Understanding Lymphoma and Chronic Lymphocytic Leukemia (CLL)

Cutaneous Lymphoma

Lymphoma Research Foundation

Lymphomas that arise in tissues or organs outside of the *lymphatic system* (tissues and organs that produce, store, and carry white blood cells) are called *extranodal* lymphomas. Extranodal lymphomas that arise and manifest in the skin are called a *cutaneous* lymphomas. When lymphomas start in the skin and there is no evidence of disease outside of the skin, they are called *primary cutaneous* lymphomas.

There are two types of primary cutaneous lymphomas depending on the type of lymphocytes (a type of white blood cell) involved (T-cells or B-cells), that are a form of non-Hodgkin lymphoma (NHL). Each type can have a different presentation (signs and symptoms), disease course (how the disease evolves with time) and prognosis (how well the patient will do with standard treatment). Both types are described in detail below.

For more information on cutaneous lymphoma diagnosis and disease staging, please view the Understanding Lymphoma and CLL Guide on the Foundation's website (visit lymphoma.org/publications).

Cutaneous T-cell lymphoma

Cutaneous T-cell lymphoma (CTCL) starts in the T cells of the skin and is the most common type of primary cutaneous lymphoma. CTCL lesions often look red and dry, can be of any size, and can affect large parts of the body. There are many subtypes of CTCL, and the most common ones are mycosis fungoides (MF), CD30-positive lymphoproliferative disorders, and Sézary syndrome (SS). Other subtypes of CTCL 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:

- Red rash or skin discoloration.
- Dry skin.
- Itching (which can be severe) sometimes with a burning sensation.
- Swelling (due to enlarged lymph nodes).
- Hair loss.
- Nail changes.

Most Common Subtypes of CTCL

Mycosis Fungoides (MF) is the most common subtype of CTCL and represents around half of all skin lymphomas. Most 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 ≥ 1 cm [half the size of a penny], 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* (a procedure to collect small samples of the affected skin) 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 and the surface markers they express) 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 cancer cells in the body.

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

Sézary Syndrome (SS) is 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). Swallen lymph nodes can be positive on a PET scan so a biopsy might be necessary to confirm if cancer cells are present in the lymph node. 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 extent and pattern of growth in the skin [patch, plaque or tumor], and if it has spread to other parts of the body). Patients with Sézary syndrome by definition have stage IV lymphoma. The clinical stages of CTCL are detailed in **Table 1**.

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 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.

Table 1: Clinical Stages of CTCL

Stages	A	B
I (disease that is limited to the skin)	Less than 10% of the skin is covered in red patches or plaques	10% or more of the skin is covered in patches or plaques
II (disease that is limited to the skin)	Any amount of the skin surface is covered with patches or plaques and lymph nodes are enlarged and inflamed, but the cancer has not spread to the lymph nodes.	One or more tumors are found on the skin, lymph nodes may be enlarged, but cancer has not spread to the lymph nodes.
III (patients with erythroderma but without significant blood involvement)	N/A	N/A
IV (disease has spread to the lymph nodes and/or the bloodstream)	Most of the skin is reddened and cancer is found in the blood; cancer may have spread to the lymph nodes but does not involve other internal organs.	Most of the skin is reddened, and cancer is found in the blood; cancer may have spread to the lymph nodes and has spread to other organs such as bone marrow (the spongy tissue inside the bones).

N/A, non-applicable.

Treatment Options

For MF, treatment is directed either at the skin (skin directed therapy) or at the entire body (systemic therapy). Skin directed therapy can be topical (in the form of creams, ointments, or gels) or full skin (ultraviolet light, skin radiation). 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 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 (drugs that stop the growth of or kill cancer cells), including:
  - Methotrexate
  - Pegylated liposomal doxorubicin
  - Fludarabine
  - 2-chlorodeoxyadenosine
  - Pentostatin
  - Chlorambucil
  - Folate analogues, like pralatrexate (Folotyn).
- Immunotherapy (drugs that use the body's immune system to fight cancer)
  - Immunomodulatory agents (drugs that work on the immune system directly by regulating [activating or slowing down] the activity of specific proteins) such as interferon alfa or gamma (with or without topical therapies)
  - Antibody-drug conjugate (ADC) such as brentuximab vedotin (Adcetris) which is a monoclonal antibody attached to a chemotherapy drug. The monoclonal antibody in the ADC recognizes and binds to a protein called CD30 on the cancer cell surface. Once the ADC is inside the cell, the chemotherapy drug separates from the ADC and kills the cancer cell by targeting cell multiplication.
  - Monoclonal antibodies (proteins made in the laboratory that bind to cancer cells and help the immune system destroy them) such as mogamulizumab (Poteligeo).
- Oral retinoids like bexarotene (Targretin).
- Targeted therapy (drugs that target molecules that the cancer cells use to grow and spread) with histone deacetylase (HDAC) inhibitors such as vorinostat (Zolinza) or romidepsin (Istodax).
- Extracorporeal photopheresis (the blood of the patient is removed, and the white blood cells are isolated, exposed to UV radiation and returned to the patient) (Therakos).
- Stem cell transplantation (SCT, the patient is treated with high-dose chemotherapy or radiation to remove their blood-forming cells or stem cells, and then receives healthy stem cells to restore the immune system and the bone marrow's ability to make new blood cells).
  - Allogeneic SCT (patients receive stem cells from a family member or unrelated donor).

Patients with more advanced-stage MF often require systemic therapies, and those with high-risk disease (advanced disease that has failed to adequately respond to multiple forms of systemic therapy) may receive an allogeneic SCT. To know more about stem cell transplantation, please view the *Understanding Cellular Therapy* guide at the Foundation'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 professionals 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 the Foundation's website (lymphoma.org/publications).

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 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.

Table 2: 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	notherapy; 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
Linperlisib	Targeted therapy; PI3K inhibitor
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
Ritlecitinib	Targeted therapy; JAK3 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; JAK3, Janus kinase 3; 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; PI3K, phosphoinositide 3-kinase.

Cutaneous B-cell lymphoma

Cutaneous B-cell lymphoma (CBCL) are rare and often indolent (slow growing), starts in the B-cells of the skin and may appear on the skin as a rash, reddish bump, lump, or nodule, usually with a raised and smooth appearance. They can appear as a single lesion (area that looks abnormal or different from the surrounding skin) or multiple lesions in either one or several body regions (areas). Many skin conditions may look similar but are not CBCLs. The disease can relapse (return after treatment) or occur in new places on the skin, but it rarely spreads outside the skin. About 50% of patients with single lesions are cured after radiation therapy. However, patients with multiple lesions are more likely to continue to have new lesions appear. This fact does not affect prognosis, which remains very good.

Subtypes of CBCL

Primary Cutaneous Follicle Center Lymphoma (PCFCL) is the most common type of CBCL. This skin lymphoma is indolent, developing slowly over months or years. It usually appears on the head, neck, or torso (upper body or chest) of the body as red pimples, nodules (bumps), or plaques (raised or flat lesions). In some cases, it can also be found on the legs. This type of CBCL is usually diagnosed in middle-aged adults and responds well to treatment.

Primary Cutaneous Marginal Zone B-Cell Lymphoma (PCMZL) is the second most common form of CBCL. This indolent lymphoma can have a similar appearance as cutaneous follicle center lymphoma, often as red to purplish large pimples, plaques, or nodules on the arms or upper body. Some cases are linked to an infection with Borrelia burgdorferi, a type of bacteria carried by ticks that causes Lyme disease. This type of CBCL is more common in older adults.

Primary Cutaneous Diffuse Large B-Cell Lymphoma (PCDLBCL), Leg-Type is a rare type of CBCL but is usually more aggressive (fast-growing), developing over weeks or months. This lymphoma usually appears as solitary or multiple nodules on the lower part of the legs, but can involve non-leg areas, such as the arms and/or torso. The lesions may ulcerate (cause sores on the skin) and spread outside the skin more frequently than slow-growing CBCLs. This type of CBCL is more common in older women and often requires intensive treatment.

Other types of PCDLBCL include a group of very rare, aggressive lymphomas, such as intravascular large B-cell lymphoma, T-cell-rich large B-cell lymphoma, plasmablastic lymphoma, and anaplastic large B-cell lymphoma. These lymphomas are not always cutaneous and usually appear on the head, torso, and extremities (arms and legs).

Treatment Options

Upon diagnosis, appropriate *staging work-up* (a procedure to evaluate how much the cancer has grown and if it has spread) should be done to make sure that the disease is limited to the skin. In general, this includes routine laboratory tests (like blood testing) and whole-body imaging studies (like CT scans). Bone marrow biopsies are not recommended for all patients with indolent CBCLs.

Treatment selection for CBCL depends on the type of CBCL, and whether the skin lesion is *solitary/regional* (single lesion or lesions that are limited to one region of the skin) or *multifocal* (widespread). Treatment also depends on how fast the lymphoma grows (indolent vs aggressive).

For indolent lymphomas with solitary/regional lesions, the most common treatment is local radiation therapy. Surgical treatment can be an option, but may result in wide, unnecessary scars. Indolent CBCLs that present as multiple lesions may be observed through an approach known as "active surveillance" or "watchful waiting," in which patients' overall health and disease are monitored through regular checkup visits that can include laboratory and imaging tests. For more information on active surveillance, view the *Active Surveillance* fact sheet on the Foundation's website (**lymphoma.org/publications**).

Treatments for this type of CBCL include:

- Intralesional corticosteroids (applied directly into the lesion).
- Topical therapies (treatment applied to the skin), such as chemotherapy, bexarotene (Targretin), and imiquimod (Zyclara).
- Surgical removal of lesions.
- Radiation therapy (applied directly to the lesions).

If lesions are very widespread and symptomatic, systemic therapies (treatment with drugs that travel through the bloodstream and reach all parts of the body) may be appropriate. This includes monoclonal antibodies (proteins made in the lab that recognize substances at the surface of cancer cells) like rituximab (Rituxan), with or without chemotherapy.

Regular skin examinations are very important, especially for indolent CBCLs, as the skin is the most common site of new lesions. General laboratory tests may also be done, but imaging is not needed unless there is a concern of systemic (widespread) disease.

For aggressive CBCLs, the patient's overall health is considered to select the best treatment option. In CDLBCL, Leg-Type, systemic chemotherapy (usually cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]) with and without rituximab (Rituxan) is often more appropriate for initial treatment, with or without radiation therapy. Regular imaging studies are usually done to evaluate treatment response or disease status.

Treatment for *relapse* of indolent CBCL can include observation, surgery, topical treatments, injected steroids, or radiation (low-dose). Indolent CBCLs usually remain indolent and relapse in the skin. Very rarely, indolent CBCLs relapse as systemic disease, most commonly in regional lymph nodes. In extremely rare cases, indolent CBCLs can transform into more aggressive types of lymphoma.

Relapsed aggressive CBCLs may be treated with chemotherapy (with or without rituximab), targeted therapies such as ibrutinib (Imbruvica), lenalidomide (Revlimid), radiation therapy, and/or radioimmunotherapy.

Treatments Under Investigation

Many new treatments (also referred to as investigational drugs) and combination therapies are currently being studied for the treatment of patients with CBCL. Results from these clinical trials may improve or change the current standard of care (the proper treatment that is widely used by healthcare professionals and accepted by medical experts). The table below lists some of these investigational drugs that can be accessed through a clinical trial. For more information on clinical trials, view the *Understanding Clinical Trials* publication on the Foundation's website (**lymphoma.org/publications**).

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 Foundation for any treatment updates that may have recently appeared.

Clinical Trials

Clinical trials are important in finding effective drugs and the best treatment doses for patients with cutaneous lymphomas. Patients interested in participating in a clinical trial should view the *Understanding Clinical Trials* fact sheet on the Foundation's website (visit **lymphoma.org/publications**), and the Clinical Trials Search Request Form at lymphoma.org, talk to their physician, or contact the Foundation's Helpline for an individualized clinical trial search by calling **(800) 500-9976** or emailing **helpline@lymphoma.org**.

Table 3: Treatments Under Investigation for CBCL in Phase 2 or 3 Clinical Trials.

Agent (drug)	Class (type of treatment)
Lenalidomide (Revlimid)	Chemotherapy
Ontorpacept (TTI-621)	Immunotherapy; fusion protein
Maplirpacept (TTI-622)	Immunotherapy; fusion protein
Pembrolizumab (Keytruda)	Immunotherapy; immune checkpoint inhibitor, anti-PD-1
Nivolumab (Opdivo)	Immunotherapy; immune checkpoint inhibitor, anti-PD-1
Varlilumab (CDX-1127)	Immunotherapy; monoclonal antibody, anti-CD27
Zanubrutinib (Brukinsa)	Targeted therapy, BTK inhibitor

BTK, Bruton's kinase inhibitor; CBCL, cutaneous B-cell lymphoma; PD-1, programmed cell death protein 1.

Follow-up

Patients with cutaneous lymphomas 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 care partners 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. The Foundation's award-winning *Focus On Lymphoma* mobile app (**lymphoma.org/mobileapp**) can help patients manage this documentation.

Lymphoma Care Plan

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. The Foundation'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**.

Patient Education Programs

The Foundation also offers a variety of educational activities, including live meetings and webinars for individuals looking to learn directly from lymphoma experts. These programs provide the lymphoma community with important information about the diagnosis and treatment of lymphoma, as well as information about clinical trials, research advances and how to manage/cope with the disease. These programs are designed to meet the needs of a lymphoma patient from the point of diagnosis through long-term survivorship. To view our schedule of upcoming programs, please visit **lymphoma.org/programs**.

Helpline

The Foundation's 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. The Foundation 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 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**).

Focus on Lymphoma Mobile App

Focus on Lymphoma is the first app to provide patients and their care partners 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 about this resource, visit our website at **lymphoma.org/mobileapp**, or contact the Foundation's Helpline at **(800) 500-9976** or **helpline@lymphoma.org**.

Lymphoma Research Foundation

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