Continuing medical education activity in *American Journal of Hematology*

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Article Title: Cutaneous T-cell lymphoma: 2011 update on diagnosis, risk-stratification, and management

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Upon completion of this educational activity, participants will be better able to discuss the current approach to diagnosing and managing Cutaneous T-cell lymphoma.

Activity disclosures

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Faculty disclosures

CME editor—Ayalew Tefferi, MD: The CME Editor has no relevant conflicts of interest.

Author—Ryan A. Wilcox, MD: The author has no relevant conflicts of interest.

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ANNUAL CLINICAL UPDATES IN HEMATOLOGICAL MALIGNANCIES:
A CONTINUING MEDICAL EDUCATION SERIES

Cutaneous T-cell lymphoma: 2011 update on diagnosis, risk-stratification, and management

Ryan A. Wilcox*

Disease overview: **Cutaneous T-cell lymphomas are a heterogenous group of T-cell lymphoproliferative disorders 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: **Tumor, node, metastasis, and blood (TNMB) staging remains the most important prognostic factor in MF/SS and forms the basis for a "risk-adapted," multidisciplinary approach to treatment. For patients with disease limited to the skin, expectant management or skin-directed therapies is 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 biologic-response modifiers, denileukin diftitox, and histone deacetylase inhibitors before escalating therapy to include systemic, single-agent chemotherapy. Multiagent chemotherapy may be used for those patients with extensive visceral involvement requiring rapid disease control. In highly-selected patients with disease refractory to standard treatments, allogeneic stem-cell transplantation may be considered. Am. J. Hematol. 86:929–948, 2011.** © **2011 Wiley-Liss, Inc.**

Disease Overview

Primary cutaneous lymphomas are a heterogenous group of extranodal non-Hodgkin lymphomas which, by definition, are largely confined to the skin at diagnosis. After the gastrointestinal tract, the skin is the second most common site of extranodal involvement in non-Hodgkin lymphoma [1]. The European Organization for Research and Treatment of Cancer (EORTC) and World Health Organization (WHO) published a consensus classification for cutaneous lymphomas in 2005, as summarized in Table I [2]. In contrast to nodal non-Hodgkin lymphoma, most of which are B-cell derived, ~75% of primary cutaneous lymphomas are T-cell derived, two-thirds of which may be classified as Mycosis fungoides (MF) or Sézary syndrome (SS) [2–4]. 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 (male:female incidence rate ratio 1.9) and African–Americans (incidence rate ratio 1.5) [3]. While CTCL may occur in children and young adults, this is very uncommon and often associated with histologic 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 fourfold 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 human T-cell lymphotropic virus-1 (HTLV-1) infection in adult T-cell leukemia/lymphoma [8–11]. 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 [12–14]. 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.

Cell of origin

It is estimated that normal human skin contains approximately one million T cells per cubic centimeter. Consequently, the skin is an important "lymphoid organ," as the skin contains twice as many T cells (~20 billion) than the peripheral blood [15]. Following antigenic activation, naïve T cells differentiate into effector and memory cells with distinct migratory patterns characterized by the expression of tissue-specific homing addressins. The overwhelming majority of skin-resident T cells are $CD45RO^+$ memory T cells expressing the skin-homing addressin CLA, which binds E-selectin on post-capillary venules in the skin and is required for lymphocyte rolling [15]. Skin-resident T cells highly express the chemokine receptors CCR4, CCR6, and CCR10, among others, required for their migration into the skin [15–17]. In contrast to central memory T cells (T_{CM}) expressing CCR7 and L-selectin, required for lymph-node homing and circulation in the peripheral blood, effector memory T cells (T_{EM}) form a persistent population of tissue-resident cells capable of rapidly responding to antigenic rechallenge and comprise 80% of T cells residing in normal skin [15]. Immunophenotyping studies demonstrate that malignant T cells in patients with leukemic CTCL variants (Sézary Syndrome) express CCR7 and L-selectin, resembling T_{CM}, while the malignant clone in MF lesions resembled T_{EM} [18]. This fundamental difference in the putative cell of origin between SS (T_{CM} derived) and MF (T_{EM} derived) is consistent with their distinct clinical behavior, as T_{CM} may be found in both the peripheral blood, lymph node and skin and are long-lived cells resistant to apoptosis, while skin-resident T_{EM} cells fail to circulate in peripheral blood, remaining fixed within the skin [18]. The contention

Conflict of interest: Nothing to report
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Received for publication 6 July 2011; Accepted 9 July 2011

Am. J. Hematol. 86:929–948, 2011.

Published online in Wiley Online Library (wileyonlinelibrary.com).
DOI: 10.1002/ajh.22139

that MF and SS originate from different T-cell subsets is consistent with comparative genomic hybridization (CGH) and gene-expression profiling data demonstrating that these CTCL subtypes are genetically distinct [19,20].

Regulatory T cells (Treg) expressing the transcription factor FoxP3 are important in the maintenance of self-tolerance and form a minor subset of skin-resident T cells. During in vitro cultures with immature dendritic cells loaded with apoptotic T cells, malignant T cells from CTCL patients upregulated the expression of activation antigens and FoxP3, leading to the suggestion that CTCL may be derived from Treg cells [21]. However, conventional T cells upregulate FoxP3 expression following activation [22,23]. Therefore, FoxP3 expression alone, particularly at low-intermediate levels, as observed in activated T cells and in some patients with CTCL, is insufficient evidence to support the claim that clonal T cells in MF or SS are Treg-derived, particularly considering the observation that conventional T cells may acquire a similar Treg-phenotype when cultured under similar conditions [24,25]. Subsequent histologic analyses of FoxP3 expression by immunohistochemical staining demonstrate that malignant T cells in CTCL lesions do not express FoxP3 to any significant degree [26,27]. As FoxP3 expression is not entirely specific for Treg cells, the definition of "Treg cells" has been, at least in part, a functional one. Therefore, the interpretation of data demonstrating that $FoxP3^+$ CTCL cells suppress conventional T cells is fraught with difficulty, as these cells may suppress conventional T cells in a FoxP3-independent fashion [28]. The finding that the FoxP3 promotor is demethylated in *bona fide* Treg has shed light on this issue [29]. Heid et al. recently demonstrated that the malignant T cells in a subset of Sézary patients may be derived from Treg cells, as the malignant clone in these patients not only expressed FoxP3 and suppressed conventional T cells but possessed a demethylated FoxP3 promoter [30]. Whether this subset of patients represents a distinct or overlapping population with the subset of Sézary patients which were recently found to express low-molecular weight splice forms of FoxP3 is unknown [28]. Therefore, a subset of CTCL patients appears to harbor a Treg-derived clone, although the prognostic and therapeutic implications of this observation remain to be defined.

In contrast to regulatory T cells, which represent a minority of skin-resident T cells, the majority of effector T cells present in the skin produce cytokines characteristic of distinct T-cell subsets, including Th1, Th2, and Th17 cells, raising the possibility that future studies may define CTCL subsets derived from these T-cell subsets [31]. Of note, MF/SS is associated with the expression of Th2-associated genes (e.g., GATA-3) and the production of Th2-associated cytokines (e.g., IL-4, IL-5, and IL-10), thus raising the possibility that a significant subset of patients may harbor Th2-derived clones [32–36]. As the cell of origin is further defined in subsets of CTCL, including MF/SS, one may anticipate that this data may have a significant impact on the classification, risk-stratification, and treatment of these diseases.

Immunopathogenesis

The establishment of long-term CTCL cell lines is challenging, as these cell frequently undergo spontaneous cell death during in vitro culture [37,38] (and personal observation). Therefore, the resistance to apoptosis observed in vivo is unlikely due to an intrinsic resistance to apoptosis alone. Rather, extrinsic factors present within the tumor microenvironment likely contribute to the growth and survival of malignant T cells, a contention supported by the observation that cytokine supplementation or the provision of T-cell costimulatory signals supports the growth of malignant T cells in vitro [37,39,40]. Both gene-expression profiling and immunohistochemistry-based studies have recently highlighted the important contribution of nonmalignant cells, including monocyte-derived lymphoma-associated macrophages, in the pathogenesis of both Hodgkin and non-Hodgkin lymphomas [41–43]. Similarly, malignant T cells in the skin are frequently associated with dendritic cells and immunohistochemistry-based studies have clearly demonstrated an abundant infiltrate of both lymphoma-associated macrophages and dendritic cells, many of which may be actively recruited into the tumor microenvironment by tumor-derived chemokines [44,45]. These monocyte-derived cells promote tumorigenesis both directly, by the production of factors which promote tumor cell growth and survival, and indirectly, by supporting tumor angiogenesis and suppressing host antitumor immunity [46]. For example, monocyte-derived dendritic cells supported the long-term survival of malignant T cells during in vitro culture [38]. More recently, peripheral blood monocytes (and their progeny) were shown to support the growth of malignant T cells in vitro, confer resistant to chemotherapy, and promote tumor engraftment in immunodeficient mice [45]. Lymphoma-derived IL-10, upregulated in patients with advanced-stage disease poorly responsive to therapy [47], impairs the maturation of lymphoma-associated dendritic cells, rendering them immunologically incompetent, thus promoting escape from host antitumor immune surveillance. In addition, lymphoma-associated dendritic cells were observed to express the T-cell coinhibitory ligand B7-H1 (PD-L1, CD274), which directly inhibits the proliferation of tumor-specific T cells, but also indirectly impairs antitumor immunity by promoting the induction of suppressive regulatory T cells [48]. Therefore, lymphoma-associated macrophages and dendritic cells appear to play an important role in cutaneous T-cell lymphomagenesis while contributing to the evasion and suppression of host antitumor immunity.

In addition to the tumor microenvironment's role, widespread impairment of cellular immunity—the tumor "macroenvironment"—has long been appreciated in CTCL and contributes to the significant morbidity and mortality associated with infectious complications observed in CTCL. Approximately 50% of patients with CTCL, particularly those with advanced stage disease, will ultimately succumb to infectious complications [49–51]. Both quantitative and qualitative defects in natural killer (NK) cell [52,53], dendritic cell [54], and T cell-mediated [55–57] immunity are observed in CTCL. In addition, CTCL is associated with a significant loss of the T-cell repertoire, analogous to that observed in HIV infection. T-cell receptor (TCR) diversity within multiple TCR beta-variable (Vβ) families was analyzed using complementarity-determining region 3 (CDR3) spectratyping and combined with a quantitative analysis of TCR-Vβ usage by flow cytometry [58]. In patients with advanced-stage disease, and half of patients with limited-stage disease, a dramatic loss of TCR diversity was observed. Whether this observation may be explained by tumor-mediated suppression of nonmalignant T cells, diminished thymic output of naïve T cells and compensatory homeostatic expansion of oligoclonal peripheral T cells, or some other mechanism, is unknown [47]. As lymphopenia is an adverse prognostic factor in many hematologic malignancies [59–64], and undoubtedly contributes to the infectious complications observed in CTCL, improved understanding of the causative mechanism(s) leading to this dramatic loss of T-cell diversity may have significant therapeutic implications.

Molecular pathogenesis

Recurrent chromosomal translocations involving the IgH gene on chromosome 14 lead to the aberrant expression of anti-apoptotic (e.g., Bcl-2) and oncogenic (e.g., cyclinD1, Myc) proteins in B-cell lymphomas. These recurrent trans-

locations arise in peripheral B cells undergoing class-switch recombination and somatic hypermutation. In contrast, the TCR gene loci, while involved in recurrent chromosomal translocations in precursor T-cell lymphoblastic leukemias/lymphomas, are rarely involved in recurrent translocations in mature T-cell lymphoproliferative disorders [65,66]. With the exception of translocations involving the interferon regulatory factor 4 (IRF4) gene (also known as MUM1) in a subset of cutaneous anaplastic large cell lymphomas, recurrent chromosomal translocations are infrequently observed in CTCL [67–71]. Despite this, a number of signaling pathways regulating cell-cycle progression and survival have been implicated in CTCL pathogenesis.

The NF-kB family of transcription factors (i.e., c-rel, p65/RelA, RelB, p50/p105, p52/p100) plays an important role in normal lymphocyte development, activation and differentiation via the regulation of target genes involved in cell growth, survival and cytokine production. Normally, NF-kB is sequestered within the cytoplasm by members of the IkB family of inhibitory proteins. A variety of cytokines, antigen-receptor engagement and other stimuli, including signaling events downstream of the HTLV-1 encoded Tax protein expressed in ATLL, culminate in NF-kB activation. Phosphorylation of IkBs by IkB kinase (IKK), composed of two catalytic subunits (IKKα, IKKβ) and a regulatory subunit (NF-kB essential modulator/IKKγ), triggers IkB ubiquitination and subsequent proteasomal degradation. In this way, NF-kB dimers are liberated and regulate gene expression following nuclear translocation. Multiple mechanisms, well described in B-cell lymphomas, lead to constitutive NF-kB activation, promoting lymphomagenesis [72]. In a similar fashion, NF-kB is constitutively activated in CTCL [73–75]. Immunohistochemical analysis of MF cases demonstrated nuclear localization of p65/RelA in over 90% of the cases examined [73]. Furthermore, pharmacologic NF-kB inhibition in CTCL cell lines decreases NF-kB DNA binding activity, thus promoting cell death [73–76]. While the molecular mechanisms leading to constitutive NF-kB activation in CTCL are poorly understood, the observation that IKK inhibition downregulates NF-kB activity implicates upstream IKK-activating elements [74,75].

The signal transducers and activators of transcription (STATs) are a family of six transcription factors which become phosphorylated by one of four upstream receptor-associated Janus kinases (JAKs) following cytokine stimulation. Nuclear localization and DNA-binding of phosphorylated STAT3 has been convincingly demonstrated in CTCL [77,78]. Following nuclear translocation, STAT3 directly regulates a number of target genes in CTCL, including regulators of apoptosis (e.g., Bcl-2/Bax), cytokines (e.g., IL-5, IL-13) and suppressors of cytokine signaling (e.g., SOCS). In addition, STAT3 indirectly regulates gene expression by inducing the expression of DNA methyltransferase 1 (DNMT1), which promotes the epigenetic silencing of tumor suppressor genes [79]. Not surprisingly then, pharmacologic inhibition of STAT3 promotes apoptosis in CTCL [77,80–82]. Cytogenetic gains involving STAT5A and STAT5B or their activation in response to cytokines present within the tumor microenvironment suggests a pathogenic role for other STATs [83–85].

Normal T cells undergo a controlled process of activation-induced cell death following antigen-dependent activation and proliferation, thus maintaining lymphocyte homeostasis. Extrinsic death receptors, including Fas (CD95), play an important role in regulating this process. A number of mechanisms, including promoter methylation [86–88], gene mutations [89] and loss of the long arm of chromosome 10 [90] result in diminished Fas expression in CTCL and reduced sensitivity to apoptosis. In addition, promoter methylation and epigenetic instability leading to the inactivation of many tumor suppressor genes, including those involved in the induction of apoptosis, appear to be commonly used mechanisms of lymphomagenesis in CTCL [91].

In addition to multiple defects in apoptosis, aberrant cell-cycle regulation, including inactivation of the CDKN2A-CDKN2B locus, is frequently observed in CTCL. The CDKN2A locus, located on chromosome 9p21, encodes for two overlapping proteins ($p16^{INK4A}$ and $p14^{ARF}$) by the selective use of two alternative first exons. The $p16^{INK4A}$ protein inhibits cyclinD1-dependent activation of cyclin-dependent kinase (CDK) 4 and CDK6, thus preventing RB1 phosphorylation and cell-cycle progression. In contrast, $p14^{ARF}$ inhibits MDM2, a ubiquitin ligase that targets p53 for proteasomal degradation, leading to the induction of p53-dependent genes, including cell-cycle regulators (e.g., $p21^{WAF1/CIP1}$). The CDKN2B locus encodes $p15^{INK4B}$ which inhibits CDK4/6 and subsequent RB1 phosphorylation. Therefore, combined deletion of CDKN2A/CDKN2B or their epigenetic silencing, leads to RB1 phosphorylation and loss of p53, culminating in cell-cycle progression. These abnormalities are frequently observed in CTCL, suggesting their early involvement in disease pathogenesis [92,93]. Cyclin upregulation, including cyclinD1, and loss of RB1 have also been described [94]. As gene-expression profiling and next-generation sequencing technologies are used, additional pathogenic pathways, including those involving transcription factors regulating T-cell differentiation [35,36], c-MYC [95,96], RAS/RAF/MEK signaling [97], among others [90,98], may be identified in subsets of CTCL.

Diagnosis

Mycosis fungoides

The definitive diagnosis of MF, particularly patch/plaque stage disease, is challenging, as many of its clinical and pathologic features are nonspecific. Many patients will have had symptoms attributed to eczema or parapsoriasis for years before obtaining a definitive diagnosis. The median time from symptom onset to diagnosis in retrospective series is 3–4 years, but may exceed four decades [99–101]. 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 (Fig. 1A). However, a broad range of MF variants have been described with differences in tropism (e.g., follicular MF), distribution (e.g., palmoplantar MF), pigmentation (e.g., hypopigmented and hyperpigmented variants) and focality (e.g., unilesional MF), some of which are formally recognized in the WHO-EORTC classification (see Table I) [2,102].

Histologically, MF is characterized by the infiltration of small to medium-sized lymphocytes with cerebriform nuclei in the upper dermis and epidermis (i.e., epidermotropism), occasionally forming intraepidermal nests, or Pautrier's microabscesses (Fig. 1B). In a retrospective review, biopsy specimens obtained from 64 patients with bona fide MF (based on their clinical course) were systematically compared with 47 non-MF biopsy specimens. On univariate analysis, seven characteristics were significantly associated with MF, including: Pautrier's microabscesses, haloed lymphocytes, exocytosis, disproportionate epidermotropism, epidermal lymphocytes larger than dermal lymphocytes, hyperconvoluted (i.e., cerebriform nuclear contour) intraepidermal lymphocytes, and lymphocytes aligned within the basal layer [103]. Of these, the presence of haloed lymphocytes was the most significant discriminator on multivariate analysis. Unfortunately, these histologic characteristics are

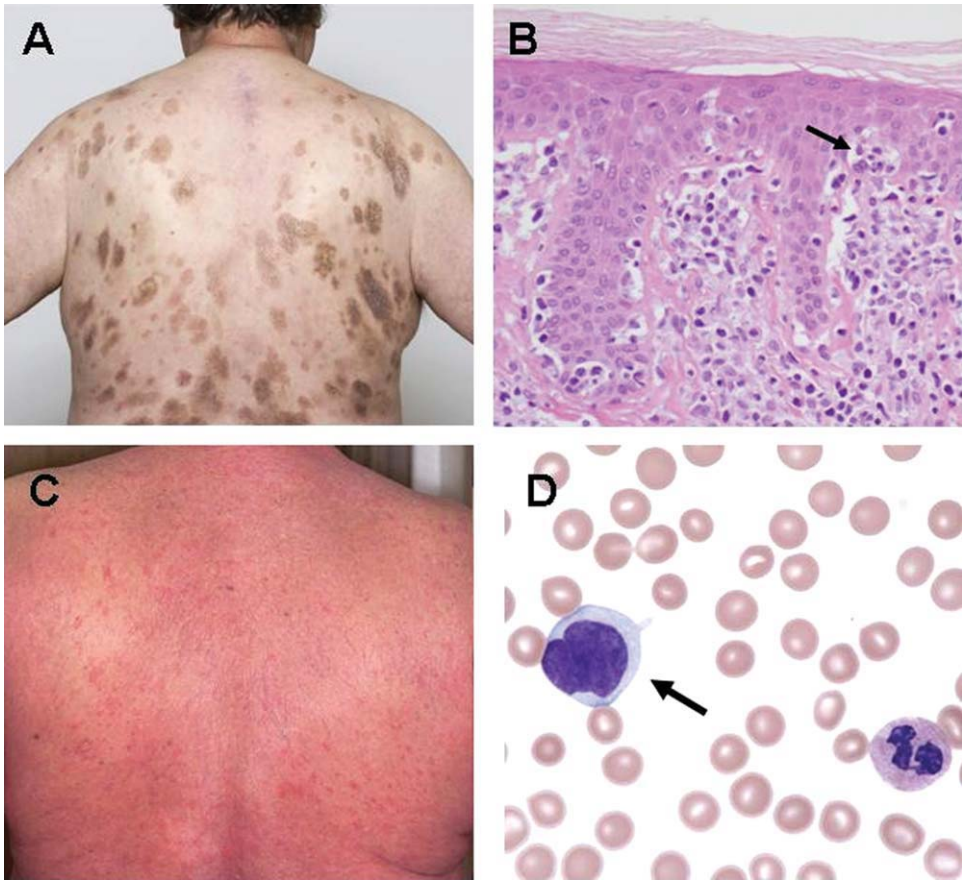

Figure 1. A patient with hyperpigmented patch-stage (stage Ib) MF is shown (A). H&E stained skin biopsy from a patient with MF demonstrates characteristic histologic findings, including epidermotropism with haloed lymphocytes aligned along the basal layer. A pautrier's microabscess is indicated by the arrow (B). A patient with erythroderma (SS) is shown (C). A Sézary cell with cerebriform nucleus is shown (D). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

neither sensitive nor specific. For example, Pautrier's microabscesses, often considered to be pathognomonic of MF, were only observed in 37.5% of MF cases, while being observed in 2.1% of non-MF cases. Conversely, spongiosis (i.e., intercellular edema between epidermal keratinocytes) may be associated with benign dermatoses, yet it was observed in 39.1% of MF cases. In a smaller series, the presence of medium to large lymphocytes with cerebriform nuclei and epidermotropism were important distinguishing features of MF [104]. 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 histologic diagnosis may be a source of frustration for clinicians unfamiliar with the challenges associated with rendering a pathologic diagnosis of MF.

While a definitive diagnosis of MF may be made on the basis of clinical and pathologic features alone, determination of T-cell clonality and assessing the aberrant loss of T-cell antigen expression upon immunohistochemical staining for CD2, CD3, CD5, and CD7 are useful ancillary studies in the diagnosis of MF (and SS). Southern blot analysis and PCR-based methods are able to detect clonal rearrangements of the T-cell receptor (TCR) in formalin-fixed, paraffin-embedded biopsy specimens [105,106]. PCR-based methods are sensitive ($\approx$1%) and should be interpreted with caution, as TCR gene rearrangements suggesting clonality may be detected in normal elderly individuals and in patients with benign dermatoses or other disease states [107–111]. However, detection of identical clones from two different sites is quite specific for MF [112]. The extent to which MF/SS may be preceded by a premalignant state, analogous to monoclonal B-cell lymphocytosis (MBL) or monoclonal gammopathy of undetermined significance (MGUS), is debatable and poorly defined [113]. 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 cells lacking CD2, CD5, and/or CD7 expression, either within the entire lesion or the epidermis alone, is highly specific (specificity $>$90%) for MF in most reported series [114,115].

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 [116]. This diagnostic algorithm is intended for classic presentations of MF and is summarized in Table II.

Sézary Syndrome

Traditionally, SS is defined as a leukemic form of CTCL associated with erythroderma (Fig. 1C). A series of studies in the early to mid-20th century, beginning with Sézary's initial landmark observation in 1938, identified a population of large lymphocytes in the peripheral blood with grooved, lobulated (i.e., "cerebriform") nuclei in patients with MF or SS (Fig. 1D) [118–123]. As in other chronic lymphoproliferative disorders, the Sezary cell count is preferably expressed in absolute terms, with $\geq$1,000 cells/μl classified

TABLE I. WHO-EORTC Classification of Primary Cutaneous Lymphomas [2]

Cutaneous T-cell and NK-cell lymphomas
Mycosis fungoides
Mycosis fungoides, variants and subtypes
Folliculotropic MF
Pagetoid reticulosis
Granulomatous slack skin
Sézary syndrome
Adult T-cell leukemia/lymphoma
Primary cutaneous $CD30^+$ lymphoproliferative disorders
Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Primary cutaneous peripheral T-cell lymphoma, unspecified
Primary cutaneous aggressive epidermotropic $CD8^+$ T-cell lymphoma (provisional)
Cutaneous γ/δ T-cell lymphoma (provisional)
Primary cutaneous $CD4^+$ small/medium-sized pleomorphic T-cell lymphoma (provisional)
Cutaneous B-cell lymphomas
Primary cutaneous marginal zone B-cell lymphoma
Primary cutaneous follicle center lymphoma
Primary cutaneous diffuse large B-cell lymphoma, let type
Primary cutaneous diffuse large B-cell lymphoma, other
Intravascular large B-cell lymphoma
Precursor hematologic neoplasm
$CD4^+/CD56^+$ hematodermic neoplasm (blastic plasmacytoid dendritic cell neoplasm)

TABLE II. Diagnostic Criteria for Classic Mycosis Fungoides and Sézary Syndrome

Disorder	Diagnostic criteria	References
Mycosis fungoides (4 points required for diagnosis)	Clinical (2 points for 1 basic + 2 additional criteria; 1 point for 1 basic + 1 additional criteria) Basic: persistent and/or progressive patches/plaques Additional: non-sun exposed location, variation in size/shape, poikiloderma Histopathologic (2 points for 1 basic + 2 additional criteria; 1 point for 1 basic + 1 additional criteria) Basic: superficial lymphoid infiltrate Additional: epidermotropism without spongiosis, lymphoid atypia (cells with large, cerebriform nuclei) Molecular biological (1 point) Clonal TCR gene rearrangement Immunopathologic (1 point for $\geq$1 criteria) $<$50% $CD2^+$, $CD3^+$ and/or $CD5^+$ T cells $<$10% $CD7^+$ T cells Epidermal/dermal discordance of CD2, CD3, CD5 or CD7	[116]
Sézary syndrome	Clonal rearrangement of the TCR (by Southern or PCR) Absolute Sézary count $\geq$ 1,000/μl Or 1 of the following if Sézary count not able to be used: Increased $CD4^+$ or $CD3^+$ T cells with CD4/CD8 ratio $\geq$10 Abnormal immunophenotype: $CD4^+CD7^-$ ratio $\geq$40% or $CD4^+CD26^-$ ratio $\geq$30%	[117]

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 [124–126]. The histologic findings in the skin often resemble those observed in MF, with less prominent epidermotropism, while lymph node involvement is characterized by complete effacement of the nodal architecture by infiltrating Sezary cells [127].

In SS, clonal T cells are generally $CD3^+CD4^+$ and $CD8^-$ by multicolor flow cytometry [128–130]. As in MF, the aberrant loss of pan-T-cell antigens, including CD2, CD3, CD4, CD5, and CD7 is frequently observed [130–132]. Of these, the aberrant loss of CD7 expression is most common, being observed in approximately two-thirds of cases [131,133,134]. Loss of CD26 expression is also useful in the identification of Sezary cells, being observed in $\sim$50% of cases [135–137]. More recently, the aberrant expression of the MHC class I-binding, killer immunoglobulin-like receptor (KIR) CD158κ, normally expressed by natural killer cells, was described in the majority of patients examined with SS [138,139]. 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 multicolor flow cytometry using a panel of antibodies specific for various TCR beta-chain variable region family members (TCR-Vβ) [140–142]. 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 [140,141]. Clark et al. recently observed that lymphocytes isolated from either peripheral blood or skin lesions of CTCL patients contained a population of cells with high forward and side scatter characteristics on flow cytometric analysis [24]. A similar population of so-called high-scatter T cells (T_{HS}) was not observed in samples obtained from patients with benign conditions. More importantly, these high-scatter T cells, upon careful immunophenotyping and analysis of clonal TCR-Vβ chain expression, were convincingly shown to represent the malignant T-cell clone. While additional confirmatory studies are warranted, detection of high-scatter T cells may be an easily performed method to detect a clonal T-cell population in patients with limited-stage MF and to monitor the response to therapy.

The currently proposed ISCL criteria for SS integrate clinical, histologic, immunophenotyping, and molecular studies. In patients with erythroderma, criteria recommended for the diagnosis of SS by the ISCL include the following: absolute sezary count $\geq$1,000/μl, a CD4/CD8 ratio $\geq$10 (due to the clonal expansion of $CD4^+$ cells), aberrant expression of pan-T-cell antigens, demonstration of T-cell clonality in the presence of a lymphocytosis by Southern blot or PCR-based methods, or cytogenetic demonstration of an abnormal clone [143]. At a minimum, the WHO-EORTC recommends the demonstration of T-cell clonality in combination with the aforementioned criteria for the diagnosis of SS, as summarized in Table II [2]. 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.

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. While a detailed description of these CTCL subtypes is beyond the scope of this update, the salient features of each are briefly summarized in Table III. Recently published overviews are also available [2].

Risk-Stratification

Staging

In contrast to many other lymphoproliferative disorders in which cytogenetic and laboratory findings play a prominent

TABLE III. Non-MF/SS Subtypes and Variants

	MF variants and subtypes				Primary cutaneous CD30+ lymphoproliferative disorders				Primary cutaneous peripheral T-cell lymphoma, unspecified*		
	Folliculotropic MF	Pagetoid Reticulosis	Granulomatous Slack Skin	Adult T-cell Leukemia Lymphoma	Primary Cutaneous Anaplastic Large Cell Lymphoma	Lymphomatoid Papulosis	Subcutaneous Panniculitis-like T-cell Lymphoma	Extranodal NK-/T-cell Lymphoma, Nasal Type	Primary Cutaneous Aggressive Epidermotropic $CD8^+$ T-cell Lymphoma	Cutaneous γ/δ T-cell Lymphoma	Primary Cutaneous CD4+ small-/medium-sized Pleomorphic T-cell Lymphoma
Clinical features:	-commonly localized to head & neck, follicular papules, alopecia, pruritus [143,144]	-single psoriaform patch or plaque -located on extremities (hands/feet) -slowly progressive	-localized areas of pendulous, lax skin, usually in groin or axillae [145] -associated with Hodgkin lymphoma and MF [146,147]	-HTLV-1 associated -endemic in Caribbean/South America and Japan -Clinical variants with varying degrees of bone marrow, blood and nodal involvement [148]: Acute Lymphoma Chronic Smoldering -skin involvement may resemble MF	-solitary papules or tumors -ulceration common -occasionally multifocal -spontaneous regression may be observed -systemic dissemination uncommon	-papules and/or nodules on trunk and extremities that may necrose, leaving a scar -relapsing-remitting course over many years -about 20% associated with another CTCL or Hodgkin lymphoma [149]	-male:female ratio 0.5 -median age 36 (19% 20 years or younger) -multifocal nodules, plaques -usually trunk and extremities -ulceration rare -B symptoms common; hemophago-cytic syndrome less common (<20%) [150]	-more common in Asia or Central and South America -stage I/II disease involving nasal cavity most common -cutaneous involvement may be "primary" or "secondary" [151,152]	-variable, including localized or disseminated disease, ranging from patch/plaque disease to ulceronecrotic tumors [153,154]	-multifocal, nodules or plaques with ulceration -B symptoms and/or hemophago-cytic syndrome common [155]	-solitary plaque or tumor involving head/neck and upper trunk -no prior history of patch/plaque disease [2,149]
Pathology:	-deep, follicular, dermal infiltrate -follicular mucinosis -$CD3^+CD4^+$ with occasional $CD30^+$ blasts -eosinophil and plasma cell infiltrate common [143]	-marked epidermal infiltrate -$CD4^+$ or $CD8^+$ -often $CD30^+$ [155]	-granulomatous dermal infiltrate -$CD4^+$ [145] -dermal elastolysis	-medium lymphocytes with polylobated nuclei (i.e., "flower" cells) -most $CD4^+$ $CD25^+CD7^-$ -subset $FoxP3^+$ (suggesting regulatory T-cell derivation) [156–160]	-diffuse, large, anaplastic (pleomorphic or immunoblastic less common), nonepider-motropic infiltrate -$CD30^+$ -t(2;5) usually absent -IRF4 translocations present in 20%, but 99% specific [69]	-variable, ranging from rare $CD30^+$ Reed-Sternberg-like cells with prominent reactive infiltrate (most common) to sheets of large $CD30^+$ cells; infiltrate similar to MF less common [161]	-express α/β TCR -$CD8^+$ $CD56^-$ beta-$F1^+$ -$CD30^-$ -express granzyme B, TIA-1 and/or perforin -subcutaneous rimming of adipocytes with neoplastic T cells characteristic [150]	-cytoplasmic $CD3^+$; surface $CD3^-$ -$CD56^+$ - express granzyme B, TIA-1 and/or perforin -angio-centric invasion with ulceration -EBV^+	-significant epidermo-tropism -involvement of adnexal structures common -angioinvasion and ulceration may be observed -$CD3^+$ $CD4^-$ $CD8^+CD30^-$	-express γ/δ TCR -$CD8^-$ $CD56^+$ beta-$F1^-$ -$CD30^-$ -express granzyme B, TIA-1 and/or perforin	-$CD3^+CD4^+$ $CD8^-CD30^-$ -diffuse infiltration of small/medium sized cells in dermis [2,149]

TABLE III. Continued

	MF variants and subtypes				Primary cutaneous CD30+ lymphoproliferative disorders				Primary cutaneous peripheral T-cell lymphoma, unspecified*		
	Folliculotropic MF	Pagetoid Reticulosis	Granulomatous Slack Skin	Adult T-cell Leukemia Lymphoma	Primary Cutaneous Anaplastic Large Cell Lymphoma	Lymphomatoid Papulosis	Subcutaneous Panniculitis-like T-cell Lymphoma	Extranodal NK-/T-cell Lymphoma, Nasal Type	Primary Cutaneous Aggressive Epidermotropic $CD8^+$ T-cell Lymphoma	Cutaneous γ/δ T-cell Lymphoma	Primary Cutaneous CD4+ small-/medium-sized Pleomorphic T-cell Lymphoma
Prognosis:	-associated with poor prognosis [7] -survival about that of T3 stage MF [143,162]	-favorable -no disease-related deaths	-indolent	-median OS for acute and lymphoma variants: <1 year -median OS for chronic and smoldering variants: years [148,163–166] -poor PS, elevated LDH, age ≥40, >3 lesions, hypercalcemia adverse prognostic factors on multivariate analysis [167] -infectious complications common -3 year OS ≤33%, even with aggressive chemotherapy or allogeneic transplant [168,169]	-5-year DFS >90% [149]	-excellent prognosis -systemic dissemination or disease-related death are rare	-indolent, with no extracutaneous disease observed in largest series [150] -5-year disease-specific survival >80% [150] -hemophago-cytic syndrome and angioinvasion poor prognostic factors [170]	-extranasal disease associated with dismal prognosis (median survival <12 months), regardless of stage [152]	-poor with median OS 2–3 years [153,154]	-dismal prognosis with few long-term survivors -2-year OS 31% [150]	-generally indolent course [171,172]
Treatment:	-less responsive to many skin-directed therapies given dermal and perifollicular infiltrate -TSEB or localized radiationtherapy [143,173]	-skin-directed therapy (e.g., radiation)	-poorly defined, but radiation thought to be helpful [146,147,174] -long-term follow up recommended	-smoldering or favorable chronic-type: observation or AZT/IFN-α (if wild-type p53, low IRF-4) -acute, lymphoma or unfavorable chronic-type: VCAP-AMP-VECP superior to CHOP [168]; AZT/IFN-α (except in lymphoma type)[175]; consider allogeneic transplantation - CNS prophylaxis -include PJP and anti-fungal prophylaxis -rule out Strongyloides [166]	-usually local therapy (radiation, surgery) -CHOP-like chemotherapy in (rare) cases of rapidly progressive nodal or cutaneous disease [149]	-observation for mild disease, with few lesions -oral methotrexate (15–20 mg/week) achieves disease control in >80% [300]	-poorly defined, responses achieved with CHOP-like chemotherapy, prednisone, or radiation to sites of local disease -CR rate 67% reported with therapy [150] -activity with denileukin diftitox reported [176]	-for localized nasal disease combined modality therapy [177] -poor results with CHOP-like regimens for advanced disease -L-asparaginase containing regimens promising [178,179] -consider autologous or allogeneic stem cell transplant [180]	-CHOP or CHOP-like regimen	-CR rate 21% in patients treated with CHOP or CHOP-like regimens [150]	-excision +/- radiation for local disease -single agents (cyclo-phosphamide, interferon-α) affective [171,181]

*Any CTCL may be given this diagnosis of exclusion if the criteria for a specific CTCL subtype are not met. These heterogenous CTCLs are associated with a variable presentation, but generally poor prognosis, despite the use of multiagent chemotherapy.[2]

TABLE IV. ISCL/EORTC Staging

	TNMB Classification				Median	10-year [7]		
Stages	T	N	M	B	OS (years)	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)

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

role in risk stratification, TNMB (tumor, node, metastasis, and 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 [143]. 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. For practical purposes, the area of one hand (including both palm and digits) represents ~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, with preference being 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. In current practice, two pathologic staging systems are used to classify the extent of nodal involvement. In the Dutch system, lymph nodes are pathologically graded based on the presence of large cerebriform nuclei (>7.5 μm) and the degree of architectural effacement [182]. In contrast, the National Cancer Institute-Veterans Administration (NCI-VA) classification uses the relative number of atypical lymphocytes (not size), along with nodal architecture to determine the extent of nodal involvement [183,184]. 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-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 [7,99,100]. 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-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 [7,185–188]. Unfortunately, median survivals from ~1–5 years are observed in these patients with more extensive disease [7]. The revised ISCL/EORTC staging for MF/SS is summarized in Table IV.

A recently reported retrospective study which included 1,398 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 IV. In addition to staging, male gender, increasing age, an elevated LDH and the folliculotropic variant of MF were also independently associated with poorer overall and disease-specific survival. In contrast to previous reports highlighting the aggressive clinical course associated with large cell transformation [189–193], defined as the presence of large, atypical lymphocytes comprising at least 25% of the total lymphoid infiltrate, large cell transformation was not an independent predictor of overall or disease-specific survival but was associated with a higher risk (hazard ratio 3.32) of disease progression [7]. 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 [143].

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 [194]. Because of 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.

Cytogenetics

In contrast to some B-cell lymphoproliferative disorders, such as chronic lymphocytic leukemia and multiple myeloma, for which gene-expression profiling and cytogenetic findings have important prognostic implications, risk-stratification in CTCL based on cytogenetic findings has only recently been described, is poorly understood, and consequently is not routinely performed in clinical practice.

Shin et al. performed a gene expression profiling analysis on lesional skin biopsy specimens obtained from 62 CTCL patients and identified three distinct gene expression clusters that were prognostically important [47], that were later confirmed by RT-PCR analysis [195]. The first cluster was associated with the upregulation of genes involved in T-cell activation, homing and tumor necrosis factor (TNF) signaling. This cluster conferred an inferior event-free survival when compared with the other two clusters. The second cluster, associated with the upregulation of genes involved in keratinocyte and epidermal proliferation and differentiation, was comprised largely of patients with limited-stage disease and was, not surprisingly, associated with superior event-free survival. Cluster 3, associated with an event-free survival intermediate between the first two clusters, was associated with the upregulation of genes involved in keratinocyte function and WNT signaling.

Array-comparative genomic hybridization techniques have revealed chromosomal copy number alterations that are prognostically relevant. First, an inverse association between survival and the absolute number of copy number alterations, reflecting genomic instability, has been observed in both tumor-stage MF and SS [196,197]. For example, in a cohort of 28 SS patients, the presence of fewer than three copy number alterations was associated with a median overall-survival of 93 months, compared with a median overall-survival of 67 months for those with three or more copy number alterations [196]. In addition to genomic complexity, specific chromosomal gains/losses have also been associated with inferior survival. Unfortunately, many of these studies are small and hindered by the inclusion of multiple histologies. For example, in a cohort of 58 patients with transformed MF, SS, or cutaneous anaplastic large cell lymphoma (cALCL), loss of the

TABLE V. Common Chromosomal Gains/Losses in MF/SS

Gain				Loss			
Gain	Frequency (%)	Candidate genes (cytogenetic band)	References	Loss	Frequency (%)	Candidate genes (cytogenetic band)	References
1p	15–45		[20]	5q	40–45	TAF9 (q13)	[20]
1q*	15–45	MCL1, CLK2, PRCC, ARHGEF11 (q21–q22); RGS1, RGS2 (q25–q31); MDM4, NAV1, KIF14 (q31–q32)	[19,20,197]	6q	17		[197]
7p	41–50	CAMK2B (p13–p14); TAX1BP1, HOXA10, CREB5 (p15-p14); RAC1, OCM (p11.2–p22);	[19,20]	9p*	30–42	CDKN2A, CDKN2B (p21)	[19,20,93,197]
7q	50–60	GTF2IRD1 (q11.2); AP1S1, HGF (q21–q22); MET (q31); BRAF, HIPK2 (q33.3–q35); FASTK (q36)	[19,20,197]	9q	30–35	UBQLN1, CDK20 (q21–q22)	[19,20,197]
8p	50	BAG4 (p11.23)	[196]	10p	17–68	NRP1, MAP3K8, ZEB1, ITGB1 (p11.22–p11.23)	[19,196,197]
8q*	32–75	MYC (q24.21); HSF1, PLEC1 (q24.3)	[19,20,197]	10q*	20–47	PTEN, FAS (q22–q24); FGFR2, CASP7 (q25–q26); MGMT (q26)	[19,20,84]
9q	17	NOTCH, TRAF2, CARD9 (q34)	[197]	11q	20	DDX10 (q22.3)	[19]
10p	17–36	GATA3, IL2R (p14)	[196,197]	13q	20–36	RB1, KLF12 (q14–q31);	[20,197]
17q	30–70	ERBB2 (q12); FMNL1, SKAP1, SUPT4H1, STAT3, STAT5A, STAT5B (q21–q25)	[19,20,197]	16q	17–35	E2F4, CBFB (q21–q22)	[19,20,197]
				17p	9–71	TP53 (p13.1)	[19,20,197]

*Associated with inferior overall survival.

CDKN2A-CDKN2B locus (at 9p21) was associated with inferior overall survival that was highly significant. However, 9p21 loss was only found in a single patient with cALCL. Therefore, when these patients were omitted from analysis, the loss of 9p21 was associated with decreased overall survival that approached, but did not reach, statistical significance [93]. Despite this, the adverse prognostic significance of 9p21 loss is supported by multiple patient cohorts including both MF and SS [19,20,197]. Additional cytogenetic abnormalities, involving gains of chromosomes 1q and 8q and losses of chromosome 10q, have been associated with inferior survival and are summarized in Table V.

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 (i.e., "watch and wait") or skin-directed therapies. A randomized trial comparing early combined modality therapy with both radiation and multiagent chemotherapy (cyclophosphamide, doxorubicin, etoposide, and vincristine) with sequential topical therapies demonstrated that combined modality therapy, while associated with a superior complete response rate, did not translate into improvements in disease-free or overall survival, but was associated with significant toxicity [198]. 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 [199–204]. Consequently, management of limited-stage disease will be summarized only briefly.

Corticosteroids, alkylating agents and bexarotene are available for topical use and are frequently utilized in the management of patients with limited-stage disease. Topical corticosteroids produce both clinical and/or pathologic complete remissions in up to 63% of patients with limited patch/plaque stage MF [205]. Nitrogen mustard (mechlorethamine) may be applied as an aqueous or ointment-based preparation and produces complete remissions in ~50–75% of patients with limited patch/plaque stage disease [206,207]. The median time to response is ~10–19 months, depending on the extent of disease, with freedom-from-progression rates exceeding 80% at 10 years [207]. Contact hypersensitivity reactions are more common with the aqueous preparation, but occur in fewer than 10% of patients with the ointment-based formulation [207]. Myelosuppression is not observed. While the risk of secondary nonmelanoma skin cancers following topical mechlorethamine alone is debatable, it may potentiate the carcinogenic affects of other therapies [208]. Topical BCNU (carmustine) is associated with complete remission rates exceeding 80% following a median of 3 months of therapy. Because of systemic absorption, it is associated with myelosuppression which requires monitoring, and in some cases dose modifications [209,210]. The most common toxicities are benign cutaneous reactions, including erythema, telangiectasias and hyperpigmentation. Bexarotene 1% gel is generally well tolerated and has been associated with an overall response rate of 63% (and complete response rate of 23%), prompting FDA approval for limited-stage CTCL in 2000 [211].

In addition to topical therapies, both ultraviolet radiation, either UVA or UVB, and total skin electron beam therapy (TSEBT) are frequently utilized in limited-stage CTCL. Psoralen, which forms DNA adducts upon photoactivation, combined with ultraviolet A (PUVA) causes tumor cell apoptosis and is associated with a complete response rate exceeding 90%, and a prolonged disease-free interval, in patients with stage IA/IB disease [212,213]. In contrast to PUVA, use of either broadband or narrowband ultraviolet B (UVB) does not require psoralen and is associated with a high clinical and pathologic complete response rate, particularly for patients with patch-stage disease [214–218]. Malignant T cells are radiosensitive. Therefore, the delivery of electrons to the entire skin surface with TSEBT is associated with response rates exceeding 90% and is potentially curative for patients with stage IA disease [219,220]. Given the limited depth of penetration, systemic toxicity is avoided with TSEBT, although hair loss and the risk of secondary skin cancers may limit its widespread use. If needed, a second coarse of TSEBT may be safe and efficacious [221]. Focal, conventional radiation therapy is useful for the palliation of local lesions.

Treatment of Advanced-Stage MF/SS

Overview

Patients with advanced-stage MF/SS require a multidisciplinary approach, as various combinations of skin-directed therapies, biologic-response modifiers and ultimately the

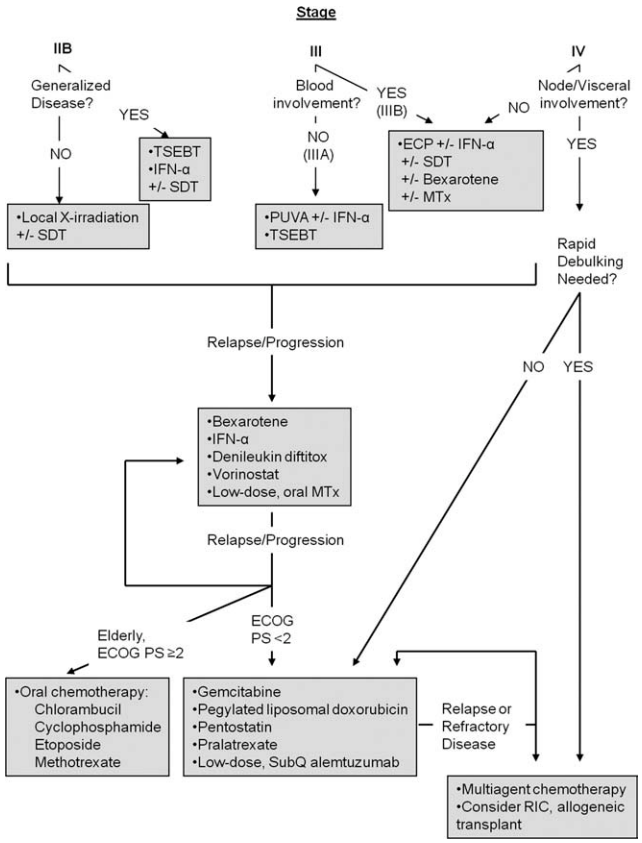

Figure 2. Approach to treatment of advanced-stage MF/SS. Abbreviations: MTx, methotrexate; RIC, reduced-intensity conditioning; SDT, skin directed therapy. Clinical trial participation, whenever possible, is encouraged.

sequential use of systemic chemotherapeutic agents are frequently used in the management of these patients. As for limited-stage disease, multiagent chemotherapy, with only few exceptions, is generally not appropriate [198]. As summarized in Fig. 2, a "risk-adapted" stage-based approach is adopted, with biologic-response modifiers (e.g., bexarotene and interferon-alpha), denileukin diftitox, and histone deacetylase inhibitors (e.g., vorinostat) generally preferred before escalating therapy to include systemic chemotherapy. Therapeutic decisions are individualized and based on a patient's age, performance status, extent of disease burden and the rate of disease progression, and previous therapies. The concise treatment algorithm provided in Fig. 2 is consistent with published treatment guidelines and expert opinion [199–204].

Bexarotene

The endogenous retinoids all-*trans* retinoic acid and 9-*cis* retinoic acid (i.e., vitamin-A-derived compounds) regulate a diverse array of biologic processes, ranging 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). Each retinoid receptor has three subtypes (α, β, γ), each of which is associated with various tissue-specific isoforms. Upon forming homodimers or heterodimers, these receptors recruit various nuclear corepressor or coactivator proteins depending whether or not they are bound by ligand. For example, in the absence of RAR ligand, RXR/RAR heterodimers recruit histone deacetylase, leading to epigenetic silencing of gene transcription. In contrast, upon engaging RAR ligand, corepressors dissociate, coactivators are recruited, and gene transcription ensues [222,223].

Multiple RAR retinoids have been used in MF/SS, either topically or systemically (reviewed in [222,224]), 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 [225,226]. In a multicenter phase II-III study, 94 patients with advanced-stage CTCL who had been previously treated with a median of five prior therapies, the vast majority of whom had disease refractory to at least one prior systemic therapy, received at least 300 mg/m^2 of oral bexarotene daily [227]. Among patients treated at the 300 mg/m^2 dose, an overall response rate of 45% was observed, only 2% of which were complete. While an improved overall response rate 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 TSH should be obtained before the initiation of therapy. In one retrospective study, all patients treated with bexarotene developed hyperlipidemia and hypothyroidism, frequently within weeks of initiating treatment [228]. Consequently, use of lipid-lowering agents (e.g., statins or fenofibrate but not gemfibrozil due to its association with increased bexarotene levels and pancreatitis) and low-dose levothyroxine (e.g., 50 μg) before initiating bexarotene is reasonable [229,230]. In clinical practice, bexarotene is frequently initiated at a lower dose of 150 mg/m^2 and subsequently titrated to full doses after 2–4 weeks of therapy, depending on patient tolerability. As most responses occur within 2–3 months of treatment initiation, treatment should be discontinued or an escalation in the dose considered for those patients with progressive disease after 2–3 months of therapy, depending on the degree of disease progression and ability to tolerate further treatment. For responding patients, treatment may be continued until disease progression and, depending on the quality of the response, adjunctive skin-directed therapies (e.g., PUVA) considered [231].

Combination therapies incorporating bexarotene are currently being explored. Bexarotene combined with denileukin diftitox provides a noteworthy example, as bexarotene was shown to increase IL-2Rβ (CD122) expression in malignant T cells [232], conferring increased sensitivity to denileukin diftitox, thus forming the rationale for a phase I study combining these two agents [233]. In this study, 14 patients with relapsed/refractory CTCL received bexarotene (75–300 mg daily) with denileukin diftitox (18 mcg/kg daily for 3 days every 21 days). Eight responses, including four complete responses, and upregulation of the IL-2 receptor following therapy were observed [233]. Future studies clarifying the optimal use of bexarotene, either in combination or sequentially with other agents, are needed.

Denileukin diftitox

Components of the trimeric IL-2 receptor complex, comprised of an alpha chain (CD25) required for high-affinity binding, beta chain (CD122), and a common gamma chain (CD132), are expressed by clonal T cells in CTCL. Targeting the IL-2 receptor with the monoclonal antibody Daclizumab was safe and partially effective in adult T-cell leukemia/lymphoma [234,235]. In hopes of improving on these

results targeting the IL-2 receptor, denileukin diftitox (Dd) was developed (reviewed in [236]). Denileukin diftitox is a fusion protein comprised of human IL-2 fused to a truncated diphtheria toxin which has high affinity for the IL-2 receptor and is internalized upon receptor binding, leading to liberation of the toxin and the induction of apoptosis. Phase I/II studies demonstrated objective responses in approximately one-third of patients [237–239], leading to a phase III study which randomized 71 patients with CD25 positive (i.e., $\geq$20% T cells positive by immunohistochemistry) CTCL, most with advanced-stage disease, to either 9 or 18 μg/kg/day of Dd given intravenously on five consecutive days every 3 weeks for up to eight cycles [240]. An objective response, 20% partial and 10% complete, was observed in 30% of patients, while an additional 32% of patients had stable disease. The median time to response was 6 weeks, with 95% of responding patients demonstrating evidence of response by week 9. The median duration of response was 7 months (range 2.7–46.1 months). Among responders, significant improvements in self-reported quality of life were observed [241]. More recently, results of a large phase III placebo-controlled trial, utilizing the same Dd dosing schedule, were reported. An overall response rate of 44% was observed and was associated with a median progression-free survival exceeding 2 years [242]. While only patients felt to have CD25 positive disease were included in these studies, biopsies obtained from different sites or at different times demonstrate significant variability, suggesting that patients with CD25 negative CTCL may benefit from treatment. In a prospective analysis, a significant difference in response rate was noted between CD25 positive and negative lymphomas, with only 20% of patients with absent or low-level expression responding to treatment, compared with a response rate approaching 80% for those with CD25 positive disease [243]. In a meta-analysis of three trials, including 307 patients, the overall response rate for Dd-treated patients that were CD25 positive was 47.5%, and was associated with a median progression-free survival exceeding 2 years [244]. In contrast, a lower response rate of 30.6%, with a progression-free survival exceeding 487 days, was observed among CD25 negative patients. For patients given placebo (n = 44), the reported response rate was 15.9% and a median progression-free survival of 4 months observed. Most of these patients (52%) experienced disease progression, compared with disease progression in 17.5% of all Dd-treated patients. In addition, responses were observed in Dd-retreated patients who relapsed after achieving an initial response.

A vascular leak syndrome leading to hypoalbuminemia, hypotension or edema has been reported in ~25% of patients, usually within the first 2 weeks of treatment. Most of these patients were retreated without further symptoms. Approximately two-thirds of patients developed evidence of hypersensitivity reactions (e.g., chest pain, hypotension, angioedema, pruritus, and rash) within 1 hr of treatment. In hopes of ameliorating these symptoms, premedication with corticosteroids was performed in 15 patients that were subsequently reported [245]. With premedication, only three patients experienced hypersensitivity reactions, while two patients developed vascular leak syndrome. Furthermore, an impressive response rate of 60% was reported. Given these toxicities, the infusion of normal saline (e.g., 500 cc) before and after Dd administration and correction of underlying hypoalbuminemia ($<$3 g/dL) before treatment is recommended. Dexamethasone premedication (e.g., 2–4 mg intravenously) is routinely provided, and patients instructed to monitor daily weights following treatment. Weight gain and edema are managed with diuretics. Routine monitoring of liver function tests, serum creatinine and albumin is recommended. Of note, Dd should not be administered in a facility ill equipped to provide cardiopulmonary resuscitation. Severe and persistent transaminitis, thyrotoxicosis, loss of visual acuity or color vision, and rhabdomyolysis have been reported but are uncommon [240,246–248]. Investigations combining Dd with conventional chemotherapeutic agents are ongoing.

HDAC inhibitors

Histone deacetylases (HDACs) catalyze the removal of acetyl groups from both histone and nonhistone 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. The 18 human HDACs may be classified as either zinc- or NAD^+-dependent and further subclassified into class I (HDAC1, 2, 3, and 8), class II (HDAC4, 5, 6, 7, 9, and 10), class III (including NAD^+-dependent sirtuins), and class IV (HDAC11) HDACs. As HDACs regulate a wide variety of processes involved in carcinogenesis, multiple mechanisms may explain the clinical activity of HDAC inhibitors [249,250], including altered gene expression of cell-cycle and apoptotic regulatory proteins [251–255], acetylation of nonhistone proteins regulating cell growth and survival [256–259], angiogenesis [260,261], aggresome formation [262], and DNA repair [263]. In addition, HDAC inhibitors may have important effects on the tumor microenvironment via reactive oxygen species [264,265], enhanced antigen presentation [266] and downregulation of immunomodulatory cytokines, like IL-10 [267].

Vorinostat (suberoylanilide hydroxamic acid, SAHA) and romidepsin (depsipeptide) inhibit class I and II HDACs (i.e., pan-HDAC inhibitors), the former being widely expressed in various lymphoma subtypes [268]. Early phase I studies of both vorinostat and romidepsin established their safety and potential efficacy in lymphoproliferative disorders, including CTCL [269], 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 [270,271]. The overall response rate was ~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 (i.e., $<$2 months) and were also noted in patients with tumor-stage disease and Sézary syndrome [272]. 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 nonhematologic 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 [273]. Prolongation of the QT interval was rarely observed, but monitoring and appropriate electrolyte replacement is recommended for those patients at risk for QT prolongation.

Romidepsin, administered as a 4-hr intravenous infusion (14 mg/m^2) days 1, 8, and 15 every 4 weeks, was evaluated in two phase II studies, the largest of which included 96 patients, most with advanced-stage disease [274,275]. The overall response rate 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 [276].

Additional HDAC inhibitors, including potent pan-HDAC inhibitors, appear to have activity in CTCL [255,277,278]. Further studies are needed to fully define the mechanisms of resistance to HDAC inhibition in CTCL [255,279–282], enabling the development of rational therapeutic combinations incorporating HDAC inhibitors in CTCL [283,284].

Interferon-alpha

Interferon-alpha (i.e., interferon-alpha 2b), a type I interferon with immunomodulatory properties, has pleiotropic effects in CTCL and is associated with an overall response rate of 50–70% and a complete response rate of 20–30%, particularly in patients with limited-stage disease [285–288]. While often considered as second-line therapy for limited-stage CTCL, interferon-alpha, frequently at doses ranging from 3 to 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. Furthermore, interferon-alpha may be successfully combined with a number of other therapeutic modalities, including PUVA, bexarotene, chemotherapy and ECP, which are frequently utilized in the management of these patients [289–302]. For example, in a cohort of 51 patients (42 of which had advanced-stage disease) treated with single-agent, low-dose, interferon-alpha, responses were observed in 34 (67%), 21 (41%) of which were complete and maintained long-term in nine patients [288]. Similarly, in a cohort of 47 patients with stage III/IV disease, 89% of which had peripheral blood involvement, a response rate exceeding 80% was observed in those treated with a combination of ECP and interferon-alpha [302]. Interferon-alpha is associated with myelosuppression, transaminitis and dose-limiting flu-like side effects, particularly at higher doses.

Extracorporeal photophoresis

During extracorporeal photophoresis (ECP), inspired by PUVA, pooled leukapheresis and plasmapheresis products are exposed to 8-methoxypsoralen (8-MOP) before extracorporeal circulation through a 1-mm thick disposable cassette exposed to UVA radiation. The irradiated leukocytes, representing ~5% of peripheral blood leukocytes, are subsequently reinfused. Psoralen covalently binds and cross-links 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 [303–305]. In contrast, ECP leads to monocyte activation, including significant changes in gene expression [306], and dendritic cell differentiation, which is thought to culminate in enhanced antigen presentation and the initiation of a host immune response [307]. In hopes of prolonging the exposure time between monocyte-derived dendritic cells and malignant lymphocytes undergoing apoptosis, investigators have developed a modified ECP protocol (i.e., "transimmunization") whereby blood products are incubated overnight following UVA irradiation and before patient infusion [308]. This novel adaptation is investigational and has not been widely used given concerns about infectious risks and lack of a proven increase in efficacy.

Following the landmark study by Edelson and colleagues describing responses in 27 of 37 patients with erythrodermic CTCL treated with ECP, ECP was approved by the Food and Drug Administration of the USA for the treatment of CTCL and is now considered the treatment of choice in the first-line management of patients with Sézary syndrome in many centers [309]. While responses vary between case series, overall response rates hover around 60%, with a complete response rate of ~20% [310,311]. As current treatment protocols no longer require the oral administration of 8-MOP, eliminating nausea, ECP is safe and generally very well tolerated. While alternative schedules have been investigated, ECP is generally performed for two consecutive days every 2–4 weeks. While the precise mechanism of action is incompletely understood, evidence suggests that ECP has immunomodulatory effects which may augment host antitumor immunity. It is not surprising then that the median time to response following the initiation of ECP is ~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 [310,312–314]. 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 [310,313]. While effective as monotherapy, ECP has also been combined with other therapeutic strategies, including interferon, bexarotene and TSEBT [292,302,312,315–317].

Monoclonal antibodies

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 [318]. 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 [319]. 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 [320]. 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 $<1{,}000/mm^3$. With the exception of a single patient whose best response was stable disease, nine 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 (i.e., 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 [321]. In addition to hematologic toxicity, conventionally dosed alemtuzumab in advanced-stage MF/SS is associated with a high incidence of infectious complications [319,320,322–325]. 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 1–2 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 [326], CD4 [327], CD25 [328], and CCR4 [329–331] are being explored and appear promising.

TABLE VI. Selected Chemotherapeutic Agents

Agents	ORR (CR/CRu) (%)	References
Pegylated liposomal doxorubicin (20–40 mg/m^2 q2–4 weeks)	56–88 (20–67)	[345–348]
Gemcitabine (1,200 mg/m^2 days 1, 8, 15 q4 weeks)	48–75 (8–22)	[340–344]
Pentostatin (various doses/schedules)	28–71 (11–25)	[349–355]

Systemic chemotherapy

Systemic chemotherapy is generally reserved for patients with advanced-stage MF/SS who have either relapsed following therapy with skin-directed therapies and the biologic-response modifiers described above or have extensive disease with visceral organ involvement. Multiple chemotherapeutic agents, including single-agent and combination chemotherapy regimens, are associated with high response rates in MF/SS and have been reviewed recently [200,202,332]. While combination chemotherapy regimens (e.g., CHOP) are associated with response rates exceeding 70–80%, the responses achieved are frequently short-lived and are associated with significant myelosuppression and infectious complications [333–335]. Therefore, with the exceptions of refractory disease or in the setting of extensive or rapidly progressive disease where a rapid treatment response may be necessary, the administration of sequential, single-agent chemotherapy, as summarized in Fig. 2, is preferred.

Low-doses of oral chemotherapy, including methotrexate (as used for limited-stage CTCL), cyclophosphamide, chlorambucil, or etoposide, may be considered for patients with minimal disease burden that is slowly progressive or for elderly patients with a poor performance status. For example, overall response rates of 58–76% (and 41% complete response rate) have been observed in patients with MF/SS treated with low-dose, oral methotrexate [336–339]. In contrast, for patients with an adequate performance status, single-agent gemcitabine [340–344], pegylated liposomal doxorubicin [345–348] and pentostatin [349–355] are frequently utilized (Table VI). Gemcitabine, a pyrimidine nucleoside analog, is associated with overall and complete response rates of 50–70% and 10–20%, respectively, but is associated with neutropenia and nonhematologic toxicities [356]. Zinzani et al. recently reported long-term outcomes in a cohort of previously treated T-cell lymphoma patients [344]. Among the 19 MF patients included in the study, an overall and complete response rate of 48 and 16%, respectively, was observed. Overall, seven of nine complete responders remained in continuous complete remission with a disease-free interval ranging from 15 months to 10 years. In the largest prospective study of pegylated liposomal doxorubicin, an overall response rate of 56%, with a complete response rate of 20%, was reported [348]. Pegylated liposomal doxorubicin is generally well tolerated, with a lower incidence of neutropenia than gemcitabine, but with occasional infusion-related and mucocutaneous toxicities, including palmoplantar erythrodysesthesia. The most durable responses with pentostatin, a purine antimetabolite which inhibits adenosine deaminase, have been reported in SS [355]. Pentostatin is associated with fewer complete responses (~10–20%) and significant lymphopenia-associated immunosuppression. Unfortunately, the duration of response with these agents is frequently measured in months. Therefore, novel therapeutic agents, either alone or in combination, are needed.

Pralatrexate, a novel antifolate with a high affinity for the reduced folate carrier (RFC-1) and novel mechanism of resistance when compared with methotrexate [357–359], was associated with an overall response rate of 29% in the PROPEL study, which was comprised largely of peripheral T-cell lymphoma patients, the majority of which had disease refractory to the most recent treatment [360]. Twelve patients with transformed MF were included in the study [361]. 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 4–5 months. Results of a dose-finding study were reported in a larger cohort of CTCL patients [362]. 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 overall response rate of 43%. In an effort to reduce the incidence of mucositis, folic acid and vitamin B12 supplementation is routinely provided in these patients [363]. Additional novel agents, including bortezomib [364], are being explored. 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.

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 versus lymphoma immune response [365,366]. A retrospective analysis of 60 patients with advanced-stage MF/SS who underwent allogeneic stem cell transplantation was recently reported [367]. In this series, patients had received a median of four prior therapies before undergoing either reduced-conditioning (73%) or myeloablative (27%) conditioning before related (75%), or matched-unrelated donor (25%) transplantation. Nonrelapse 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 3-year overall survival (68% vs. 46%). Given the differences in nonrelapse 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-versus-lymphoma effect in MF/SS. In contrast to the experience with B-cell non-Hodgkin lymphomas, chemotherapy sensitivity before transplantation or the

extent of disease burden did not influence overall survival. The estimated 3-year progression-free and overall survivals were 34 and 53%, respectively. Therefore, allogeneic stem-cell transplantation may be considered for young patients with disease refractory to standard treatments.

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.

Acknowledgments

The author thanks Thomas M. Habermann (Division of Hematology, Mayo Clinic, Rochester, MN), Mark R. Pittelkow (Department of Dermatology, Mayo Clinic, Rochester, MN) and David A. Wada (Department of Dermatology, Mayo Clinic, Rochester, MN) for their thoughtful review of this manuscript. The Sézary cell photomicrograph shown in Fig. 1 is courtesy of David A. Wada.

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