Cutaneous T-Cell Lymphoma: Pathogenesis and Treatment

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Cutaneous T-cell lymphoma (CTCL) is a malignancy of a distinctive subset of T-helper cells designated “cutaneous T cells” because of their central role in the normal functioning of the skin immune system. Guided by

Introduction

Cutaneous T-cell lymphoma (CTCL) is an umbrella term used to describe a spectrum of clinical and histologic variants characterized by a malignant population of cutaneous T cells that have a predilection for the skin. As such, CTCL may be viewed as analogous to another life-threatening cancer that commonly begins in the skin—malignant melanoma. Whereas malignant melanoma is a cancer of melanocytes, a cell population that normally resides in the skin to perform an important function (eg, to protect against ultraviolet insult), CTCL is a malignancy of a distinctive subset of T cells of the skin immune system that normally patrol the skin’s environment (eg, to protect against infection).

The primary dermal and epidermal infiltrating cell in the skin of CTCL patients was first identified 20 years ago as having a T-helper phenotype.[1] Since that time, the advancement and application of sensitive tools of immunology and molecular biology have allowed for the organization of CTCL variants into a more logical classification than had previously been possible. The use of polymerase chain reaction (PCR) to amplify T-cell receptor genes has greatly enhanced our ability to detect the presence of a clonal population of T cells.[2] This has allowed for an earlier and more sensitive means of diagnosing CTCL, as well as the identification of several previously poorly classified CTCL variants.

Here again, CTCL is analogous to malignant melanoma, which can present with different, important-to-recognize variations, all of which reflect the dominant cellular features of the malignant melanocytes. Similarly, CTCL can present with a spectrum of clinical variations—all manifestations of the features of the dominant set of malignant cutaneous T cells. Nevertheless, it should be emphasized that even the most innocuous-appearing of these clinical variations (for example, focal patch/plaque involvement) are malignancies of cutaneous T cells.

Despite the advent of PCR technology, it may be difficult at times to make the diagnosis of CTCL or to pigeonhole cases into a particular CTCL clinical variant, for several reasons. First, there exist several clinical presentations that may demonstrate a predominant T-cell clone by molecular analysis or immunoassay but that only rarely progress to clear-cut CTCL. These entities have been termed premycotic CTCL, and may represent a premalignant state of CTCL.

Second, there is often clinical overlap between variants of CTCL and/or transformation from one variant to another. This transformation between the different clinical forms of CTCL may represent either the natural evolution of more aggressive subclones of the original malignant cutaneous T cell or partial reversal of disease progression by therapeutic inhibition of the most aggressive subclone(s).

Thus, a definitive diagnosis of CTCL can be made when the lymphoma shows evidence of T-cell clonality in addition to a clinical and histologic picture that is highly suggestive of one or more of the CTCL variants.

Skin Immune System and CTCL Pathogenesis

Emergence of the concept of a skin immune system[3] has shed light on the pathogenesis of CTCL. It is now clear that, in the normal state, T cells can circulate from the peripheral blood, through the selective barrier of endothelial cells bearing adhesion molecules into the dermis, to regional lymph nodes via the lymphatic vessels, and back into the peripheral circulation through high endothelial venules in the lymph-node cortex (Figure 1).

The key to this skin-blood-lymph node-specific cycling appears to be T-cell expression of the
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Cutaneous lymphocyte antigen (CLA) marker. Naive (ie, CD45Ra-positive) T cells that encounter their specific antigen in draining lymph nodes of the skin differentiate into activated/memory (ie, CD45Ro-positive) T cells and express CLA. Once returned to the blood, CLA-positive T cells can encounter their ligand E-selectin on dermal endothelial cells for recruitment back into the skin during an inflammatory response.

During normal homeostasis, this system performs an immunosurveillance function as part of the defense against cutaneous insults and infection. However, under abnormal circumstances, CLA-positive T cells mediate many inflammatory skin disorders, including psoriasis, atopic dermatitis, and cutaneous graft-vs-host disease.[4] Although often referred to as a primary cutaneous lymphoma to distinguish it from, eg, Hodgkin’s disease, which may eventually involve the skin, CTCL is perhaps more accurately viewed as a lymphoma arising from skin-homing, CLA-positive memory T cells of the skin immune system.

Understanding that CTCL is a malignancy of the skin immune system helps one to better understand the pathogenesis of this lymphoma. For example, while the insidious patch/plaque CTCL (discussed below) usually persists for years in patients in the absence of obvious leukemia (ie, with normal peripheral lymphocyte subset counts and without any abnormalities present by flow cytometry) or lymphadenopathy, it is incorrect to view this condition as a lymphoma confined to the skin. It is not unusual for such patients to present with multiple cutaneous patch and/or plaque lesions. Immunohistochemical and molecular analysis of infiltrating T cells demonstrates a common clonal population of CD4-positive, CD45Ro-positive memory T cells in each of the discrete lesions. (Each patch/plaque lesion of mycosis fungoides has the same clone.) The presence of multiple lesions with intervening normal skin is indirect evidence that, even in this early-stage patch/plaque disease, CTCL is a lymphoma of T cells of the skin immune system (ie, cycling among the skin, peripheral blood, and skin-draining lymph nodes).

In patients with early patch/plaque CTCL, in whom the vast majority of malignant T cells home to and reside in the skin, it is possible, using PCR, to detect the same malignant clone in the peripheral blood and lymph nodes, thus confirming that this is a systemic lymphoma.[5] At this stage, skin-directed therapy (eg, psoralen plus ultraviolet A light [PUVA], electron-beam radiation, or topical carmustine [BCNU]) may be sufficient to prevent disease progression or induce apparent cure. This suggests the strong tendency of the malignant T cells to home to the skin, as well as their dependence on the cutaneous environment to maintain their growth. In more advanced stages of CTCL, the malignant T cells apparently lose their dependence on the skin environment, and more of them are found in the peripheral blood (ie, leukemic CTCL) and lymph nodes. Under such circumstances, skin-directed therapies alone are insufficient to control disease, and systemic therapy is warranted.

While the presence of a malignant clone of CLA-positive, CD4-positive cutaneous T cells can be demonstrated in the skin of patients with patch/plaque CTCL, it is important to note that these cells usually represent a minority of the T-cell dermal infiltrate, which includes other nonmalignant activated CD4-positive, as well as CD8-positive, T cells. Several clinical findings have supported the hypothesis that the malignant cells of CTCL are immunogenic. CD8-positive tumor-infiltrating lymphocytes present within CTCL lesions tend to be more plentiful in early-stage disease. Their proportion correlates positively with improved survival, suggesting that they may exert an antitumor host response.[6]

In addition, cyclosporine (Neoral, Sandimmune), a potent immunosuppressive agent that is specific for T cells, can promote rapid disease progression, possibly through the downregulation of antitumor T cells.[7,8] Perhaps most importantly, results of treatment of CTCL with photopheresis (discussed below) are consistent with the stimulation of an antitumor immune response.[9]

Clinical and Histologic Features

Parapsoriasis

The terminology and delineation of the various forms of parapsoriasis are unclear. A pattern of large, atrophic, erythematous plaques on the trunk with histologic features that are nondiagnostic of CTCL has been called large-plaque parapsoriasis. Treatment of large-plaque parapsoriasis, most effectively with PUVA, will generally clear these lesions. The apparent progression over years of a portion of these cases to obvious CTCL, if left untreated, and the ability to detect clonal dominance by PCR, suggests that large-plaque parapsoriasis is, in fact, patch/plaque CTCL from the outset, rather than a premalignant condition.[10-12]
This fact notwithstanding, it appears that patients who present with much smaller lesions, as in so-called small-plaque parapsoriasis, do not readily progress to CTCL, although a dominant T-cell clone may be detectable by PCR.\(^5\),\(^{13}\) Since T-cell clonality may be detectable in several other T-cell-mediated inflammatory conditions of the skin, such as pityriasis lichenoides et varioliformis acute (PLEVA; Mucha-Habermann disease)\(^{14}\), without any evidence of progression to CTCL, molecular testing must be interpreted in light of the clinical and histologic findings.

**Patch/Plaque CTCL Variants**

- **Classic Patch/Plaque CTCL**—The most common variant of CTCL, classic patch/plaque CTCL (also known as, mycosis fungoides\(^*)\) presents with single or multiple, erythematous patches or thin plaque (Figure 2). Lesions are typically well defined and round, oval, or arcuate in shape, but many have nondiscrete borders. Color may vary from bright red, to red-brown, to orange, to pink, to violaceous. In early mycosis fungoides, there is a predilection for involvement of non-sun-exposed areas (eg, buttocks, medial thighs, and breasts), although any area of skin may be affected. Disease progression is slow, and, thus, it is not uncommon for patch/plaque CTCL to go undiagnosed for over 10 years.

Patch/plaque CTCL is most often misdiagnosed as chronic contact dermatitis, atopic dermatitis, or psoriasis. When the diagnosis of such conditions becomes uncertain due to atypical clinical findings or poor response to typical treatment modalities, the possibility of patch/plaque CTCL should be thoroughly investigated by performing multiple cutaneous biopsies every 3 months until a definitive diagnosis can be made. Patch lesions are present for months to years before progressing to plaques. More often found on the trunk, plaques may become variably indurated, may coalesce to form larger plaques, or may undergo partial involution to leave residual arcuate or other figurate plaques.

Patients with patch/plaque CTCL may manifest lesions of hypopigmentation, atrophy, poikiloderma, or alopecia mucinosa. Patients in whom such lesions predominate over patch/plaque lesions are considered to have one of the clinicopathologic variants of patch/plaque CTCL (Table 1).

The major histologic features of patch/plaque CTCL\(^{15}\) are a lymphocytic infiltrate in the superficial dermis, with evidence of epidermotropism (exocytosis), and formation of epidermal collections of several or more lymphocytes termed \[^{[}Pautrier\]s microabscesses.\[^{[}\] The lymphocytes may exhibit varying degrees of atypia (ie, with pleomorphic, hyperchromatic, and convoluted nuclei). Many dermatopathologists will summarize the histologic findings into various categories, such as \[^{[}diagnostic of,\[^{[} consistent with,\[^{[} or \[^{[}suggestive of\[^{[} CTCL, depending on the number and degree of characteristic features observed. Multiple biopsies from various lesions at various times will increase the likelihood of making an accurate diagnosis. In any event, a clinicopathologic correlation is strongly warranted, especially given the degree of clinical and histologic variation that may occur in CTCL.

**Clinicohistologic Variants of Patch/Plaque CTCL**

- **Hypopigmented Patch/Plaque CTCL**—The development of hypopigmented patches, typically in dark-skinned individuals, likely allows for earlier detection of CTCL than would have occurred otherwise (Figure 3). While recurrences are common, they have a benign course within most patients, showing an excellent response to phototherapy with repigmentation.\(^{16,17}\)

Hypopigmented patch/plaque CTCL has been reported in Caucasians as well.\(^{18-20}\) Of note, many of these cases occur in individuals under 20 years of age,\(^{19,20}\) and, thus, such patients may be initially misdiagnosed as having vitiligo, pityriasis alba, or postinflammatory hypopigmentation.

- **Granulomatous Slack Skin**—Although it is not uncommon for granulomatous inflammation to be present on histologic analysis in patients with CTCL, granulomatous slack skin is a rare form characterized clinically by the development of circumscribed, erythematous, lax skin lesions, especially in the body folds, and histologically by a granulomatous T-cell infiltrate and loss of elastic fibers.\(^{21}\) Granulomatous slack skin has also been associated with other antecedent or subsequent lymphomas, including Hodgkin\[^{[}s disease.\[^{[}\] Lax skin changes are permanent, despite adequate treatment of the lymphoma. Molecular studies have confirmed the presence of the T-cell malignant clone in these lesions.\(^{23,24}\)

- **Pagetoid reticulosis (Woringer-Kolopp disease)** presents as a slow-growing, chronic, solitary plaque. Although the indolent nature of pagetoid reticulosis has led to controversy over whether this represents a true variant of patch/plaque CTCL, these lesions demonstrate histologic and immunophenotypic findings of CTCL and T-cell clonality by molecular analysis.\(^{25}\)

Histologically, pagetoid reticulosis lesions demonstrate a marked epidermotropism of lymphomatous T cells, and must be distinguished from Paget\[^{[}s disease and pagetoid melanoma. The malignant T cells demonstrate a marked expression of CLA (a ligand for E-selectin expressed on endothelial
cells), as well as integrin α<sub>e</sub>β<sub>7</sub> (a ligand for E-cadherin expressed on keratinocytes).[26]

Poikilodermatous Patch/Plaque CTCL

In this variant, lesions of patch/plaque CTCL predominantly demonstrate the clinical features of a pigmented purpura, with varying degrees of atrophy, hypopigmentation, and hyperpigmentation.[27] The buttocks and trunk may be particularly affected, especially the skinfolds in these areas (Figure 4). The differential diagnosis includes steroid atrophy, collagen vascular disease, and capillaritis.

Alopecia Mucinosa

Patients with alopecia mucinosa present with clusters of erythematous or flesh-colored follicular papules with associated hair loss (Figure 5); these follicular plaques may coalesce into cobblestone-like or nodular plaques. Alopecia mucinosa lesions demonstrate the histologic pattern of follicular mucinosis, characterized by accumulation of mucin (ie, mucopolysaccharides) in sebaceous glands and outer root sheaths of follicles. Because alopecia mucinosis, and its histologic counterpart follicular mucinosis, may occur as a reaction pattern in nonmalignant dermatoses (eg, chronic atopic dermatitis), confirming the diagnosis of CTCL is often difficult and may take years.[28-30] Thus, close clinical follow-up and repeat biopsies for histologic examination and T-cell rearrangement status are warranted in patients with alopecia mucinosa.

Pilotropic (Follicular) CTCL

Like patients with alopecia mucinosa, those with pilotropic CTCL initially manifest follicular papules and patchy alopecia. However, patients with pilotropic CTCL also develop comedo-like lesions and multiple epidermoid cysts.[31,32] Histologically, lesions demonstrate folliculotropism of atypical lymphocytes, sometimes forming follicular Pautrier’s microabscesses, without epidermotropism and follicular mucinosis.

Immunophenotypic Variants of CTCL

Immunohistochemical phenotyping and molecular analysis of T-cell gene rearrangements have demonstrated that most forms of CTCL have an activated/memory T-helper cell phenotype as the malignant clone and a surface expression pattern characterized by surface expression of CD3, CD4, CD8, CD45Ro, and T-cell receptor-alpha-beta (TCR-alpha-beta). However, several other immunophenotypic patterns have been observed in CTCL.

CD8-Positive T-Cell Lymphoma (Cytotoxic T-Cell Lymphoma)

Rare patients with CTCL have been reported with a malignant T-cell clone of the CD8-positive immunophenotype. In such patients, the lymphoma may follow a course not dissimilar to that of the classic patch/plaque CTCL and its variants that are typically mediated by malignant, CD4-positive T cells. However, several CD8-positive lymphomas have demonstrated a more aggressive course, characterized by visceral metastases and a median survival of less than 3 years, and, thus, likely represent a distinct variant.[33]

Gamma-Delta T-cell Lymphoma

The vast majority of the peripheral T cells utilize rearranged alpha and beta TCR genes to produce a heterodimeric alpha-beta receptor and are CD4 positive or CD8 positive. However, a smaller population of these cells utilizes delta and gamma genes and are double-negative (ie, CD4 negative and CD8 negative). Cases of gamma-delta T-cell CTCL have demonstrated that the malignant T cells are epidermotropic, cytolytic, and capable of producing interferon-gamma[34,35] but do not likely comprise a distinct clinicopathologic entity.

Erythrodermic CTCL

Patients with erythrodermic CTCL may present with an exfoliating, diffuse, bright red cutaneous erythema (ie, erythroderma), which apparently develops de novo or progresses from established patch/plaque CTCL. The skin may be completely involved, or there may be islands of skin that are spared. The patient complains of fever and chills, intense pruritis, and malaise. Multiple biopsies may be necessary to confirm the diagnosis, since evidence of epidermotropism varies and secondary changes of epidermal hyperplasia due to scratching can cloud the findings. The term Sézary syndrome is used to describe the combination of frank lymphocytic leukemia, lymphadenopathy, and generalized exfoliative erythroderma. Patients with this syndrome typically demonstrate enlarged, hyperchromatic, malignant T cells in the peripheral circulation and on skin histology, and the diagnosis of CTCL may be confirmed by Southern hybridization analysis of the TCR genes. In erythrodermic patients without lymphocytosis, it is imperative to perform the molecular test of TCR rearrangement status (ie, by PCR analysis of the peripheral blood or skin) since the differential diagnosis of erythroderma includes severe forms of psoriasis, atopic dermatitis, and allergic drug reaction.

Tumor-Stage CTCL

Lymphomatous tumors may develop anywhere on the skin in patients with any form of CTCL. The most common scenario is the development of nodules and tumors arising within preexisting affected patches or plaques, suggesting that affected lesions have given rise to more aggressive malignant
subclones, or that the local environment (eg, antitumor immune response) has been altered. Newly forming tumors in the absence of any previous lesion suggest direct hematologic seeding of the skin, but may have arisen from a subclinical patch. Histologically, a dense dermal polymorphous infiltrate may be seen extending into the subcutaneous tissue. There may be a thin area of sparing (ie, grenz zone) in the uppermost dermis just below to the epidermal junction, even if there is overlying epidermotropic involvement. Other cases may show monomorphic lymphocytic infiltrates with varying degrees of nuclear atypia. In such cases, a secondary B-cell lymphoma should be ruled out.

Non-Patch/Plaque CTCL

Rarely, patients may present with CTCL tumors without previous clinical or histologic evidence of patch/plaque CTCL.[36] Such patients can be divided on the basis of CD30 (Ki-1) expression (ie, CD30-positive vs CD30-negative T-cell lymphoma), and cytomorphology (ie, pleomorphic small-cell vs medium-cell CTCL).

- **CD30-Positive vs CD30-Negative CTCL** Patients with tumor-stage variants of CTCL present with tumors showing central ulceration, and must be distinguished clinically and histologically as lymphomatoid papulosis.[37,38] Although the presence of the CD30-positive marker on tumor cells typically suggests a better prognosis, and a small percentage of CD30-positive lymphomas will undergo spontaneous resolution,[39] a more aggressive behavior is possible.[40] Until further delineation can be made to reliably predict prognosis, such cases are best treated with aggressive radiotherapy from the outset.

- **Pleomorphic Small-Cell vs Medium-Cell vs Large-Cell CTCL** These variants are distinct, in that patients develop dermal and subcutaneous infiltrates of malignant pleomorphic small-, medium-, or large-sized T cells, manifesting clinically as red-purple nodules and tumors. Typically, there is no coincident or preceding patch/plaque disease. Small- and medium-sized variants tend to behave like low-grade lymphomas and have a prognosis better than that of CD30-negative large-cell variants.[41]

**Pathogenesis: A Working Hypothesis**

The mechanisms by which normal cutaneous T cells are transformed into malignant clones of CTCL are unknown. It is noteworthy that adult T-cell lymphoma/leukemia (ATLL), which closely resembles CTCL with respect to primary involvement of the epidermis and malignant T-cell phenotype, is endemic in southwestern Japan and the Caribbean region and is caused by the retrovirus human T-cell lymphotrophic virus type 1 (HTLV-1).[42] Although no clear association of CTCL with a related retrovirus has yet been established, the similarities between ATLL and CTCL raise the possibility that an as yet unidentified retrovirus could play an etiologic role in the latter lymphoma as well. If this proves to be the case, the epidemiology of CTCL would differ from that of ATLL, since no geographic localization of the former has been evident, nor does spousal transmission appear to be a factor. The tendency of malignant CTCL cells to congregate around Langerhans cells in the epidermis early in the evolution of the malignancy[43] suggests that presentation of antigens to CD4-positive T cells may contribute to the proliferation of CTCL cells. If so, it remains necessary to explain the localization of the initial plaques to defined, well-demarcated specific lesions. If antigen presentation is a pathogenic factor, therefore, the stimulant must be present in significant quantity only in very discrete sites.

We suggest the working hypothesis that a retrovirus, of very low contagious potential, may reside in the Langerhans cells of such discrete skin sites. Cutaneous T cells with specificity for antigenic determinants of these retroviruses or their protein products may be stimulated by the Langerhans cells to proliferate in the microenvironment of the epidermis. As these cutaneous T cells proliferate, they may become susceptible to the transforming properties of the occult retrovirus, with an occasional T cell then giving rise to a CTCL clone.

This working hypothesis is attractive for several reasons. It not only may account for the pathognomonic localization of proliferating malignant cells in clusters in the epidermis around Langerhans cells but also may explain why the lesions tend to recur in exactly the same spots in which they were originally localized. Finally, this hypothesis suggests a possible explanation for why ultraviolet light exposure, which can greatly diminish the number of Langerhans cells, may be of marked therapeutic benefit in early disease. It will be important to test this and other hypotheses in the near future to aid in the refinement of staging and therapeutic approaches to CTCL.

**Staging**
Unlike most other lymphomas, the staging of CTCL is complicated by the fact that it is a lymphoma of T cells of the skin immune system and, as such, involves the skin, blood, and lymph nodes even in the earliest stages of disease. The widely used TNM classification (Table 2) was adopted by the North American Mycosis Fungoides Cooperative Study Group in 1975 and was subsequently modified by the Cutaneous T-Cell Lymphoma Workshop. In addition to TNM ratings, a B (for peripheral blood) rating is typically given, emphasizing the propensity for leukemic involvement in CTCL. Recently, Zackheim et al[44] reported on the survival of 489 patients with CTCL based on tumor stage at diagnosis. For patients with stage T2, T3, or T4 disease, the 10-year survival rates relative to aged-matched controls were 67%, 39%, and 41%, respectively. Interestingly, no statistically significant difference in survival was noted for T1 patients relative to disease-free age-matched controls. This speaks to the insidious nature of limited patch/plaque CTCL and to the likely existence of an effective antitumor immune response in early disease. Whether longer follow-up studies may eventually bear out a survival difference for T1 patients, especially if one considers age at presentation, has yet to be determined. Several studies have shown that prognosis is independently affected by the level of tumor burden, cellular atypia, and immunocompetence of the patient.

**Treatment**

An understanding of the pathogenesis of CTCL helps guide the selection of therapy (Table 3). In our working hypothesis of pathogenesis (see above), the malignant T cells are critically dependent on stimulation by epidermal Langerhans cells. Thus, while the presence of a T-cell clone may be demonstrable even in early-stage patch/plaque CTCL, skin-directed therapy is highly effective. Conversely, as the T-cell clone grows more independent of the need for this stimulation, and is more likely to cause leukemia (as in Sézary syndrome), systemic therapies, including immunomodulatory and cytotoxic treatments, must be utilized.

Commonly used treatments for early-stage (patch/plaque) CTCL include topical corticosteroids, PUVA and ultraviolet light B (UVB). Total-skin electron-beam therapy is indicated for widespread infiltrated plaque and tumor-stage disease. Low-dose methotrexate is often useful for resistant patch/plaque CTCL and erythrodermic CTCL. Interferon-alfa is indicated for methotrexate failures and recurrent tumors following total-skin electron-beam therapy. Photopheresis may be helpful for early-stage erythrodermic CTCL but is very costly. Retinoids may be of value for early and moderately advanced CTCL, particularly in combination with other therapies, such as interferon-alfa and PUVA. Systemic disease usually requires combination chemotherapy, such as that used for non-Hodgkin’s lymphoma. However, responses are usually short lived.

**Skin-Directed Therapy**

For limited (< 20% body surface area) patch/plaque CTCL, topical chemotherapeutic agents (eg, mechlorethamine [Mustargen], carmustine) have a proven track record of efficacy.[45,46] These agents are limited by the development of irritant and allergic contact dermatitis. In addition, several studies have shown the utility of topical corticosteroids and topical retinoids in the management of early patch/plaque CTCL. However, we recommend PUVA or UVB as a first-line therapy for most cases of patch/plaque CTCL, since phototherapy treats even subclinical lesions. Treatments can be tapered slowly from three times weekly to once monthly. For patients whose disease proves resistant to phototherapy or who have more extensive (> 50%) body surface involvement, total-skin electron-beam radiotherapy may be warranted. Despite the fact that early CTCL forms appear to depend on the skin environment for continued stimulation and are therefore treatable with skin-directed therapies, close patient monitoring for disease progression is essential.

**Systemic Therapy**

Cutaneous T-cell lymphoma is a malignancy of slow-growing, mature T cells that continue to function, as evidenced by their ability to (1) cycle between skin, blood, and lymph node compartments; (2) secrete and respond to cytokines; and (3) interact with other cells of the immune system (eg, CD8-positive T cells, Langerhans cells). For these reasons, CTCL responds to immunomodulatory treatments.

[Photopheresis](#), or extracorporeal photochemotherapy, first demonstrated efficacy in the treatment of Sézary syndrome in 1980.[46] The therapy consists of removing a portion of the patient’s blood via an intravenous needle, separating out the leukocytes by centrifugation, and
exposing these cells to UVA light in the presence of psoralen. The photochemically altered cells, as well as the untreated red blood cell and plasma portion, are reininfused through the same intravenous needle from which they were obtained. The observation that patients can attain a complete remission with photopheresis alone, despite the fact that approximately 10% of the peripheral leukocytes are exposed to treatment during each treatment session (typically given on 2 consecutive days every 4 weeks), is consistent with a tumor vaccination mechanism.

- **Bexarotene**: Oral bexarotene (Targretin) is a retinoic X receptor (RXR)-specific retinoid that has demonstrated efficacy when used as monotherapy in CTCL regardless of stage, and was recently approved by the Food and Drug Administration (FDA) for the treatment of CTCL. For patients who do not respond to or cannot tolerate skin-directed therapies such as PUVA or electron-beam therapy, oral bexarotene is a practical alternative.

While patients with erythrodermic CTCL will show skin improvement when treated with bexarotene, it is important to note that the drug has a limited effect on any associated leukemia. Close monitoring for hypertriglyceridemia and hypothyroidism is necessary. The role of bexarotene in combination therapy has yet to be determined.

- **DAB\(_{389}\)IL-2 (Ontak)**, a “magic bullet” of a 389-amino acid portion of diphtheria toxin conjugated to interleukin-2 (IL-2), was recently approved by the FDA for the treatment of CTCL. Since CTCL is a lymphoma of mature, activated T cells, the malignant cells often express the IL-2 receptor. Such cells readily take up the DAB\(_{389}\)IL-2 molecules; once inside the malignant cells, the toxin is cytoplasmically cleaved and can inhibit cell protein synthesis. DAB\(_{389}\)IL-2 is administered intravenously at a dose of 9 or 18 mg/kg/d for 5 days every 3 weeks for up to 8 cycles. DAB\(_{389}\)IL-2 demonstrated a 10% complete response rate and a 30% partial response rate, in patients with CTCL who had received a median of five prior therapies. Toxicities of hypersensitivity reactions and capillary leak syndrome can be attenuated through premedication with systemic corticosteroids.

**Summary and Future Directions**

Even in its earliest stages, CTCL involves the skin, lymph nodes, and the blood because it is a lymphoma of T cells that normally cycle within these compartments. A growing understanding of the factors that stimulate the malignant T cells to become independent of the skin’s stimulation, and an increase in the ability to detect clonal T cells within the different tissues, will help shape a more refined staging system and more effective therapies for this unique lymphoma.

The principal lesson to be learned from the clinical success of photopheresis in treating CTCL is that the malignant T cells bear clinically relevant tumor-specific antigens, which occasionally can be used to stimulate quite potent antitumor responses. Perhaps the greatest challenge of the immediate future for CTCL researchers is to learn how to use these tumor antigens in immunotherapeutic regimens in order to help a larger percentage of the patients afflicted with this malignancy. A clear understanding of the distinctive biological features of malignant CTCL cells will likely lead to major future advances in our ability to manage this serious lymphoma.

*Although still widely used, the term “mycosis fungoides” is in our opinion outdated and misleading. Coined long before the discovery of the T cell, mycosis fungoides is an obvious misnomer in that this condition is not pathogenically related to a fungal infection and clinically only remotely resembles such. Because mycosis fungoides connotes a benign entity and deemphasizes that this condition is a lymphoma, the term “patch/plaque CTCL” will be used throughout this review.*

**References:**


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