All About Cutaneous T Cell Lymphoma (CTCL)

What is the lymph system, and what are lymph nodes?
The lymph system is essentially the "housekeeping system" of the body. It is a network of vessels (tubes), which connect the lymph nodes. These nodes can vary in size, but are normally up to about 2 centimeters in width. They contain cells that clear bacteria and other foreign debris from the body. Lymph is a watery liquid that flows between cells in the body, picking up foreign debris and taking it into the lymph node for filtering. From the lymph node, the debris may pass through several more nodes in the system before being dumped into the bloodstream to ultimately be cleared by the liver. The lymph system flows throughout the body, and also includes the spleen and thymus gland.

What is a lymphocyte?
Lymphocytes are a type of white blood cell. These cells (called B cells and T cells) are important in fighting infection and mount what is called the "immune response". B cells produce proteins called antibodies, which move through the bloodstream and attack a specific target, as directed by the B cell. They start their lives in the bone marrow and then develop fully in the lymph nodes. T cells are developed in the thymus gland and directly attack the cells identified as foreign by the B cells. In addition, both of these cells are able to remember bacteria from previous infections, and thus respond quicker to future infections.

What are the non-Hodgkin's lymphomas?
Simply put, the non-Hodgkin's lymphomas (NHLs) are a group of cancers that affect the various parts of the immune system, the very system that is supposed to protect our body against disease. NHLs begin in the lymph nodes and are made up of malignant (cancerous) lymphocytes (either B cells or T cells). In 2001, the World Health Organization developed a comprehensive classification system for the 30+ different types of non-Hodgkin's lymphomas (NHLs), which are then further divided according to the cell type involved (either B cell or T cell). These 30+ types of NHLs are different in their growth rates and aggressiveness, and are often treated differently.

What are cutaneous T-cell lymphomas?
Cutaneous T-cell lymphomas (CTCLs) are a group of lymphomas that affect the skin as their primary site. There are multiple types or "classifications" of CTCL (see below), with varying prognoses and appearance under the microscope (histology). Mycosis fungoides is the most common. This article will focus on mycosis fungoides and Sézary syndrome, the two most common CTCLs. The other subtypes seen in the table below are considered quite rare.

The World Health Organization (WHO) and the European Organization for...
Research and Treatment of Cancer (EORTC) Classification of CTCL (T-type)

**Indolent Clinical Behavior**

- Mycosis fungoides variants include: folliculotrophic mycosis fungoides, hypopigmented/vitiligenous mycosis fungoides, Pagetoid reticulosis and granulomatous slack skin.
- Subcutaneous panniculitis-like T-cell lymphoma
- Primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoma

**Aggressive Clinical Behavior**

- Sezary syndrome
- Primary cutaneous CD8+ aggressive epidermotropic T-cell lymphoma
- Primary cutaneous gamma/delta T-cell lymphoma
- Extranodal natural killer/T-cell lymphoma, nasal type

**Variable Clinical Behavior**

- Primary cutaneous peripheral T-cell lymphoma, unspecified.

(Found at: https://www.lls.org/sites/default/files/file_assets/cutaneoustcelllymphoma.pdf)

The World Health Organization (WHO) and the European Organization for Research and Treatment of Cancer (EORTC) Classification of CTCL (B-type)

Included within the CTCL classifications are the cutaneous B-cell lymphomas (CBCLs). The WHO-EORTC classification recognizes 4 types of CBCLs, and each varies in histology, presentation, treatment and prognosis, compared to other CTCLs and the 5 types themselves.

**Indolent clinical behavior**

- Primary cutaneous marginal zone B-cell lymphoma
- Primary cutaneous follicle center lymphoma
Intermediate-aggressive clinical behavior

- Primary cutaneous diffuse large B-cell lymphoma, leg type
- Primary cutaneous diffuse large B-cell lymphoma
- Intravascular large B-cell lymphoma

(Found at: https://www.lls.org/sites/default/files/file_assets/cutaneouscelllymphoma.pdf)

What causes CTCL and am I at risk?

CTCL accounts for about 4% of non-Hodgkin’s lymphomas. CTCL is twice as common in men than women and more common in blacks than whites. The incidence increases with age, with an average age of diagnosis between 50 and 60. However, childhood cases have been reported. The incidence has increased over the past 30 years, which may, in part, be due to better diagnosis. There is no accurate reporting system for CTCL diagnoses, but experts estimate there are 16,000-20,000 cases in the U.S. annually.

Experts think the cause is related to some type of viral infection resulting in a chronically heightened immune state. Other theories include genetic changes and chemical exposure, but the actual causes remain unknown.

How can I prevent CTCL?

Because it is not definitively known what causes CTCL there are no known prevention measures.

What screening tests are available?

This is a rare cancer; therefore specific screening tests do not exist, though a thorough skin exam by the healthcare provider can detect early lesions.

What are the signs of CTCL?

The signs of CTCL are dependent upon whether you have MF or SS type. Mycosis fungoides (MF) is a slowly progressive disease in which cancerous T cells accumulate in the skin. This causes the red (erythematous) patches or plaques that most patients present with. Patches are flat lesions, whereas a plaque describes a thicker, raised lesion. MF patches or plaques tend appear round or ring shaped, red to pink in color, may be dry, flaky or itchy and typically occur on skin that is not often exposed to sunlight. The lesions may remain the same size for many years, grow slowly or disappear spontaneously. The median time to diagnosis is about 6 years for CTCL, demonstrating that it's benign behavior and appearance may cause the lesions to be ignored by the patient or to go undiagnosed by the physician. In more advanced stages, the skin lesions can form mushroom-appearing tumors (this is called tumor stage MF), which is how the name mycosis fungoides came about.

Sézary syndrome (SS) is a more aggressive form of CTCL. Patients diagnosed with SS have red patches or generalized redness on the skin, but more importantly, cancerous T cells in the bloodstream. These malignant cells can ultimately involve lymph nodes, bone marrow and other organs. SS can be a result of the progression of existing MF or, more commonly, a new diagnosis (called de novo). The diagnosis of SS is made by detecting the presence of abnormal T-cells, called Sézary cells, in
the bloodstream. The skin in SS is often very itchy, appears "thickened" and may appear scaly. Palms and soles may be very red and thickened, with cracks in the skin (called fissures). In addition, these patients can have alopecia (hair loss), nail abnormalities and eye changes (blepharoconjunctivitis and ectropion).

How is CTCL diagnosed?

It can take years for CTCL to be diagnosed since in its early stages it mimics many common skin conditions such as eczema and psoriasis. An incisional skin biopsy, and in some cases more than one, is necessary to determine a CTCL diagnosis. Your provider will remove a small portion of a lesion and look at it under a microscope to determine if the cells are that of CTCL or a different skin disorder. You will receive a full physical exam including palpation of your lymph nodes, as well as blood work to check for malignant lymphocytes. In some cases of SS, malignant cancer cells can be seen in the blood. You may also have a CT, MRI or PET scan to check for metastasis (spread) to lymph nodes and organs.

How is CTCL staged?

The staging of a cancer describes how much it has grown before the diagnosis is made. Staging documents the extent of disease. Cancers cause problems because they spread and can disrupt the functioning of normal organs. MF and SS are staged using a TNM staging system (see below).

The TNM breakdown is quite technical, but is provided here for your reference. Your healthcare provider will use the results of the diagnostic work up to assign the TNM result and then a stage.

<table>
<thead>
<tr>
<th>TNMB</th>
<th>TNMB Classification and Staging of Mycosis Fungoides and Sezary Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Limited patches, papules, and/or plaques covering less than 10% of the skin surfaces</td>
</tr>
<tr>
<td>T2</td>
<td>Patches, papules, and/or plaques covering less than or equal to 10% of the skin</td>
</tr>
<tr>
<td>T2a</td>
<td>Patch only</td>
</tr>
<tr>
<td>T2b</td>
<td>Plaque with or without patch</td>
</tr>
<tr>
<td>T3</td>
<td>One or more tumors (?1 cm in diameter)</td>
</tr>
<tr>
<td>T4</td>
<td>Confluence of erythema ? 80% body surface area</td>
</tr>
<tr>
<td>Node</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>No abnormal lymph nodes; biopsy not required</td>
</tr>
<tr>
<td>N1</td>
<td>Abnormal lymph nodes; histopathology Dutch Gr 1 or NCI LN 0-2</td>
</tr>
<tr>
<td>-----</td>
<td>------------------------------------------------------------</td>
</tr>
<tr>
<td>N2</td>
<td>Abnormal lymph nodes; histopathology Dutch Gr 2 or NCI LN3</td>
</tr>
<tr>
<td>N3</td>
<td>Abnormal lymph nodes; histopathology Dutch Gr 3-4 or NCI LN4</td>
</tr>
<tr>
<td>NX</td>
<td>Abnormal lymph nodes; no histologic confirmation</td>
</tr>
</tbody>
</table>

**Visceral**

<table>
<thead>
<tr>
<th>M0</th>
<th>No visceral organ involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>Visceral involvement (must have pathology confirmation and organ involvement should be specified)</td>
</tr>
<tr>
<td>MX</td>
<td>Abnormal visceral site; no histologic confirmation</td>
</tr>
</tbody>
</table>

**Blood**

<table>
<thead>
<tr>
<th>B0</th>
<th>Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes or &lt;250/mcL are atypical (Sezary) cells or &lt;15% CD4+/CD26- or CD4+/CD7- cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>Low blood tumor burden: &gt;5% of peripheral blood lymphocytes are atypical (Sezary) cells but do not meet the criteria of B2</td>
</tr>
<tr>
<td>B2</td>
<td>High blood tumor burden</td>
</tr>
</tbody>
</table>

(Found at: http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf)

The disease often has a long, slow course and may remain confined to the skin. In fact, patients with T1 disease have a similar life expectancy compared with same age persons without CTCL. Some patients may have more rapidly progressing CTCL and about 10% of cases will ultimately spread to lymph nodes or other organs. The diseases are often described as chronic, requiring long-term management by an interdisciplinary team of healthcare providers.

T1 and T2 are often referred to as the patch/plaque stage, T3 as the tumor stage and T4 the erythrodermic stage. Those with SS and advanced MF are chronically immunosuppressed due to the disease's affect on T cells. This leads to infections being a chronic problem that can ultimately be the cause of death.

**How is CTCL treated?**

While early stage CTCL is potentially curable, for most patients this is a chronic disease, progressing over many years. There
are no less than 30 treatments for CTCLs, with many more possible combinations of these therapies. Unlike some cancers, progression on one therapy does not mean that the same therapy cannot be successful again in the future. While early (patch/plaque) stage disease may respond well to topical therapy alone, more advanced cases may require a combination of topical and systemic therapies to be successful.

### Topical therapies

Topical therapies are applied several times a day as an ointment, cream or gel to the affected areas. Corticosteroids of varying strengths can be used to treat small areas with few side effects, but are not usually applied to the entire body. They should be applied only to the affected areas and can cause thinning of the skin after long-term use. Nitrogen Mustard, a chemotherapy agent, can be incorporated into an ointment for application to large areas of the skin. Nitrogen Mustard can cause itching, redness or rash and should be applied using gloves and only to the skin that is affected.

Topical retinoids such as bexarotene (gel and oral) and tazarotene interfere with the production of tumor cells and are available in topical (gel) and oral formulations. Retinoids work by encouraging tumor cell death and boosting the immune reaction. Almost all patients taking oral bexarotene will develop hypothyroidism (underactive thyroid) and elevated cholesterol levels, both of which can be treated with another medication, which in some practices are started prior to the bexarotene therapy. These problems reverse after the medication is stopped. Other side effects include: headache, nausea, fatigue, and sun sensitivity. Diabetics may experience hypoglycemia and should monitor their blood sugar carefully.

PUVA (psoralen plus UVA light) and UVB are types of phototherapy, which uses either UVA (with psoralen) or UVB ultraviolet rays to damage the cancer cells. Psoralen, a photosensitizer, is given about 90 minutes before PUVA therapy to make the T cells more sensitive to the damaging effects of the light. The skin is then exposed to UVA rays from a "light box" in the dermatologist's office. The psoralen remains in the system for 24 hours, so precautions need to be taken to protect the skin and eyes from sunlight during that time. There is an increased risk of cataracts and nausea from the psoralen and red, dry or itchy skin from the UVA rays. As with any UVA/B exposure, there is a risk for melanoma, basal and squamous cell cancers due to this therapy. UVB therapy does not penetrate the skin as deeply as UVA and can be used (without a photosensitizer) for thin skin lesions. Side effects include redness or burning of the skin.

Electron beam radiation therapy is a type of x-ray therapy that delivers radiation to the outer layers of the skin, sparing deeper tissues from damage. This therapy is quite effective at clearing the skin lesions and in some cases, can be administered to the whole body. Side effects of therapy include skin burn, itching and fatigue. Long term effects can include skin cancers, changes in color or hair distribution and a loss of sweat/oil secretion from the area treated.

### Systemic Therapies

Systemic therapies are those that treat the entire body by circulating via the blood stream. These include photopheresis, bexarotene and various other medication therapies, which can be given alone or in combination with other systemic or topical therapies.

Photopheresis is a therapy used to treat patients with erythrodermic stage or blood involvement of the disease. It is basically a form of PUVA for the blood. The patient has two IV catheters placed, one used to remove blood, the other to return the treated blood to their system. The blood is passed through a machine that separates the white blood cells from the rest of the blood, mixes them with a liquid form of psoralen (photosensitizer), exposes them to UVA light and returns them to the body. The process damages the cancerous T cells, but other types of white blood cells are immune to the damage and help induce an
immune response in the body. The procedure takes 3-4 hours and is done on two consecutive days about once a month. It has minor side effects, including fever, increased skin redness and dizziness.

Interferons are substances the body produces normally to stimulate the immune system. By giving synthetic forms of interferon alpha (called interferon alfa 2b and alfa 2a), the body's immune system is stimulated to attack the cancer cells. It is given by injection several times a week, often in conjunction with other therapies and may have a synergistic effect with photopheresis. Side effects are related to the stimulation of the immune system and include fever, chills, muscle aches and fatigue—often called "flu-like" symptoms. Other side effects include depression, sleep disturbances, anxiety, hair loss and nausea. If patients have failed to or stopped responding to interferon alfa, a synthetic form of interferon gamma may be used.

Other Therapies

Advanced cases of CTCL may be treated with chemotherapy. Your provider will create a regimen for you including which drugs you will receive, the dose of each drug and how often you will receive them. The first line therapies typically used include: brentuximab, gemcitabine, liposomal doxorubicin, pralatrexate. Some other less commonly used chemotherapies include chlorambucil, pentostatin, etoposide, cyclophosphamide, temozolomide and methotrexate.

Denileukin difitox, alemtuzumab and vorinostat are targeted therapies, which attack a specific target present in the cancerous cells, resulting in fewer side effects compared to traditional chemotherapy. For a limited number of patients allogeneic stem cell transplant may be an option. Allogenic stem cell transplants are thought to be the only cure for advanced stages of CTCL.

Clinical Trials

There are clinical research trials for most types of cancer, and every stage of the disease. Clinical trials are designed to determine the value of specific treatments. Trials are often designed to treat a certain stage of cancer, either as the first form of treatment offered, or as an option for treatment after other treatments have failed to work. They can be used to evaluate medications or treatments to prevent cancer, detect it earlier, or help manage side effects. Clinical trials are extremely important in furthering our knowledge of this disease. It is through clinical trials that we know what we do today, and many exciting new therapies are currently being tested. Talk to your provider about participating in clinical trials in your area. You can also explore currently open clinical trials using the OncoLink Clinical Trials Matching Service.

Follow Up Care and Survivorship

Your follow-up care will depend upon whether you have completed treatment or if you will require continued treatment. Therefore, your plan for follow-up care will be unique to your situation. Your provider will follow you closely, perform a physical exam and monitor your skin for any recurring or new lesions. Depending upon how you are doing you may be required to have blood tests and in some cases imaging tests. It is important for you to go to your appointments and to speak to your provider about any recurring or new side effects you are experiencing. If you are continuing treatment for CTCL your provider will continue or change your treatment plan as needed, depending upon how the disease is responding to your current treatment.

Cancer survivorship is a relatively new focus of oncology care. With some 15 million cancer survivors in the US alone, there is a need to help patients transition from active treatment to survivorship or to live with chronic cancers. What should you know and do to live healthy going forward? A survivorship care plan can be a first step in educating yourself about navigating life after (or with) cancer and helping you communicate knowledgeably with your healthcare providers. Create a survivorship care plan today on OncoLink.
Resources for More Information

**Cutaneous Lymphoma Foundation**

Resources for patients and health care providers including educational programs, research opportunities and assistance with finding a treatment center.

[www.clfoundation.org](http://www.clfoundation.org)

**The Leukemia and Lymphoma Society**

Provides educational material for patients and caregivers along with information about research and resources.

[www.lls.org](http://www.lls.org)

**Lymphoma Research Foundation**

Provides educational material and information about clinical trials.

[www.Lymphoma.org](http://www.Lymphoma.org)