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Cutaneous T-cell lymphoma: 2016 update on diagnosis, risk-stratification, and management

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Abstract

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—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, 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 or histone deacetylase inhibitors prior to escalating therapy to include systemic, single-agent chemotherapy. In highly-selected patients, allogeneic stem-cell transplantation may be considered, as this may be curative in some patients.

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. 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). 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). 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 (2). While CTCL may occur in children and young adults, this is very uncommon and often associated with histopathologic variants of MF (4–6). The incidence of CTCL increases

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significantly with age, with a median age at diagnosis in the mid-50's and a four-fold increase in incidence appreciated in patients over 70 (2, 6).

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 (7). Recent studies, however, have suggested that medications may induce an antigen-driven T-cell lymphoproliferation or dyscrasia (8, 9). 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 (9). 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 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 (10–12). 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 (13–16).

Cell of origin

Naïve T cells, upon encountering antigen in skin-draining lymph nodes, inducibly express the E-selectin ligand cutaneous lymphocyte antigen (CLA) and chemokine receptors (e.g. CCR4, CCR8, CCR10) that are required for their subsequent trafficking to the skin (17–19). Clonal expansion of activated T cells is followed by their differentiation into multiple subsets of effector and memory cells. Central memory cells (T_{CM}) retain the ability to access the peripheral blood and lymph nodes. Effector memory cells (T_{EM}), in contrast, migrate into extranodal sites, including the skin, where a subset will remain, as tissue-resident memory cells (T_{RM}). The majority of T cells in the skin are T_{RM} (17, 20), express a high-affinity antigen receptor (21), and have a distinct gene-expression profile (22). Clonal T cells in MF are commonly T_{RM} derived, thus explaining their tendency to remain confined to the skin (23). Immunophenotyping studies demonstrate that malignant T cells in patients with leukemic CTCL variants (Sézary Syndrome and MF with secondary leukemic involvement) express CCR7 and L-selectin, resembling T_{CM} (24). This fundamental difference in the putative cell of origin between SS (T_{CM} derived) and MF (T_{RM} 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_{RM} cells fail to circulate in peripheral blood, remaining fixed within the skin (24).

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In addition, a population of recirculating $CCR7^{+}$L-$selectin^{-}$ migratory memory T cells (T_{MM}) has been described in the skin (20). Therefore, a subset of MF patients with secondary leukemic involvement, poorly demarcated patches/plaques, more significant dermal involvement, and dermatopathic lymphadenopathy may harbor a T_{MM}-derived clone (20). The contention that MF subtypes 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 (25, 26).

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. Heid et. al. 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 (27). Uncertainties remain as to whether or not a subset of Sézary patients harbor a clone that is derived from *bona fide* skin resident Treg cells, or whether these cells aberrantly acquire a Treg phenotype during disease evolution (28). For example, immature dendritic cells, which are prevalent in CTCL (29), may upregulate FoxP3 expression in malignant T cells (30). Therefore, a subset of SS patients appears to harbor a Treg-derived (or “Treg-like”) 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 T cells in the skin produce cytokines characteristic of distinct effector T-cell subsets, including Th1, Th2 and Th17 cells. This effector T-cell heterogeneity raises the possibility that future studies may subclassify CTCL based on these T-cell subsets (31, 32). 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, IL-13), raising the possibility that a significant subset of patients may harbor Th2-derived clones (33–37). Alternatively, recurrent mutations activating specific signaling pathways (e.g. NFAT, NFκB, JAK/STAT) may promote the acquisition of a particular phenotype independent of the cell of origin (38). T-cell differentiation is associated with considerable plasticity. Therefore, the phenotype of malignant T cells may be both heterogeneous and highly dependent upon cues within the microenvironment (30, 39, 40). As the genetic landscape and the putative cell of origin are 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 cells frequently undergo spontaneous cell death during *in vitro* culture (41, 42)(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* (41, 43, 44).

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Both gene-expression profiling and immunohistochemistry-based studies have recently highlighted the important contribution of non-malignant cells, including monocyte-derived lymphoma-associated macrophages, in the pathogenesis of both Hodgkin and non-Hodgkin lymphomas (45–47). Similarly, malignant T cells in the skin are frequently associated with dendritic cells and immunohistochemistry-based studies have clearly demonstrated an abundance of both lymphoma-associated macrophages and dendritic cells, many of which may be actively recruited into the tumor microenvironment by tumor-derived chemokines (29, 48). 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 anti-tumor immunity (49). For example, monocyte-derived dendritic cells supported the long-term survival of malignant T cells during *in vitro* culture (42). 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 (29). Lymphoma-derived IL-10, which is upregulated in patients with advanced-stage, refractory disease (50), impairs the maturation of lymphoma-associated dendritic cells, rendering them immunologically incompetent, thus promoting escape from host anti-tumor immune surveillance. In addition, lymphoma-associated dendritic cells were observed to express the T-cell co-inhibitory ligand B7-H1 (PD-L1, CD274), which directly inhibits the proliferation of tumor-specific T cells, and indirectly impairs anti-tumor immunity by promoting the induction of suppressive regulatory T cells (51). 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 anti-tumor 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 (52–54). Both quantitative and qualitative defects in natural killer (NK) cell (55, 56), dendritic cell (57) and T cell-mediated (58–60) 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 (61). 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 non-malignant T cells, diminished thymic output of naïve T cells and compensatory homeostatic expansion of oligoclonal peripheral T cells, or some other mechanism, is unknown (50). As lymphopenia is an adverse prognostic factor in many hematologic malignancies (62–67), 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.

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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 translocations 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 (68, 69). 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 (70–74). 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. Multiple mechanisms, well described in B-cell lymphomas, lead to constitutive NF-kB activation, promoting lymphomagenesis (75). In a similar fashion, NF-kB is constitutively activated in CTCL (76–78). Immunohistochemical analysis of MF cases demonstrated nuclear localization of p65/RelA in over 90% of the cases examined (76). Furthermore, pharmacologic NF-kB inhibition in CTCL cell lines decreases NF-kB DNA binding activity, thus promoting cell death (76–79). 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 (77, 78).

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 (80, 81). 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 (82). Not surprisingly then, pharmacologic inhibition of STAT3 promotes apoptosis in CTCL (80, 83–85). 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 (40, 86–88).

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 (89–91), gene mutations (92) and loss of the long arm of chromosome 10 (93) 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

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involved in the induction of apoptosis, appear to be commonly employed mechanisms of lymphomagenesis in CTCL (94).

In addition to multiple defects in apoptosis, aberrant cell-cycle regulation, including inactivation of the CDKN2A-CDKN2B locus, is frequently observed in CTCL (95, 96). Cyclin upregulation, including cyclinD1, and loss of RB1 have also been described (97). As gene-expression profiling and next-generation sequencing technologies are employed, additional pathogenic pathways, including those involving transcription factors regulating T-cell differentiation (36, 37), c-MYC (98, 99), RAS/RAF/MEK signaling (100), among others (93, 101), may be identified in subsets of CTCL. For example, a gain of function mutation (S345F) in the phospholipase C, gamma 1 (PLCG1) gene was recently observed in 19% of CTCL cases (38). This mutation was associated with NFAT activation, and suggests that calcineurin inhibitors may be a rationale therapeutic approach in these patients.

Diagnosis

Mycosis fungoides

The definitive diagnosis of MF, particularly patch/plaque stage disease, is challenging, as many of its clinical and pathologic features are non-specific. Many patients will have had symptoms attributed to eczema or parapsoriasis for years prior to obtaining a definitive diagnosis. The median time from symptom onset to diagnosis in retrospective series is 3–4 years, but may exceed four decades (102–104). 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 histopathologic 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 histopathologic features alone, 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). 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, while sensitive, should be interpreted with caution, as clonal TCR gene rearrangements 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 pre-malignant 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). 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

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frequently large (>5 cm), pruritic and multifocal in “classical” MF. 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. hypo- and hyperpigmented variants) and focality (e.g. unilesional MF), some of which are formally recognized in the WHO-EORTC classification (1, 116). 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 (117).

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 (that is, “cerebriform”) nuclei in patients with MF or SS (118–123). As in other chronic lymphoproliferative disorders, the Sezary cell count is preferably expressed in absolute terms, 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 (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 multi-color flow cytometry (128–131). As in MF, the aberrant loss of pan-T-cell antigens, including CD2, CD3, CD4, CD5 and CD7 is frequently observed (130, 132–134). Of these, the aberrant loss of CD7 expression is most common, being observed in approximately two-thirds of cases (132, 135, 136). Loss of CD26 expression is also useful in the identification of Sezary cells, being observed in the majority of cases (131, 137–139). 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 (140, 141). 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) (142–144). 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 (142, 143). 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 (145). 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

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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 ≥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 (130). 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.

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 recently summarized (1, 146).

Risk-stratification

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 (147). 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 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, 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 (148). In contrast, the NCI-VA classification uses the relative number of atypical

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lymphocytes (not size), along with nodal architecture to determine the extent of nodal involvement (149, 150). 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 (6, 102, 103). At diagnosis, the majority of MF patients will have limited-stage disease (6). 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 (6, 151–154). Unfortunately, median survivals from approximately 1–5 years are observed in these patients with more extensive disease (6). The revised ISCL/EORTC staging for MF/SS is summarized in Table 1.

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 (6). 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. 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 (155–159), 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 (6). 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 (147).

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 (160). 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.

Cytogenetics

In contrast to some B-cell lymphoproliferative disorders, like 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.

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Shin et. al. performed a gene expression profiling analysis on lesional skin biopsy specimens obtained from 62 CTCL patients and identified 3 distinct gene expression clusters that were prognostically important (50), that were later confirmed by RT-PCR analysis (161). 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 (162, 163). For example, in a cohort of 28 SS patients, the presence of fewer than 3 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 3 or more copy number alterations (162). 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 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 (96). Despite this, the adverse prognostic significance of 9p21 loss is supported by multiple patient cohorts including both MF and SS (25, 26, 163). Additional cytogenetic abnormalities, involving gains of chromosomes 1q and 8q and losses of chromosome 10q, have been associated with inferior survival (146).

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, including 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 and was associated with significant toxicity (164). The limited efficacy associated with chemotherapy was recently highlighted in a large retrospective study in which the median time to next treatment following single or multiagent chemotherapy was <4 months(165). Therefore, patients with limited-stage disease who require therapy are best

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approached with skin-directed therapies, usually under the direction of a dermatologist and/or radiation oncologist. Excellent reviews and treatment guidelines are available (146, 166–171).

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 sequential use of systemic chemotherapeutic agents are frequently employed in the management of these patients. As for limited-stage disease, multiagent chemotherapy, with only few exceptions, is generally not appropriate (164). A “risk-adapted” stage-based approach is adopted, with biologic-response modifiers (e.g. bexarotene and interferon-alpha) and histone deacetylase inhibitors (e.g. vorinostat) generally preferred prior to escalating therapy to include systemic chemotherapy (172). 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 (166–171).

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). 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 (173, 174)), 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 (175, 176). 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 (177). 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 prior to the initiation of therapy. In one retrospective study, all patients treated with bexarotene developed hyperlipidemia and hypothyroidism, frequently within weeks of initiating treatment (178). Consequently, use of lipid-lowering agents (e.g. fenofibrate) and

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low-dose levothyroxine (e.g. 50 micrograms) prior to initiating bexarotene is generally recommended (179–181). 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 2–3 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 (e.g. PUVA, interferon) should be considered (182). Guidelines describing appropriate laboratory monitoring, supportive care, and safe clinical prescribing of bexarotene have been recently published (181). Future studies clarifying the optimal use of bexarotene, either in combination or sequentially with other agents, are needed.

HDAC inhibitors

Histone deacetylases (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 (183, 184), including altered gene expression of cell-cycle and apoptotic regulatory proteins (185–189), acetylation of non-histone proteins regulating cell growth and survival (190–193), angiogenesis (194, 195), aggresome formation (196) and DNA repair (197). In addition, HDAC inhibitors may have important effects on the tumor microenvironment via reactive oxygen species (198, 199), enhanced antigen presentation (200) and downregulation of immunomodulatory cytokines, like IL-10 (201).

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 (202). Early phase I studies of both vorinostat and romidepsin established their safety and potential efficacy in lymphoproliferative disorders, including CTCL (203), 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 (204, 205). The overall response rate 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 (i.e. <2 months) and were also noted in patients with tumor-stage disease and Sézary syndrome (206). 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, 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 (207). Prolongation of the QT

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interval was rarely observed, but monitoring and appropriate electrolyte replacement is recommended for those patients at risk for QT prolongation (208).

Romidepsin, administered as a 4-hour 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(209, 210). The overall response rate was 38% for patients with advanced-stage disease, with a median duration of response that exceeded one 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 (211).

Additional HDAC inhibitors, including potent pan-HDAC inhibitors, appear to have activity in CTCL (189, 212, 213). Further studies are needed to fully define the mechanisms of resistance to HDAC inhibition in CTCL (189, 214–218), enabling the development of rational therapeutic combinations incorporating HDAC inhibitors in CTCL (219, 220).

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 (221–224). 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(165, 225). 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 (226–239). 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 9 with a long-term remission (224). 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 (239). Interferon-alpha is associated with myelosuppression, transaminitis and dose-limiting flu-like side effects, particularly at higher doses.

Extracorporeal photophoresis

During extracorporeal photophoresis (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 (240–242). In contrast, ECP leads to monocyte activation,

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including significant changes in gene expression (243), and dendritic cell differentiation, which is thought to culminate in enhanced antigen presentation and the initiation of a host immune response (244). 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 prior to patient infusion (245). This novel adaptation is investigational and has not been widely employed 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 out 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 (246). While responses vary between case series, overall response rates hover around 60%, with a complete response rate of approximately 20% (247–250). 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 2 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 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 (247, 251–253). 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 (247, 249, 252). While effective as monotherapy, ECP has also been combined with other therapeutic strategies, including interferon, bexarotene and TSEBT (229, 239, 251, 254–256).

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 (257). 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 (258). 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 (259). 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

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exception of a single patient whose best response was stable disease, 9 out of 10 patients treated in this manner achieved a response, 3 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 six weeks (260). In addition to hematologic toxicity, conventionally dosed alemtuzumab in advanced-stage MF/SS is associated with a high incidence of infectious complications (258, 259, 261–264). 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 (265), CD4 (266), CD25 (267) and CCR4 (268–270) are being explored and appear promising. 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 overall response rate of 37%. A similar response rate of 29% (2/7), all partial, was observed in a phase II Japanese study (270, 271). In addition to ADCC-mediated clearance of malignant T cells, mogamulizumab may inhibit T_{reg}-mediate immune suppression (272, 273), and may warrant further investigation with immunomodulatory therapies, including immune checkpoint blockade (274). A randomized, phase III clinical trial comparing mogamulizumab and vorinostat in relapsed/refractory CTCL is ongoing in the US (NCT01728805). While capable of binding skin-resident T cells, monoclonal antibodies like mogamulizumab and alemtuzumab may be most efficacious in MF/SS patients with recirculating (and T_{MM} or T_{CM}-derived) clones (20). Brentuximab vedotin is an antibody-drug conjugate in which an anti-CD30 monoclonal antibody is linked with an anti-tubulin agent (monomethyl auristatin E). In a phase II study, 19 patients with relapsed/refractory MF received brentuximab vedotin. Among the 13 patients with stage IB or IIB disease, a response rate of 92% (all partial) was observed (275). As a single partial response was observed among the 6 patients with Stage IV disease, an overall response rate of 68% for the entire cohort was observed. Interestingly, quantitative image analysis for CD30 expression demonstrated CD30 positivity in all cases available for review, including those that were deemed CD30 negative by conventional immunohistochemistry. The response to brentuximab vedotin was not associated with CD30 expression in this cohort. As anticipated, neuropathy was the most common toxicity observed. A randomized, phase III clinical trial comparing brentuximab vedotin with an investigator's choice (methotrexate or bexarotene) is ongoing (NCT01578499). Resimmune, a second-generation immunotoxin in which the catalytic and

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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 (276). Much like its predecessor, resimmune is associated with a vascular leak syndrome (146).

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, while associated with high response rates in MF/SS (167, 169, 277), are infrequently durable (165), and frequently associated with significant myelosuppression and infectious complications (165, 278–280). 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 is preferred. Many oral and intravenous chemotherapeutic agents have been utilized in MF/SS (281–301). 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 (302–304), was associated with an overall response rate of 29% in the PROPEL study. This study was comprised largely of peripheral T-cell lymphoma patients, most of whom had refractory disease (305). Notably, twelve patients with transformed MF were included in the study (306). Many of these patients had received more than 5 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 (307). 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 (308). Additional therapeutic approaches, including proteasome inhibition (309), immunomodulatory strategies (310), and more targeted approaches warrant further investigation (311). 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 (312,

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313). A retrospective analysis of 60 patients with advanced-stage MF/SS who underwent allogeneic stem cell transplantation was recently reported (314). In this series, patients had received a median of 4 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 3 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 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-versus-lymphoma effect in MF/SS. In contrast to the experience with B-cell non-Hodgkin lymphomas, chemotherapy sensitivity prior to transplantation or the extent of disease burden did not influence overall survival. The estimated 3-year progression-free and overall survival were 34% and 53%, respectively. Given the possibility of complete and durable remissions, allogeneic stem-cell transplantation in conjunction with total skin electron beam therapy may be considered in selected patients (225, 315).

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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TABLE 1

ISCL/EORTC Staging

	TNMB Classification					10-year(6)		
Stage	**T**	**N**	**M**	**B**	**Median 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 year)	18 (5 year)	82 (5 year)

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

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