

Understanding Lymphoma

Cutaneous T-Cell Lymphoma

Cutaneous T-cell lymphoma (CTCL) is a general term for T-cell non-Hodgkin's lymphomas (NHLs) that mainly involve the skin. There are many subtypes of CTCL, and the most common ones are mycosis fungoides (MF) and Sézary syndrome (SS). Other subtypes of CTCL (like CD30-positive lymphoproliferative disorders) are less frequent and can be more *aggressive* (fast-growing). CTCL affects men more often than women and usually occurs in people in their 50s and 60s.

Aside from the skin, MF and SS can also affect the blood, *lymph nodes* (small bean-shaped structures that help the body fight disease), and other internal organs. Symptoms can include:

- Dry skin.
- Itching (which can be severe).
- Red rash or skin discoloration.
- Swelling (due to enlarged lymph nodes).

The type of treatment used also depends on the subtype of CTCL, skin symptoms and appearance.

MOST COMMON SUBTYPES OF CTCL

Mycosis Fungoides (MF) is the most common subtype of CTCL and represents around half of all skin lymphomas. The majority of patients with MF experience only skin symptoms. This type of CTCL is usually *indolent* (grows slowly). In many patients, the disease is limited to the skin. However, MF may progress (become worse or spread in the body) more rapidly in some patients and spread to the lymph nodes, blood, and/or internal organs.

MF may look different in each patient as skin symptoms can appear in different forms:

- Patches (usually are flat, sometimes scaly, and look like a rash).
- Plaques (thick, raised, and often itchy lesions that can be mistaken for other skin conditions like *eczema*, *psoriasis*, or *dermatitis*).
- Tumors (raised bumps or nodules with a diameter or height \geq 1 cm, that may become an open sore or *ulcer*).
- *Erythroderma* (reddening and scaling of more than 80% of the skin).

It is possible to have more than one type of skin symptom. For instance, patients with erythrodermic MF also have scaly red skin lesions that can be very itchy.

A medical history, physical examination, and skin biopsy are needed for diagnosis. A physician will examine lymph nodes, order various blood tests, and may conduct other screening tests, such as blood flow *cytometry* (a technique that detects and counts different types of blood cells, according to their physical and chemical characteristics) or a whole-body imaging study (such as a computed tomography [CT] or positron emission tomography [PET] scan). A PET scan is a form of imaging that uses a special dye to locate the lymphoma cells in the body.

MF is difficult to diagnose in its early stages because the symptoms and skin biopsy findings are similar to those of other skin conditions.

Sézary Syndrome (SS) is usually more aggressive (grows faster) and harder to treat than MF. Patients with SS may experience the following signs and symptoms:

- *Erythroderma*.
- Sézary cells (large T cells with an abnormal shape) in the blood.
- Enlarged lymph nodes.
- A red and itchy skin rash, often with shedding of the outer layer of the skin (exfoliation).

- Feeling cold (loss of temperature control by the skin).
- Patches and tumors (in some patients).
- Severe itching.
- Frequent skin infections (for instance, with *Staphylococcus aureus*).
- *Keratoderma* (the skin of the hands and feet becomes very thick and cracked).
- Changes in the nails, hair, or eyelids.

DIAGNOSIS AND STAGING OF CTCL

Many of the same procedures (tests and exams) used to diagnose and stage other subtypes of CTCL are used in SS. Blood flow cytometry is essential to diagnose and stage SS, and whole-body imaging often is needed to determine if the cancer has spread to the lymph nodes or other organs. These tests may include a CT scan, a PET scan, and/or *magnetic resonance imaging* (MRI, a procedure that takes detailed pictures of areas inside the body using a powerful magnet and radio waves). A *bone marrow biopsy* (a procedure to collect small samples of the spongy tissue inside the bone) may also be performed but is not always necessary.

Once the diagnosis is made, patients undergo exams to assess the disease stage (how much the cancer has grown, what is the pattern of growth [patch, plaque or tumor], and if it has spread to other parts of the body). The clinical stages of CTCL are the following:

- Stages I (A and B) and II (A and B): disease that is limited to the skin.
- Stage III: patients with erythroderma but without significant blood involvement.
- Stage IV (A and B): disease has spread to the lymph nodes and/or the bloodstream. The disease may have spread to the bone marrow (the spongy tissue inside the bones) and additional organs.

Because it is a rare disease, patients should be referred to a health care team that specializes in this type of lymphoma. The patients' clinical stage is important to select the best treatment. The treatment is individually chosen for each patient and may be adjusted frequently depending on how effective the treatment is and how well the patient tolerates it.

The clinical stage is also important to determine the *prognosis* (how well the patient will do with standard treatment) and treatment options. Keep in mind that no two patients are alike and that statistics can only predict how a large group of patients will do (not what will happen to an individual patient). The doctor most familiar with the patient's situation is in the best position to interpret these statistics and understand how well they apply to a patient's particular situation.

TREATMENT OPTIONS

For MF, treatment is directed either at the skin (topical therapy) or at the entire body (*systemic* therapy). The disease is not considered curable and follows a chronic course (lasts for a long period of time), but it can be managed with treatment and become undetectable (remission). Some patients with early-stage MF are able to remain in remission for long periods of time.

Since SS is systemic (cancer has spread to the bloodstream), it is usually not treated with skin-directed therapies alone. Treatments may be prescribed alone or in combination to achieve the best long-term treatment response.

Topical therapies generally are used for earlier-stage disease and are useful to treat patients who have patches and limited plaques. These therapies include:

- Topical corticosteroids (most frequently used topical therapy).
- Topical chemotherapy (for example, mechlorethamine [Valchlor]).
- Topical retinoids like bexarotene (Targretin).
- Topical immunotherapy (drugs that use the body's immune system to fight cancer) with imiquimod (Zyclara).
- Local or total skin radiation therapy.
- Phototherapy (with ultraviolet light).

Corticosteroids are the most commonly used topical treatment for CTCL. Bexarotene gel (Targretin) and mechlorethamine gel (Valchlor) have been approved by the U.S. Food and Drug Administration (FDA) as a topical treatment for Stages 1A and 1B CTCL in patients who have received previous skin treatment.

Systemic treatment may be used in more advanced-stage disease and in patients with earlier-stage disease who did not respond to or did not tolerate topical therapies.

Systemic treatments include:

- Chemotherapy with methotrexate, pegylated liposomal doxorubicin, fludarabine, 2 chlorodeoxyadenosine, pentostatin, chlorambucil or folate analogues like pralatrexate (Folotyn)
- Immunotherapy with interferon alfa or gamma (with or without topical therapies), brentuximab vedotin (Adcetris) or mogamulizumab (Poteligeo)
- Oral retinoids like bexarotene (Targretin)
- Targeted therapy (drugs that target molecules that the cancer cells use to grow and spread) with vorinostat (Zolinza) or romidepsin (Istodax)
- Extracorporeal photopheresis, where the blood of the patient is removed and the white blood cells are isolated, exposed to UV radiation and returned to the patient (Therakos)

Patients with more advanced-stage MF often require systemic therapies, and those with *high-risk* disease (more likely to spread across the body) may receive an *allogeneic stem cell transplant* (patients receive stem cells from a family member or unrelated donor after a course of high dose chemotherapy with or without radiation). To know more about stem cell transplantation, please view the *Understanding Cellular Therapy* guide at LRF's website (lymphoma.org/publications).

Combination chemotherapy regimens are for those with refractory (does not respond to treatment) or advanced disease or that has spread from the skin to other parts of the body. Some of the systemic therapies can be combined to improve the response. Patients also often use skin-directed treatments in conjunction with systemic therapies.



TREATMENTS UNDER INVESTIGATION

Many yet-to-be-approved treatments (also referred to as investigational drugs) and combinations are currently being tested in clinical trials for CTCL. Results from these clinical trials may improve or change the current standard of care (the proper treatment that is widely used by health care professional and accepted by medical experts). The table below lists some of these treatments that can be accessed through a clinical trial. For more information about clinical trials, view the *Understanding Clinical Trials* publication on LRF's website (lymphoma.org/publications).

Table 1. Selected Agents Under Investigation for CTCL in Phase 2 or 3 Clinical Trials.

Agent (Drug)	Class (Type of treatment)
Atezolizumab (Tecentriq)	Immunotherapy; immune checkpoint inhibitor, anti-PD-L1
ASTX660	Targeted therapy; IAP inhibitor
CD30 biAb-AATC	Immunotherapy; bispecific antibody, anti-CD30 & -CD3.
Cemiplimab (Libtayo)	Immunotherapy; immune checkpoint inhibitor, anti-PD-1
Lacutamab (IPH4102)	Immunotherapy; monoclonal antibody, anti- KIR3DL2
Lenalidomine (Revlimid)	Immunotherapy; immunomodulatory drug
Nivolumab (Opdivo)	Immunotherapy; immune checkpoint inhibitor, anti-PD-1
Pembrolizumab (Keytruda)	Immunotherapy; immune checkpoint inhibitor, anti-PD-1
Resminostat (4SC-201, RAS2410)	Targeted therapy; HDAC inhibitor
Sintilimab (Tyvyt)	Immunotherapy; immune checkpoint inhibitor, anti-PD-1
Talimogene laherparepvec (Imlygic)	Immunotherapy; oncolytic viral therapy

CTCL, cutaneous T-cell lymphoma; HDAC, histone deacetylase; IAP, inhibitor of apoptosis proteins; KIR3DL2, killer cell immunoglobulin like receptor three Ig domains and long cytoplasmic tail 2; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

It is important to remember that scientific research is always evolving. Treatment options may change as new treatments are discovered and current treatments are improved. Therefore, it is important that patients check with their physician or with the Lymphoma Research Foundation (LRF) for any treatment updates that may have recently appeared. It is also very important that all patients with CTCL consult a specialist to clear up any questions.



CLINICAL TRIALS

Clinical trials are important in finding effective drugs and the best treatment doses for patients with CTCL. Patients interested in participating in a clinical trial should view the *Understanding Clinical Trials* fact sheet on LRF's website (visit lymphoma.org/publications), and the *Clinical Trials Search 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 CTCL should have regular visits with their physician. During these visits, medical tests (such as blood tests, CT scans, and PET scans) may be required to evaluate the need for additional treatment.

Some treatments can cause long-term side effects (occur **during** treatment and continue for months or years) or late side effects (appear only months, years or decades **after** treatment has ended). These can vary depending on the following factors:

- Duration of treatment (how long the treatment has lasted).
- Frequency of treatment (how often the treatment was administered).
- Type of treatment given.
- Patient's, age and, gender.
- Patient's overall health of each patient at the time of treatment.

A physician will check for these side effects during follow-up care. Visits may become less frequent the longer the patient stays in remission (no signs or symptoms of disease).

Patients and their caregivers are encouraged to keep copies of all medical records. This includes test results as well as information on the types, amounts, and duration of all treatments received. Medical records are important for keeping track of any side effects resulting from treatment or potential disease recurrences. LRF's award-winning *Focus On Lymphoma* mobile app (lymphoma.org/mobileapp) can help patients manage this documentation.

LRF CARE PLAN AND PATIENT EDUCATION PROGRAM

Keeping your information in one location can help you feel more organized and in control. This also makes it easier to find information pertaining to your care and saves valuable time. LRF's Lymphoma Care Plan document organizes information on your health care team, treatment regimen, and follow-up care. You can also keep track of health screenings and any symptoms you experience to discuss with your health care provider during future appointments. The Lymphoma Care Plan document can be accessed by visiting lymphoma.org/publications. LRF also offers a variety of educational activities, including live meetings and webinars for individuals looking to learn directly from lymphoma experts. To view our schedule of upcoming programs, please visit lymphoma.org/programs.

LRF Helpline

The LRF Helpline staff are available to answer your general questions about lymphoma and treatment information, as well as provide individual support and referrals to you and your loved ones. Callers may request the services of a language interpreter. LRF also offers a one-to-one peer support program called the Lymphoma Support Network and clinical trials information through our Clinical Trials Information Service. For more information about any of these resources, visit our website at lymphoma.org, or contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org.

Para información en Español, por favor visite lymphoma.org/es. (For Information in Spanish please visit lymphoma.org/es).

LRF FOCUS ON LYMPHOMA MOBILE APP

Focus on Lymphoma is the first app to provide patients and their caregivers with tailored content based on lymphoma subtype, and actionable tools to better manage diagnosis and treatment. Comprehensive lymphoma management, conveniently in one secure and easy-to-navigate app, no matter where you are on the care continuum. Get the right information, first, with resources from the entire Lymphoma Research Foundation content library, use unique tracking and reminder tools, and connect with a community of specialists and patients. To learn more this resource, visit our website at lymphoma.org/mobileapp, or contact the LRF Helpline at 800-500-9976 or helpline@lymphoma.org.

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