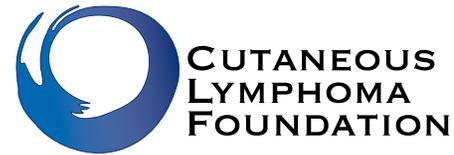


UNDERSTANDING TREATMENT OPTIONS IN CUTANEOUS LYMPHOMA



A Supplement to the
Patient's Guide to Understanding Cutaneous Lymphoma



Welcome

Living with cutaneous lymphoma and understanding the diversity of the treatment options available can be challenging. The good news is that there are many treatment options available today. Making informed decisions about which treatment is best for you at a given point in time is why this supplement was created.

As your resource for valuable information, we hope you find this information helpful as you learn more about the treatment options available. Armed with knowledge and information, you can be prepared for discussions with your healthcare provider about the best treatment options for you.

In addition to this printed supplement, there is a companion treatment table available on our website (www.clfoundation.org), which provides additional details about the specific treatments available. We want you to have access to as much information as possible so that you understand your options and are comfortable making informed treatment decisions.

You are not alone. You are part of a knowledgeable, caring, resourceful, and compassionate community, and we are here to help you.

Reach out any time we can be of additional help. We hope to hear from you or meet you at one of our patient events.

All the best in your journey.

The Staff and Board of Directors of the Cutaneous Lymphoma Foundation

Understanding Treatment Options in Cutaneous Lymphoma

This supplement is an educational resource published by the Cutaneous Lymphoma Foundation providing general information on cutaneous lymphoma and treatment options. Publication of this information is not intended to take the place of medical care or the advice of your physician(s). Patients are strongly encouraged to talk to their physician(s) for complete information on how their disease should be diagnosed, treated, and followed. Before starting treatment, patients should discuss the potential benefits and side effects of therapy.



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ABOUT THIS BOOKLET

There are many treatment options, both old and new, for cutaneous lymphomas. This booklet provides an overview of the treatment choices available that you can discuss with your healthcare provider to decide which treatment options may suit you best. The information in this booklet provides an overview of cutaneous lymphoma, as well as detailed sections on cutaneous T-cell lymphoma and cutaneous B-cell lymphoma.

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Additional information on cutaneous lymphoma and treatment options, including more detailed information on particular drug treatments, is available at www.clfoundation.org.

SECTION 1: UNDERSTANDING TYPES OF TREATMENT

Lymphoma is a family of cancers of white blood cells called lymphocytes. There are 2 types of lymphocytes: B cells and T cells. Both types of lymphocytes work to fight infections in the body. When one type of lymphocyte cell mutates and multiplies uncontrollably, it becomes a lymphoma.

Most types of lymphoma develop in lymph nodes, where lymphocytes typically function. However, lymphocytes travel to many sites in the body during their normal function, including the skin. When a lymphocyte residing in the skin develops a mutation resulting in cancer it is called cutaneous lymphoma. There are several varieties of cutaneous lymphomas depending on the type of white blood cell that developed the original cancerous mutation. Cutaneous T-cell lymphomas (CTCLs) develop from mutations in T cells. Similarly, cutaneous B-cell lymphomas (CBCLs) develop from altered B cells and are less common than CTCLs. Both CTCLs and CBCLs are further divided into various subtypes, as discussed in the sections for each of these diseases.

Treatment Decision

Treatments for cutaneous lymphomas vary based on several factors. These include whether it is a CTCL or CBCL, an early or advanced cancer, and any prior treatments for the lymphoma. As a result, treatments are personalized and tailored to each patient's particular situation.

The goal of treatment for cutaneous lymphoma is to:

- Clear up all patches, plaques, or tumors
- Eliminate or reduce the number of cancerous lymphocytes in the skin and blood
- Prevent migration of malignant cells from skin to other organs
- Block the growth of tumor cells
- Restore immune balance and competence
- Improve the patient's quality of life by relieving symptoms such as pain, itching, burning, and redness

While this booklet presents common themes in treatment approaches, a particular patient's treatment plan may vary based on the specifics of their lymphoma, previous treatments and experiences, the patient's health and particular situation, and overall needs. There have been very few studies done to compare the effectiveness of one therapy for cutaneous lymphoma with another, so it is often a matter of trial and error until your healthcare team finds the right treatment or combination of treatments that work for you. It is necessary to discuss the benefits and disadvantages of treatment options with your healthcare team before making a decision on your individual treatment course. For less common forms of cutaneous lymphomas, physicians may select a treatment that has been used successfully in other, more common types of cutaneous lymphoma.

It is important to understand that some cutaneous lymphomas will respond to a treatment temporarily, but the patient may not maintain a permanent remission. Constant monitoring and maintenance may be required, but maintenance therapy may also be sufficient to prevent progression. For patients whose lymphoma has recurred, the treatment used previously may still be effective at controlling the disease. For others, the previous treatment may not be effective and a new treatment approach is needed.

Local/Skin-Directed Therapies

Generally, early, localized disease is treated with skin-directed therapies that are administered directly to the affected area. Localized therapy or skin-directed treatment includes topical therapies like topical steroids, phototherapy, radiation, intralesional therapy, and surgical removal (excision) of lesions. These kinds of treatments are applied to limited areas of the skin with little or no effect on other regions of the body. This approach can limit the side effects of treatments.

Systemic Therapies

Systemic therapies, given orally, intravenously, or subcutaneously (injected under the skin), are distributed across the entire body, reaching and affecting cells all over the body to kill cancer cells wherever they are located, including the skin, blood, and organs. These are typically administered for more advanced disease. There are several different types of systemic therapies.

Targeted Therapies

Targeted therapies are agents that act directly and specifically against particular molecules needed for cancer growth. Targeted therapies usually affect fewer normal cells and therefore may result in fewer side effects. However, not all cutaneous lymphomas develop in the same way and patients' disease may develop along different pathways. If a particular patient's disease does not have the specific target exploited by the drug (for example, a specific marker on the surface of the cancer cell) due to the pathway along which it developed, then the drug will not be effective. Targeted therapies represent a new area of interest in cutaneous lymphoma treatments and are leading to increasingly individualized treatments where each patient can receive therapy that is specific for their individual disease.

Biologic Therapies

Biologic therapy is a kind of systemic targeted therapy that works with the body's normal cell functions to fight cancer. These drugs repair, stimulate, or enhance the action of the patient's healthy immune cells. Specific biologic agents target specific characteristics of cancer cells.

Therapies used for CTCL and CBCL are described in more detail in the sections for each disease. Further information is also available at the Cutaneous Lymphoma Foundation's website at www.clfoundation.org.

Cutaneous T-Cell Lymphoma Subtypes

Cutaneous T-cell lymphomas (CTCLs) account for 75%–80% of all cutaneous lymphomas. Mycosis fungoides is slow growing and is the most common type, accounting for about 44% of all CTCLs.¹ Primary cutaneous CD30+ lymphoproliferative disorders are the second most common group of CTCLs, accounting for about 20% of all cases; they can be slow growing (lymphomatoid papulosis) or fast growing (primary cutaneous anaplastic large-cell lymphoma). Sézary syndrome is the most common fast-growing CTCL and accounts for about 3% of all CTCLs. **Table 1** shows the different types of CTCLs.

Table 1. Types of CTCLs

Cutaneous T-Cell Lymphomas (75%–80% of cutaneous lymphomas)	Mycosis fungoides
	Sézary syndrome
	Primary cutaneous CD30+ lymphoproliferative disorders
	Lymphomatoid papulosis
	Primary cutaneous anaplastic large-cell lymphoma
	Subcutaneous panniculitis-like T-cell ($\alpha\beta$) lymphoma
	Primary cutaneous extranodal natural killer/T-cell lymphoma, nasal type
	Primary cutaneous peripheral T-cell lymphoma
	Primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoma
	Primary cutaneous aggressive CD8+ T-cell lymphoma
Cutaneous γ/δ T-cell lymphoma	

Additional information about the subtypes of CTCL can be found at www.cfoundation.org.

Disease Classification/Staging

CTCLs are classified into stages IA through IVB using the T (tumor, which for CTCL is patches or plaques), N (lymph node), M (presence of metastasis) (TNM) system.² The level of disease is evaluated based on the size of the plaques or patches of affected skin (T1–T4); the presence or number of cancer cells in lymph nodes (N0–N3); and the presence of metastasis (M0–M1) (**Table 2**). Stages IA, IB, and IIA are considered early-stage disease, meaning that the cancer is not widespread. Stages IIB through IVB are considered advanced-stage disease, where the cancer is more widespread and/or has moved outside the skin to other places in the body such as the lymph nodes or other organs.

Since mycosis fungoides and Sézary syndrome include involvement of the blood, staging of these cutaneous lymphomas includes this additional criteria based on the presence of Sézary cells in the blood.² B₀ represents an absence of significant blood involvement, B₁ represents a low blood tumor burden, and B₂ represents a high blood tumor burden.

Table 2. Staging of CTCLs by the TNM System^a

		Tumor (T)			
		T1: Limited patches/plaques (<10% BSA)	T2: Generalized patches/plaques limited to 1 or 2 contiguous body regions (≥10% BSA)	T3: Generalized skin involvement, or 1–2 tumors ≥1 cm in diameter	T4: ≥80% of BSA affected
Lymph nodes (N)					
Metastasis present (M)					
N0: No nodes are clinically involved	M0	IA	IB	IIB	IIIA
N1: Nodes enlarged, histologically uninvolved	M0	IIA			IIIB
N2-3: Nodes clinically normal (N2) or enlarged (N3), histologically involved	M0	IVA			
N0-3: Visceral involvement	M1	IVB			

^aThe grey-shaded regions indicate early-stage disease, whereas the blue-shaded areas indicate advanced disease.²

BSA, body surface area.

Treatment Options

Patients with CTCL who have early-stage disease can be treated effectively with skin-directed therapies.³ Skin-directed treatments for CTCL include topical therapies like topical steroids, phototherapy, and radiation. Topical treatments are applied to the skin directly and are mostly active on the surface of the skin, without much absorption into the bloodstream. This can limit side effects. Patients can often use skin-directed therapies for a long time.^{4,5} Although the disease will probably come back (relapse), the same treatment that worked previously often works again. Skin-directed therapies are recommended alone or in combination for treating mycosis fungoides and other early-stage CTCLs (**Figure 1**).

For patients with large areas of skin involvement or lymphoma that has spread beyond the skin or has relapsed, systemic therapies that can move through the bloodstream and extend throughout the entire body to reach cancer cells wherever they are located, such as oral retinoids, interferon, or extracorporeal photopheresis, might be used early on in combination with skin-directed treatments,^{6,7} depending on the individual patient's clinical circumstances.

Common Combination Therapies ^a	
Skin-directed + Systemic	Systemic + Systemic
Phototherapy + retinoid	Retinoid + interferon
Phototherapy + interferon	Photopheresis + retinoid
Phototherapy + photopheresis	Photopheresis + interferon
Total skin electron beam + photopheresis	Photopheresis + retinoid + interferon

^aThis list should not be considered exhaustive. Patients and physicians may decide on other combinations that are appropriate for their particular situation.

The National Comprehensive Cancer Network® (NCCN®, www.nccn.org), a not-for-profit alliance of 25 of the world's leading cancer centers, develops guidelines on the treatment of cancers including cutaneous lymphoma. An overview of the NCCN CTCL guidelines are shown in **Figure 1**.⁵

Figure 1. Treatment of CTCLs Based on the NCCN Guidelines^a

Stage	IA	IB	IIA	IIB	IIIA	IIIB	IVA	IVB
Skin-Directed Therapies^b →								
<ul style="list-style-type: none"> • Ointments, creams, or lotions • Phototherapy • Radiation 								
Systemic/Novel Therapies →								
<ul style="list-style-type: none"> • Extracorporeal photopheresis • Retinoids • HDAC inhibitors • Interferon • Denileukin diftitox • Single-agent/multiagent chemotherapy • Monoclonal antibodies 								
Stem Cell Transplant →								
Clinical Trials →								

^aFrom the National Comprehensive Cancer Network Guidelines in Oncology; Non-Hodgkin Lymphomas, V3.2011. Available at: http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf

^bPatients with stage IA, IB, or IIA who have refractory disease may receive other types of treatments as well.

HDAC, histone deacetylase.

SKIN-DIRECTED THERAPIES

Topical Corticosteroids

Topical corticosteroids (sometimes referred to simply as steroids) are one of the more established treatments for CTCL. These agents cause the immune system to become more active and also have anti-inflammatory effects. There are many options in steroid treatment, and multiple formulations are available including creams, gels, ointments, and lotions. With modest efficacy,^{8,9} steroids can be particularly useful in reaching some areas of the skin that are more difficult to reach with other forms of treatment, such as under the arms. They are also helpful in alleviating symptoms of itching. However, steroids are associated with several side effects such as thinning of the skin (atrophy), stretch marks/striae (irregular areas of skin that look like bands, stripes, or lines), acne/pimples, and hair growth, which should be considered when evaluating this option. Although they may be used independently, steroids are frequently used in combination with other treatments.

Topical Chemotherapy

Alkylating agents are a class of chemotherapy that act by chemically modifying DNA and preventing cancer cells from growing. Mechlorethamine (Mustargen[®] and Valchlor[™]), commonly known as nitrogen mustard, and carmustine (BiCNU[®]) are examples of these. They have been mixed into solution or compounded into ointments and used topically to treat CTCL.¹⁰⁻¹² Recently, a gel form of mechlorethamine (Valchlor[™]) has become available for treatment of CTCL. During the course of topical chemotherapy, patients sometimes experience redness, irritation, and/or allergy (dermatitis), development of fine, dilated blood vessels (telangiectasias), or darkening of the skin (hyperpigmentation) in the treated area. Dermatitis and hyperpigmentation may cause physicians and patients to choose another treatment when the affected area is visual, such as the face.

Imiquimod

Topical imiquimod (Aldara[®]) is a cream that works by stimulating the release of interferon and cytokines, which have anti-tumoral effects.¹³ While the exact mechanism behind the anti-tumoral response is still unclear, imiquimod is thought to stimulate dendritic cells, which leads to immune activation. Although large clinical trials are needed, there is mounting evidence from clinical practice that imiquimod has activity against CTCL. In most cases reported to date, imiquimod was used for patients who had failed at least one other topical therapy, suggesting imiquimod may be beneficial in disease for which the initial treatment has stopped working (resistant or refractory disease).^{14,15} One current limitation is that this cream is distributed in small packets, making it difficult to use over larger areas of the body.

Retinoids

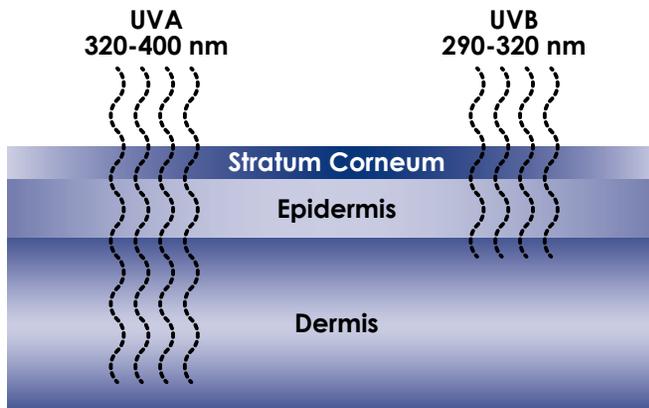
Retinoids are another, newer class of agents that are available as topical or oral formulations, which include bexarotene (Targretin[®]) and tazarotene gel (Tazorac[®]). These vitamin A-derived agents regulate a wide range of biological processes, including cell growth and death.¹⁶ Retinoids have been shown to be effective at killing cancer cells and inhibit the ability of cancer cells to move into the skin, which helps with itching and redness.¹⁷ Topical bexarotene is approved by the US Food and Drug Administration (FDA) for the treatment of Stage 1A and 1B CTCL in patients who have not responded to or tolerated other

therapies.¹⁸ There are also oral forms available (see **Systemic Therapies** on page 12). Common side effects with the topical form of bexarotene include redness, itching, warmth of the skin, swelling, burning, scaling, and other skin irritations. The treated areas should also be protected from prolonged exposure to sunlight or other sources of ultraviolet (UV) light, such as tanning lamps.

Phototherapy

Phototherapy involves the use of UV light—the same rays that are in sunlight—to treat the skin.¹⁹ Phototherapy is generally used for patients with CTCL who have lesions classified as T2 (eg, generalized patches or plaques, limited to 1 or 2 contiguous body regions).⁵ There are several different types of phototherapy, including 1) psoralen-ultraviolet A light (PUVA), which utilizes UVA spectrum light¹⁹; 2) broad-band ultraviolet B light (bbUVB), which uses UVB spectrum light; and 3) narrow-band ultraviolet B light (nbUVB), which also uses UVB spectrum light.^{20,21} UVA radiation is considered less powerful than UVB, but UVA penetrates deeper into the skin than UVB rays (**Figure 2**). UVA and UVB both cause T cells to self-destruct.

Figure 2. Skin Penetration of UVA and UVB Light



PUVA

Psoralens are photosensitizing agents found in plants. Methoxsalen (Oxsoalene-Ultra[®]) is an example of one of these agents. Psoralen is taken orally prior to exposure to UV light. Exposure to UV light then causes the ingested psoralen to become toxic to the malignant cells.

PUVA phototherapy is effective in early-stage disease, but it is most effective for thicker skin lesions that involve large surface areas. Twenty to 40 treatments given 2 to 3 times per week are usually needed to produce clearing. In order to protect the eyes from photosensitive reactions, patients are required to wear UV-protective eye shields for 24 hours after each treatment. Oral psoralens can cause stomach upset in some patients. Long-term complications of PUVA phototherapy include the development of skin cancers. PUVA phototherapy may be combined with other forms of systemic therapy.^{22,23}

nbUVB and bbUVB

UVB phototherapy has been shown to be effective in thinner skin lesions or “patches.”^{20,24} Treatments are typically conducted in a dermatology office with the use of a specially calibrated light box; however, these boxes can be purchased for treatment at home. Improvement in skin lesions are often not observed until the patient has received approximately 20 to 40 treatments. UVB phototherapy begins with small doses of light given 2 to 3 times per week, with gradual increases in dose over time. Side effects of phototherapy include sun burn or temporary redness or burning of the skin. Prolonged phototherapy administration can increase overall skin cancer risk.

Radiation Therapy

Radiation therapy is considered the most effective single treatment for primary cutaneous lymphoma.^{25,26} Advances in radiation therapy have led to the use of low-energy orthovoltage X-rays and electron beam radiotherapy. Orthovoltage X-rays can successfully treat recurrent lesions; however, these rays will also penetrate and damage the underlying tissues, such as blood vessels, muscles, and bone marrow. Local radiation therapy is typically used for patients with limited extent tumors (T3) with or without patches and/or plaques.

Total skin electron beam (TSEB) therapy is a type of radiation therapy that has shown high response rates, particularly in early-stage disease.²⁷⁻³¹ Patients usually receive only one TSEB treatment. However, repeat treatments after disease relapse are possible when other therapies have failed. This treatment penetrates only the superficial portions of the skin, limiting damage to underlying tissues. This is a complicated treatment that requires a skilled multidisciplinary team of oncologists, physicists, radiographers, nurses, and

dermatologists experienced in the management of cutaneous lymphoma. There are also risks including infection, blisters, skin discoloration, and pain.³² TSEB therapy is commonly used in combination with chemotherapy.³³⁻³⁵

Brachytherapy, also known as internal radiotherapy, is a newer method for delivering radiation in cancer treatment. The term “brachy” is from the Greek word “brachys,” meaning short distance. Very small radioactive seeds or sources called implants are placed in or near the tumor by computer-controlled delivery through a thin plastic catheter or metal tube called an applicator. The implants are about the size of a grain of rice. A computer controls where the seeds are delivered and how long they remain in any location. They are located so as to harm as few healthy cells as possible. The radioactive material may be left for a short time or more permanently. The applicator may be left until all treatments are completed. The procedure, which is done in a hospital operating room, may only last a few minutes. Locating the radiation source so close to the cancerous tissue helps to spare surrounding healthy tissue from radiation exposure. Short-range radiation sources are used. It can be used alone or in combination with other therapies such as surgery, external beam radiotherapy, or chemotherapy. One trial investigating the use of brachytherapy in the treatment of patients with mycosis fungoides analyzed 23 facial lesions in 10 patients. This trial reported dramatic clinical improvement and no recurrences in these patients during the 6.3-month follow-up period; however, longer-term follow-up is still needed.³⁶

SYSTEMIC THERAPIES

Extracorporeal Photopheresis

Extracorporeal photopheresis is a treatment for disease that has traveled beyond the skin and into the bloodstream. This treatment has similarities to phototherapy. It is a 1.5- to 5-hour procedure, depending on the equipment used, during which a portion of the patient’s blood is removed from the vein and placed into a portable machine that separates the white blood cells, mixes them with a photosensitizing drug (methoxsalen), and exposes them to UVA light. The cells that are returned to the body are better able to fight infection. Patients are typically treated on 2 successive days, 3 to 4 weeks apart.

Biologics

Interferon

Interferon is a cytokine, a naturally occurring protein in the body that is normally present in very small amounts. Interferon can also be made in a laboratory and used as a drug. Interferon may be given as an injection into a vein or muscle, or under the skin. Interferon alfa (Intron® A [interferon alfa-2b] or Roferon®-A [interferon alfa-2a]) or gamma stimulate the body’s immune system to fight some types of cancer. Although how it works is not fully understood, it is thought that these molecules interact with receptors on the surface of cells, where they may interfere with the cancer cell’s ability to divide or reduce the ability of the cancer cells to protect themselves from the immune system, and/or they may strengthen the patient’s immune system. The most common side effects are flu-like syndrome, fatigue, low blood cell counts, low calcium or high glucose or triglycerides, changes in liver enzyme levels, weight loss, and hair loss.^{37,38} Some patients, especially the elderly, might experience cognitive effects that may include difficulty concentrating and remembering. Peripheral neuropathy (numbness and tingling of hands and feet and sometimes loss of taste) can also occur, which usually slowly resolves when the medication is stopped.

Retinoids

Bexarotene is a retinoid that is available as a capsule that is taken orally, as well as being used in a skin cream. Oral bexarotene is approved by the FDA for the treatment of patients with refractory or persistent CTCL after trying at least one other therapy. The most common side effects with use of oral bexarotene are an increase in blood lipids and an underactive thyroid gland. When taking oral bexarotene, your skin may become more sensitive to sunlight, so you must wear sunscreen and protective clothing while in the sun. Grapefruit or grapefruit juice may interact with bexarotene and could cause additional side effects. Other drugs can also interact with oral bexarotene. Patients should check with their doctor or pharmacist to make sure they are avoiding products containing ketoconazole, itraconazole, gemfibrozil, or erythromycin, or any other medications that may interact with bexarotene.

Antibodies

Monoclonal antibodies are the most common biologic agents used for lymphoma therapy. The immune system uses antibodies to recognize and destroy foreign invaders such as bacteria and viruses. Scientists can now produce “monoclonal antibodies” in the laboratory that recognize certain kinds of cancer cells. Once in the blood, monoclonal antibodies travel throughout the body and attach themselves to their specific target. Antibodies are thought to work by stopping or slowing the growth of cancer cells, or by making it easier for the person’s immune system to destroy the tumor cell. Healthy cells can also be affected by the antibody, but the body can usually replace these cells after the treatment with biologic therapy has stopped. However, patients taking a biologic treatment may be susceptible to infection. Alemtuzumab (Campath®) is a monoclonal antibody that targets the CD52 antigen on the cell surface of cancerous lymphocytes. Alemtuzumab can be given as a low-dose regimen that can reduce malignant T cells without affecting healthy T cells.³⁹⁻⁴³ Mogamulizumab, a bioengineered, humanized monoclonal antibody against CCR4, is a newer antibody treatment being tested in CTCL.⁴⁴

Monoclonal antibodies can also be made with a chemotherapy drug, radioactive particle, or toxin attached to it. These antibodies bring the drug, radioactive particle, or toxin to its target on the malignant cell. One example of this is brentuximab vedotin (Adcetris®), a monoclonal antibody that targets the CD30 antigen on cancer cells.⁴⁵ This antibody is attached to a drug (monomethyl auristatin E) that can kill the cancer cell after the antibody attaches to it. Common side effects experienced by patients receiving brentuximab were fatigue, fever, diarrhea, and nausea. This drug is being tested in primary cutaneous CD30-positive CTCLs.⁴⁶

Denileukin diftitox is a “fusion protein,” meaning that it is made of 2 different molecules: a biologic agent called interleukin 2 and diphtheria toxin.⁴⁵ The interleukin 2 attaches to the cancer cell, and the diphtheria toxin kills the cell. Denileukin diftitox is used to treat persistent or recurrent CD25-positive CTCL. The supply of denileukin diftitox (Ontak®) for general use is on hold and it is currently available only through a clinical trial.

Targeted Therapy

Histone Deacetylases

Histone deacetylase (HDAC) inhibitors like vorinostat (capsule)^{47,48} and romidepsin (intravenous)⁴⁹ are a newer group of drugs that are thought to work by blocking enzymes in cells called histone deacetylases. Stopping these enzymes changes the amount of proteins made in cells, which affects the rate at which these cells can grow and divide. The FDA approved vorinostat, which showed a 30% response rate in patients with CTCL highly resistant to therapy; however, the duration of response is mixed and limited.⁴⁷ There are also serious side effects associated with treatment, including diarrhea, nausea, and thrombocytopenia (low platelets). Romidepsin, also approved by the FDA for treatment of CTCL,⁵⁰ showed 40% responses in CTCL highly resistant to therapy with higher duration of response, sometimes exceeding 20 months. Clearing of skin lesions and blood and nodal disease was also observed in patients with advanced forms of CTCL.

Chemotherapy

Most chemotherapy drugs for CTCL have been in use for decades, but several have been developed more recently. While these agents are frequently used in combination for the treatment of many cancers, they are mostly used in CTCL as “single agents,” meaning they are given independently. Chemotherapy agents used for CTCL include methotrexate (an anti-metabolite), liposomal doxorubicin,⁵¹ cyclophosphamide, and gemcitabine⁵² (agents that interfere with the DNA of cancer cells), pentostatin (a kind of antibiotic), chlorambucil, etoposide, temozolomide, and pralatrexate.⁵³ Combination chemotherapies are reserved for patients whose disease does not respond to single agents or for selected patients who have solid organ involvement. More information on the details of each agent can be found at www.clfoundation.org.

STEM CELL TRANSPLANTATION

If cutaneous lymphoma recurs after treatment and numerous other treatments have been tried and are no longer effective, a stem cell transplant may be considered. A stem cell is an immature cell in the bone marrow that can develop into mature blood cells. Stem cell transplantations are serious treatments that should not be taken lightly or considered early in a patient's disease journey and may not be suitable for all patients. For a stem cell transplant, patients are given high doses of chemotherapy or radiation, which kills stem cells in the bone marrow that develop into blood cells. The bone marrow cells are then replaced with the patient's own healthy stem cells stored prior to treatment (autologous stem cell transplantation) or those from a genetically matched donor (allogeneic stem cell transplantation). Of these 2 types of transplants, allogeneic stem cell transplantation is the only procedure used for patients with CTCL. These stem cells will form new, healthy white blood cells.

The ability to transplant stem cells allows physicians to use higher doses of chemotherapy to treat the cancer than the patient could normally tolerate. High-dose chemotherapy can destroy not only cancer cells, but also healthy bone marrow needed to maintain a patient's blood cells. After high-dose chemotherapy, which is sometimes given with radiation, blood cell counts are low, which increases a patient's risk of infection, and the ability of the blood to clot is reduced, which may increase the risk of bleeding. In addition, because the chemotherapy doses are higher, side effects from the chemotherapy may be more intense, especially immediately following transplantation and for a few weeks afterward. Patients with adverse health conditions or those who are more advanced in age may be at higher risk while undergoing this procedure.⁵⁴

Because patients with adverse health conditions and/or those with more advanced age are put at higher risk when their bone marrow is destroyed, they may be candidates for reduced-intensity transplantation (also called non-myeloablative or mini-allogeneic stem cell transplantation). During this procedure, reduced-intensity treatment kills some of the cancer cells and some of the bone marrow, suppressing the immune system just enough to allow the donor's stem cells to be taken up. The cells from both the donor and the patient exist together in the patient's body. Slowly, the donor's cells take over the

patient's bone marrow. These new donor cells may be capable of responding to the cutaneous lymphoma by helping the patient's immune system kill the cancer cells. This is a less intense approach than full stem cell transplantation. This approach is being investigated more thoroughly and may become adopted by more physicians for the treatment of a broader range of patients if it proves to be sufficiently effective in healthier patients.

With allogeneic stem cell transplantation, there is a risk of graft-versus-host disease (GVHD). Immune cells are able to detect "foreign" tissues. GVHD occurs when the new stem cells from the donor see the recipient's body cells as foreign and attack them. GVHD is a common condition that can either be a minor problem or a very serious one. It is usually controlled with drugs that suppress the immune cells to keep them from attacking the recipient's cells.

Stem cell transplantation is an area of great interest to many leaders in the field. There is significant discussion and investigation into determining the best approach for treating patients with CTCL.

SECTION 3: CUTANEOUS B-CELL LYMPHOMAS

Cutaneous B-cell lymphomas (CBCLs) occur less frequently than cutaneous T-cell lymphomas and account for 20%–25% of all cutaneous lymphomas. There are 4 primary types of CBCLs; the most common is primary cutaneous marginal zone B-cell lymphoma (PCMZL), followed by primary cutaneous follicle center lymphoma (PCFCL), primary cutaneous diffuse large B-cell lymphoma, leg type (PCLBCL-LT), and primary cutaneous diffuse large B-cell lymphoma, non-leg type (**Table 3**). Both PCMZL and PCFCL are slow-growing forms of CBCL, with an estimated 5-year survival rate of more than 95%.⁵⁵ On the other hand, while PCLBCL-LT is a rare type of CBCL, it grows into large tumors and is more likely to spread to other parts of the body. It has an estimated 5-year survival rate of approximately 59%.

Table 3. Types of CBCLs

Cutaneous B-Cell Lymphomas	Primary cutaneous follicle center lymphoma (PCFCL)
	Primary cutaneous marginal zone B-cell lymphoma (PCMZL)
	Primary cutaneous diffuse large B-cell lymphoma, leg type (PCLBCL-LT)
	Primary cutaneous diffuse large B-cell lymphoma, non-leg type

Classification

Although a staging system for CBCLs has not been developed yet, the World Health Organization and the European Organization for Research and Treatment of Cancer developed a system for classifying the 3 major CBCL entities (PCMZL, PCFCL, and PCLBCL-LT) in a TNM system that considers the amount of skin involvement of the tumor (T), involvement of the lymph nodes (N), and whether the tumor has metastasized (M) to involve other lymph nodes (**Table 4**).^{1,56} Comprehensive lymphoma staging with laboratory imaging and bone marrow biopsy are important for determining the prognosis.

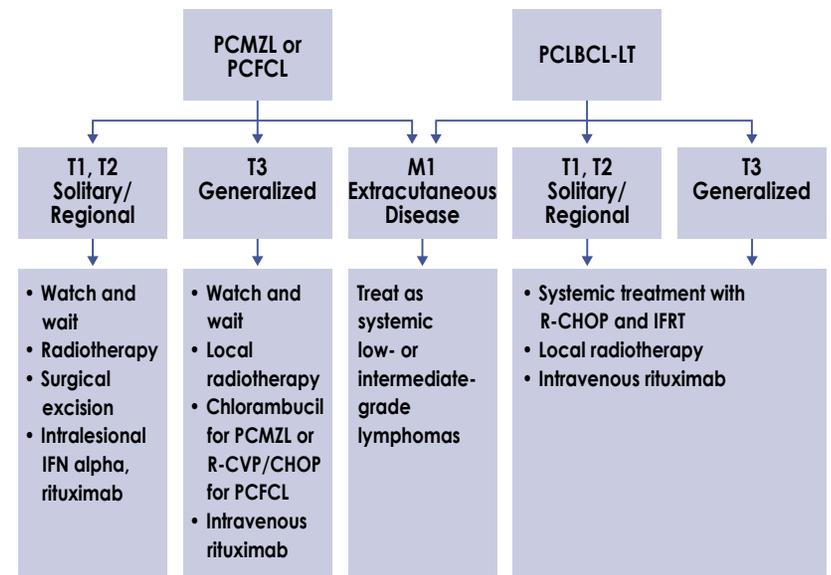
Table 4. TNM System for CBCLs⁵⁶

Tumor (T)
T1: Single sites of skin involvement
T2: Regional skin involvement, multiple lesions limited to 1 body region or 2 adjacent body regions
T3: Generalized skin involvement of 2 noncontiguous body regions or ≥ 3 body regions
Lymph Node Involvement (N)
N0: No lymph node involvement
N1: Involvement of 1 lymph node in the area of skin involvement
N2: Involvement of ≥ 2 lymph node regions or any lymph node not in the area of skin involvement
N3: Involvement of central lymph nodes
Metastasis (M)
M0: No evidence of extracutaneous non-lymph node disease
M1: Extracutaneous non-lymph node disease present

Treatment Options

The treatment for CBCL is based on the histology (what the cells look like under the microscope), where the lesions are located on the body, and the size and number of lesions.⁵⁵ Depending on these factors, the types of therapies can vary from a “watch and wait” approach to surgical removal of the lesion, intralesional therapy (injections into the lesion), radiation, biologic agents, or chemotherapy. Treatment options for CBCLs depend on which specific slow-growing or fast-growing disease is diagnosed and the TNM classification of the disease (**Figure 3**).

Figure 3. Treatment of CBCLs Is Based on the Type of Lymphoma and TNM Classification^{55,57}



IFN, interferon; IFRT, involved field radiotherapy; R-CHOP, rituximab, cyclophosphamide, hydroxy doxorubicin, Oncovin, and prednisone; R-CVP, rituximab, cyclophosphamide, vincristine, and prednisone.

The most commonly used therapies for CBCLs include surgical excision, radiation therapy, rituximab (Rituxan[®]), or systemic chemotherapy. The slow-growing forms of CBCL often relapse after treatment.

Watch and Wait

For patients with CBCL who are not experiencing symptoms and who have a low tumor burden, it is often recommended that treatment be reserved for when symptoms appear. This approach is called “watchful waiting” or “watch and wait.” Although patients do not initially receive anti-lymphoma treatment, the lymphoma is not being ignored. By contrast, the patients’ overall health and disease are monitored through regular checkup visits through an active observation strategy to closely follow the disease. Laboratory and imaging tests are performed just as often as follow-up evaluations for active treatment would be. When and if the patient begins to develop symptoms or there are signs that the disease is progressing, active treatment is started.

The advantages of watch and wait over active treatment for disease that is not progressing are that patients do not experience the many possible side effects associated with anti-cancer treatments, which can negatively impact patients' quality of life. Treatments are also associated with expenses and lifestyle burdens for the patient.

Surgical Excision

If only a few skin lesions are present, surgery can be performed to remove the lesions. Surgical excision is a commonly used treatment for CBCL^{57,58} and is usually sufficient to control stage T1 and T2 disease.⁵⁵ Surgical removal of lesions can completely remove the lesion and may prevent the same lesion from coming back. However, there is up to a 43% likelihood that the tumor will reappear or a new tumor will develop somewhere else.⁵⁷ In patients with a solitary or localized skin lesion, surgical excision is still considered a simple and effective choice of treatment.

Radiation Therapy

Radiation therapy has a high rate of effectiveness, with most patients having a complete response (100% clearance of skin lesions).^{57,58} However, about one-half of patients will experience a recurrence of the tumor, usually in another location.⁵⁸ Patients who have more than one lesion have a higher risk of recurrence than those with a single lesion.

External beam radiation therapy is a type of radiation where a special beam of radiation is aimed directly at the lesion. This type of therapy is a local therapy that only treats a specific area of the body. Patients are given a radiation dose through a special machine that rotates around the patient. This rotation allows the lesion to be accessed from different angles, which provides a more complete treatment. In one study of 18 patients, almost three-quarters of patients responded to a low-dose treatment.⁵⁹ However, some patients had to be retreated after a few months because the lesion remained or recurred.

Intralesional Therapy

When many small lesions are present, a small amount of drug—usually interferon,³⁷ corticosteroid, or the monoclonal antibody rituximab (Rituxan®; described on the next page)⁶⁰—can be injected directly into the lesion.⁵⁵ This

type of treatment has only been tested in a limited number of patients, so there is much that is still not well understood. However, in the limited studies that have been done, patients did not experience adverse reactions except pain at the injection site. The rates of complete remission with this treatment are high and, in some cases, lesions other than the one injected showed regression. However, recurrences were also common.

Chemotherapy

Multiagent chemotherapies used to treat non-Hodgkin B-cell lymphomas are also commonly used for CBCL. CVP (also called COP) and CHOP are alternate chemotherapies given for CBCLs. CVP is a combination therapy consisting of cyclophosphamide (Cytosan®), vincristine (Oncovin®), and prednisone. One of the most common chemotherapy regimens for CBCL is called CHOP, which is a combination of Cytosan® (cyclophosphamide), hydroxy doxorubicin (Adriamycin®), Oncovin® (vincristine), and prednisone. Most patients will respond to one of these chemotherapies, but the rates of relapse are high.⁵⁸

Chlorambucil, CVP, and CHOP are often given in combination with rituximab (Rituxan®).⁶¹ The response rates of these treatments is slightly better than those of the chemotherapy regimens used without rituximab.⁵⁸

Biologic Therapies

Rituximab was the first monoclonal antibody approved by the US Food and Drug Administration (FDA) for cancer. Rituximab targets the CD20 antigen, which is on the surface of both normal and abnormal cells. The CD20 molecule is a key target for anti-cancer therapies because it is highly expressed in most B-cell malignancies. Rituximab is the most common biologic drug used in lymphoma treatment regimens, either alone or in combination with standard chemotherapy regimens. For example, rituximab is used as first-line therapy with CHOP for aggressive B-cell lymphomas. With systemic rituximab therapy, there is a drop in the number of normal B cells as well as a decrease in the malignant lymphoma cells. This is a reasonable treatment for patients with multiple and/or symptomatic lesions, widespread disease, and involvement of sites that are not appropriate for radiotherapy, such as the head. Most patients respond to treatment for 4 to 39 months before relapse.^{55,62-64}

Radioimmunotherapy

Radioimmunotherapy (RIT) is a targeted delivery system to help kill cancerous cells. With this treatment, a monoclonal antibody is attached to a radioactive element. The monoclonal antibody recognizes the cancer cells and takes the radioactive element to the cancer cell to kill it.

RIT consists of a targeted therapy such as rituximab with a source of radiation attached. RIT acts as a “guided missile” to destroy cancer cells by attaching to the lymphoma cell and delivering small doses of medicine and radioactivity to it. There are 2 RIT products currently approved by the FDA: yttrium-90 (⁹⁰Y)-ibritumomab tiuxetan (Zevalin®)⁶⁵ and tositumomab (Bexxar). Both treatments recognize the specific antigen CD20 on the surface of cancer cells in patients with B-cell non-Hodgkin lymphoma. In general, ⁹⁰Y-ibritumomab tiuxetan and tositumomab cause fewer side effects than traditional chemotherapy agents. GlaxoSmithKline recently announced plans to discontinue the manufacture and sale of tositumomab in 2014, so the availability of this RIT will be limited. For both ⁹⁰Y-ibritumomab tiuxetan and tositumomab, serious complications may include skin infections, severe allergic reactions, and temporary lowering of blood cell counts. These drugs are usually given when patients do not respond to rituximab.

Antibiotics

The possibility of treating PCMZL associated with *B. burgdorferi* has been considered. However, the efficacy of antibiotic treatment is poorly documented.^{57,58} Some patients reported achieving a response following an antibiotic regimen. There is some evidence to suggest that cephalosporins might be superior to high-dose tetracyclines; however, this is based on very limited experience from a few patients.

SECTION 4: CLINICAL TRIALS

Scientific research is continuously evolving, and the best treatment options may change as new drugs and combination drug strategies are discovered. It is important for patients to check with their physician for any treatment updates that may have recently emerged. Patients who join clinical trials are given the best cancer treatment options available and more frequent examinations and disease evaluations. Patients may have the chance to receive a new treatment being considered, which could be better than the current standard of care, and contribute valuable information for improving cancer care. Sugar pills (also called placebos) are rarely used in cancer clinical trials and are never used in place of treatment.

As scientists learn more about what changes occur in the cells of patients with different cutaneous lymphomas, drugs are being developed and tested that can potentially target and stop or reverse these changes. There are a number of agents being investigated for the treatment of cutaneous lymphoma. There are also studies looking into new combinations of treatments and new formulations of existing treatments, and there are trials to study the efficacy of drugs currently approved to treat other types of cancer.

Proteasome inhibitors block the action of proteasomes, which are large cellular protein complexes that help destroy other cell proteins when they are no longer needed. Bortezomib (Velcade®) and carfilzomib (Kyprolis®) are proteasome inhibitors already approved for multiple myeloma that are undergoing clinical trials for treatment of cutaneous T-cell lymphomas (CTCLs). Also, newer proteasome inhibitors with improved safety profiles are in clinical development. Lenalidomide (Revlimid®), an immunomodulating agent that affects the way the immune system functions, is being investigated as a treatment for relapsed or refractory primary cutaneous large B-cell lymphoma, leg type, a rare form of the disease, as well as in recurrent/refractory CTCLs. Agents that target immune checkpoints that allow the body's immune system to fight cancer, such as anti-PD-1 and anti-PD-L1, are in development and being tested in cutaneous lymphoma. Studies are also underway to assess brentuximab vedotin

(Adcetris®), an immunoconjugate (monoclonal antibody with a chemotherapy drug attached) that targets a marker on the surface of T-cell and B-cell tumors. Once brentuximab vedotin enters cells, it releases a chemotherapy agent to destroy the cell.

As clinical trials reveal what agents are effective in the treatment of cutaneous lymphoma, new agents are being developed and studied in classes of drugs that have shown promise. Novel histone deacetylase (HDAC) inhibitors such as quisinostat (JNJ-26481585) for the treatment of CTCL and a novel pan-deacetylase inhibitor, panobinostat (LBH589), for treatment of CTCLs are undergoing clinical trials.

As researchers learn more about how cancer cells work, other classes of novel agents that target specific tumor cell signaling, transduction, proliferation, and survival pathways, such as agents that target phosphoinositide 3-kinase (PI3K) and mammalian target of rapamycin (mTOR), are also being developed and evaluated in preclinical and clinical trials. Ibrutinib (PCI-32765), an oral Bruton's tyrosine kinase inhibitor for treatment of B-cell malignancies, including cutaneous B-cell lymphoma, is being tested in clinical trials.

For more details on active clinical trials in CTCL, please visit the Cutaneous Lymphoma Foundation's website at www.clfoundation.org/clinicaltrials.

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