commonly occurs in children and young adults.

Other subtypes of MF that are less common include:

- Erythrodermic MF
- Ichthyosiform MF
- MF palmaris et plantaris
- Papillomatous MF
- Papular MF
- Solitary or unilesional MF
- Purpuric MF
- Pustular MF
- Verrucous MF
- Granulomatous MF
- Interstitial MF
- MF with large-cell transformation
- Invisible MF
- MF with eruptive infundibular cysts
- Syringotropic MF
- Poikilodermal MF
- Bullous MF
- Anetodermic MF

SEZARY SYNDROME (SS)

SS is the second most common type of CTCL. It is similar to MF in that it affects the skin, causing skin redness and lesions (see the Symptoms section). SS also affects the blood and lymph nodes and can also spread to other organs in the body. A high number of malignant T cells in the skin (called Sezary cells) can also be found in the blood. SS is a more aggressive type of CTCL. Those with this lymphoma often have weakened immune systems which increases the risk for infection.

PRIMARY CUTANEOUS ANAPLASTIC LARGE CELL LYMPHOMA (PCALCL)

PCALCL is an indolent (slow-growing) type of CTCL that usually develops as a single tumour. In approximately 10% of cases, PCALCL spreads to other organs of the body. If this occurs, it is treated as a systemic anaplastic large cell lymphoma (SALCL).

LYMPHOMATOID PAPULOSIS (LYP)

LyP falls under the umbrella of cutaneous T-cell lymphomas, but it is known as a 'lymphoproliferative disorder'. This is a non-cancerous condition where lymphocytes grow abnormally but their overall behaviour is harmless. It can cause similar symptoms to other CTCLs such as skin lesions, but these often go away on their own or with light treatment. People with LyP are at greater risk for developing other types of skin lymphomas.

Symptoms

The first signs and symptoms of CTCL can vary depending on the disease subtype. However, there are some symptoms that are common to most types of CTCLs.

Patients may experience only one symptom or a combination of multiple symptoms. These include:

- **Patches** are usually flat, scaly areas on the skin that may be pink or red in colour. Patches can also be regions of lighter (hypopigmented) or darker (hyperpigmented) skin compared to your normal skin colour. Patches may disappear and then reappear, or they may remain stable.
- **Plaques** are raised, thickened rashes on the skin. The bumps often itch. They may be smooth, scaly or ulcerated, and can be red, purple or brown in colour.
- **Papules** are small bumps that may look like pimples or a rash. They may be pink, red, purple or brown in colour.
- **Tumours** are solid, dome-shaped masses that are at least 1 cm in thickness. They are thicker and deeper than plaques. These can ulcerate and scab over. You may have one or several tumours.
- **Reddening of the skin (erythrodema)** is a general redness of the skin which can be very dry, itchy and scaly.

In Mycosis Fungoides, the first signs and symptoms are usually smaller lesions, such as small patches and plaques. These lesions often first appear in areas of the body that are not usually exposed to sun. These are often mistaken for other skin conditions including psoriasis, eczema, or dermatitis. Over time, these may slowly grow into larger lesions that are more widespread, and may turn into sores (ulcerate) and be painful. Rarely, MF can spread from the skin to internal regions, causing variable symptoms depending on where in the body it has spread to.

Sezary Syndrome is characterized by erythroderma on most or all of the skin. This may be accompanied by other skin lesions. Since SS affects the blood and lymph nodes, enlarged lymph nodes, enlarged spleen (splenomegaly) and/or an enlarged liver (hepatomegaly), are common symptoms. Other symptoms of SS can include hair loss, thickening of the skin on the palms and soles of the feet, outward turning of the eyelid (ectropia) and changes to the fingernails and toenails.

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 called ALCL tumours, and they grow slowly. These tumours may ulcerate and become painful. This subtype of lymphoma can result in a solitary tumour or multiple tumours, and they can appear on any part of the body.

Diagnosis

A diagnosis of CTCL is typically confirmed by a biopsy of a tumor 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). Diagnosing CTCLs is often not straightforward, and you may require multiple skin biopsies as well as additional tests and imaging scans to confirm a diagnosis.

It is important that tests that look at the entire body to find all of the lymphoma. This is usually done by performing blood tests, such as blood flow cytometry (which measures the characteristics of cells), and whole-body imaging scans which can include a computed tomography (CT) scan, positron emission tomography (PET) scan and/or magnetic resonance imaging (MRI) scan. A bone marrow biopsy or lymph node biopsy may also be performed to look for the presence of lymphoma cells in the bone or lymph nodes. .

Staging

Staging describes a cancer based on how much cancer is in the body and where it is located when first diagnosed. CTCLs are 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.

Staging for most CTCLs, particularly mycosis fungoides and sezary syndrome, take into consideration the extent of tumours present, whether the lymphoma is in the lymph nodes, whether it has spread to other internal organs (visceral involvement), and the amount of blood involvement. This is known as the Tumour-Node-Metastasis-Blood (TNMB) classification which involves nine stages (IA-IVB). Stages IA to IIA are considered early stages. Stages IIB to IVB are considered advanced stages. This staging system is presented in the following table.

STAGE	T (TUMOUR)	N (NODES)	M (METASTASIS)	B (BLOOD)
IA	**T1** Patches and plaques ‹10% of body surface area	**N0** No palpable nodes or histological evidence of MF	**M0** No visceral involvement	**B0** ‹5% lymphocytes are atypical **B1** ›5% lymphocytes are atypical, but ‹1000μ/l
IB	**T2** Patches and plaques ›10% of body surface area	**N0**	**M0**	**B0-1**
IIA	**T1-T2**	**N1** No histological evidence of MF **N2** Early involvement of MF, atypical cell aggregations with preservation of nodal structure	**M0**	**B0-1**
IIIA	**T4** Erythroderma ›80% body surface area involved	**N0-2**	**M0**	**B0**
IIIB	**T4**	**N0-2**	**M0**	**B1**
IVA1	**T1-T4**	**N0-2**	**M0**	**B2** ›1000μ/l circulating atypical lymphocytes
IVA2	**T1-T4**	**N3** Lymph nodes involved with loss of normal structure	**M0**	**B0-2**
IVAB	**T1-T4**	**N0-3**	**M1** Metastsis	**B0-2**

Prognosis

WHAT IS PROGNOSIS?

Prognosis is the medical term used to describe how the disease is expected to 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 CTCL. 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.

Unlike most types of lymphoma, there is no prognostic index to aid in predicting the outcome and survival for those with cutaneous T-cell lymphomas. However, there are certain indicators that doctors may use to help determine the prognosis (outcome and survival) of your disease.

Some of these factors include:

- Stage of lymphoma
- Age
- Sex
- Extent of skin involvement
- Presence of extracutaneous disease (spread of disease outside of the skin)
- Extent of peripheral blood involvement
- Presence of large cell transformation (LCT)
- Cutaneous histologic features of folliculotropism
- CD30 (a protein that can be found on the surface of T cells) positivity
- Proliferation index (a measure of the number of cells in a tumour that are dividing)
- Lymphocyte count
- Presence of identical T cell clones in the blood and skin
- Thickness of skin lesions (plaques/tumours versus patches)

Treatment Options

The type of treatment you will receive for your CTCL will depend on the subtype that you have and the stage of your disease. Some treatments are **localized**, meaning that they only target the affected skin. Other treatments are **systemic**, meaning that they travel throughout the entire body. Depending on your lymphoma, your doctor may decide to use localized treatments, systemic treatments, or a combination of the two.

For early stage, indolent CTCLs that are isolated to the skin, such as most cases of early stage mycosis fungoides and primary ALCL, localized treatment is typically used. Localized treatment will directly target small areas of skin lesions.

Some commonly used localized treatments include:

- **Topical Corticosteroidsn -** corticosteroids can reduce many of the associated symptoms of CTCL. These drugs reduce the swelling and inflammation associated with rapidly growing tumors and other skin lesions. They may also alleviate itchiness and redness of the skin.
- **Topical Chemotherapy -** some chemotherapy drugs can be applied directly to the skin to slow the growth of cancer cells. A commonly used topical chemotherapy drug is mechlorethamine.
- **Topical Retinoids -** retinoids are drugs that regulate skin cell growth. Topical retinoids can slow the growth of some types of cancer cells.
- **Local Radiation Therapy -** electron beam therapy is a form of radiation therapy that is used to treat skin lesions. The radiation does not penetrate deeply into the body, so it is less likely to harm the tissue and organs beneath the skin.
- **Phototherapy -** phototherapy, or light therapy, is a treatment that uses ultraviolet (UV) light to target cancer cells. There are two mains types of phototherapy: narrowband ultraviolet B (UVB) phototherapy and psoralen + ultraviolet A (PUVA) phototherapy. PUVA penetrates the skin more deeply than UVB, so it is used on larger, deeper lesions whereas UVB is used on smaller, thinner lesions.
- **Surgery -** surgery may be required to remove larger lesions such a tumours.

You may be treated with one or several of the above localized treatments. For some patients, localized treatments may result in remission. For others, this may not be enough, and a systemic treatment may be required. A systemic treatment is typically used for advanced stage or aggressive CTCLs, such as sezary syndrome or advanced stage mycosis fungoides, in which lymphoma has spread from the skin to the blood or other organs. Systemic treatments will target lymphoma cells that are present throughout your whole body.

Some commonly used systemic treatments for CTCL include:

- **Oral Retinoids -** Retinoids are drugs that regulate skin cell growth. Some retinoids can be taken orally, such as bexarotene (Targretin), to slow the growth of some types of cancer cells.
- **Photophoresis -** is a systemic treatment that involves extracting lymphocytes and treating the lymphocytes with psoralen + ultraviolet A (PUVA). Psoralen is a light-sensitive drug that makes the cells more sensitive to UVA light. Once the lymphocytes are treated, they are returned back to the circulating blood.
- **Extracorporeal photophoresis (ECP) -** ECP is a leukapheresis-based therapy that involves the collection of blood from a patient through a vein. The white blood cells are then separated from the other cells in the blood. These white blood cells are treated with a photosensitizing agent and then passed through a machine where they are exposed to ultraviolet-A (UVA) light. The treated cells are then infused back into the patient to help their immune system fight against their CTCL.
- **Interferon Immunotherapy -** immunotherapy enhances your body's immune system to target cancer cells. Interferons are a type of immunotherapy. An interferon is a protein molecule that is naturally produced by the body's immune system to help fight infection and kill cancer cells in the body. Synthetic interferons have been produced and are used to treat CTCL.
- **Monoclonal Antibodies -** these are immunotherapy drugs that are designed to target specific proteins in cancer cells to limit the growth and spread of cancer while minimizing harm to healthy cells. An example of a monoclonal antibody that may be used to treat CTCL is alemtuzumab (Campath).
- **Targeted Therapy -** targeted therapy uses drugs to target specific molecules on the surface of cancer cells. By targeting certain molecules, the drugs can limit the growth and spread of cancer cells. An example of a targeted therapy drug is brentuximab vedotin (Adcentris).
- **Chemotherapy -** chemotherapy is the most commonly used systemic treatment. Chemotherapy drugs may be given on their own (single-agent) or in combination with other chemotherapy drugs. The following drugs are typically used to treat CTCLs:
    - Single agent traditional chemotherapy drugs such as methotrexate, gemcitabine (Gemzar), liposomal doxorubicin (Doxil), chlorambucil (Leukeran), cyclophosphamide;
    - Other more novel chemotherapy agents such as pralatrexate (Folotyn), vorinostat (Zolinza), romidepsin (Istodax).

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 CTCL are also 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 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 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 CTCL is often shared between your cancer specialists, dermatologist 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 your cancer care. It is very important to go to all of your follow-up appointments. Your schedule of visits and the tests and procedure that you will undergo during your follow-up are tailored to your individual lymphoma.

Cutaneous T-cell lymphomas are generally considered incurable, however, these lymphomas are treatable and are not life-threatening in most cases. Typically, the goals of treatment are to relieve symptoms, achieve remission and postpone disease progression. If you do go into remission after treatment, your lymphoma may relapse in the future. Your doctor will tell you to watch for specific signs or symptoms of relapse or recurrence such as worsening skin lesions and swelling of the lymph nodes.

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 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.

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

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