LYMPHOMA RESEARCH • FOUNDATION

Understanding Cutaneous T-Cell Lymphoma

T-cell lymphomas account for five to ten percent of all NHLs in the United States. There are many different forms of T-cell lymphomas, some of which are extremely rare. Most T-cell lymphomas can be classified into two broad categories: *aggressive* (fast-growing) or *indolent* (slow-growing).

Cutaneous T-cell lymphoma (CTCL) is a general term for T-cell lymphomas that primarily involve the skin. There are many subtypes of CTCL, and the most common ones are mycosis fungoides (MF) and Sézary syndrome (SS). The next most frequent subtype is a spectrum of T-cell neoplasms called the CD30-positive lymphoproliferative disorders. Some of the rare CTCL subtypes can be very aggressive. The skin symptoms and appearance, as well as the kind of treatment used, vary depending on the subtype of CTCL.

MF and SS can involve the blood, lymph nodes, and other internal organs. Symptoms can include dry skin, itching (which can be severe), a red rash, and enlarged lymph nodes. CTCL affects men more often than women and usually occurs in people in their 50s and 60s.

SUBTYPES OF CTCL

MYCOSIS FUNGOIDES (MF)

Mycosis Fungoides (MF) is the most common subtype of CTCL, accounting for approximately one-half of all CTCLs. The majority of patients with MF experience only skin symptoms. Early-stage MF may not ever progress to later stages in some patients, while it may progress rapidly in others, with the cancer spreading to the lymph nodes, blood, and/or internal organs.

MF may look different in each patient, with skin symptoms that can appear as patches, plaques, tumors, or *erythroderma* (reddening of more than 80 percent of the skin). Patches usually are flat, possibly scaly, and look like a rash; plaques are thicker, raised, often itchy lesions that can be mistaken for eczema, psoriasis, or dermatitis; and tumors are raised bumps or nodules that are 1 cm or greater in diameter or height that may or may not *ulcerate* (become an open sore). It is possible to have more than one type of skin symptom. Patients with erythrodermic MF have diffuse scaly red skin eruptions that can be very itchy.

A medical history, physical examination, and skin biopsy are essential for diagnosis. A physician will examine lymph nodes, order various blood tests, and may conduct other screening tests, such as blood flow cytometry or a whole-body imaging study (such as a computed tomography [CT] or positron emission tomography [PET] scan).

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

SÉZARY SYNDROME (SS)

Sézary Syndrome (SS) is characterized by the presence of erythroderma, by the presence of a significant number of lymphoma cells in the blood, and sometimes by enlarged lymph nodes. An extensive red, itchy rash typically appears on the skin, often with sloughing off of the superficial layer of the skin (called exfoliation). Loss of temperature control by the skin is common, and patients often feel cold. In certain patients, patches and tumors appear. Patients often experience severe itching and frequently have *Staphylococcus aureus* skin infections. The skin of the hands and feet can become extremely thick and cracked (called keratoderma). Patients can also experience changes in their nails, hair, or eyelids.

Many of the same procedures used to diagnose and stage other subtypes of CTCL are used in SS. In addition, blood flow cytometry is essential to diagnose SS and to follow the severity of the disease in the blood, 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 bone marrow biopsy may also be performed but is not always necessary.

TREATMENT OPTIONS

Once the diagnosis is made, patients undergo a staging work-up to assess the extent of their lymphoma, which determines the final clinical stage and prognosis. Disease stage refers to how much the disease has spread to other parts of the body. Stages I and II are considered limited disease involving only select groups of lymph nodes. More advanced stages (III and IV) are characterized by widespread involvement across the lymphatic system. The bone marrow and additional organs may be involved. Because it is a rare disease, CTCL management should be done at centers with expertise and experience in treating it or in close partnership with such centers. The patients' clinical stage is the primary factor for selecting the optimal treatment. Many other factors are also considered in identifying the most appropriate treatment for each patient, including the extent of skin involvement, the type of skin lesion, and whether the cancer involves the blood, lymph nodes, or other internal organs. The treatment is highly tailored for each patient and may be adjusted frequently depending on the treatment response and tolerability.

For MF, treatment is directed either at the skin or at the entire body (*systemic* [throughout the body]). Many patients with early-stage MF live normal lives while their disease is being treated, and some are able to remain in remission for long periods of time. However, the disease is not considered curable and follows a chronic course, with treatments adjusted to address symptoms when it is active. Patients with advanced-stage MF often require systemic therapies at some point in their treatment course, and those with high-risk disease may receive an *allogeneic stem cell transplant* (patients receive stem cells from a donor).

Since SS is systemic, a disease in which both blood and skin involvement is noted, it usually is not treated with skin-directed therapies alone. Treatments may be prescribed alone or in combination to achieve the best long-term benefit.

Skin-Directed Therapies generally are used for earlier-stage disease and typically are useful for symptoms that appear as patches and limited plaques. These therapies include topical corticosteroids, topical chemotherapy (for example, mechlorethamine), topical retinoids, or imiquimod, local or total skin radiation therapy, and ultraviolet light. Among these, 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 MF in patients who have received previous skin treatment. However, the most frequently used skin-directed treatment is topical corticosteroids at different strengths for different parts of the body and for different levels of severity of the skin disease.

Systemic treatment may be used in more advanced-stage disease and in patients with earlier-stage disease in whom skin-directed therapies did not help, were not tolerated, or are not available.

Systemic treatments include milder systemic agents (such as bexarotene retinoid), low-dose methotrexate, interferons, extracorporeal photopheresis (ECP), histone deacetylase inhibitors (romidepsin and vorinostat), brentuximab vedotin (antibody-drug conjugate), mogamulizumab (monoclonal antibody), and single-agent chemotherapies. Combination chemotherapy regimens are reserved for those with *refractory* (does not respond to treatment) or advanced disease or those who have severe/extensive extracutaneous involvement. Some of the systemic therapies can be combined to improve the response. Patients also often use skin-directed treatments in conjunction with systemic therapies. Systemic therapies in MF/SS include:

- Acitretin (Soriatane)
- Bexarotene capsules (Targretin)
- Brentuximab vedotin (Adcetris)
- Extracorporeal photopheresis
- Gemcitabine (Gemzar)
- Interferons (alpha or gamma)
- Liposomal doxorubicin (Caelyx or Myocet)
- Methotrexate tablets
- Mogamulizumab (Poteligeo)
- Pralatrexate (Folotyn)
- Romidepsin (Istodax)
- Vorinostat (Zolinza)

TREATMENTS UNDER INVESTIGATION

Many treatments at various stages of drug development currently are being tested in clinical trials and for various stages of CTCL, including E7777, MRG-106, carfilzomib (Kyprolis), lenalidomide (Revlimid), anti-PD-1 antibodies, anti-CD47 antibodies, anti-KIR3DL2 monoclonal antibody, PI3-kinase inhibitors, and others.

It is critical to remember that today's scientific research is continuously 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 emerged.

CLINICAL TRIALS

Clinical trials are crucial in identifying effective drugs and determining optimal doses for patients with lymphoma. Patients interested in participating in a clinical trial should view the *Understanding Clinical Trials* fact sheet on LRF's website at 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 lymphoma should have regular visits with a physician who is familiar with their medical history and the treatments they have received. Medical tests (such as blood tests, CT scans, and PET scans) may be required at various times during *remission* (disappearance of signs and symptoms) to evaluate the need for additional treatment.

Some treatments can cause long-term side effects or late side effects, which can vary based on the duration and frequency of treatments, age, gender, and the 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 disease remains in remission.

Patients and their caregivers are encouraged to keep copies of all medical records and test results as well as information on the types, amounts, and duration of all treatments received. This documentation will be 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.

Resources

LRF offers a wide range of resources that address treatment options, the latest research advances, and ways to cope with all aspects of lymphoma, including our award-winning mobile app. LRF also provides many educational activities for people with lymphoma, from in-person meetings to webinars, as well as patient guides and e-Updates that provide the latest disease-specific news and treatment options. To learn more about any of these resources, visit our website at lymphoma.org, or contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org.

The Cutaneous Lymphoma Foundation is dedicated to supporting every person affected by cutaneous lymphoma by promoting awareness and education, advancing patient care, and fostering research for the best possible outcomes. To accomplish this, the Foundation provides an array of resources for patients, caregivers, and physicians, including guide books, an online learning center with current videos and articles, as well as numerous live events for in-depth learning and social networking. For more information about this independent nonprofit patient advocacy organization, please visit: www.clfoundation.org.

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