Understanding Treatment Options in Cutaneous Lymphoma

Second Edition

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

CUTANEOUS LYMPHOMA FOUNDATION

Welcome

Living with cutaneous lymphoma and understanding the range of treatments can be challenging. The good news is that there are many therapy 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 navigate the treatment landscape. Armed with knowledge and information, you can prepare proactively for discussions with your healthcare providers about the best choices for you.

In addition to this printed supplement, companion treatment pages are available on our website. New pages are added as treatments change (www.clfoundation.org). These pages provide additional details about individual therapies and give you easy access to information to understand your options and be comfortable making informed treatment decisions.

You are not alone. You are part of a knowledgeable, caring, capable, and compassionate community. The Cutaneous Lymphoma Foundation is here to support you.

We also provide a place where you can interact with others facing the same challenges as you via the Cutaneous Lymphoma Community Connections. Community Connections is an online community open exclusively to patients and their loved ones. The platform provides privacy and encourages open communication with others and directly with the staff from the Foundation. Visit www.clfoundation.org/connections to learn more. Please reach out any time we can be of additional help. We encourage you to connect with us by participating in an educational event, or directly by phone or email.

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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EDITORIAL REVIEW BOARD

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.

This booklet is structured as follows:

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 two main types of lymphocytes: B cells and T cells. Both of the lymphocytes work to fight infections in the body. When the genetic material (i.e., DNA) in lymphocytes mutates, it can lead to the transformation of normal lymphocytes to lymphoma cells.

Most types of lymphomas develop in the lymph nodes or bone marrow, where lymphocytes typically function. However, lymphocytes travel to many sites in the body during their normal function, including the skin. When lymphocytes residing in the skin develop mutations in their DNA resulting in cancer, it is called cutaneous lymphoma. There are several subtypes of cutaneous lymphomas, depending on the type of white blood cells that developed the original cancerous mutations. Cutaneous T-cell lymphomas (CTCLs) develop from transformed-carrying mutations. 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 stage, 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. Due to the lack of available treatments over the decades that are approved by the regulatory authorities (US, Canada & Europe primarily), some of the first FDA approved treatments were never approved for use in other countries, making comparison clinical trials challenging. As a result, 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 risks, benefits and alternatives 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 lymphomas.

It is important to understand that some cutaneous lymphomas will respond to a treatment temporarily, but the patient may not maintain a permanent remission. Long-term 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 stage, 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, retinoids, mechlorethamine, phototherapy, radiation, intralesional injection, and surgical removal (excision) of lesions. These kinds of treatments are applied to 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 which may lead 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. Detailed information relating to specific therapies are available at the Cutaneous Lymphoma Foundation's website at www.clfoundation.org.

SECTION 2: CUTANEOUS T-CELL LYMPHOMAS

2

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 CTCL's.[1] Primary cutaneous CD30+ lymphoproliferative disorders are the second most common group of CTCLs, accounting for about 20% of all cases; they can be benign entities (lymphomatoid papulosis, lymphoproliferative diseases) or fast growing lymphomas (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
	Folliculotropic mycosis fungoides (FMF)
	Lymphomatoid papulosis
	Primary cutaneous anaplastic large-cell lymphoma
	Subcutaneous panniculitis-like T-cell (αβ) 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.clfoundation.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 may include involvement of the blood, staging of these cutaneous lymphomas includes blood class (TNMB), this additional criteria is based on the presence of Sézary cells in the blood.[2] B_0 represents an absence of significant blood involvement, B_1 represents a low blood tumor burden, and B_2 represents a high blood tumor burden of Sézary syndrome.

Table 2. Staging of CTCLs by the TNM System[a]

<table>
<tr><th colspan="2" rowspan="2"></th><th colspan="4">Tumor (T)</th></tr>
<tr><th colspan="2">Lymph nodes (N)
Metastasis present (M)</th><th>T1: Limited patches/plaques (<10% BSA)</th><th>T2: Generalized patches/plaques limited to 1 or 2 contiguous body regions (≥10% BSA)</th><th>T3: Generalized skin involvement, or 1–2 tumors ≥1 cm in diameter</th><th>T4: ≥80% of BSA affected</th></tr>
<tr><td>N0: No nodes are clinically involved</td><td>M0</td><td>IA</td><td>IB</td><td rowspan="2">IIB</td><td>IIIA</td></tr>
<tr><td>N1: Nodes enlarged, histologically uninvolved</td><td>M0</td><td colspan="2">IIA</td><td>IIIB</td></tr>
<tr><td>N2-3: Nodes clinically normal (N2) or enlarged (N3), histologically involved</td><td>M0</td><td colspan="4">IVA</td></tr>
<tr><td>N0-3: Visceral involvement</td><td>M1</td><td colspan="4">IVB</td></tr>
</table>

[a] The darker grey-shaded regions indicate early-stage disease, whereas the lighter grey-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 (**Table 3**).

Table 3. Common Combination Therapies[a]

Common Combination Therapies	
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

[a]This list should not be considered exhaustive. Patients and physicians may decide on other combinations that are appropriate for their particular situation.

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.

Please go to the Cutaneous Lymphoma Foundation website for additional information on treatments at www.clfoundation.org/treatment-basics.

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 is shown in **Table 4**.[5]

Table 4. Treatment of CTCLs Based on the NCCN Guidelines[a]

Stage	IA	IB	IIA	IIB	IIIA	IIIB	IVA	IVB
Skin-Directed Therapies[b] → • Ointments, creams, or lotions • Phototherapy • Radiation								
				Systemic/Novel Therapies → • Extracorporeal photopheresis • Retinoids • HDAC inhibitors • Interferon • Denileukin diftitox • Single-agent/multiagent chemotherapy • Monoclonal antibodies				
				Stem Cell Transplant →				
Clinical Trials →								

[a]From the National Comprehensive Cancer Network Guidelines in Oncology; Non-Hodgkin Lymphomas, V3.2011.

[b]Patients with stage IA, IB, or IIA who have refractory disease may receive other types of treatments as well.

HDAC, histone deacetylase.

The European Organisation for Research and Treatment of Cancer (EORTC), an independent, non-governmental, non-profit cancer research organisation, established consensus recommendations for the treatment of cutaneous lymphoma in collaboration with the International Society for Cutaneous Lymphomas. The EORTC-Cutaneous Lymphoma Task Force reviews, recommends and publishes revisions to these treatment guidelines (www.eortc.org/research_field/cutaneous-lymphoma/).

Skin-Directed Therapies

Topical Corticosteroids

Topical corticosteroids (sometimes referred to simply as steroids) are frequently used in skin lymphomas and help with symptoms of pain, redness, and itch, and may also treat early lesions. 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. They have been mixed into a solution or compounded into ointments and used topically to treat CTCL.[10-12] 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.

Retinoids

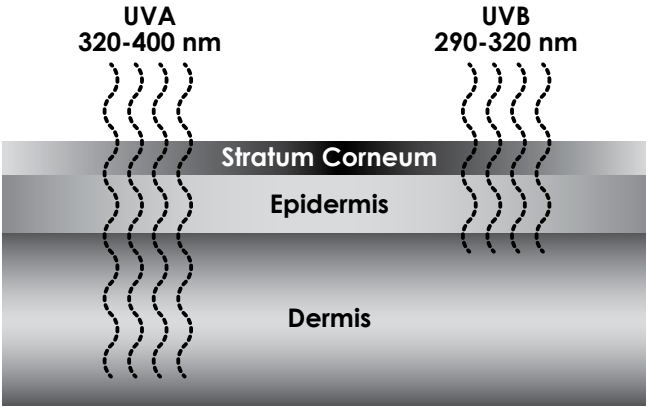
Retinoids are another, newer class of agents that are available as topical or oral formulations. These vitamin A-derived agents regulate a wide range of biological processes, including cell growth and death.[16] Retinoids have been shown to be effective at killing cancer cells and inhibit the ability 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 13). 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 (e.g., 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 light.[19] 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 1**). UVA and UVB both cause T cells to self-destruct.

Figure 1. Skin Penetration of UVA and UVB Light



Psoralen with UVA (320-400nm) (PUVA)

Psoralens are photosensitizing agents found in plants. 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]

Narrowband UVB (nbUVB) and Broadband Ultraviolet B (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 sunburn or temporary redness or burning of the skin. Prolonged phototherapy administration can increase overall skin cancer risk.

Fluorescent Light Therapy

Fluorescent light therapy is a treatment process using a new topical photosensitizing agent (synthetic hypericin) and fluorescent light. Positive results were announced for the FLASH Study, a phase 3 clinical trial in CTCL. SGX301 is a novel first-in-class photodynamic therapy utilizing safe visible light for activation. The active ingredient in SGX301 is synthetic hypericin, a potent photosensitizer that is topically applied to skin lesions, is taken up by the malignant T-cells, and then activated by fluorescent light 16 to 24 hours later. This treatment approach avoids the risk of secondary malignancies (including melanoma) inherent with the frequently employed DNA-damaging chemotherapeutic drugs and other photodynamic therapies that are dependent on ultraviolet exposure. In a published Phase 2 clinical study in CTCL, patients experienced a statistically significant ($p=0.04$) improvement with topical hypericin treatment in comparison to the placebo. SGX301 has received orphan drug and fast track designations from the US Food and Drug Administration (FDA), as well as orphan designation from the European Medicines Agency (EMA).[45,46]

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] This treatment penetrates only the superficial portions of the skin, limiting damage to underlying tissues. Although the treatment is usually very effective, many patients get their disease back slowly over time.

TSEB 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 can be used on its own or as part of a protocol for stem cell transplantation. TSEB therapy is also 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 brachyther-

apy 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 two 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 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 symptoms, 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.

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.

Targeted Therapy

Histone Deacetylases

Histone deacetylase (HDAC) inhibitors 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.

Chemotherapy

Chemotherapy tends to be reserved for the most aggressive or resistant skin lympho-

mas. Immunotherapies tend to be used before. 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.

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.[39]

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.

Notes

SECTION 3: CUTANEOUS B-CELL LYMPHOMAS

Cutaneous B-Cell Lymphoma Subtypes

Cutaneous B-cell lymphomas (CBCLs) occur less frequently than cutaneous T-cell lymphomas and account for 20%–25% of all cutaneous lymphomas. There are 3 primary types of CBCLs; the most common is primary cutaneous marginal zone B-cell lymphoma (PCMZL), followed by primary cutaneous follicle center lymphoma (PCFCL), and primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT) (**Table 5**). Both PCMZL and PCFCL are slow-growing forms of CBCL, with an estimated 5-year survival rate of more than 95% with low intensity therapy.[40] On the other hand, while PCDLBCL-LT is a rare type of CBCL, it grows into large tumors and is more likely to spread to other parts of the body. Despite its name, 10-15% of cases first appear in cutaneous sites other than the legs. It has an estimated 5-year survival rate of approximately 74% with intensive rituximab containing chemotherapy.[13]

Table 5. Types of CBCLs

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

Disease Classification

The International Society for Cutaneous Lymphomas and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer developed a system for classifying the 3 major CBCL entities (PCMZL, PCFCL, and PCDLBCL-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 sites other than the skin and lymph nodes (**Table 6**).[1,41] Depending on the patient's presentation, comprehensive lymphoma staging with blood tests, radiographic imaging, and bone marrow biopsy may be performed.

Table 6. TNM System for CBCLs[41]

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

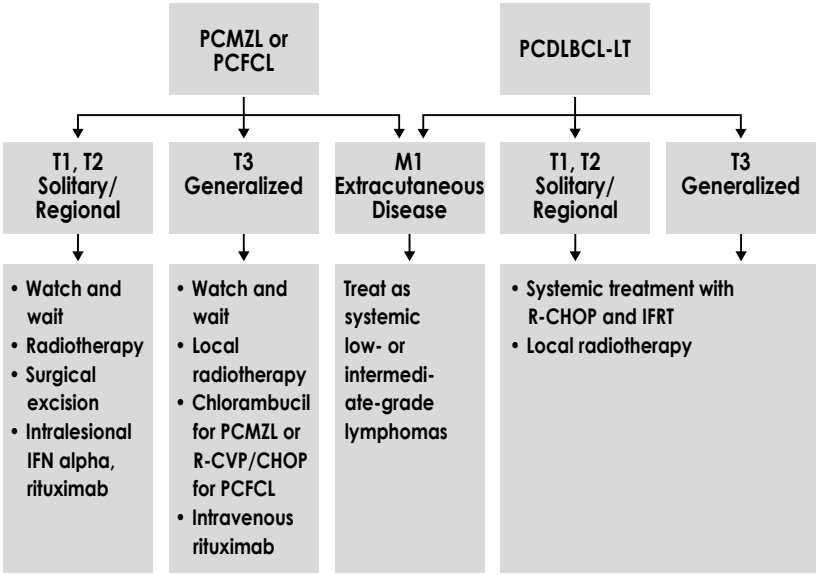
Treatment Options

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.[40] 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 2**).

The most commonly used therapies for the slow growing CBCLs (PCMZL, PCFCL) include surgical excision, radiation therapy, or observation. It is relatively common (30-46%)[14] for patients to develop recurrent lesions on other areas of the skin, often close to initial sites of involvement. When a relapse occurs, it is treated with the same therapeutic options, and prognosis continues to be excellent.

Primary cutaneous diffuse large B-cell lymphoma (PCDLBCL), leg-type, is a more aggressive lymphoma that is treated with multi-agent chemotherapy, such

Figure 2. Treatment of CBCLs is Based on the Type of Lymphoma and TNM Classification[40,42]



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

as R-CHOP, often followed by radiation to the localized site of disease involvement. The goal of treatment is cure and any relapse would require more aggressive chemotherapy.

Please go to the Cutaneous Lymphoma Foundation website for additional information on treatments at www.clfoundation.org/treatment-options-cutaneous-b-cell-lymphoma

Watch and Wait (Observation)

For patients with slow growing CBCL (PCMZL or PCFCL) who are not experiencing symptoms and who have a low tumor burden, observation without immediate therapy is reasonable. 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.

This approach is not used for PCDLBCL-LT.

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 slow growing CBCL (PCMZL, PCFCL)[42,43] and is usually sufficient to control stage T1 and T2 disease.[40] 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.[42] 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 for slow growing CBCL (PCMZL or PCFCL), with most patients having a complete response (100% clearance of skin lesions).[42,43] However, about one-half of patients will experience a recurrence of the tumor, usually in another location.[43] 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.[44] However, some patients had to be re-treated after a few months because the lesion remained or recurred.

Intralesional Therapy

When indolent CBCL is present, a small amount of a drug — usually corticosteroid, interferon, or an antibody drug — can be injected directly into the lesion.

In the limited studies that have been done with intralesional therapies for indolent CBCL, 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.[15] However, as with other therapies, recurrences were also common.

Chemotherapy

Classic chemotherapy tends to be reserved for the most aggressive (PCDLBCL-LT) or resistant skin lymphomas. The most commonly used regimen for PCDLBCL-LT is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone).

Biologic Therapies

Biologic therapy is a kind of 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. Rituximab is probably the most commonly used biologic therapy in the treatment of CBCL. This is a very well tolerated drug that is usually given intravenously or as an injection. This would more commonly be used as a single agent in a patient with a slow growing CBCL (PCFCL, PCMZL) that has relapsed multiple times or has more extensive skin involvement.

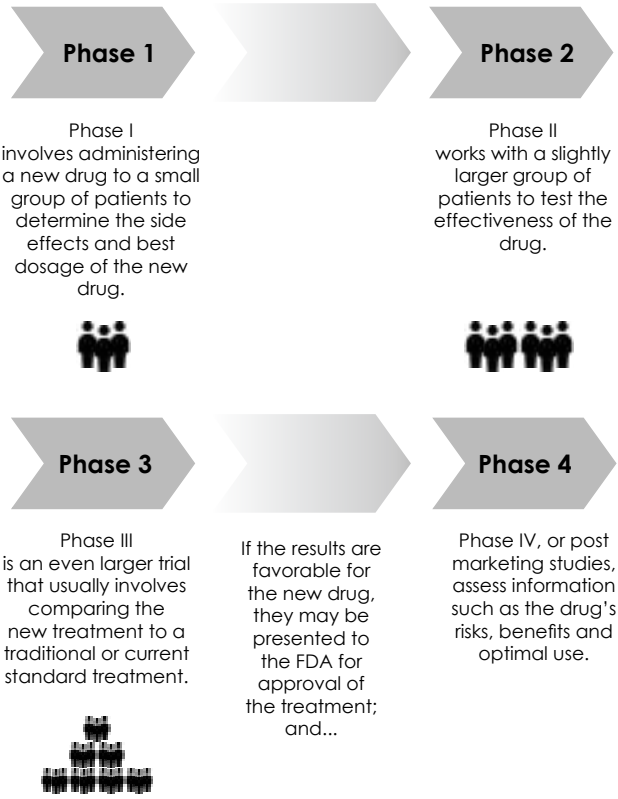
Antibiotics

The possibility of treating PCMZL associated with antibiotics has been considered. However, the efficacy of antibiotic treatment is poorly documented.[42,43] Some patients reported achieving a response following an antibiotic regimen.

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 close monitoring and more frequent examinations and disease evaluations. Patients will have the chance to receive a new treatment, 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.

Phases of a Clinical Trial



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.

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.

Clinical trials cannot happen without patients to participate. Involvement in a clinical trial can contribute greatly to medical research, helping both the participating patient and others with the same disease. Patients may get access to therapies not readily available and play a more active role in their own treatment.

For more details on active clinical trials in cutaneous lymphoma, please visit the Clinical Trial page under the Research and Publications section on the Cutaneous Lymphoma Foundation's website at www.clfoundation.org/directory.

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