someday is today | LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers

Cutaneous T-Cell Lymphoma Facts

No. 5 in a series providing the latest information for patients, caregivers and healthcare professionals

www.LLS.org • Information Specialist: **800.955.4572**

Highlights

- Cutaneous T-cell lymphomas (CTCLs) constitute a group of non-Hodgkin lymphomas (NHLs) of the skin. The overall annual age-adjusted incidence of CTCL is approximately six cases per one million.
- CTCLs are cancers of the T lymphocytes (a type of white blood cell) that mainly affect the skin but can also involve the blood, lymph nodes and/or internal organs in patients with advanced disease.
- There are many types of CTCL. The two main subtypes are mycosis fungoides (MF) and Sézary syndrome (SS). Initial signs of MF include skin patches, plaques or tumor nodules. SS is a type of CTCL that affects both the skin and the blood.
- MF and SS are more often diagnosed in men than in women and usually are first diagnosed in people between the ages of 50 and 60 years.
- The type of treatment prescribed for patients who have MF or SS is based on a number of factors, including the patient's health, age and disease stage (how far the cancer has progressed). There is treatment for early-stage patients as well as treatment for advanced stages. The National Comprehensive Cancer Network (NCCN) NHL treatment guidelines (available at www.nccn.org) provide a standard that often governs health insurance carriers' coverage.
- Other than allogeneic stem cell transplantation, there are no curative therapies for MF and SS. However, recent research has led to the development of more effective biologic and targeted therapies for patients who have CTCL that may lead to a more lasting remission or cure.
- Optimal management of CTCL patients involves a collaborative effort among oncologists, dermatologists and primary care providers. It is important for you and members of your medical team to discuss treatment options, including treatments being studied in clinical trials.

This publication was supported in part by a grant from Celgene

Introduction

"Lymphoma" is the name for many different types of cancer that arise in the lymphocytes (immune cells). There are three types of lymphocytes: B lymphocytes (B cells), T lymphocytes (T cells) and natural killer (NK) cells. B lymphocytes make antibodies to fight infection; T lymphocytes have many functions, including helping B lymphocytes; and natural killer cells attack cancer cells and viruses. Lymphoma may arise in any of these types of lymphocytes. In general, B-cell lymphomas are more common than T-cell lymphomas; however, in the skin, T-cell lymphomas are the most common type.

About 20 percent of the white cells in the blood are lymphocytes. Most lymphocytes are found in the lymphatic system, the major part of the body's immune system. The lymphatic system consists of a network of organs, including the spleen, the lymph nodes (small bean-shaped structures located throughout the body), the lymphatic vessels and areas in the gastrointestinal tract.

Lymphoma is divided into two major categories: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Cutaneous T-cell lymphomas (CTCLs), cancers of the T lymphocytes, are a rare group of NHLs that arise primarily in the skin and have various signs and symptoms, outcomes and treatment options.

While the term "cutaneous T-cell lymphoma" can describe a number of different diseases, this fact sheet provides descriptions of the two main subtypes of CTCL: mycosis fungoides (MF) and Sézary syndrome (SS). It also includes specific information on the diagnosis, stages and treatment of these diseases, new drugs being studied in clinical trials and support resources.

For additional information about subtypes of NHL, please see the free The Leukemia & Lymphoma Society (LLS) booklets *Non-Hodgkin Lymphoma* and *The Lymphoma Guide: Information for Patients and Caregivers.*

About Cutaneous T-Cell Lymphoma

Cutaneous T-cell lymphomas (CTCLs), or "skin T-cell lymphomas," account for about 4 percent of all cases of NHL and, as the term indicates, primarily affect the skin. The overall annual age-adjusted incidence of CTCL is approximately six cases per one million. CTCL is twice as common in men as in women. The incidence of CTCL increases with age, with an average onset between 50 and 60 years. Although this disease is less prevalent in children, people of all ages can be affected.

Normally, there is a balance in the body by which new cells replace old ones, and each cell carries out its specific tasks. This balance ensures that the body functions properly. In lymphoma, malignant lymphocytes (cancer cells) grow uncontrollably. Malignant cell division is not balanced by cell death. Malignant T lymphocytes differ from normal resident skin T lymphocytes in that they accumulate in the skin and form patches, plaques, or tumor nodules. In early stages, the CTCL cells are found primarily in the skin. In patients with advanced stages of disease, the cells may also accumulate in the marrow, blood, the lymph nodes and/or solid organs.

Research is under way to determine a cause for CTCL. At this time, no definitive factor or factors have been found. Lymphoma results from a change(s) directly to the DNA in a single cell, which then becomes malignant, or indirectly, by affecting the cell's control mechanism. So far, studies have failed to prove an inherited genetic connection to the disease or establish links to chemical exposure, the environment, pesticides, infectious agents, radiation or occupations. CTCL is not contagious. Researchers are exploring genetic or epigenetic abnormalities (see *Treatments Under Investigation* on page 7) that may be responsible for the development and progression of this cancer.

The two most common subtypes of CTCL are mycosis fungoides (MF), which is often indolent (slow-growing) in early stages, and a more aggressive form called "Sézary syndrome" (SS). Other less common CTCL subtypes include

- Cutaneous CD30+ expressing anaplastic large cell lymphoma
- Panniculitis-like T-cell lymphoma
- Cutaneous CD8+ expressing aggressive epidermotropic T-cell lymphoma
- Gamma-delta T-cell lymphoma
- Hypopigmented/vitiligenous mycosis fungoides—more common in children with darker skin types, especially children who are African American, Latino and Middle Eastern/Indian.

A smaller number of skin lymphomas arise from a malignant change in a B lymphocyte and are referred to as "primary cutaneous B-cell lymphomas" (PCBCL). In most cases, patients with PCBCL respond well to treatment and have relatively good outcomes. The only exception is the rare subset called "diffuse large B-cell lymphoma, leg type," where the skin lymphoma behaves aggressively and usually requires more intensive systemic therapy.

Most cases of MF start with dry skin and a red rash, with or without itching. For some people, the initial sign is either redness or light or dark patches on the skin. In patients with extensive rash/erythroderma (total body skin redness often with scaling, as in SS), itching may be severe and make sleeping difficult. There may be red patches or raised areas of the skin, referred to as "plaques," that often have scaling on the surface and cover either small or large portions of the skin. Large bumps or tumor nodules with significant thickness may develop initially or later in disease progression. There may be breaks in the skin that do not heal well and become infected. In later stages, the skin tumors may become ulcerated and infected.

In some cases, the malignant lymphocytes may enlarge a lymph node so that it can be felt or seen if located close to the surface of the skin. Malignant lymphocytes may travel to other lymph nodes, which can also become enlarged. In advanced disease, malignant lymphocytes may also spread to other parts of the body, including the liver, spleen and lungs.

Because CTCLs are so rare, it is best to seek treatment at a medical center specializing in the diagnosis and treatment of NHL. See the free LLS fact sheet *Choosing a Blood Cancer Specialist or Treatment Center* for more information.

Signs and Symptoms

Mycosis fungoides (MF) is the most common type of CTCL. The name comes from the mushroom-like skin tumors that may appear in the advanced stages of the disease. There is no relation to a "fungus." MF often remains confined to the skin. About 70 to 80 percent of patients are diagnosed in early stages with skin involvement only, and the disease does not progress to the lymph nodes or internal organs. Also, in most patients diagnosed with early-stage (patches/plaques) disease, the skin involvement does not progress to show tumor lesions, seen in patients diagnosed with advanced stages, provided that they are given appropriate therapy. For a small number of patients, MF does slowly progress.

Sézary syndrome is a more aggressive, leukemic form of CTCL, with widespread skin effects, enlarged lymph nodes and the presence of significant numbers of malignant lymphocytes (called "Sézary cells") in the blood. The disease is characterized by an extensive red rash, itchiness and sometimes loss (sloughing) of the exterior layers of the skin. These patients often have skin infections due to the extensively compromised skin.

Mycosis fungoides and Sézary syndrome symptoms may include

- A scaly red rash or light or dark patches in areas of the body that are not usually exposed to the sun
- Thin, reddened, eczema-like rash
- Thickened scaly, red skin (or plaques) or psoriasis-like rash

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

Cutaneous T-Cell Lymphomas

Indolent clinical behavior

- Mycosis fungoides[1]: variants include
  - Folliculotropic mycosis fungoides
  - Hypopigmented/vitiligenous mycosis fungoides
  - Pagetoid reticulosis
  - Granulomatous slack skin
- Subcutaneous panniculitis-like T-cell lymphoma
- Primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoma

CD30+ Lymphoproliferative Disorders

- Primary cutaneous anaplastic large cell lymphoma
- Lymphomatoid papulosis[2]

Aggressive clinical behavior

- Sézary 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

Cutaneous B-cell Lymphomas

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, other
- Intravascular large B-cell lymphoma

[1] Aggressive clinical behavior will be seen in patients with advanced-stage mycosis fungoides or in those with large-cell transformation. Folliculotropic MF has also been shown to have worse prognosis.
[2] In patients with lymphomas, lymphomatoid papulosis may develop either before, after or at the same time the lymphoma is diagnosed. However, lymphomatoid papulosis itself does not have a malignant behavior and is considered a lymphoproliferative disorder with recurrent, self-healing lesions.

Source: Swerdlow SH, Campo E, Harris NL, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (ed 4th)*. Lyon, France: IARC Press; 2008.

- Tumors (with significant thickness) on the skin, which may develop ulcers and become infected
- Total body skin redness often with scaling and severe itching (erythroderma).

Symptom Management

Supportive therapy may be used to help manage MF and SS symptoms.

The itching that accompanies the skin tumors can be difficult to control. Supportive therapies that help manage MF and SS symptoms may include

- Antihistamines, particularly Benadryl® (diphenhydramine) or Atarax® (hydroxyzine), may relieve itching to some extent. The major side effect of these drugs is drowsiness. A patient will usually start at a lower dose of the medication and be increased to a higher dose as tolerated and as needed.
- Gabapentin (Neurontin®) may be effective in patients with severe itching, especially those with Sézary syndrome, and it may have fewer side effects than antihistamines. A patient will usually start at a lower dose of the medication and be increased to a higher dose as tolerated and as needed.
- Mirtazapine (Remeron®), an antidepressant or aprepitant (Emend®), an antinausea may help.
- Application of skin emollients and/or corticosteroid ointments may also help relieve itching.
- Some patients may benefit from using corticosteroid ointments with either sauna suits or as part of "soak and smear" (a regimen in which the patient soaks in a plain water bath followed by an application of the corticosteroid ointment to the moist skin, followed by damp and dry layers of cotton pajamas).
- Antibiotics are given if the skin becomes infected. Patients with long-standing, troublesome symptoms may require treatment for depression or insomnia.

Diagnosis

A diagnosis of MF or SS is usually made by a dermatologist following a series of diagnostic tests and procedures, including

- A physical examination and history (eg, rash does not respond to common eczema treatments)
- Blood tests (eg, to check for malignant lymphocytes)
- A skin biopsy and/or lymph node biopsy (the removal of a small piece of tissue) for examination under a microscope by a pathologist (a doctor who studies tissues and cells to identify diseases)
- A series of imaging tests such as computerized tomography (CT), magnetic resonance imaging (MRI) and/or positron emission tomography (PET) to determine whether the cancer has spread to lymph nodes or other organs.

Immunophenotyping, a process used to identify antigens, or markers, on the surface of the cells in the blood, may also be done to identify specific types of lymphoma by comparing the cancer cells to normal cells of the immune system. Also, in selected cases, molecular tests may be helpful in establishing the diagnosis. The results from these special tests must be interpreted with caution as there are many overlaps between benign cells and malignant cancer cells. Bone marrow biopsies are included as an option in NCCN guidelines but are often not useful in staging.

In advanced stages of MF and SS, the malignant cells may transform into more aggressive large cell types, a process referred to as "large cell transformation." Lymphoma cells may start to produce a protein called "CD30." Patients who undergo this type of cell transformation may need more aggressive treatment.

Treatment Planning

Every patient's medical situation is different and should be evaluated individually by a dermatologist and/or hematologist/oncologist who specializes in treating NHL. The optimal management of a patient's evaluation and treatment for cutaneous lymphoma involves a collaborative, multidisciplinary approach. It is important for you and members of your medical team to discuss all treatment options, including treatments being studied in clinical trials.

Staging

The following staging system is used to determine the extent of MF and SS:

Stage I

- Stage IA—Less than 10 percent of the skin surface is covered with patches and/or plaques.
- Stage IB—10 percent or more of the skin surface is covered with patches and/or plaques.

Stage II

- Stage IIA—Any amount of the skin surface is covered with patches and/or plaques. Lymph nodes are enlarged but do not contain cancerous cells.
- Stage IIB—One or more tumor lesions are found on the skin. Lymph nodes may be enlarged but do not contain cancerous cells.

Stage III

Erythrodermic skin, defined as a diffuse pattern of skin involvement, where greater than 80 percent of the body surface is involved with red patches or plaques. Lymph nodes may be enlarged but do not contain cancerous cells.

Stage IV

- Stage IVA and IVB—Any amount of the skin surface is covered with patches, plaques or tumors. Cancer involves lymph nodes and/or blood. Cancer involves other organs in the body (stage IVB). Patients with SS have a significant level of circulating cancer/Sézary cells as determined by special evaluation of the blood, either by flow cytometry (measures cancer-specific markers) or blood smear.

Treatment

There are several factors that determine a patient's treatment plan, including the person's general health, age and the stage of the disease. While patients with early-stage MF or SS may respond well to skin-directed therapies alone, patients with more advanced disease may require a combination of skin-directed (topical) and systemic (affecting the entire body) therapies to be successful. When appropriate, allogeneic stem cell transplantation should be considered in patients with advanced, refractory (resistant to therapy) and/or aggressive disease. Consensus practice guidelines are available for doctors treating patients who have CTCL; the most commonly used guideline is the National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline available at NCCN.org.

An individual patient's prognosis depends on

- The stage of the cancer and whether the disease involves the lymph nodes, the blood or other organs in the body
- The type and extent of skin lesions present (patches, plaques or tumors)
- The number of Sézary cells in the blood
- Transformation to large cell type or folliculotropic (involving the hair follicles) MF.

Treatment options for MF and SS include phototherapy, radiation (local and entire skin surface), topical therapy, systemic therapy (affecting the entire body), biologic or immune therapies, systemic single-agent chemotherapies and combined therapies. Combination chemotherapies are reserved for patients whose disease does not respond to single agents or for selected patients who have solid organ involvement. Some treatments are standard of care for MF or SS, and some are being tested in clinical trials.

In general, patients with early-stage disease, stages I-IIA, are managed mostly with skin-directed therapies.

Systemic therapies are used

- If skin-directed treatments no longer benefit the patient
- In patients with advanced stage of disease, stages IIB-IV, either in combination with skin-directed and/or other systemic agents.

Each treatment described in the following section has benefits and risks (side effects) for the patient. The selection of a specific therapy or therapies should be individualized, carefully weighing the risks versus the benefits.

Specific treatments include

Skin-Directed Therapies

- Topical corticosteroids—These drugs are a type of steroid and are used to relieve red, swollen and inflamed skin. They also have anti-proliferative (can stop the growth or multiplying of new cells or tissue) effects and can eliminate cancerous T cells in CTCL. Topical corticosteroids may be prescribed in a cream, lotion, foam, gel or ointment formulation. The strength of the topical steroid should be appropriate and matched for the body area being treated. Long-term use of topical corticosteroids can have negative effects such as skin thinning and weakening. This risk increases with the strength of topical corticosteroid.
- Topical chemotherapy—Nitrogen mustard (mechlorethamine HCl, Valchlor gel®) is FDA approved for the topical treatment of Stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma in patients who have received prior skin-directed therapy. Carmustine (BCNU) is an off-label topical CTCL treatment. Both agents can be administered as a compounded ointment (petrolatum-based vehicle). These ointments are applied daily either to affected areas of the skin or to all skin surfaces. Sometimes, these topical medications can cause skin irritation or allergic reaction. So, a patient should use caution when applying on sensitive skin areas such as face or folds. NEVER apply to genital skin.
- Retinoids—Topical retinoids, including bexarotene (Targretin®) and tazarotene (Avage®, Tazorac®), are drugs related to vitamin A; they work by encouraging the tumor cells to die faster and boosting immune reactions. Bexarotene is available as a skin-directed (gel formulation) and systemic therapy (oral therapy). Topical retinoids can frequently cause skin irritation.
- Phototherapy (light therapy)
  - Narrow-band UVB therapies—These types of therapies are used to treat thin lesions (patches and/or thin plaques) and are similar to PUVA (psoralen plus ultraviolet A) except that UVB rays do not penetrate the skin as deeply as UVA rays and are used without a photosensitizing drug.
  - PUVA (psoralen plus ultraviolet A)—This type of cancer therapy uses a skin-sensitizing medicine psoralen (taken by mouth) and exposure to ultraviolet (UV) light to kill cancer cells. Treatment is usually given two to three times a week for a few months and less frequently thereafter. Maintenance treatment is usually continued for a year or more.

PUVA or UVB phototherapy is also used in combination with the biologic agents interferon or bexarotene.

It is important to note that long-term phototherapy is associated with an increase in UV-associated skin cancer (basal cell and squamous cell cancers and melanoma). Thus, patients who have a strong personal or family history of these skin cancers should discuss the risks and benefits of phototherapy with their doctor.

- Other skin-directed therapies used include topical imiquimod cream, photodynamic therapy, and excimer laser. Imiquimod (Aldara®) and photodynamic therapy are each used to treat UV-associated skin damage (precancers and skin cancers) but also have been shown to be effective in MF. Excimer laser offers localized UV therapy. These treatments are less commonly used and require close oversight and follow-up by your doctor.

Radiation Therapy

- Electron beam radiation—Conventional radiation therapy penetrates the skin and reaches areas inside the body. Electron beam therapy can be applied to the entire skin surface, or to a localized area, without affecting internal organs. The dose (amount) of radiation can be lowered to reduce side effects whether the patient is receiving local or total skin electron beam therapy. Localized radiation therapy has been helpful for patients who have localized skin tumors or those who have had a poor response to treatment. The tumors often heal after treatment and the dead tissue resolves, reducing the risk of infection. Total skin electron beam therapy is appropriate for patients with widespread thick plaques with or without skin tumors. Some patients appear to have long-standing regression of their skin tumors following this type of treatment. Radiation

therapy, local or total skin, is effective at low doses in MF/SS, thus it is important that unnecessary higher doses are avoided.

Radiation therapy can be used alone, combined or used sequentially with other skin-directed or systemic therapies. As with phototherapy, radiation will increase risk of skin damage, thus risks and benefits should be discussed in patients with extensive photo-damage and history of multiple UV-associated skin cancers.

Systemic Therapies

- Biologic or immune therapies—These are milder forms of systemic therapies that aim to encourage cancer cells to die faster (facilitate apoptosis) or to enhance the patient's own immune system to fight off cancer cells. Examples include oral retinoids such as bexarotene (Targretin®), interferons, extracorporeal photopheresis (ECP), and targeted antibody therapies. Side effects of these biologic therapies are, in general, reversible and manageable. The profile of side effects depends on the specific agent.
  - Oral bexarotene is FDA approved in CTCL when at least one prior systemic therapy has not worked. Side effects include increased lipid levels (cholesterol, triglyceride) and lowering of thyroid hormone measurements, thus medications to address these side effects may be needed.
  - Interferons have common flulike symptoms.
  - Extracorporeal photopheresis (ECP) is an FDA-approved treatment for CTCL and is available only at selected centers that offer this treatment; it is a very well-tolerated therapy. In this procedure, blood is removed through a patient's vein. The white cells, which include circulating CTCL cells, are isolated and treated with a liquid form of psoralen, which sensitizes the cells to UVA light. The UVA rays irradiate the cells, and this, together with the drug, damages the DNA of the CTCL cells. The cells are then returned to the patient through a vein. The process injures the cancerous T cells and helps induce an immune response in the body. This procedure must be repeated multiple times to obtain the full effect. ECP is most effective in patients with blood involvement such as SS.
- Chemotherapy—Conventional chemotherapies kill cancer cells that divide rapidly. These treatments may also affect healthy dividing cells, so careful monitoring of blood counts and other laboratory test results are needed. Chemotherapy can be given as a single agent or in combination with multiple agents. Conventional chemotherapy has not been able to cure widespread skin lymphoma, and studies using chemotherapy combined with radiation therapy in patients with early stages of disease have not been very successful. Thus, chemotherapy in patients with early stages of disease should be avoided. However, selected single-agent chemotherapies have been shown to benefit patients with very aggressive disease (especially, large cell transformation) or patients whose disease does not respond to milder systemic therapies.

Some effective systemic chemotherapies for patients with aggressive skin disease and/or with involvement of the lymph nodes or other organs or for those with SS include

  - Methotrexate, pralatrexate (Folotyn®)—anti-folate agents that interfere with the growth of tumor cells; pralatrexate is FDA approved for the treatment of relapsed or refractory peripheral T-cell lymphoma. In 2011, the NCCN updated the non-Hodgkin lymphoma Clinical Practice Guidelines and the Drug and Biologics Compendium to include Folotyn® for the treatment of CTCL patients with MF and SS. Mouth sores, also called "mucositis" or "stomatitis," can be seen in some patients with anti-folate agents; this side effect can be prevented or reduced with folate and vitamin B_{12} supplementation.
  - Gemcitabine (Gemzar®), pentostatin (Nipent®)—purine analogues that interfere with the tumor growth.
  - Liposomal doxorubicin (Doxil®)—a chemotherapy that binds to DNA.
  - Chlorambucil (Leukeran®), cyclophosphamide (Cytoxan®)—alkylating agents, which interfere with the growth of cancer cells.
  - Etoposide (VP-16, VePesid®, Etopophos®), temozolomide (Temodar®)—antineoplastic, which interferes with the growth of cancer cells.
- Targeted therapies—These agents target a specific molecule on the cancer cell killing the cancer cells and not the healthy cells.
  - Alemtuzumab (Campath®)—alemtuzumab is a monoclonal antibody (a type of protein that can bind to tumor cells) that is FDA approved to treat chronic lymphocytic leukemia (CLL) but it can also be useful in managing patients with SS. Alemtuzumab therapy can lead to serious infections, thus it must be used carefully along with antimicrobials to lower the risk of infections. In SS, alemtuzumab is used in very low doses to reduce the risk of infections.
- Fusion toxin—Denileukin diftitox (Ontak®) is a fusion toxin (interleukin-2 [IL-2] linked with diphtheria toxin) that is FDA approved to treat persistent or recurrent CTCL in patients whose malignant cells express the CD25 component of the IL-2 receptor. Supply of Ontak for general use is on hold and currently available only through a clinical trial.
- Histone deacetylase (HDAC) inhibitors—These drugs target "epigenetic" changes (changes that affect certain cell processes without changing the genetic makeup of the cell).

- Vorinostat (Zolinza®), romidepsin (Istodax®)—vorinostat, an oral agent, is FDA approved to treat CTCL in patients whose CTCL gets worse, does not go away or comes back after treatment with two systemic therapies. Romidepsin, an intravenous therapy, FDA approved for the treatment of CTCL in patients who have received at least one prior systemic therapy. Side effects of HDAC inhibitors include fatigue, nausea, abnormal taste (dysgeusia), and decrease in platelet count.

Allogeneic Stem Cell Transplantation

Allogeneic stem cell transplantation involves receiving peripheral blood stem cells from a matched donor. There is a reduced-intensity (or nonmyeloablative) transplant that uses less intensive conditioning treatment and may be used for older patients. Multiple studies have shown successful results with reduced-intensity allogeneic stem cell transplantation in patients with MF and SS. Many centers are performing this type of transplant in patients who have advanced disease and have failed standard therapies or in very high-risk disease patients.

Combination therapies include

- Phototherapy and bexarotene (Targretin®)
- Phototherapy and interferon
- Phototherapy and ECP (extracorporeal photopheresis)
- Total skin electron beam radiation and photopheresis
- Bexarotene and interferon
- Bexarotene and denileukin diftitox (Ontak®) (Supply of Ontak for general use is on hold and currently available only through a clinical trial.)
- Photopheresis and bexarotene
- Photopheresis and interferon
- Photopheresis, bexarotene and interferon.

Side Effects of Treatment for Mycosis Fungoides and Sézary Syndrome

The side effects of treatment will depend on many factors including type of treatment (such as the location of radiation treatment) and dosage, the age of the patient and coexisting medical conditions. Therapy may induce fatigue, nausea, fever, chills, dizziness, blood clots, infertility and other effects. Some treatment options, such as retinoids, can cause birth defects; it is strongly suggested that women be on birth control when using these drugs. Side effects management is important. If you are having any concerns about your side effects, talk to your doctor to get help. Most side effects are temporary and resolve when treatment is completed. For specific drug and side effects information, see the free LLS booklet *Understanding Side Effects of Drug Therapy.*

Treatments Under Investigation

More research for types of CTCL over the last several years has resulted in better treatment options for patients; new therapies are constantly emerging. These trials, conducted under rigorous guidelines, help researchers to determine the benefits and risks of new treatments. Studies are also conducted to evaluate new indications for therapies that are already approved for other cancers or types of diseases. For more information about clinical trials, see the free LLS publication *Understanding Clinical Trials for Blood Cancers* or visit www.LLS.org/clinicaltrials. NCCN encourages patients to participate in clinical trials whenever appropriate.

Some of the classes of novel therapies and drugs under investigation include

- Antifolate inhibitors, agents that target a folate-dependent enzyme. Pralatrexate (Folotyn®), a drug approved for the treatment of relapsed or refractory peripheral T-cell lymphoma, is under study in patients with refractory MF and SS. It is also being studied in patients with refractory/relapsed disease in combination with bexarotene (Targretin®).
- Proteasome inhibitors, which block the action of proteasomes. A proteasome is a large cell protein that helps destroy other cell proteins when they are no longer needed. Bortezomib (Velcade®), an agent approved to treat patients with multiple myeloma or mantle cell lymphoma, is being evaluated in clinical trials in combination with an HDAC inhibitor (eg, vorinostat, romidepsin), chemotherapies, or other targeted agents. Also newer proteasome inhibitors with improved safety profiles are in clinical development.
- Many other agents that target specific tumor cell signaling, transduction, proliferation, and survival pathways are in preclinical and clinical development. This includes PI3k and mTOR pathway inhibitors.
- Numerous immune stimulatory/augmenting strategies are in development including new toll-like receptor (TLR) agonists and agents that target immune checkpoints (the breaks in our antitumor response), thus leading to enhancement of immune response against tumor cells. Examples of antibodies that target immune checkpoints include anti-PD-1 and anti-PD-L1 monoclonal antibodies.
- Monoclonal antibodies, such as
  - Mogamulizumab (KW-0761) that targets CCR4 molecule on tumor cells is currently undergoing a phase 3 clinical trial to obtain FDA approval. The phase 1/2 study results show promising results especially for patients with SS but without the risk of infections observed with alemtuzumab therapy.

- Brentuximab vedotin (Adcetris®) is a novel antibody-drug-conjugate where a monoclonal anti-CD30 antibody is linked to a potent tubulin-disrupting agent, monomethyl auristatin-E (MMAE). It targets and binds to tumor cells with CD30 expression, which then leads to tumor cell killing. Brentuximab vedotin is FDA approved for Hodgkin lymphoma and systemic anaplastic large cell lymphoma. Currently, there are multiple clinical trials available in CTCL, including the phase 3 trial for FDA approval in CTCL.

- Allogeneic stem cell transplantation and reduced-intensity (or nonmyeloablative) transplant involve receiving peripheral blood stem cells from a matched donor. Multiple studies have shown successful results with reduced-intensity allogeneic stem cell transplantation in patients with MF and SS. Clinical trials are under way to determine whether milder or alternative regimens of allogeneic stem cell transplants in CTCL may improve clinical benefit and reduce the harmful outcome of graft-versus-host disease, which can be a complication in allogeneic transplantation. High-dose therapy followed by autologous stem cell transplantation has not been effective in MF and SS. For more information about transplantation, see the free LLS booklet *Blood and Marrow Stem Cell Transplantation.*

Treatment Outcomes

The prognosis for patients with MF or SS depends on a number of factors, including patient age, disease type and stage, rate of disease progression and response to therapy. Some patients may have stable or slowly progressive disease, while others may have a more rapidly progressive form, especially with large cell transformation. Many patients will have disease limited to the skin. Some may have involvement of other organs.

Patients may live normal lives for many years while being treated for their disease and some are able to remain in remission for long periods of time. A minority will experience progressive disease with lymph node and/or internal involvement with serious complications. The risk of progression (worsening disease) depends on the initial extent and type of skin involvement (T-classification), how well the skin disease is controlled with therapy and the disease course. Patients who are initially diagnosed with mild/limited disease (stage IA) are unlikely to experience progression of their skin disease or to be at risk for lymph nodes, blood or other organ involvement. However, patients with MF who present with extensive thick skin disease (thick plaques or tumor nodules) or total skin redness (erythroderma) have more threatening disease and are at increased risk for disease progression, including lymph node, blood or internal organ involvement. Patients with SS also have a worse prognosis because they have significant blood involvement. It is important to emphasize that prognosis/outcome for a patient with advanced or progressive disease is improving as a result of better/new treatment options.

Acknowledgement

LLS gratefully acknowledges

Youn H. Kim, MD

Joanne and Peter Haas Jr. Professor for Cutaneous Lymphoma Research

Director, Multidisciplinary Cutaneous Lymphoma Research

Co-Director of Lymphoma Research Program

Stanford Cancer Center & School of Medicine

Stanford, CA

for her review of *Cutaneous T-Cell Lymphoma Facts* and her important contributions to the material presented in this publication.

LLS also gratefully acknowledges members of the staff of the Cutaneous Lymphoma Foundation for their important contributions to the material presented in this publication.

We're Here to Help

LLS is the world's largest voluntary health organization dedicated to funding blood cancer research, education and patient services. LLS has chapters throughout the country and in Canada. To find the chapter nearest to you, visit our website at www.LLS.org or contact

The Leukemia & Lymphoma Society
1311 Mamaroneck Avenue
White Plains, NY 10605
Contact an Information Specialist at (800) 955-4572
Email: infocenter@LLS.org

LLS offers free information and services for patients and families touched by blood cancers. The following lists various resources available to you. Use this information to learn more, to ask questions, and to make the most of your health care team's knowledge and skills.

Consult with an Information Specialist. Information Specialists are master's level oncology social workers, nurses and health educators. They offer up-to-date disease and

treatment information. Language services are available. For more information, please

- Call: (800) 955-4572 (M-F, 9 a.m. to 9 p.m. EST)
- Email: infocenter@LLS.org
- Live chat: www.LLS.org
- Visit: www.LLS.org/informationspecialists.

Free Materials. LLS offers free education and support publications that can either be read online or downloaded. Free print versions can be ordered. For more information, please visit www.LLS.org/publications.

Información en Español (LLS information in Spanish). For more information, please visit www.LLS.org/espanol.

Telephone/Web Education Programs. LLS offers free telephone/Web education programs for patients, caregivers and healthcare professionals. For more information, please visit www.LLS.org/programs.

Co-Pay Assistance Program. LLS offers insurance premium and medication co-pay assistance for certain eligible patients. For more information, please

- Call: (877) 557-2672
- Visit: www.LLS.org/copay.

Online Blood Cancer Discussion Boards and Chats. Online discussion boards and moderated online chats can provide support and help cancer patients to reach out, and share information. For more information please visit www.LLS.org/getinfo.

LLS Chapters. LLS offers community support and services in the United States and Canada including the *Patti Robinson Kaufmann First Connection Program* (a peer-to-peer support program), in-person support groups, and other great resources. For more information about these programs or to contact your chapter, please

- Call: (800) 955-4572
- Visit: www.LLS.org/chapterfind.

Clinical Trials (Research Studies). New treatments for patients with CTCL are under way. Patients can learn about clinical trials and how to access them. For more information, please

- Call: (800) 955-4572 to speak with our LLS Information Specialists who can help conduct clinical-trial searches
- Visit: www.LLS.org/clinicaltrials and click on TrialCheck®.

Advocacy. The LLS Office of Public Policy (OPP) enlists volunteers to advocate for policies and laws to speed new treatments and improve access to quality medical care. For more information, please

- Call: (800) 955-4572
- Visit: www.LLS.org/advocacy.

Other Resources

Cutaneous Lymphoma Foundation

(248) 644-9014
www.clfoundation.org

The Cutaneous Lymphoma Foundation is an independent, nonprofit patient advocacy organization dedicated to supporting every person with cutaneous lymphoma by promoting awareness and education, advancing patient care and facilitating research. The Foundation offers patient educational forums and programs and services that help patients, caregivers, physicians and others who are affected by cutaneous lymphoma.

The National Cancer Institute (NCI)

(800) 422-6237
www.cancer.gov

The National Cancer Institute, part of the National Institutes of Health, is a national resource center for information and education about all forms of cancer, including cutaneous T-cell lymphomas (CTCLs). The NCI also provides a clinical-trial search feature, the PDQ® Cancer Clinical Trials Registry, at www.cancer.gov/clinicaltrials, where CTCL patients can look for clinical trials for their specific subtype.

The National Comprehensive Cancer Network (NCCN)

www.nccn.org
For current practice guidelines visit www.nccn.org, NCCN Clinical Practice Guidelines in Oncology to see what MF or SS treatments are being used and are most likely covered by insurance companies.

References

Bloom T, Kuzel TM, Querfeld C, et al. Cutaneous T-cell lymphomas: a review of new discoveries and treatments. *Current Treatment Options in Oncology*. 2012;13(1):102-121.

Geskin Larisa J, "Chapter 105. Cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome)." Lichtman MA, Kipps TJ, Seligsohn U: *Williams Hematology*. 8th ed. Available from: AccessMedicine. Accessed April 3, 2014.

Guenova E, Hoetzenecker W, Rozati S, et al. Novel therapies for cutaneous T-cell lymphoma: what does the future hold? *Expert Opinion on Investigational Drugs*. 2014; 23(4):457-467.

Imam MH, Shenov PJ, Flowers CR, et al. Incidence and survival patterns of cutaneous T-cell lymphomas in the United States. *Leukemia and Lymphoma*. 2013; 54(4):752-759.

National Cancer Institute. Mycosis fungoides and Sézary syndrome Treatment PDQ®. www.cancer.gov/cancertopics/pdq/treatment/mycosisfungoides/Patient/page1/AllPages. Accessed June 11, 2014.

National Comprehensive Cancer Network. Practice Guidelines in Oncology v.1.2014. Non-Hodgkin. Lymphoma. Guidelines can be accessed here: www.nccn.org/professionals/physician_gls/f_guidelines.asp

Pinter-Brown LC, Schwartz RA, et al. Cutaneous T-cell lymphoma. *Medscape*. 2013. emedicine.medscape.com/article/1098342-overview. Accessed June 11, 2014.

Swerdlow E, Campo N, Harris NL, et al. WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues. 4th ed. IARC Press Lyon, France; 2008.

Wollina U. Cutaneous T-cell lymphoma: update on treatment. *International Journal of Dermatology*. 2012:51(9):1019-1036.