Chapter 14
Cutaneous T-Cell Lymphoma: Mycosis Fungoides and Sézary Syndrome

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Disease Overview

Cutaneous T-cell lymphomas (CTCLs) include a heterogeneous group of rare, extranodal, non-Hodgkin lymphomas (NHLs), primarily defined by malignant T-lymphocyte invasion of the skin. The clinical presentation ranges from a single patch or plaque to erythroderma involving over 80% of the body or widespread cutaneous tumors. They are almost always pruritic in nature, which can be associated with interrupted sleep, weight loss, and depression [1]. CTCL is a chronic disease for which, in most instances, there is no cure; therefore, patients typically require long-term therapy often with a combination of topical and systemic medications.

The 2017 World Health Organization (WHO) classification of lymphoid neoplasms expanded the CTCL classification to include 13 distinct clinical entities [2, 3]. Here we will focus on the most common: mycosis fungoides (MF) and its

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leukemic variant, Sézary syndrome (SS). The cutaneous CD30+ lymphoproliferative disorders (primary cutaneous anaplastic large-cell lymphoma and lymphomatoid papulosis) are important to distinguish from MF but are not fully addressed here.

Mycosis fungoides (MF) was first described in 1825 in a patient with diffuse patches, plaques, and mushroomlike tumors of the skin [4]. Almost a century later, Sézary and Bouvrain described a patient with generalized exfoliative erythroderma and abnormal lymphoid cells in the blood, a condition that eventually became known as Sézary syndrome [5]. It was not until 1975 that CTCLs were defined as a distinct clinical entity rather than a cutaneous manifestation of systemic peripheral T-cell lymphomas [6].

CTCLs are rare lymphomas with a reported annual incidence in the United States of 5.6–6.4 cases per million persons [7]. It has been hypothesized that persistent antigenic stimulation by allergens may be associated with the development of CTCL, particularly MF [8], but epidemiologic studies have not shown a definitive association between environmental exposures and MF [9–11]. However, MF/SS incidence does increase with age with a median age at diagnosis in the mid-50s. Males are affected almost twice as often as females, and there is a higher rate observed in African Americans [7].

Immunopathogenesis

CTCL is characterized by clonal expansion of mature, tissue-resident T-cells. Upon encountering an antigen, naïve T-cells residing in lymph nodes draining from the skin undergo clonal expansion and differentiation into a variety of effector and memory T-cells. During this process, T-cells induce the expression of an E-selectin ligand cutaneous lymphocyte antigen as well as a variety of chemokine receptors (CCR4, CCR8, CXCR6, CCR10) necessary for migration to the skin [12–14]. Effector T-cells migrate to extranodal sites such as the skin, where a small subset of differentiated T-cells will remain as tissue-resident memory cells (T_{RM}). While the majority of T-cells undergoing clonal expansion differentiate into effector T-cells and migrate to the skin, a subset of T-cells differentiate into central memory T-cells (T_{CM}), which retain the ability to access the peripheral blood via CCR7 and L-selectin upregulation [15–17].

Immunophenotyping studies in patients with CTCL have shown that CTCL subtypes arise from separate mature T-cell compartments. Previously, it was believed that SS represented a transformation from MF; however, recent data with respect to molecular expression and genomic alteration provides evidence to the contrary. Biopsy samples from patients with MF have demonstrated clonal T-cell profiles consistent with a T_{RM} phenotype, strongly expressing CCR4 and E-selectin ligand cutaneous lymphocyte antigen [18]. In contrast to a T_{RM} phenotype, patients with SS, which is characterized by leukemic involvement, appear to express CCR7 and L-selectin, resembling the phenotype of T_{CM}. This further supports the theory of separate disease states arising from separate cells of origin. Further evidence sup-

porting subtype-specific cell of origin can be found in gene expression profiling with comparative genomic hybridization. There appears to be a strong discordance with respect to genomic alterations when comparing MF to SS as well as cutaneous anaplastic large-cell lymphoma [19, 20]. Given that disease subtypes within CTCL may develop from specific and differing cells of origin, this may provide rationale for differing clinical presentations, disease behavior, and response to therapy.

Clinical and Histopathologic Features

The diagnosis of MF/SS can be difficult to make and requires consideration of clinical presentation plus histopathologic features. Given the variable clinical presentations, the differential diagnosis for these patients may include psoriasiform dermatitides (e.g., psoriasis, pityriasis rubra pilaris, seborrheic dermatitis), spongiotic dermatitides (e.g., eczema, allergic contact dermatitis), infectious processes (e.g., tinea), or drug eruptions [21]. Initially, limited skin involvement is often presumptively treated as eczema, psoriasis, or other inflammatory dermatitis based on physical appearance. Even once MF is suspected, multiple biopsies are often required to make a definitive diagnosis. The median time from onset of symptoms to diagnosis of MF is approximately 4 years [22].

Mycosis Fungoides

Mycosis fungoides is the most common CTCL and represents approximately 50% of cases. The majority of lesions present in relatively sun-protected locations (e.g., hip girdle, buttocks, skinfolds) [1]. Classic histopathologic findings for MF include epidermotropism (lymphocytes present in the epidermis without spongiosis) as well as formation of epidermal clusters of lymphocytes around Langerhans cells, termed *Pautrier microabscesses* (Fig. 14.1a–c). Proving T-cell clonality is not essential to establishing a diagnosis, however, detection of clonal T-cell receptors (TCRs) from two different biopsy locations is specific for MF. Persistence of a TCR clone over time (when comparing to past biopsy specimens) also strongly supports an MF diagnosis. Immunophenotyping of biopsy samples commonly show an aberrant loss of T-cell antigens such as CD2, CD3, CD5, and CD7 [23, 24].

Although several clinical variants of mycosis fungoides have been described (e.g., bullous, hypopigmented, or poikilodermatous MF), most have a similar clinical behavior to classical MF. However, the WHO-EORTC classification recognizes three variants with distinct clinicohistopathologic features: folliculotropic MF, pagetoid reticulosis, and the extremely rare granulomatous slack skin. Folliculotropic MF is characterized by the presence of malignant T-cell lymphocyte tropism to dermal hair follicles. This variant commonly spares the epidermis, which is typically involved in classical MF (Fig. 14.1d). The clinical presentation is characterized by either grouped follicular papules, acneiform lesions, or indu-

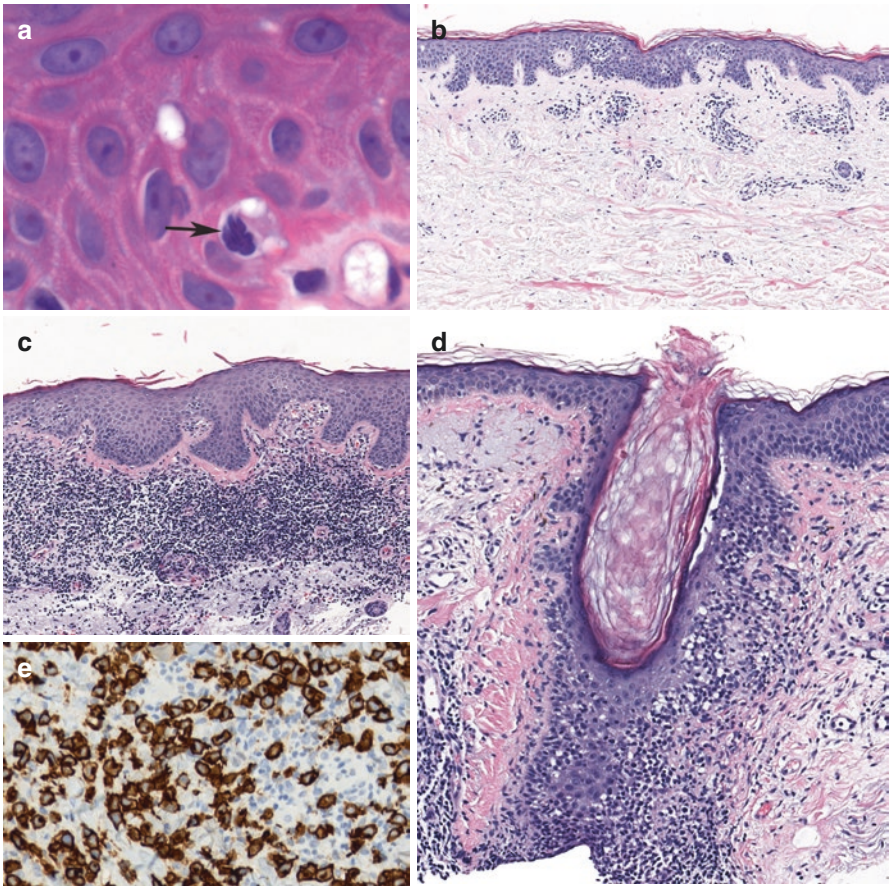

Fig. 14.1 (**a**) Intraepidermal lymphocyte with hyperconvoluted nucleus (arrow). Small- or medium-sized, atypical lymphocytes showing nuclear hyperchromasia and epidermotropism are diagnostic features of cutaneous T-cell lymphoma of the mycosis fungoides pattern. (hematoxylin and eosin, 1000×). (**b**) Patch pattern of mycosis fungoides. Atypical T lymphocytes are present in the papillary dermis and show epidermotropism with Pautrier abscess formation. The deeper dermis and subcutis are minimally uninvolved. (**c**) Plaque pattern of mycosis fungoides. Atypical T lymphocytes fill the papillary dermis and portions of the reticular dermis. Epidermotropism is typically present but may sometimes be minimal. (**d**) Folliculotropic cutaneous T-cell lymphoma. Atypical, hyperchromatic T lymphocytes accumulate within the epithelium of hair follicles. Mucin may also be visible in the follicular epithelium (follicular mucinosis). (**e**) The superposition of accumulations of large atypical T-cells in a patient with mycosis fungoides is termed large-cell transformation. The large cells account for 25% or more of the T-cells in the infiltrate. These large cells sometimes are CD30 positive. (Photos courtesy of Paul Googe, MD)

rated plaques which preferentially involve the head and neck. The presence of plaques involving the eyebrows with associated alopecia is highly specific for folliculotropic MF. The 5-year overall survival (OS) has been found to be approximately 70–80%, which is worse than early-stage MF, and more consistent with tumor-stage MF [25, 26].

Pagetoid reticulosis describes localized patches or plaques with marked intraepidermal proliferation of neoplastic T-cells. Lesions are often solitary and follow an exceptionally indolent course with little to no risk of extracutaneous spread [2]. Pagetoid reticulosis should only be used to describe localized disease (Woringer-Kolopp type), as generalized skin involvement should raise suspicion for a more aggressive form of CTCL.

Granulomatous MF is a very rare subtype of MF characterized by diffuse infiltration of malignant T-cell lymphocytes throughout the entire dermis with perivesicular granuloma formation. A minority of patients with granulomatous infiltration develop granulomatous slack skin, characterized by progressive development of pendulous lax skin with predilection for skinfolds, often in the axilla and groin [27–30].

Sézary Syndrome

Sézary syndrome is a rare, although clinically significant, variant accounting for 3–5% of CTCL cases. It has classically been defined by the presence of erythroderma, generalized lymphadenopathy, and neoplastic T-cells (called Sézary cells) in the peripheral blood [31]. Morphologically, Sézary cells are described as large lymphocytes with grooved, lobulated, or cerebriform nuclei [32, 33]. Although previously thought to be a leukemic progression of MF, recent immunophenotyping and genetic studies support that SS exists as a distinct disease process [18–20]. The typical immunophenotype of Sézary cells is CD3+, CD4+, and CD8−. Aberrant loss of CD7 and CD26 has been found in up to 57% and 86% of cases, respectively. In cases where both CD7 and CD26 lack expression, there is a high sensitivity and specificity for SS [34–36]. The presence of Sézary cells is not diagnostic for SS because small numbers of Sézary cells can be found in benign conditions such as actinic reticuloid and drug-induced pseudolymphoma [37–39].

Diagnostic criteria for SS include an absolute Sézary cell count of 1000 cells/mm^3 in peripheral blood, a CD4/CD8 ratio $\geq$ 10, evidence of a T-cell clone in the peripheral blood, and demonstration of a chromosomally abnormal T-cell clone [40]. Although no minimum criteria must be met to confirm diagnosis, the WHO-EORTC recommends at least establishing TCR clonality as well as one additional criteria above prior to diagnosing SS [2].

Sézary syndrome has a poor overall prognosis. Median survival is 2–4 years with a disease-specific 5-year survival rate of 24% [2]. Due to ineffective T-cell immunity and significant immunosuppression with therapies, infection is a frequent cause of death.

Staging, Risk Stratification, and Prognosis for MF/SS

Staging in CTCL uses a modified tumor, node, metastasis (TNM) classification system [41, 42], which includes a fourth marker, the presence of circulating tumor cells

in the blood, termed the B (blood) rating. Stage is determined at diagnosis. However, the patient's updated TNMB classification should be reported throughout treatment to provide information about ongoing tumor burden and response to therapy [43, 44].

Recommended staging studies include physical exam with attention to type and extent of skin disease as well as a thorough lymph node exam. Blood should be sent for a Sézary cell count and/or flow cytometry. Computed tomography (CT) scans and/or a fluorodeoxyglucose (FDG) positron emission tomography (PET) scan should be performed in patients with nodal or blood involvement or ≥ T2 skin disease. Lymph node biopsies should be performed if there is a node ≥1.5 cm in diameter or that is firm, irregular, clustered, or fixed [43].

Skin Stage (T)

Tumor staging of MF is determined by extent of skin involvement, and, therefore, a detailed complete skin exam is a requirement for appropriate staging. T1 is defined as patches, plaques, and papules covering <10% of total body surface area (BSA). T2 is defined as patches, plaques, and papules covering ≥10% of total BSA (Fig. 14.1). These stages can be further stratified into T1a/T2a (patch only disease) and T1b/T2b (plaque disease with or without patches) (Fig. 14.2a). Tumor-stage disease (T3) is defined by the presence of at least one tumor ≥1.5 cm in diameter (Fig. 14.2b). T4 disease is erythrodermic involvement of MF, affecting ≥80% of BSA (Fig. 14.2c) [43].

Patients with T1 disease at diagnosis have an excellent prognosis. The risk of progression at 5 years is only 10% [45], and 10-year OS is similar to matched population controls without MF [46]. In contrast, T4 stage at diagnosis correlates with higher risk of disease progression (48% at 5 years) and lower 10-year OS of only 41% compared to normal controls (Table 14.1) [45, 46].

Node Staging (N)

Nodal staging is based on physical exam and pathologic staging. Peripheral lymph nodes on physical exam that are firm, irregular, clustered, fixed, or >1.5 cm in diameter [43] are considered abnormal. Palpable peripheral lymphadenopathy has been shown in multiple studies to be an independent poor risk factor [47–49]. However, the presence or absence of central lymph node enlargement is not included in N staging. Biopsy of enlarged nodes will frequently demonstrate reactive or dermatopathic nodes without frank involvement by CTCL [50]. Dermatographic nodes without identifiable CTCL involvement are still considered nodal involvement and classified as N1 [51–53].

In the most recent ISCL/EORTC clinical classification guideline, N1–N3 are differentiated by the degree of atypical lymphocyte involvement in the node. There are two separate, validated grading systems for lymph node involvement, the NCI/VA

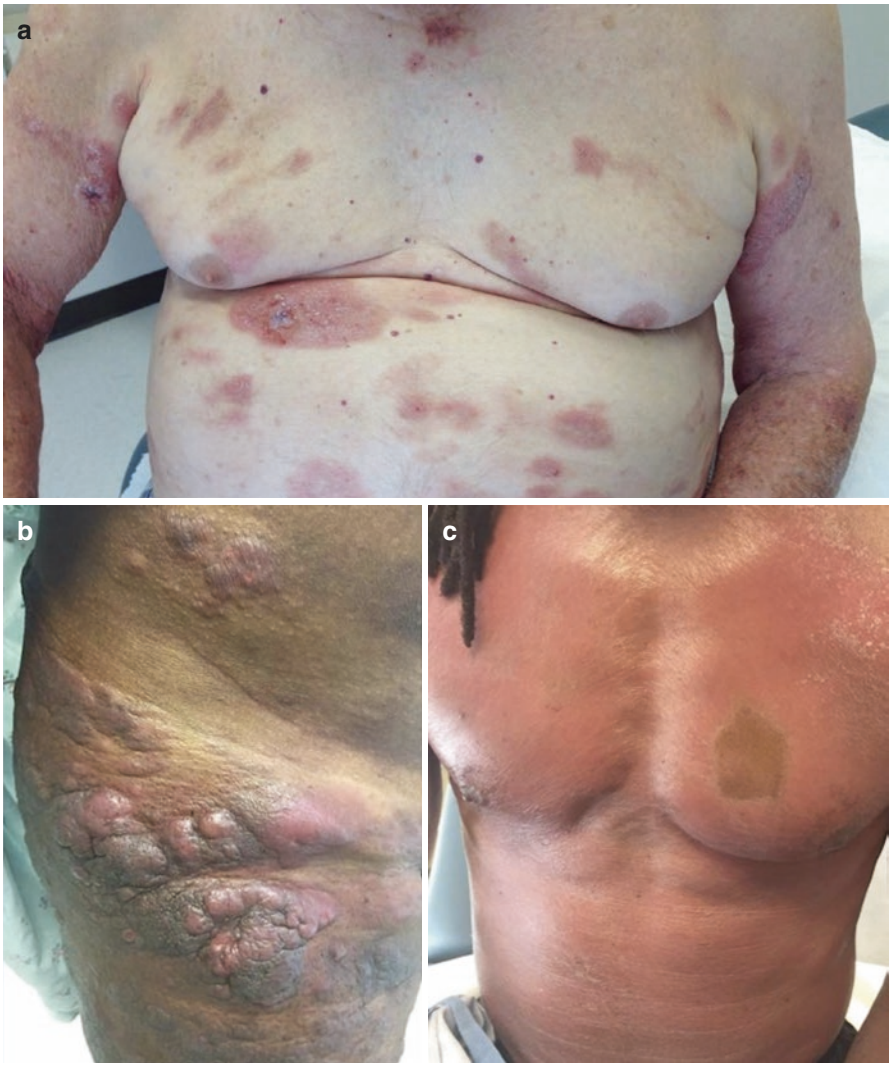

Fig. 14.2 Clinical T stage mycosis fungoides. (**a**) Patches and plaques of mycosis fungoides (Stage T2 disease). (**b**) Tumor-stage (T3) mycosis fungoides. (**c**) Erythroderma associated with mycosis fungoides (Stage T4 disease). (Photos courtesy of Edith Bowers, MD, PhD)

classification system and the Dutch classification system. The NCI/VA system uses a smaller size criteria, defining atypical lymphocytes as ≥6 μm with cerebriform, irregularly folded nuclei. Lymph nodes are then assessed for location of atypical lymphocytes as either occasionally present (LN_1), many atypical lymphocytes or clusters of three to six cells (LN_2), aggregates with preserved nodal architecture (LN_3), or partial to complete effacement of nodal structure by atypical lymphocytes (LN_4) [51, 52]. The Dutch system only considers large atypical cells with an irregular cerebriform nuclei measuring a minimum diameter of 7.5 μm. The Dutch grad-

Table 14.1 ISCL/EORTC clinical staging and overall survival

ISCL/EORTC staging [43, 44]					Overall survival [45, 56, 57]		
Stage	T	N	M	B	Median (years)	5 year (%)	10 year (%)
IA	1	0	0	0–1	35.5	94	88
IB	2	0	0	0–1	21.5	84	70
IIA	1–2	1	0	0–1	15.8	78	47
IIB	3	0–2	0	0–1	4.7–5.6	47–57	34
IIIA	4	0–2	0	0	4.7	47–60	37
IIIB	4	0–2	0	1	3.4–5.2	40–55	25
IVA1	1–4	0–2	0	2	3.8–4.4	37–48	18
IVA2	1–4	3	0	0–2	2.1–2.4	18–32	15
IVB	1–4	0–3	1	0–2	1.4–2.7	18	–

ing is as follows: grade 1 for dermatographic lymphadenopathy, grade 2 with early involvement of atypical lymphocytes, grade 3 with partial effacement of the lymph node, and grade 4 with complete effacement of the lymph node [53].

Prognosis has been clearly linked to either partial or complete effacement of lymph nodes [54]. Therefore, this becomes the major distinction for N1–N3 classification. N1 disease is characterized by the presence of small atypical lymphocytes without effacement (i.e., Dutch grade 1 or NCI/VA LN_1–LN_2). N2 disease is characterized by the presence of large atypical lymphocytes (i.e., Dutch grade 2) or small atypical lymphocyte aggregates without effacement (i.e., NCI/VA LN_3). Finally, N3 disease is classified by any evidence of lymph node effacement (i.e., Dutch grade 3–4 or NCI/VA LN_4). Complicating N staging further, both N1 and N2 can be further subclassified based on the presence of a T-cell clone within the lymph node (e.g., N1 can be either N1a without a clone or N1b with a clone) [43].

Metastatic Staging (M)

Visceral metastases of MF are almost never seen in T1–T3, N0, or B0 disease. Visceral disease is most commonly found as either liver or splenic involvement. The presence of splenomegaly is considered M1 disease and does not require a biopsy. The bone marrow is an infrequent site of metastatic disease in CTCL; therefore, bone marrow biopsies are not routinely performed but can be considered in B2 disease [43, 55].

Blood Staging (B)

In the amended TNMB staging criteria from the ISCL/EORTC in 2007, blood involvement is categorized based on prognostically significant blood involvement by Sézary cells; B0 is the absence of significant blood involvement (≤%5 Sézary

cells); B1 represents detectable, but low blood tumor burden (>5% Sézary cells, but does not meet B2 criteria); and B2 is defined as a detection of a clonal TCR rearrangement in the blood and either ≥1000 cells/mm^3 Sézary cells or one of two secondary criteria (CD4/CD8 ratio >10 or increased CD4+ cells with >40% CD4+/CD7− or >30% CD4+/CD26− ratio) [43].

Impact of Staging and Other Factors on Prognosis

Patients with early-stage disease have an excellent survival. Stage IA disease is associated with minimal impact on long-term OS, and patients with less than Stage IIA disease have a median OS greater than 15 years. Stage IIB is an important distinction given the dramatic drop in median OS to only 4.7 years (Table 14.1). The prognosis associated with higher stage CTCL becomes progressively more grim with Stage IVB disease associated with a median OS of only 1.5 years and most deaths attributable to lymphoma [45, 56].

In 2015, the Cutaneous Lymphoma International Consortium (CLIC) published a retrospective study of 1275 patients with advance MF/SS and identified four independent prognostic markers of worse survival: Stage IV disease, age >60 years, large-cell transformation (LCT), and increased lactate dehydrogenase [57]. LCT is defined by an atypical lymphoid infiltrate in either the skin or lymph nodes with >25% of cells characterized as large cells (Fig. 14.1e) [58, 59]. LCT occurs in around 7% of all patients with MF/SS [60] and up to 56–67% of patients with Stage IV MF/SS. Identifying LCT is of clinical importance as it is associated with a median OS of less than 24 months and may require more aggressive treatment with cytotoxic chemotherapy [61–64].

Treatment of MF/SS

The care of patients with MF/SS requires a multidisciplinary team consisting of dermatologists, oncologists, radiation oncologists, pathologists, and wound care specialists.

Skin-directed therapies such as topical steroids, phototherapy, localized radiation therapy, and mechlorethamine are recommended for the first-line management of Stage IA–IIA MF. Second-line therapy for these early disease stages may include systemic retinoids or interferon, total skin electron beam therapy (TSEBT), or low-dose methotrexate (MTX). In Stage IIB–IVB MF, systemic therapies are recommended in the first-line setting [3]. However, even advanced-stage patients on systemic therapy often benefit from concurrent skin-directed therapy such as topical steroids either alone or in combination with phototherapy.

Once systemic treatment is required, most patients will require therapy indefinitely; therefore, it is imperative to balance toxicity of treatment with clinical benefit. Furthermore, because complete remissions are rare, the goals of MF treatment

Table 14.2 Systemic therapy options for CTCL

Systemic treatment	ORR (%)	CR (%)	PFS (months)	FDA approval (as of 1/01/19)
Systemic retinoids [99, 100]	45–66	9–13	3.4–7.3	Approved
Interferon-α + PUVA [79, 103, 104]	80–90	62–74	28–32	Off label
HDACi [108–111]	23–34	5–6	4.9–15	Approved
ECP [112, 113]	36–73	14–26	14–30	Approved
Brentuximab [117]	56	16	16.7	Approved
Alemtuzumab [119–124]	55–84	32–47	6–12	Off label
Mogamulizumab [126, 127]	37–47	3	7.7	Approved
Liposomal doxorubicin [128–130]	41–56	6–20	6–7	Off label
Gemcitabine [131–133]	62–68	8	8–10	Off label
Methotrexate [134, 135]	33–76	12–41	15–22	Approved
Pralatrexate [136]	60	11	12.8	Off label

should focus on improving quality of life and symptoms such as pruritus rather than complete clearance of disease. Minor or partial responses are not considered failures as long as the patient had some clinical benefit from therapy. Even in advanced-stage CTCL, multi-agent chemotherapy has not demonstrated improved survival compared to more conservative therapy [65]; therefore, sequential single-agent therapy is the preferred management approach. Due to the lack of large, randomized clinical trials in CTCL, there is a paucity of data to guide decisions about which therapies should preferentially be used, and in which order. Choices must be made based on provider experience and side effect profile (Table 14.2).

Consensus recommendations of response criteria were created in 2011 by the International Society of Cutaneous Lymphomas. Separate scoring systems are available for skin response, lymph node response, visceral response, and blood response. Skin response is typically assessed by the modified Severity Weighted Assessment Tool (mSWAT) which combines both percent of body surface area involved and a modifier for either plaque-, patch-, or tumor-stage lesions [66]. However, this can be time-consuming and is typically used more in research trials than in clinical practice. Both lymph node and visceral response are typically assessed by serial CT scan. Timing and intervals of CT imaging are determined by each treating physician keeping in mind radiation exposure to recurrent CT imaging. A FDG-PET scan can be useful in selected clinical scenarios but likely results in increased false-positive results from infection and inflammation. Blood response is assessed by either Sézary cell quantification or flow cytometry of T-cell subsets consistent with Sézary cells. Combining these four distinct response scoring systems, a global response score can be determined for overall disease response to therapy [67]. However, decisions about continuation of a particular treatment depend more on clinical response and improvement of symptoms than on the global response score.

Skin-Directed Therapy

Topical Corticosteroids

Topical corticosteroids are an affordable, readily available, and effective choice for many patients. Overall response rates (ORR) >90% and complete response (CR) rates >60% have been reported in Stage T1 patients treated with class I corticosteroids [68, 69].

The choice of topical corticosteroid, both potency and vehicle (e.g., ointment, cream, solution, etc.), depends on the body area being treated and patient preference. Topical corticosteroids are applied once or twice daily to affected areas only. Once clearance is achieved to a given area, they should be stopped and only resumed when patches or plaques recur. Overuse of topical steroids should be avoided to prevent skin atrophy. Response is expected within a few months of use; if control is not achieved within 3 months, alternate therapies should be considered.

Topical Mechlorethamine

Mechlorethamine, commonly known as nitrogen mustard, is an alkylating agent that has been administered topically for the treatment of MF since the 1950s. Approximately 70–80% of patients with Stage T1 disease experience a clinical response, typically achieving skin clearance in 6–10 months [70–73]. Durable remissions lasting at least 10 years occur in 20–25% of patients [72, 73]. Irritant and allergic contact dermatitis are common side effects and are managed by reducing the frequency or strength of application or by using topical corticosteroids. Long-term use of mechlorethamine may lead to the development of secondary cutaneous malignancies, particularly squamous cell carcinoma. However, this is difficult to demonstrate absolutely as many such patients were also treated with other therapies that may alter skin cancer risk, such as phototherapy or radiation [73, 74].

Topical Retinoids

Topical bexarotene is available as a 1% gel and is approved by the US Food and Drug Administration (FDA) for the treatment of patients with Stage IA/IB MF who either have failed or not tolerated other therapies. In patients with Stage IA–IIA MF, ORR of 44–63% has been reported with CR rates of approximately 20% [75, 76]. Initially, it is often administered once daily or every other day, but applications may be titrated up to four times daily if tolerated. Irritant dermatitis at the application site is common and typically limits its use to those patients who have <15% body surface area involvement. Bexarotene is contraindicated in pregnancy.

Phototherapy

Ultraviolet light therapy is widely used and highly efficacious for the treatment of early-stage MF. Phototherapy is particularly advantageous to those patients whose skin involvement is too diffused to practically manage with topical medications. For many patients, phototherapy can also be a safe alternative to systemic treatments. However, treatments are frequent (two to three times per week), and long-term maintenance therapy is often needed, so it may not be a feasible for patients who do not live near a treatment center. Furthermore, phototherapy may not be appropriate for patients with a history of melanoma or extensive non-melanoma skin cancers.

Psoralen Plus Ultraviolet A (PUVA) Photochemotherapy

The combination of psoralen, a plant-derived phototoxic compound, with UVA (320–400 nm) radiation, known as PUVA, has been used for decades to treat MF. The term PUVA typically refers to oral 8-methoxypsoralen (8-MOP) photochemotherapy, although it is sometimes used to describe the topical application of 8-MOP or the use of other psoralen compounds prior to UVA exposure.

Treatment consists of an oral dose of 8-MOP (0.5–0.6 mg/kg) taken 1.5–2 h prior to exposure to UVA light in an office-based phototherapy unit. The entire body is treated, except for a few body areas that are protectively shielded (i.e., eyes and genitalia). Treatments are repeated two to three times per week until clearance is achieved and then gradually tapered.

PUVA is very effective as monotherapy for early-stage MF with reported CR rates of 65–85% [77]. Time to achieve CR is 2–6 months [78, 79], and some patients experience long-term remission of ≥10 years [80]. Complete response rates for advanced-stage disease are much lower: 28% for tumor-stage disease and 43% for erythrodermic MF [77].

Acute complications of PUVA include erythema, photosensitivity, pruritus, blistering, pain, and xerosis. Patients must protect their eyes and skin from sunlight for a minimum of 24 h after 8-MOP intake because of the increased photosensitivity. Patients who are treated long-term with PUVA are at increased risk of developing melanoma [81] and non-melanoma skin cancers [82].

Narrowband Ultraviolet B (UVB)

In patients with patches or thin plaques, narrowband UVB (311 nm) can be used as a safe and effective alternative to PUVA. However, because the depth of penetration of UVB is less than UVA, it is not ideal for patients with thick plaque lesions.

The average CR rate reported in the literature for narrowband UVB as monotherapy is 84% [77]. Similar to PUVA, treatments are administered two to three

times weekly until clearance is achieved, after which frequency may be slowly tapered. Acute complications include erythema, but this is shorter-lived and less severe than with PUVA [83]. Although there is a concern for increased photocarcinogenicity, studies have not shown an association between narrowband UVB and skin cancer [84, 85].

Radiation Therapy

Radiation therapy (RT) is one of the most effective treatment modalities for MF and has several different clinical applications. For the rare patient with unilesional disease (or a few clustered lesions), radiation therapy alone is potentially curative. Almost all such patients achieve a complete response (94–100%) with reported 10-year relapse-free survival (RFS) rates of 50–86% [86–88]. A dose of ~30 Gy is recommended in this clinical scenario.

Even patients with more advanced cutaneous disease, with a few symptomatic plaques or tumors, often benefit from local radiation therapy. Several retrospective studies have demonstrated complete response rates >95% for individual MF lesions treated with abbreviated courses of radiation therapy [86–89]. A common fractionation regimen used in low-grade lymphomas (2 Gy × 2, total dose 4 Gy) is not particularly efficacious in mycosis fungoides [90]. However, a slightly more intense regimen (4 Gy × 2, total dose 8 Gy) leads to a complete response in most patients (>90%) [90]. A single 7–8 Gy fraction is similarly efficacious [91]. It has been suggested that more protracted regimens, utilizing total doses of ~30 Gy, are associated with a lower risk of local failure [89]. Thus, the total dose and fractionation scheme should be tailored to the individual circumstances of the patient taking into account the extent and activity of disease, other ongoing treatments, and overall prognosis.

Many patients with MF present with diffuse symptomatic cutaneous disease or will develop such during the course of their illness. Total skin electron beam therapy (TSEBT) can be utilized in such circumstances, particularly in the setting of thick plaques or tumors that may not respond well to other skin-directed therapies. TSEBT is a technically challenging procedure and requires special commissioning (i.e., configuring) of a linear accelerator and significant support from medical physics. Thus, this treatment is generally only available at larger centers that treat many patients a year. As with local radiation therapy, TSEBT is very effective with nearly all patients experiencing significant clinical improvement. For patients with T2 disease, the CR rate has been reported to be 75–85% with 50% RFS at 5 years, but only 10% at 10 years [92–94]. With T3 disease, CR rates of 43–78% have been reported with nearly all patients eventually experiencing recurrent disease [94, 95]. Both conventional courses of TSEBT (30–36 Gy) and low-dose TSEBT (12–15 Gy) are effective, though CR rates are higher with conventional doses.

Systemic Therapies

Systemic Retinoids

Bexarotene, a synthetic retinoid, is FDA approved for use in patients with CTCL refractory to ≥1 systemic therapy. Bexarotene selectively binds and activates RXR nuclear receptors, leading to cell cycle inhibition, decreased proliferation, and increased apoptosis of malignant cells [96–98].

Patients with refractory disease, either early or late stage, treated with bexarotene, have reported ORR of approximately 50% [99, 100]. Recommended dosing is typically 300 mg/m^2 by mouth daily, although some providers start at lower doses and titrate up based on individual patient response and tolerance of side effects.

Similar to other systemic retinoids, bexarotene is teratogenic and is contraindicated in pregnancy. Bexarotene requires frequent lab monitoring of liver function, cell counts, serum lipid levels, and thyroid function throughout therapy. Acquired hypertriglyceridemia and central hypothyroidism, requiring medical management, are common [101]. Other potential side effects include cataracts, xerosis, photosensitivity, myalgias, arthralgias, or headache.

Interferon-α

Interferon-alpha (IFN-α) is commonly prescribed for management of advanced-stage MF and achieves a superior time to next treatment compared to chemotherapy regardless of disease stage [102]. It is administered subcutaneously either daily or three times weekly in doses of 3–9 million units. When used as monotherapy, IFN-α results in an ORR of 64% and CR rate of 27% [79]. Commonly, IFN-α is administered in combination with other skin-directed or systemic therapies. The combination of IFN-α and PUVA has been reported to achieve improved complete response rates of 62–76% with a median duration of response of 28–32 months [79, 103, 104]. Adverse effects of IFN-α include flu-like symptoms, depression, and bone marrow suppression.

Histone Deacetylase Inhibitors (HDACi)

Histone deacetylases (HDACs) are a group of enzymes which function normally to remove acetyl groups form both histone and nonhistone proteins. The epigenetic downregulation of tumor suppressors due to HDACs has been linked to a variety of malignancies [105, 106]. HDAC inhibitors (HDACi) function to maintain histone acetylation and thus transcription of tumor suppressor proteins. HDACi therapy has been found to have clinical activity in advanced-stage MF and SS [107].

Vorinostat is an oral HDACi that is FDA approved, at a dose of 400 mg/day, for recurrent, refractory, or persistent CTCL after ≥2 prior therapies. The ORR in heav-

ily pretreated patients is 24–30% [108, 109]. In clinical trials, the median time to response was 12 weeks, and median time to progression was 30–34 weeks. Romidepsin is an intravenous HDACi that is FDA approved for CTCL after ≥1 prior therapy at a dose of 14 mg/m^2 on days 1, 8, and 15 every 4 weeks. Clinical trials demonstrated an ORR of 34% and CR rate of 6% with a median duration of response (DOR) of 13.7–15 months [110, 111]. Forty-three percent of patients had improvement in pruritus lasting a median of 6 months. Vorinostat and romidepsin have a similar adverse event profile consisting of GI symptoms (nausea, vomiting, and diarrhea) and grade 3 hematologic toxicities (lymphopenia, granulocytopenia, anemia, and thrombocytopenia).

Extracorporeal Photopheresis

Extracorporeal photopheresis (ECP) is FDA approved for use in advanced-stage CTCL patients. ECP involves three distinct steps: separation of a portion of the patient's white blood cells (WBC), which includes the circulating malignant CD4+ cells, through an apheresis procedure, the treatment of the collected white blood cells with 8-methyloxypsoralen and ultraviolet A (UVA) radiation, and reinfusion of treated WBCs to the patient. The mechanism of action is not completely elucidated but is believed to be through induction of antitumor immunity. The 8-MOP intercalates into the WBC DNA which, when exposed to UVA, leads to apoptosis. This causes maturation of monocytes into dendritic cells, which appears to be the cornerstone of the therapy. ECP is also thought to decrease CD4 + FOXP3 + CD25− cells and increase functional CD8+ cells [112].

The reported ORR is 36–73% with CRs in 14–26% of patients. Responses have been associated with shorter duration of disease, fewer circulating malignant cells, and early response of skin lesions to the ECP treatments (>50% regression in 6 months or less) [113].

Typically, one to two treatment cycles of ECP are administered per month with each cycle consisting of two treatments on 2 consecutive days. The median time to maximum response is 5–6 months, but responses have been seen up to 10 months from the start of the therapy. ECP in combination with other modalities has been associated with quicker response time in some cases. Once maximal response is achieved, the interval between treatment cycles can be extended to one cycle every 6–12 weeks. If the patient's disease worsens, the schedule can return to one cycle every 2–4 weeks [113].

ECP is generally very well-tolerated and there are few contraindications. It does not cause systemic immunosuppression. Rarely, during the ECP procedure, hypotension can occur due to volume shifts, and patients can have low-grade fevers a few hours after the procedure. For 24 h after a treatment, the patient is sensitive to light and must wear clothes that cover his/her skin as well as sunscreen and sunglasses [112–114].

Brentuximab Vedotin

Brentuximab vedotin (BV) is an antibody-drug conjugate therapy in which a CD30-directed recombinant IgG1 antibody is conjugated to a microtubule disrupting agent, monomethyl auristatin E [115, 116]. BV is FDA approved for treatment of patients with cutaneous anaplastic large-cell lymphoma (c-ALCL) or CD30+ MF who have received prior systemic therapy.

Approval was largely based on a phase III, randomized trial of BV versus physician choice, of oral methotrexate or bexarotene, in patients with MF or c-ALCL. An ORR lasting at least 4 months occurred in 56% of patients treated with BV versus 12% for physician's choice with CR rates of 16% and 2%, respectively. Median PFS was 15 months in BV and 4 months with physician's choice. Importantly, patient-reported burden of symptoms also showed significantly more improvement in the BV arm. The most frequent toxicity caused by BV is peripheral neuropathy (usually grade 1 or 2) reported in up to 67% of patients [117]. CTCL has significant variation in CD30 expression from strongly expressed to very low expression. Interestingly, the ORR for patients with MF was independent of the level of CD30 expression.

Alemtuzumab

Alemtuzumab is a humanized recombinant IgG1 monoclonal antibody directed against CD52, which is widely expressed by T-cells [118]. Alemtuzumab has been studied in two small phase II studies of patients with Stage IIIA–IVB MF or SS who were administered alemtuzumab 30 mg, three times per week for up to 12 weeks. The ORR was 55–84% with 32–47% CR and a suggestion of more responses in patients with erythroderma and SS [119]. However, there was also a significant rate of infectious complications, approximately 50% either during or shortly after therapy. Infectious complications included reactivation of cytomegalovirus (CMV) in 18% of patients reported in one of the studies [119–122].

With an aim of maintaining efficacy and reducing toxicity, several trials were developed with a reduced dose of alemtuzumab. Bernengo et al. treated 14 patients with SS with a reduced dose of 3 mg subcutaneously on day 1 and then 10 mg on alternating days. ORR was 86% with 21% complete responses. No patients in this reduced dose study developed hematologic toxicity or infections [123]. Furthermore, this dose has subsequently been proven to be safe in elderly patients (80–87 years old) with SS [124]. The clinical responses seen with alemtuzumab are compelling; however, it is imperative that patients are closely monitored for CMV reactivation during therapy.

Mogamulizumab

Mogamulizumab is a humanized monoclonal antibody targeting CC chemokine receptor 4 (CCR4). MF cells strongly express CCR4 (T_{RM} phenotype), which appears to play an important role in T-cell homing to the skin [125]. Mogamulizumab binds with high affinity for CCR4 and is thought to induce cytotoxicity via antibody-dependent cellular toxicity due to NK cell activity.

In August 2018, the international, randomized, phase III study of mogamulizumab versus vorinostat in Stage IB–IV CTCL after at least one prior therapy reported a prolonged median PFS of 7.7 months compared to 3.1 months with vorinostat. This led to FDA approval for all adult patients with relapsed or refractory MF or SS after at least one line of therapy. Mogamulizumab is administered at a dose of 1 mg/kg weekly for 4 weeks and then every 2 weeks as maintenance until disease progression. The best overall global response was 35% for mogamulizumab and only 6% for vorinostat [126]. Responses had previously been reported to be higher in patients with SS (47%). In patients with blood involvement, 94% had a hematologic response [127]. Interestingly, responses were independent of tissue CCR4 expression prior to therapy. Mogamulizumab was very well-tolerated, and the most common adverse events were limited to grade 1–2 nausea, chills, headaches, and infusion reactions.

Cytotoxic Chemotherapy

The role of conventional systemic chemotherapy in the management of CTCL is limited due to short duration of responses and increased toxicities. Therefore, chemotherapy is generally reserved for advanced-stage MF or SS, usually after multiple relapses to other therapeutic agents. Multi-agent chemotherapy has a limited role due to higher rates of significant toxicities with limited improvement in durable responses. However, several drugs such as liposomal doxorubicin, gemcitabine, or folic acid analogs have demonstrated efficacy in MF and SS when administered as single agents.

Pegylated liposomal doxorubicin resulted in ORR of 41–56%, CR rates of 6–20%, and PFS of 6–7 months in patients with relapsed, refractory Stage II–IV MF [128–130]. Gemcitabine has also been studied in advanced MF and SS with an ORR of 62–68% and CR rate of 8% [131–133].

Low-dose oral methotrexate (MTX) has been studied in early-stage MF with an ORR of 33% and a CR rate of 12%. Despite a relatively low response rate in early-stage MF, it can be effective in SS. In patients with SS treated with low-dose oral MTX, high response rates have been reported (ORR 76%; CR rate 41%) [134, 135]. Pralatrexate, which is FDA approved for relapsed/refractory peripheral T-cell lymphoma, has shown some efficacy in MF as well. In a phase I/II study of 34 patients with Stage IV MF, SS, or c-ALCL, the combination of pralatrexate and oral bexarotene showed an ORR of 60% with a 11% CR rate. Furthermore, median progression-free survival was longer than most other systemic therapies, reported at 12.8 months [136].

Hematopoietic Stem Cell Transplant

Hematopoietic stem cell transplantation (SCT) is rarely used in the management of MF/SS. The data available is limited to case reports and retrospective reviews which raises questions about its efficacy, optimal timing in the disease course, and ideal

patient population. The evidence for high-dose chemotherapy followed by autologous SCT rescue is limited to a small case series. Results showed a reasonable response rate; however, over half of the patients developed an early relapse [137]. Allogeneic SCT is more frequently used in MF/SS patients but is a high-risk procedure with a reported 1-year non-relapse mortality of 14–40% depending on conditioning regimen and donor type. In one report, patients who underwent allogeneic SCT with a reduced intensity conditioning regimen and a matched-related donor were found to have a 3-year OS of 63% [138]. Responses have been found to be strongly dependent on graft versus lymphoma effect, and many patients required donor lymphocyte infusions after SCT [139]. Given the high treatment-related morbidity and mortality, SCT is typically limited to younger, healthy patients with high-risk disease and a suitable matched donor.

Summary

Cutaneous T-cell lymphomas represent a wide range of clinical entities with differing pathogenesis and responses to treatment. Establishing a clear diagnosis along with staging and risk stratification is critical prior to recommending appropriate therapeutic interventions. Assessments and treatment recommendations are best delivered by a multidisciplinary team involving dermatology, dermatopathology, medical oncology, and radiation oncology. Early-stage CTCL is typically managed with skin-directed therapies, often achieving durable, long-term remissions and disease control. Advanced-stage MF and SS typically require systemic therapy; however, therapy does not typically lead to durable responses. While many new therapies have recently been studied and approved, well-designed clinical trials are needed in the future to optimize disease response and survival.

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