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ANNUAL CLINICAL UPDATES IN HEMATOLOGICAL MALIGNANCIES

# Mycosis fungoides and Sézary syndrome: 2019 update on diagnosis, risk-stratification, and management

Alexandra C. Hristov[1] | Trilokraj Tejasvi[2] | Ryan A. Wilcox[3]

[1]Departments of Pathology and Dermatology, University of Michigan, Ann Arbor, Michigan

[2]Department of Dermatology, University of Michigan, Ann Arbor, Michigan

[3]Division of Hematology/Oncology, Department of Internal Medicine, University of Michigan Rogel Cancer Center, Ann Arbor, Michigan

**Correspondence**
Ryan Wilcox, Division of Hematology/Oncology, Department of Internal Medicine, University of Michigan Rogel Cancer Center, 1500 E. Medical Center Drive, Room 4310 CC, Ann Arbor, MI 48109-5948.
Email: rywilcox@med.umich.edu

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## Abstract

**Disease Overview:** Cutaneous T-cell lymphomas (CTCL) are a heterogenous group of T-cell neoplasms involving the skin, the majority of which may be classified as Mycosis fungoides (MF) or Sézary syndrome (SS).

**Diagnosis:** The diagnosis of MF or SS requires the integration of clinical and histopathologic data.

**Risk-Adapted Therapy:** TNMB (tumor, node, metastasis, blood) staging remains the most important prognostic factor in MF/SS and forms the basis for a "risk-adapted," multi-disciplinary approach to treatment. For patients with disease limited to the skin, skin-directed therapies are preferred, as both disease-specific and overall survival for these patients is favorable. In contrast, patients with advanced-stage disease with significant nodal, visceral or blood involvement are generally approached with systemic therapies. These include biologic-response modifiers, histone deacetylase (HDAC) inhibitors, or antibody-based strategies, in an escalating fashion. In highly-selected patients, allogeneic stem-cell transplantation may be considered, as this may be curative in some patients.

## 1 | INTRODUCTION

Primary cutaneous lymphomas are a heterogeneous group of extranodal non-Hodgkin lymphomas which, by definition, are confined to the skin at diagnosis. The European Organization for Research and Treatment of Cancer (EORTC) and World Health Organization (WHO) published a consensus classification for cutaneous lymphomas in 2005[1] that was recently updated.[2] In contrast to nodal non-Hodgkin lymphoma, most of which are B-cell derived, approximately 75% of primary cutaneous lymphomas are T-cell derived, two-thirds of which may be classified as *Mycosis fungoides* (MF) or Sézary syndrome (SS).[1,3,4] The incidence of cutaneous T-cell lymphomas (CTCL) has been increasing, and is currently 6.4 per million persons, based on Surveillance, Epidemiology, and End Results (SEER) registry data, with the highest incidence rates being reported among males and African-Americans.[3] While CTCL may occur in children and young adults, this is very uncommon and often associated with histopathologic variants of MF.[5-7] The incidence of CTCL increases significantly with age, with a median age at diagnosis in the mid-50s and a 4-fold increase in incidence appreciated in patients over 70.[3,7]

Epidemiological studies have failed to consistently identify environmental or virally associated risk factors for most CTCL subtypes, with the notable exception of HTLV-1 infection in adult T-cell leukemia/lymphoma.[8] Recent studies, however, have suggested that medications may induce an antigen-driven T-cell lymphoproliferation or dyscrasia.[9,10] A recent case series examined a subset of hypertensive MF patients using hydrochlorothiazide. When compared to hypertensive MF patients not using hydrochlorothiazide, these patients were more likely to have stage I disease, and were less likely to have a clonal TCR gene rearrangement.[10] More importantly, in a subset of these patients, a complete or partial response was observed upon discontinuation of hydrochlorothiazide. In three patients, CTCL recurred upon reinitiating hydrochlorothiazide, and subsequently receded with its discontinuation. While these findings could be interpreted as a drug reaction, more specifically a drug-induced pseudolymphoma, the authors of this single center study speculate that hydrochlorothiazide may be associated with

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antigen-driven T-cell lymphoproliferation and could serve as a trigger for MF. Consequently, a therapeutic trial off hydrochlorothiazide may be warranted in selected patients. Moreover, as a variety of other medications may initiate a reaction mimicking MF, a careful medication history should be performed in these patients with a trial off any suspected offending drug. Individual genetic features have also been implicated in the development of CTCL. Rare reports of familial MF, and the detection of specific HLA class II alleles in association with both sporadic and familial MF, suggest that host genetic factors may contribute to MF development.[11-13] While the role of environmental and host genetic factors in CTCL pathogenesis remains unclear, significant insights into disease ontogeny, molecular pathogenesis and disease-associated immune dysregulation have been realized.[14-17] Recently performed next-generation sequencing studies have demonstrated a high frequency of C > T transitions. This is in contrast to the T > G transversions observed in B-cell lymphproliferative disorders, a signature associated with ultraviolet B (UVB) exposure in melanoma (reviewed in 18).

The cell of origin, molecular pathogenesis, and genetic landscape associated with MF/SS have been elucidated,[19] and have significant therapeutic implications [reviewed in[18]].

## 2 | DIAGNOSIS

### 2.1 | Mycosis fungoides

The definitive diagnosis of MF, particularly patch/plaque stage disease, is challenging, as many of its clinical and pathologic features are nonspecific and overlap with reactive processes. Many patients will have had symptoms attributed to eczema, psoriasis or parapsoriasis for years prior to obtaining a definitive diagnosis. The median time from symptom onset to diagnosis in a retrospective series is 3to 4 years, but may exceed four decades.[20-22] Given the importance of clinicopathological correlation in the diagnosis of MF, and the variable association of specific histologic findings with the diagnosis, biopsy reports are not infrequently "suggestive of" the diagnosis. This occasional uncertainty implied in biopsy reports, and apparent lack of a more definitive histopathologic diagnosis, may be a source of frustration for clinicians unfamiliar with the challenges associated with rendering a pathologic diagnosis of MF. Drug reactions, chronic spongiotic dermatitis, connective tissue diseases, lichen sclerosus et atrophicus, and pigmented purpuric dermatoses, are just a few of the conditions that may mimic MF.[23,24] Treatment with topical steroids, ultraviolet light, or systemic immunosuppressants diminish or eliminate neoplastic T-cells and critical histopathologic findings for 2 to 4 weeks, and patients may be receiving these therapies at the time of biopsy. A definitive diagnosis of MF may be made on the basis of clinical and histopathologic features alone. However, determination of T-cell clonality and assessment for the aberrant loss of T-cell antigen expression by immunohistochemical staining for CD2, CD3, CD5, and CD7, are useful ancillary studies in the diagnosis of MF (and SS). The PCR-based methods are able to detect clonal rearrangements of the T-cell receptor (TCR) in formalin-fixed, paraffin-embedded biopsy specimens.[25,26] The PCR-based methods, while sensitive, should be interpreted with caution. The clonal TCR gene rearrangements may be detected in normal elderly individuals, and in patients with benign dermatoses or other disease states.[27-31] However, detection of identical clones from two different sites is quite specific for MF.[32] Even this feature is not without complications. Rare reactive processes display what appears to be an identical T-cell clone by PCR-based gene rearrangement studies in multiple biopsies over time. The extent to which MF/SS may be preceded by a pre-malignant state, analogous to monoclonal B-cell lymphocytosis (MBL), or monoclonal gammopathy of undetermined significance (MGUS), is debatable and poorly defined.[33] The malignant lymphocytes in MF/SS are usually $CD3^+CD4^+$ and $CD8^-$, but frequently lose the expression of other pan-T-cell antigens. Therefore, demonstration of a significant population of $CD4^+$ cells lacking CD2, CD5, and/or CD7 expression is highly specific (specificity >90%) for MF in most reported series.[34,35] However, reactive dermatoses may also show a predominance of CD4-positive T-cells, and diminished expression of CD7, the T-cell antigen most frequently lost in MF, and these results must be interpreted with caution.[24,35] Finding a marked predominance of CD4-positive T-cells, especially by epidermotropic T-cells, helps to support a diagnosis of MF.[24,35] Similarly, finding extensive loss of CD7, preferential loss of pan T-cell antigens by epidermal T-cells, or loss of multiple pan T-cell markers favors a diagnosis of MF in challenging cases.[24,35] Clinically, patch/plaque stage MF is frequently characterized by persistent and progressive lesions that develop in a "bathing suit" distribution and vary in size, shape and color. These lesions are frequently large (>5 cm), pruritic and multifocal in "classical" MF. However, a broad range of MF variants have been described with differences in tropism (eg, follicular MF), distribution (eg, palmoplantar MF), pigmentation (eg, hypo- and hyperpigmented variants) and focality (eg, unilesional MF), some of which are formally recognized in the WHO-EORTC classification.[1,36] Histopathologically, patch/plaque MF is characterized by enlarged, epidermotropic lymphocytes, with irregular nuclei that often show a band-like distribution in the dermis, where they are associated with dense strips of collagen ("wiry" fibrosis). Aggregates of neoplastic T-cells in the epidermis, termed Pautrier microabscesses, are seen in a minority of cases, but are a helpful clue to the diagnosis. Folliculotropism and/or syringotropism may be seen in a minority of cases. Given the need for uniform diagnostic criteria in MF, the International Society for Cutaneous Lymphoma (ISCL) recently proposed a point-based diagnostic algorithm which integrates clinical, histopathologic and immunophenotyping data with an assessment of T-cell clonality.[23]

### 2.2 | Sézary syndrome

Traditionally, SS is defined as a leukemic form of CTCL associated with erythroderma. A series of studies in the early to mid-20th century, beginning with Sezary's initial landmark observation in 1938, identified a population of large lymphocytes in the peripheral blood with grooved, lobulated (ie, "cerebriform") nuclei in patients with MF or SS.[37-42] As in other chronic lymphoproliferative disorders, the Sezary cell count is preferably expressed in absolute terms. That is with ≥1000 cells/μl classified as B2 disease in the current ISCL/EORTC TNMB staging

classification. The morphologic detection of Sezary cells in the peripheral blood is not specific for CTCL, as Sezary cells may be found in peripheral blood from normal donors and in benign conditions.[43-45] The histopathologic findings in the skin often resemble those observed in MF, with less prominent epidermotropism, though findings in skin biopsies may be paradoxically subtle and non-specific. As in MF, immunohistochemical studies showing a CD4 predominance and loss of pan T-cell markers may be helpful. Lymph node involvement is characterized by complete effacement of the nodal architecture by infiltrating Sezary cells.[46]

In SS, clonal T cells are generally $CD3^+CD4^+$ and $CD8^-$ by multicolor flow cytometry.[47-50] As in MF, the aberrant loss of pan-T-cell antigens, including CD2, CD3, CD4, CD5, CD7 and/or CD26 is frequently observed.[49,51-54] Of these, the aberrant loss of CD7 and/or CD26 expression is most common, being observed in most cases.[50,51,55-59] The loss of CD7 (≥40%) and/or CD26 (≥80%) is sensitive (>80%) and highly specific (100%) for SS.[54] The aberrant expression of the MHC class I-binding, killer immunoglobulin-like receptor (KIR) CD158κ (and less commonly CD158a or CD158b), normally expressed by natural killer cells, was described in the majority of patients examined with SS.[54,60,61] Molecular studies, including detection of a clonal TCR gene rearrangement by PCR and the presence of a clonal cytogenetic abnormality, provide evidence of T-cell clonality. An alternative approach to demonstrate T-cell clonality incorporates multi-color flow cytometry, using a panel of antibodies specific for various TCR beta-chain variable region family members (TCR-Vβ).[62-64] This approach is successful in identifying a clonal population of T cells if this population is significantly higher than the background frequency of polyclonal T cells harboring the same Vβ chain.[62,63]

The currently proposed ISCL criteria for SS integrate clinical, histopathologic, immunophenotyping and molecular studies. In patients with erythroderma, criteria recommended for the diagnosis of SS by the ISCL include the following: absolute Sezary count ≥1000/μl, a CD4/CD8 ratio ≥10 (due to the clonal expansion of $CD4^+$ cells), aberrant expression of pan-T-cell antigens, demonstration of T-cell clonality by Southern blot or PCR-based methods, or cytogenetic demonstration of an abnormal clone.[49] At a minimum, the WHO-EORTC recommends the demonstration of T-cell clonality in combination with the above-mentioned criteria for the diagnosis of SS.[1] In addition to the ISCL criteria, the most recent WHO classification requires erythroderma, generalized lymphadenopathy, and clonally related T-cells (Sézary cells) in the skin, peripheral blood, and lymph nodes. On rare occasions, SS may be preceded by a prior history of classic MF. The ISCL recommends that such cases be designated as "SS preceded by MF." Conversely, patients with MF, but without erythroderma, may meet hematologic criteria for SS. In these cases, the designation "MF with leukemic involvement" is recommended.

### 2.3 | Non-MF/SS subtypes of CTCL

An important goal during a patient's initial diagnostic evaluation is to distinguish non-MF/SS CTCL subtypes from MF/SS, as the natural history, prognosis, and treatment approach for each of the non-MF/SS lymphomas is highly variable. A detailed description of these CTCL subtypes is beyond the scope of this update, but the salient features of each have been previously summarized.[2,65]

## 3 | RISK STRATIFICATION

### 3.1 | Staging

In contrast to many other lymphoproliferative disorders in which cytogenetic and laboratory findings play a prominent role in risk stratification, TNMB (tumor, node, metastasis, blood) staging remains an important prognostic factor in MF/SS, and forms the basis for a "risk-adapted" approach to treatment. In 2007, the ISCL and EORTC revised the TNMB staging of MF/SS.[66] Patients with only patches and plaques have stage I disease, but may be further divided into stage IA (<10% body surface area involved or T1) or stage IB (>10% body surface area involved or T2) based on the extent of skin involvement, and by the presence of patch- (T1a/T2a) or plaque-stage (T1b/T2b) disease. For practical purposes, the area of one hand (including both palm and digits) represents approximately 1% of body surface area. Current staging and diagnostic recommendations do not require a biopsy of clinically normal lymph nodes. However, an excisional biopsy of any abnormal lymph nodes (≥1.5 cm in diameter or firm/fixed) is recommended. Preference is given either to the largest lymph node draining an area of skin involvement, or to the node with the greatest standardized uptake value (SUV) on FDG-PET imaging.[67-69] Patients with patch/plaque stage disease (T1/T2), and architectural preservation of any clinically abnormal lymph nodes are classified as stage IIA. Collectively, patients with stage I-IIA disease have "limited (or early)-stage" disease, as the overall survival in these patients is measured in decades, with survival in patients with stage IA disease resembling that of normal age-matched controls.[7,20,21] At diagnosis, the majority of MF patients will have limited-stage disease.[7] In contrast, patients with tumor stage disease (T3), erythroderma (T4), nodal involvement characterized by partial or complete architectural effacement (N3), visceral metastases (M1), or significant leukemic involvement (B2) have "advanced" or late "late-stage" disease. Detection of a clonal TCR gene rearrangement by PCR, which has been incorporated into the revised ISCL/EORTC node(N) and blood(B) staging classification, is an adverse prognostic factor.[7,70-73] Unfortunately, median survivals from approximately 1 to 5 years are observed in these patients with more extensive disease.[7] The revised ISCL/EORTC staging for MF/SS is summarized in Table 1.

A retrospective study including 1398 MF patients, 71% with patch/plaque stage disease, and 104 SS patients has validated the revised ISCL/EORTC staging classification.[7] On univariate and multivariate analyses, the revised T, N, M and B classification were significantly associated with overall and disease-specific survival. The median survival, disease-specific survival and risk of disease progression, by clinical stage, are summarized in Table 1. For those with early-stage disease, male gender, age > 60, plaque-stage or folliculotropic disease, and nodal stage N1/Nx were adverse prognostic factors and were utilized to generate the cutaneous lymphoma international prognostic index (CLIPi) for patients with early-stage disease.[74] Ten-year OS was 90.3% for those with low-risk (0-1 risk factors) disease, and 48.9% for those

**TABLE 1** ISCL/EORTC staging

| Stage | TNMB classification | | | | Median OS Years | 10-year (7) | | |
|---|---|---|---|---|---|---|---|---|
| | T | N | M | B | | OS (%) | DSS (%) | RDP (%) |
| IA | 1 | 0 | 0 | 0,1 | 35.5 | 88 | 95 | 12 |
| IB | 2 | 0 | 0 | 0,1 | 21.5 | 70 | 77 | 38 |
| IIA | 1, 2 | 1 | 0 | 0,1 | 15.8 | 52 | 67 | 33 |
| IIB | 3 | 0-2 | 0 | 0,1 | 4.7 | 34 | 42 | 58 |
| IIIA | 4 | 0-2 | 0 | 0 | 4.7 | 37 | 45 | 62 |
| IIIB | 4 | 0-2 | 0 | 1 | 3.4 | 25 | 45 | 73 |
| IVA1 | 1-4 | 0-2 | 0 | 2 | 3.8 | 18 | 20 | 83 |
| IVA2 | 1-4 | 3 | 0 | 0-2 | 2.1 | 15 | 20 | 80 |
| IVB | 1-4 | 0-3 | 1 | 0-2 | 1.4 | 18 (5 years) | 18 (5 years) | 82 (5 years) |

Abbreviations: OS, overall survival; DSS, disease-specific survival; RDP, risk of disease progression.

with high-risk (3-5 risk factors) disease. Similarly, male gender, age > 60, stage B1/B2 or N2/N3 disease, and visceral involvement were adverse prognostic factors for patients with late-stage disease. Ten-year OS was 53.2% for low-risk patients, and 15.0% for high-risk patients.[74] In a large, international series (n = 1275) of late-stage MF/SS, stage IV disease, age > 60, large-cell transformation, and elevated LDH were identified as independent adverse prognostic factors, and were similarly combined in a prognostic index.[75] Patients with low-risk (0-1 risk factors) disease experienced superior 5-year OS (68%), compared with the 5-year OS observed (28%) among those with high-risk (3-4 risk factors) disease.[7,76-80] Given the importance of the TNMB classification in risk stratification and defining disease burden, the ISCL/EORTC recommends its use in defining the initial, maximum and current burden of disease, which will ultimately play an important role in the selection of either skin-directed or systemic therapies.[66] In the future, it is anticipated that improved understanding of the genetic landscape will further improve risk-stratification and lead to a more personalized approach for treatment selection in CTCL.[18]

Recognizing that the staging system used for MF/SS is less helpful for non-MF/SS cutaneous lymphomas, a new TNM classification was also proposed for these CTCL variants.[81] Due to the significant heterogeneity of these lymphomas, this staging system does not provide prognostic information, but is intended to provide a uniform description of the disease burden.

## 4 | TREATMENT OF LIMITED-STAGE MF

As the majority of CTCL patients present with patch/plaque stage MF and have an excellent prognosis, the initial goal of therapy is to improve symptoms and quality of life while avoiding treatment-related toxicity. For many patients, this may involve either expectant management (ie, "watch and wait") or skin-directed therapies. A randomized trial compared early combined modality therapy, including both radiation and multi-agent chemotherapy (cyclophosphamide, doxorubicin, etoposide, and vincristine), with sequential topical therapies. It demonstrated that combined-modality therapy, while associated with a superior complete response rate, did not translate into improvements in disease-free or overall survival, and was associated with significant toxicity.[82] The limited efficacy associated with chemotherapy has been highlighted in retrospective studies in which the median time to next treatment following single or multiagent chemotherapy was ≤4 months.[83,84] Therefore, patients with limited-stage disease who require therapy are best approached with skin-directed therapies, usually under the direction of a dermatologist and/or radiation oncologist. Excellent reviews and treatment guidelines are available.[65,85-90]

### 4.1 | Topical therapies

The first-line treatment for limited stage MF is topical steroids. In an uncontrolled prospective study, topical clobetasol propionate was used in 85% of patients with stage 1A/B disease, had an overall response rate (ORR) of 94%, and is associated with minimal to no toxicity.[91,92] An alternative topical medication is mechlorethamine 0.02% gel. In a phase 2 trial, patients with stage IA-IIA MF were treated with 0.02% gel daily for up to 12 months. A response was observed in 58.5% of patients, with 13.8% achieving a complete response. A sustained response was observed in 85.5% patients, and the most common adverse effects are contact dermatitis and irritant dermatitis.[93] For refractory and persistent cutaneous lesions, bexarotene 1% topical gel may be considered. Prospective trials have demonstrated an ORR between 44% and 63%.[94] Topical toll-like receptor (TLR) agonists, which lead to local production of interferons, and other cytokines, induce cell death and promote host anti-tumor immunity,[95] and have demonstrated efficacy in limited stage MF. For example, 20 patients with stage 1A-2B disease were treated with 5% imiquimod, a TLR7 agonist. An ORR of 80%, including 45% complete responses, was observed. Toxicities are limited, including localized pain, redness, ulceration, and pruritus. Systemic symptoms, including flu-like symptoms and fatigue, while reported, are rare. Most adverse events are self-limited, and resolve after the first few weeks of treatment.[95,96] Resiquimod, a potent TLR7/8 agonist, was examined in a phase 1 trial using 0.03% and 0.06% topical resiquimod gel. Among the 12 patients treated, clinical improvement was observed in 75% of treated lesions, and 90% of patients had a reduction in malignant T-cell clones in the

treated lesions, and an abscopal, and presumably immune-mediated, effect was observed.[97]

### 4.2 | Phototherapy

Phototherapy is an important treatment modality that may be used alone, or in combination with topical therapies, in patients with limited-stage disease, and includes narrowband UVB (NBUVB, 311 nm), and 8-methoxypsoralen plus ultraviolet A (PUVA). Narrow band UVB is used in both patch and plaque stage MF, PUVA is the modality of choice in skin of color. Phototherapy is widely available and has demonstrated efficacy in many retrospective and prospective studies,[98,99] and a comprehensive consensus statement on the use of phototherapy was recently published.[100]

### 4.3 | Radiation

The MF/SS are radiosensitive, thus radiation therapy, with curative intent, may be considered in patients with localized, unilesional MF. For those with more widespread disease, palliative local radiation or low-dose total skin electron beam therapy (TSEBT) are effective [reviewed in, 101,102].

## 5 | TREATMENT OF ADVANCED-STAGE MF/SS

### 5.1 | Overview

Patients with advanced-stage MF/SS require a multidisciplinary approach, as various combinations of skin-directed therapies, biologic-response modifiers and ultimately the sequential use of systemic chemotherapeutic agents, are frequently employed in the management of these patients. As for limited-stage disease, multi-agent chemotherapy, with only few exceptions, is generally not appropriate.[82] A "risk-adapted" stage-based approach, consistent with NCCN guidelines, is adopted. This is done with biologic-response modifiers (eg, bexarotene and interferon-alpha), and histone deacetylase (HDAC) inhibitors (eg, romidepsin, vorinostat), generally preferred prior to escalating therapy to include systemic chemotherapy.[103] Therapeutic decisions are individualized and based on a patient's age, performance status, extent of disease burden, the rate of disease progression, and previous therapies.[85-90]

### 5.2 | Bexarotene

The endogenous retinoids all-*trans* retinoic acid and 9-*cis* retinoic acid (ie, vitamin-A-derived compounds) regulate a diverse array of biologic processes. They range from embryonic development to cell growth, differentiation and survival, upon binding two families of steroid hormone receptors; the retinoic acid receptors (RAR) and retinoid X receptors (RXR). Upon forming homo- or heterodimers, these receptors recruit various nuclear co-repressor or co-activator proteins depending whether or not they are bound by ligand. Multiple RAR retinoids have been used in MF/SS, either topically or systemically (reviewed in,[104,105] with response rates exceeding 50%. However, in 1999 the oral RXR-selective "rexinoid" bexarotene was FDA approved for CTCL, and was later approved as a topical gel formulation. Laboratory studies demonstrate that bexarotene promotes cell cycle arrest and apoptosis in CTCL cell lines.[106,107] In a multicenter phase II-III study, there were 94 patients with advanced-stage CTCL who had been previously treated with a median of five prior therapies. The vast majority had disease refractory to at least one prior systemic therapy, and they received at least 300 mg/m$^2$ of oral bexarotene daily.[108] Among patients treated at the 300 mg/m$^2$ dose, an ORR of 45% was observed, only 2% of which were complete. While an improved ORR was noted with the use of higher doses, this difference was not statistically significant, and dose-limiting toxicity was far more common (50% vs 89%) in these patients. While a dose-response relationship is likely, the 300 mg/m$^2$ dose appears to provide the optimal risk-benefit ratio. The most common toxicities associated with therapy were hypertriglyceridemia (in 82%) and central hypothyroidism (29%). Myelosuppression is infrequent and usually uncomplicated. Pancreatitis secondary to hypertriglyceridemia may be rarely observed, but is reversible upon discontinuation of treatment. Therefore, a baseline lipid panel and free T4/TSH should be obtained prior to the initiation of therapy. In one retrospective study, all patients treated with bexarotene developed hyperlipidemia and central hypothyroidism, frequently within weeks of initiating treatment.[109] Consequently, use of lipid-lowering agents (eg, fenofibrate) and low-dose levothyroxine (eg, 50 micrograms) prior to initiating bexarotene is generally recommended.[110-112] In clinical practice, bexarotene is frequently initiated at a lower dose of 150 mg/m$^2$, and subsequently titrated to full doses after 4 weeks of therapy, depending upon patient tolerability. Most responses occur within 2 to 3 months of treatment initiation, but may be delayed. Therefore, in the absence of disease progression or toxicity, treatment should be continued for up to 6 months. For responding patients, treatment should be continued until disease progression, and depending upon the quality of the response, adjunctive skin-directed therapies (eg, PUVA, interferon) should be considered.[113] Guidelines describing appropriate laboratory monitoring, supportive care, and safe clinical prescribing of bexarotene have been recently published.[112] Future studies clarifying the optimal use of bexarotene, either in combination or sequentially with other agents, are needed.

### 5.3 | HDAC inhibitors

HDACs catalyze the removal of acetyl groups from both histone and non-histone proteins. As histone acetylation is associated with an open chromatin configuration associated with active gene transcription, HDACs contribute to histone deacetylation and the epigenetic repression of gene transcription. As HDACs regulate a wide variety of processes involved in carcinogenesis, multiple mechanisms may explain the clinical activity of HDAC inhibitors.[114,115] Those include altered gene expression of cell-cycle and apoptotic regulatory proteins,[116-120] acetylation of non-histone proteins regulating cell growth and survival,[121-124] angiogenesis,[125,126] aggresome formation[127] and DNA repair.[128] In addition, HDAC inhibitors may have important effects on the tumor microenvironment via reactive oxygen species,[129,130] enhanced antigen

presentation[131] and downregulation of immunomodulatory cytokines, like IL-10.[132]

Vorinostat (suberoylanilide hydroxamic acid, SAHA) and romidepsin (depsipeptide) inhibit class I and II HDACs (ie, pan-HDAC inhibitors), the former being widely expressed in various lymphoma subtypes.[133] Early phase I studies of both vorinostat and romidepsin established their safety and potential efficacy in lymphoproliferative disorders, including CTCL,[134] thus paving the way for larger phase II studies. An earlier phase II study established 400 mg of oral vorinostat once daily as the optimal dose that was investigated further in 74 previously treated patients with CTCL, most of whom (>80%) had advanced-stage disease.[135,136] The ORR was approximately 30% for patients with advanced-stage disease, and was associated with a median duration of response estimated to exceed 185 days. Most responses were rapid (ie, <2 months), and were also noted in patients with tumor-stage disease and SS.[137] Patients who failed to achieve an objective response appeared to derive some clinical benefit, including stable disease, decreased lymphadenopathy and pruritis relief, with treatment. The most common non-hematologic adverse events, observed in almost 50% of patients, were gastrointestinal toxicities (nausea, vomiting, and diarrhea). Hematologic toxicities, including anemia or thrombocytopenia, were observed in up to 20% of patients. Among responding patients, long-term therapy with vorinostat appears to be well tolerated.[138] Prolongation of the QT interval was rarely observed, but monitoring and appropriate electrolyte replacement is recommended for those patients at risk for QT prolongation.[139]

Romidepsin, administered as a four-hour intravenous infusion (14 mg/m$^2$) days one, eight and 15 every 4 weeks, was evaluated in two phase II studies, the largest of which included 96 patients, most with advanced-stage disease.[140,141] The ORR was 38% for patients with advanced-stage disease, with a median duration of response that exceeded 1 year. A toxicity profile similar to that described for vorinostat was observed. Intensive cardiac monitoring in a subset of these patients failed to demonstrate any clinically significant cardiotoxicity.[142] A subset of MF/SS patients, after induction with romidepsin at the standard dose, may anticipate a durable remission with attenuated "maintenance" (every two or four-weeks) dosing. For example, among 38 MF/SS patients, 17 achieved a durable (>6 months) remission, nine of which were maintained with an attenuated, dose-sparing schedule.[143] Among the patients achieving a durable remission, the median duration of treatment was 15 months (range: 7-34 months).

Additional HDAC inhibitors, including potent pan-HDAC inhibitors, appear to have activity in CTCL.[120,144,145] Further studies are needed to fully define the mechanisms of resistance to HDAC inhibition in CTCL,[120,146-150] enabling the development of rational therapeutic combinations incorporating HDAC inhibitors in CTCL.[151,152]

## 5.4 | Interferon-alpha

Interferon-alpha (ie, interferon-alpha 2b), a type I interferon with immunomodulatory properties, has pleiotropic effects in CTCL, and is associated with an ORR of 50%-70%. It has a complete response rate of 20%-30%, particularly in patients with limited-stage disease.[153-156] While often considered as second-line therapy for limited-stage CTCL, interferon-alpha, frequently at doses ranging from 3-10 million units daily to three times weekly, is a treatment to be considered in the first-line setting in patients with advanced-stage disease. Responses, which may be achieved within a few months, are observed in patients with tumor-stage MF and SS, and are occasionally durable.[83,157] Furthermore, interferon-alpha may be successfully combined with a number of other therapeutic modalities frequently utilized in the management of these patients, including PUVA, bexarotene, chemotherapy and ECP.[158-171] For example, in a cohort of 51, mostly advanced-stage patients treated with single-agent, low-dose, interferon-alpha, responses were observed in 34 (67%), including 21 (41%) with a complete response, and nine with a long-term remission.[156] Similarly, in a cohort of 47 patients with stage III/IV disease, 89% of whom had peripheral blood involvement, a response rate exceeding 80% was observed in those treated with a combination of ECP and interferon-alpha.[171] Interferon-alpha is associated with myelosuppression, transaminitis and dose-limiting flu-like side effects, particularly at higher doses.

## 5.5 | Extracorporeal photophoresis (ECP)

During ECP, pooled leukapheresis and plasmapheresis products are exposed to 8-methoxypsoralen (8-MOP), prior to extracorporeal circulation through a 1 mm thick disposable cassette exposed to UVA radiation. The irradiated leukocytes, representing approximately 5% of peripheral blood leukocytes, are subsequently reinfused. Psoralen covalently binds and crosslinks DNA following UVA exposure, leading to the induction of apoptosis in the majority of treated lymphocytes by multiple mechanisms involving bcl-2 family members, disruption of the mitochondrial membrane potential and extrinsic cell death pathways.[172-174] In contrast, ECP leads to monocyte activation, including significant changes in gene expression,[175] and dendritic cell differentiation, which is thought to culminate in enhanced antigen presentation and the initiation of a host immune response.[176]

Following the landmark study by Edelson and colleagues describing responses in 27 out of 37 patients with erythrodermic CTCL treated with ECP, it was approved by the Food and Drug Administration of the USA for the treatment of CTCL. It is now considered the treatment of choice in the first-line management of patients with SS in many centers.[177] Furthermore, retrospective series demonstrate that ECP is associated with superior time to next treatment, when compared with most systemic therapies, including HDAC inhibitors.[84] While responses vary between case series, ORRs hover around 60%, with a complete response rate of approximately 20%.[178-181] As current treatment protocols no longer require the oral administration of 8-MOP, eliminating nausea, ECP is safe and generally very well tolerated. Long-term use of ECP may cause iron deficiency anemia due to the small residual blood volume that is not returned to the patient.[182] While alternative schedules have been investigated, ECP is generally performed for two consecutive days every 4 weeks, although alternative schedules have been adopted at some centers. While the precise mechanism of action is incompletely understood, evidence suggests that ECP has immunomodulatory effects which may augment host

anti-tumor immunity. It is not surprising then that the median time to response following the initiation of ECP is approximately 6 months. Median survival exceeding 8 years has been observed in ECP treated patients and among complete responders, many experience durable responses which may permit, for some, weaning from CTCL-directed therapies.[178,183-185] While patient- or disease-specific factors which may predict a response to therapy are imperfect, patients for whom treatment is initiated promptly after diagnosis who have circulating Sézary cells, but without significant nodal or visceral disease, may be more likely to respond. In addition, patients without profound immune deficiencies, reflected by normal or near-normal cytotoxic T-cell and CD4/CD8 values, and the absence of prior exposure to systemic chemotherapy, may be more likely to respond to therapy.[178,180,184] While effective as monotherapy, ECP has also been combined with other therapeutic strategies, including interferon, bexarotene and TSEBT.[161,171,183,186-188]

## 5.6 | Monoclonal antibodies and immunotoxins

In contrast to many B-cell lymphoproliferative disorders, where the incorporation of CD20-targeting monoclonal antibodies has become the standard of care, additional studies are needed to identify the optimal approach targeting T-cell specific antigens in advanced-stage MF/SS. Alemtuzumab is a humanized IgG1 monoclonal antibody directed against CD52, an antigen widely expressed by B-cells, T-cells and monocytes.[189] In a phase II study in 22 patients with advanced-stage MF/SS, overall and complete response rates of 55% and 32%, respectively, were observed, with a median time to treatment failure of 1 year.[190] Given the significant risk of infectious complications, low-dose subcutaneous alemtuzumab was investigated in 14 patients with SS, most of whom had relapsed/refractory disease.[191] Most patients in this study received 3 mg of subcutaneous alemtuzumab on day 1, followed by a 10 mg dose on alternating days until the Sézary count was <1000/mm$^3$. With the exception of a single patient whose best response was stable disease, 9 out of 10 patients treated in this manner achieved a response, three of which were complete. For most patients, the time to treatment failure exceeded 12 months. What is notable, however, is that infectious complications were not observed in patients treated with the lowest dose (ie, 10 mg) of alemtuzumab. Similar results, with no infectious complications, were recently reported in a small cohort of patients treated with modified, low-dose, subcutaneous alemtuzumab for 6 weeks.[192] In addition to hematologic toxicity, conventionally dosed alemtuzumab in advanced-stage MF/SS is associated with a high incidence of infectious complications.[190,191,193-196] Overall, infectious complications have been observed in two-thirds of treated patients, most of which are bacterial, including sepsis. Cytomegalovirus (CMV) reactivation is the most common viral infection. In addition, *Pneumocystis jirovecii* pneumonia and invasive fungal infections have also been observed. Therefore, trimethoprim-sulphamethoxazole and acyclovir should be routinely administered for PJP and HSV/VZV prophylaxis, respectively, in patients receiving alemtuzumab. In addition, CMV surveillance should be performed every 1 to 2 weeks by quantitative PCR, and suppressive therapy with ganciclovir or oral valganciclovir initiated in response to viral reactivation. Low-dose, subcutaneous alemtuzumab appears to be safe and efficacious in selected patients with advanced-stage MF/SS provided with appropriate supportive care. Monoclonal antibodies targeting additional T-cell specific antigens, including CD2,[197] CD4,[198] CD25[199] and CCR4[200-202] are being explored and appear promising. Resimmune, a second-generation immunotoxin in which the catalytic and translocation domains of diphtheria toxin ($DT_{390}$) have been fused to CD3-specific single chain antibody fragments [bisFv(UCHT1)], is associated with a response rate of 36% (16% complete), and is particularly active in patients with limited-stage disease.[203] Much like its predecessor, resimmune is associated with a vascular leak syndrome.[65]

## 5.7 | Mogamulizumab

Mogamulizumab (KW-0761) is a humanized monoclonal antibody specific for the chemokine receptor CCR4 that has been defucosylated and is consequently associated with enhanced antibody-dependent cell-mediated cytotoxicity (ADCC). In a phase I/2 study, mogamulizumab was well tolerated and was associated with an ORR of 37%. A similar response rate of 29% (2/7), all partial, was observed in a phase II Japanese study.[202,204] In addition to ADCC-mediated clearance of malignant T cells, mogamulizumab may inhibit $T_{reg}$-mediate immune suppression,[205,206] and may warrant further investigation with immunomodulatory therapies, including immune checkpoint blockade (CPB).[207] A randomized, phase III clinical trial comparing mogamulizumab and vorinostat in relapsed/refractory CTCL (MAVORIC) demonstrated a significant improvement in progression-free survival among MF/SS patients randomized to mogamulizumab.[208] Overall responses in patients treated with mogamulizumab were higher in the blood compartment (68%) when compared with those observed in the skin (42%) or lymph nodes (17%). Not surprisingly then, the ORR was highest among Sezary syndrome (SS) patients (37%). Overall, treatment with mogamulizumab was well tolerated, with few ≥grade 3 adverse events (AE's). Infusion-related reactions were the most common grade 1 or 2 AE's and were observed in 32%. These positive findings led to mogamulizumab's approval by the FDA in 2018 for MF/SS patients who have failed at least one prior systemic therapy.

## 5.8 | Brentuximab vedotin

Given the promising response rates observed with brentuximab vedotin (BV) in phase II studies,[209-211] a randomized, phase III clinical trial (ALCANZA) comparing BV with an investigator's choice (methotrexate or bexarotene) was performed, and demonstrated a significantly improved PFS (>12 months vs 3.5 months) for patients randomized to BV, and led to its FDA approval in previously treated CTCL.[212] Among MF patients with limited-stage disease treated with BV, a response lasting at least 4 months (ORR4) was observed in 40%, whereas an ORR4 of 63% was observed among patients with tumor-stage (stage IIB) disease. Consistent with prior experience in "CD30 high" lymphomas, an ORR4 of 89% was observed among patients with primary cutaneous ALCL with disease confined to the skin.

### 5.9 | CPB

Durable remissions may be achieved with immunomodulatory therapies, including ECP and interferon-α. While largely anecdotal, these observations suggest that host immunity, when properly harnessed, can lead to durable responses in selected patients. These observations, coupled with high-level PD-L1 expression in a substantial minority of patients, provide a strong rationale for CPB in CTCL.[213,214] While few CTCL patients have been included in early phase clinical trials, durable responses have been observed, including two responding CTCL patients who achieved responses that were ongoing at 24+ and 50+ weeks.[215] Preliminary data from an ongoing phase II study with pembrolizumab in relapsed/refractory MF and SS appears similarly promising. There is an ORR of 33% in MF/SS, including in patients with advanced-stage disease.[214] These encouraging preliminary results, in conjunction with the smorgasbord of currently available immunomodulatory agents, including HDAC inhibitors, may lend themselves to future combinatorial strategies.[214]

### 5.10 | Systemic chemotherapy

Responses to conventional chemotherapeutic agents are rarely durable in CTCL,[65] being associated with a median time-to-next treatment that is measured in months.[83,84] Consequently, >90% of patients treated in this manner will require additional therapy within the first year of therapy. Furthermore, first-line treatment with systemic chemotherapy has been associated with increased mortality.[216] Therefore, multi-agent chemotherapy is rarely utilized, and is generally reserved for patients with bulky and rapidly progressive disease. Therefore, novel therapeutic agents, including clinical trial participation, are preferred. As there is no standard of care for patients with MF/SS requiring systemic chemotherapy and the decision to initiate therapy is individualized, including consideration of responses and complications related to prior therapies, participation in a well-designed clinical trial is always worth consideration.

Pralatrexate, a novel antifolate with a high affinity for the reduced folate carrier (RFC-1) and novel mechanism of resistance when compared with methotrexate,[217-219] was associated with an ORR of 29% in the PROPEL study. This study was comprised largely of peripheral T-cell lymphoma patients, most of whom had refractory disease.[220] Notably, 12 patients with transformed MF were included in the study.[221] Many of these patients had received more than five prior systemic therapies, including CHOP or CHOP-like regimens. With only a single exception, these patients were refractory to their most recent therapy. Responses, as assessed by the study investigators, were observed in 58% of patients with a median duration of response and progression-free survival of 4 to 5 months. Results of a dose-finding study were reported in a larger cohort of CTCL patients.[222] In this study, the optimal dose was identified as 15 mg/m$^2$, given weekly 3 weeks out of 4, and was associated with an ORR of 43%. In an effort to reduce the incidence of mucositis, folic acid and vitamin B12 supplementation is routinely provided in these patients.[223] Additional therapeutic approaches, including proteasome inhibition,[224] immunomodulatory strategies,[225] and more targeted approaches warrant further investigation.[226,227]

### 5.11 | High-dose chemotherapy and hematopoietic stem cell transplantation

The available experience with high-dose chemotherapy and autologous stem cell transplantation, largely confined to case series, suggests that responses following treatment are frequently transient. In contrast, the durable remissions observed following allogeneic transplantation may be explained by the graft vs lymphoma immune response.[228,229] A retrospective analysis of 60 patients with advanced-stage MF/SS who underwent allogeneic stem cell transplantation was recently reported.[230] In this series, patients had received a median of four prior therapies prior to undergoing either reduced-conditioning (73%) or myeloablative (27%) conditioning, prior to related (75%) or matched-unrelated donor (25%) transplantation. Non-relapse mortality at 1 year was 14% for patients receiving reduced-intensity conditioning or HLA identical/related donor stem cells and 38-40% for those undergoing myeloablative conditioning or receiving match-unrelated donor grafts. Transplantation during an early phase of disease (defined as first or second remission or relapse following three or fewer systemic therapies) was associated with lower relapse rates (25% vs 44% at 1 year), and a statistically insignificant increase in three-year overall survival (68% vs 46%). Given the differences in non-relapse mortality, both reduced-intensity conditioning and use of matched-related donors were associated with superior overall survival (63% at 3 years). Seventeen out of 26 patients who relapsed received donor-lymphocyte infusions. Of these, 47% achieved a complete remission, thus providing evidence for a graft-vs-lymphoma effect in MF/SS. The estimated three-year progression-free and overall survival were 34% and 53%, respectively. In a larger series from the CIBMTR (n = 129), non-relapse mortality and disease progression at 1 year were 19% and 50%, respectively, and 5 years PFS and OS were 17% and 32%, respectively.[231] Given the possibility of complete and durable remissions, allogeneic stem-cell transplantation may be considered in highly selected patients.[157,232,233]

## 6 | SUMMARY

Establishing a definitive diagnosis of CTCL, accurate disease staging and risk-stratification, and the selection of appropriate therapy requires a multidisciplinary approach. While high response rates may be achieved with systemic chemotherapy, these responses are frequently short-lived and associated with significant toxicities. As treatment of advanced-stage MF/SS is largely palliative, a stage-based approach utilizing sequential therapies in an escalated fashion is preferred. Participation in a well-designed clinical trial is encouraged, as the introduction of novel agents will continue to expand the therapeutic options available in the management of CTCL.

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## CONFLICT OF INTEREST

Nothing to report.

## ORCID

*Ryan A. Wilcox* https://orcid.org/0000-0002-6420-0760

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