Cutaneous T-Cell Lymphomas

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Introduction

Cutaneous T cell lymphomas (CTCL) are T cell non-Hodgkin lymphomas (NHL) with primary cutaneous involvement. Mycosis fungoides (MF) and Sézary syndrome (SS) are subsets of CTCL [1]. Although MF and SS are uncommon forms of NHL, they are the most common lymphomas with primary involvement of the skin. The annual incidence in the United States is estimated at 0.96 cases per 100,000 with approximately 3,000 new cases per year in the United States [2]. While MF and SS occur in children and young adults, the median age at diagnosis is between 55 and 60 years [3]. There is 2:1 male predominance, and black patients have a twofold greater risk for developing MF/SS than white. The diagnosis and work-up for MF and SS are outlined in the National Comprehensive Cancer Network (NCCN) practice guidelines.

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Clinical Presentation

MF is the most common type of CTCL with a unique clinical–pathologic presentation. The initial cutaneous presentation of MF can be as patches or plaques that may subsequently evolve into tumors or generalized erythroderma; however, some patients may present with tumors or generalized erythroderma (Fig. 10.1). The most common initial cutaneous presentation is patch and plaque disease with approximately 30% of patients presenting with limited patch and plaque disease (less than 10% of the skin surface involved) and 35–40% with generalized patch and plaque (greater than or equal to 10% of the skin surface involved) [4]. Patches or plaques in MF are often localized, typically affecting flexural areas and the buttocks ("bathing trunk" distribution), although any cutaneous area of the body can be involved. The typical patches of mycosis fungoides are slightly scaling and mildly erythematous. More infiltrated lesions evolve into palpable plaques. These plaques are erythematous and slightly scaling, with well-defined borders. The shape and distribution of lesions are variable. Pruritus is the most common symptom even in the early phases of the disease and is often the problem that prompts a visit to the dermatologist.

However, the skin involvement can be much more extensive with infiltrated plaques evolving into ulcerating or fungating tumors or generalized erythroderma involving the entire skin surface. Fifteen to 20% of patients with MF present

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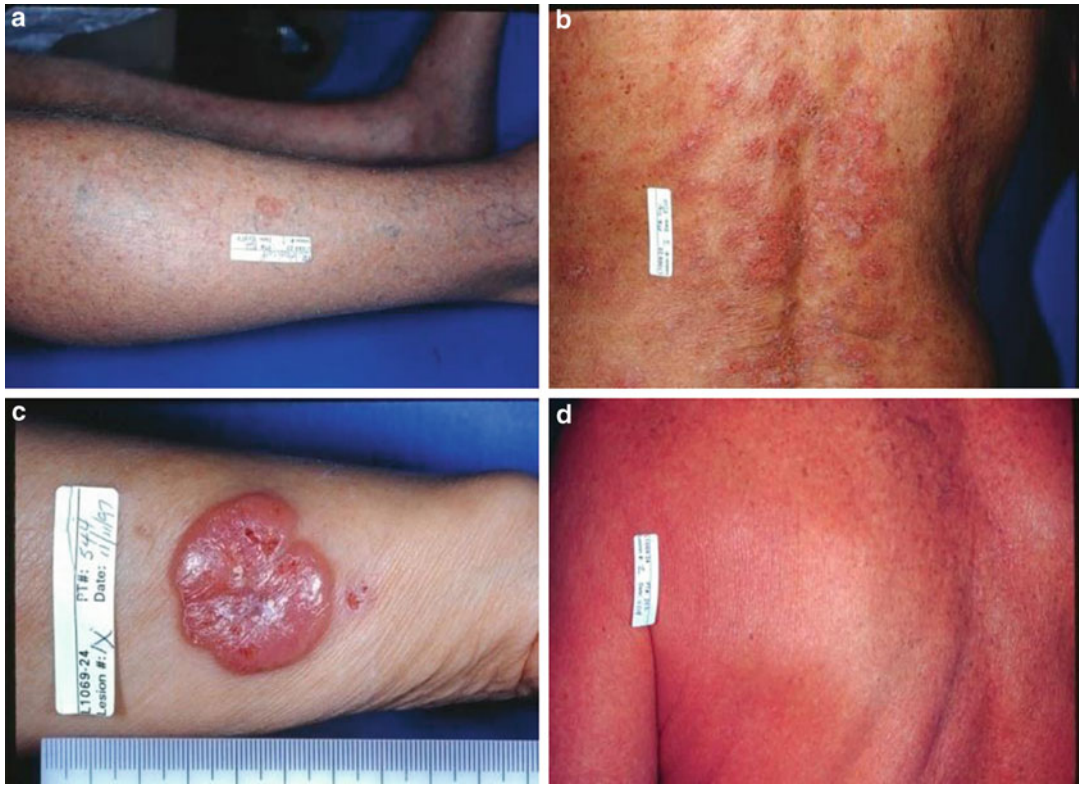

Fig. 10.1 Clinical manifestations of mycosis fungoides. (**a**) Patch stage disease. (**b**) Cutaneous plaques and patches. (**c**) Tumor stage disease. (**d**) Erythroderma

with tumorous lesions [4]. Tumors often become infected, and sepsis secondary to infection is often the cause of death in individuals so affected. Generalized dermal thickening from infiltrative disease may cause the classic but very unusual leonine facies of mycosis fungoides.

Another manifestation of skin involvement in mycosis fungoides is generalized erythroderma, with 15% of patients presenting as such [4]. The erythema may be accompanied by either atrophic or lichenified plaques or tumors. In the more generalized presentations, keratoderma may develop, nails may become dystrophic, and scalp involvement can result in alopecia [1]. These patients are almost always intensely symptomatic from pruritus and scaling and often have lymphadenopathy due to diffuse and severe skin involvement. SS is a distinct subtype of CTCL which is characterized by the triad of erythroderma, lymphadenopathy, and neoplastic T cells (or Sézary cells). The presence of all three is not required for the diagnosis. However, the presence of blood involvement is required for the definitive diagnosis of this syndrome. Sézary cells have the same microscopic appearance and immunophenotypic and genotypic characteristics as the cells that infiltrate the epidermis. Sézary cells in the peripheral blood meet the criteria of significance either by morphology, flow cytometry, or molecular analysis [5, 6]. For a definitive diagnosis, Sézary cells should number at least 1,000 per mm^3 [3, 5]. Additional ancillary tests, which help to define the diagnosis, include an expanded peripheral blood $CD4^+$ population with increased ratio of CD4 to CD8 T lymphocytes (greater than 10:1), expanded populations of abnormal T-cells with $CD4^+/CD7^-$ or $CD4^+/CD26^-$ phenotype, and molecular evidence of a relevant T-cell receptor gene rearrangement in the peripheral blood [5]. Patients may present initially with all components of SS or with only one component, e.g., generalized erythroderma,

and subsequently progress to develop other clinical features of SS [7]. Patients with SS have a worse prognosis than erythrodermic patients with mycosis fungoides who do not have the other findings of the SS [7].

The median duration from the onset of skin symptoms to a diagnosis of mycosis fungoides may be 5 years or longer [8]. In many patients, the disease presents initially in a premycotic phase with nonspecific, slightly scaling skin lesions that wax and wane over a period of years. Biopsies are generally nondiagnostic during this phase of disease, and patients may respond to treatment with topical corticosteroids. Clinically and histologically, the patients may be confused with a nonspecific dermatitis. Some of these patients will experience an evolution of their disease and develop more typical patches or infiltrated plaques, from which a definitive diagnostic biopsy may be obtained. Repeated biopsies must be obtained from patients suspected of having mycosis fungoides, even when an initial biopsy is negative. In addition, ancillary tests such as immunohistochemistry and T-cell receptor gene rearrangements may be helpful (Fig. 10.1).

Pathogenesis, Histology, Immunophenotype, and Molecular Diagnosis

The etiology of MF and SS remains undetermined. Various studies and case reports have suggested an association with genetic factors, environmental exposure, or an infectious etiology, but none has confirmed a causal association. The immunopathogenesis has been a focus of much research in the last decade. The malignant lymphocytes in mycosis fungoides are $CD4^+$ T cells that express the skin-homing receptors CLA and CCR4. The malignant cells are associated with increased T helper type 2 and reduced T helper type 1 cytokine production [9]. However, whether cytokine abnormalities are primarily involved or are secondary processes in the pathogenesis is unclear. The trigger of T cell activation and subsequent clonal expansion of the malignant T cells in the skin remains unclear.

Genetic aberrations that contribute to the development and progression of mycosis fungoides or SS are becoming better elucidated. Cytogenetic studies have yet to disclose a consistent chromosomal change in all patients with mycosis fungoides, but alterations to 10q, including loss of heterozygosity and microsatellite instability, are reported [10]. These may result in the loss of function of a tumor suppressor gene (or genes) found in this region, such as PTEN. Other studies have found evidence that p16(INK4a), a tumor suppressor gene located on 9p, may be selectively inactivated with progression of mycosis fungoides from patch to tumor stage [11]. Recurrent chromosomal or genetic abnormalities have been reported in SS. In particular, utilizing high-resolution array-based comparative genomic hybridization, the SS genome was characterized by gross chromosomal instability with highly recurrent gains and losses. Prominent among deregulated genes are those encoding c-myc, c-myc regulating proteins, mediators of myc-induced apoptosis, and IL-2 signaling pathways components [12]. Preliminary data from transcriptional analysis with oligonucleotide microarrays in mycosis fungoides revealed promising clinically relevant gene signatures predictive of survival, disease progression, and response to therapy [13]. However, further prospective long-term studies are needed to validate these early findings.

In patch lesions of mycosis fungoides, there is a perivascular or band-like infiltrate of small- to medium-sized atypical lymphocytes with hyperchromatic and convoluted (cerebriform) nuclei. The atypical cells exhibit epidermotropism, with individual lymphocytes arranged along the dermal–epidermal junction in a single-file pattern or scattered throughout all layers of the epidermis in the absence of spongiosis. There may also be small intraepidermal collections of neoplastic lymphocytes known as Pautrier's microabscesses (Fig. 10.2a). Although such collections are virtually pathognomonic of mycosis fungoides, in early patch-stage lesions, Pautrier's microabscesses may not be present (Fig. 10.2b). As lesions evolve from patches to plaques, the density of neoplastic cells within the dermis

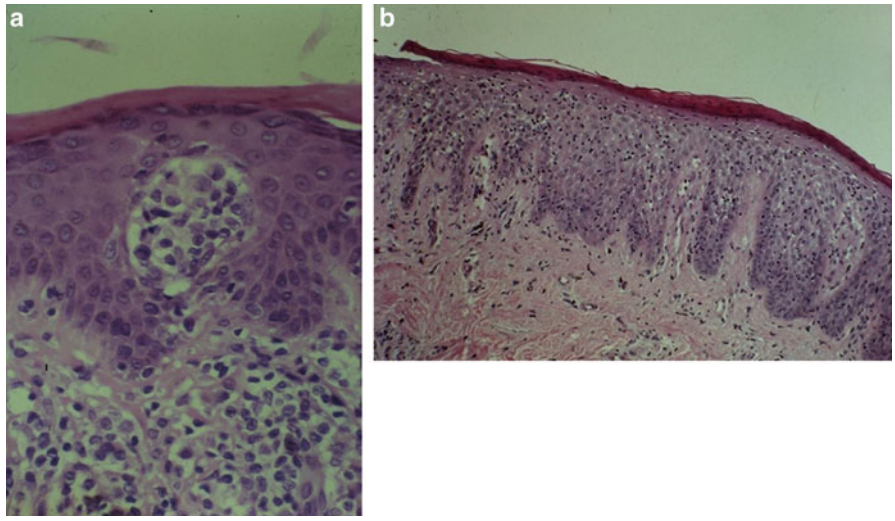

Fig. 10.2 Histopathologic features of mycosis fungoides. (**a**) Epidermotropism, Pautrier microabscesses, atypical cells with hyperconvoluted nuclei. (**b**) Epidermotropism, spongiosis, no Pautrier's microabscesses, minimal dermal infiltrate

increases, and the degree of epidermotropism becomes more exaggerated. In tumorous lesions, the dermal infiltrate is very dense, involving the full breadth of the dermis, often extending into the subcutaneous fat, and epidermotropism tends to diminish. Biopsies of patients with erythroderma show very similar histology to that of patch mycosis fungoides, but the infiltrate is typically more sparse, and the diagnosis is more difficult to establish [14]. Most cases of conventional mycosis fungoides exhibit the following immunophenotype: $CD2^+$, $CD3^+$, $CD4^+$, $CD8^-$, $CD5^+$, $CD7^-$, $CD25^{-/+}$, $CD30^{-/+}$, and T-cell receptor alpha/$beta^+$. Some cases exhibit a $CD8^+$/$CD4^-$ immunophenotype.

Both Southern blot and polymerase chain reaction analyses are capable of detecting clonally rearranged T-cell receptor gene sequences in clinical material from patients with mycosis fungoides. In normal and neoplastic T-cell ontogeny, the γ region of the T-cell receptor gene is rearranged early on, such that most T-cell malignancies have detectable T-cell–receptor γ chain rearrangements, despite the fact that the alpha/beta heterodimer is more often expressed at the cell surface. For various practical reasons, polymerase chain reaction analysis of the gamma-chain region of the T-cell receptor (T-cell receptor gamma) has proved more useful than Southern blot analysis in the evaluation of T-cell lymphoproliferative disorders. Polymerase chain reaction of T-cell receptor gamma represents a very useful adjunct to the histopathologic diagnosis of various cutaneous T-cell malignancies, especially early patch-stage mycosis fungoides, and, at present, the sensitivity of the assay is approximately 70%. Beta-chain region of the T-cell receptor is also rearranged early on in T-cell development. However, the beta-chain region is much larger with more possible rearrangements. The T-cell receptors rearrangements in both the beta region and the gamma region have identical sensitivity (64%) and specificity (84%) when analyzed as individual assays [15]. It is well established that nonneoplastic inflammatory dermatoses can exhibit detectable T-cell receptor gene rearrangements. The false-positive rate reported in the literature is quite variable, but the overall specificity is probably approximately 80–90% [16]. Recently reported data suggest that the false-positive rate becomes lower when tissue samples from two anatomically different sites or different time points demonstrate presence of identical clones [17].

Involved lymph nodes in mycosis fungoides or SS show a range of histologic features. The disease may cause regional nodes to develop the changes of dermatopathic lymphadenitis, with or

without scattered individual atypical cerebriform lymphocytes (category N_1). Category N_2 lymph nodes demonstrate dermatopathic lymphadenitis with clusters of more than ten cytologically atypical lymphocytes confined to the paracortex. Category N_3 is reserved for lymph nodes that demonstrate partial or total effacement of lymph node architecture by atypical lymphocytes [5]. Because reactive lymph nodes can sometimes exhibit non-neoplastic lymphocytes with cerebriform nuclei, and because the diagnosis of early lymph node involvement by mycosis fungoides (i.e., category I) can be very difficult on histologic grounds alone, molecular methods for demonstrating T-cell clonality are gaining wide acceptance. Recent studies even suggest that patients with lymph nodes exhibiting rearranged T-cell receptor genes by molecular methods have a worse prognosis, regardless of the histologic grade [5].

Staging of Mycosis Fungoides/Sézary Syndrome

Along with a revised clinical staging system for patients with mycosis fungoides and SS, a consensus recommendation for staging evaluation has been established [5]. Accurate staging is important because therapeutic approaches in MF are largely based on the clinical stage of the disease. The standard clinical staging system for MF and SS is based on the extent and type of skin involvement (T classification), the presence of lymph node (N classification) or visceral disease (M classification), and the detection of abnormal (Sézary) cells in the peripheral blood (B classification) [5]. Tables 10.1 and 10.2 summarize the revised TNMB categories and staging classification.

Many patients with mycosis fungoides have only cutaneous disease. Only 15–20% of patients with mycosis fungoides develop clinical problems related to extracutaneous disease. The most commonly identified site of extracutaneous disease is the regional lymphatics, usually in areas that drain significant sites of skin involvements and the blood compartment. Visceral disease may be identified subsequently. Any visceral site can be involved with MF and SS, the most common of which are the lungs, bone marrow, gastrointestinal tract, liver, and central nervous system [18].

The risk of extracutaneous disease tends to correlate with the extent and type of skin involvement [19, 20]. The extent and type of skin involvement are defined in the T-classification in the revised staging system [5]. T1 disease is defined as less than 10% of the skin surface involved with patches or plaques while T2 disease is defined as greater than 10% but less than 80% of the skin surface involved with patches or plaques. T3 disease is defined as tumor (nodular) disease, and T4 disease is erythroderma with at least 80% of the skin surface diffusely involved. Extracutaneous involvement at presentation is exceedingly rare in patients with T1 disease, infrequent in patients with T2 disease (2%), and (more) likely in patients with T3 (13%) or T4 (24%) disease [4, 20]. Patients who present with limited cutaneous involvement (T1) may never progress to more advanced T classification, especially when appropriate treatment is administered [19, 21, 22]. Although MF may be a systemic disease from the outset, the clinical behavior is such that progression of skin disease precedes onset of clinical symptoms at extracutaneous sites.

Conventional staging for patients with mycosis fungoides includes a comprehensive physical examination with careful examination of the skin (including the scalp, palms, soles, and perineum) and lymph nodes, a complete blood count with Sézary cell studies, screening chemistries (including lactate dehydrogenase), and chest X-ray. Additional imaging studies for patients with T1 or T2 skin involvement are not recommended unless the patient has very extensive skin disease, lymphadenopathy or parameters associated with worse clinical outcome, such as folliculotropic disease, large cell transformation, or blood involvement. However, patients with T3 or T4 disease are at increased risk for extracutaneous involvement, and further imaging, such as a contrast-enhanced chest/abdomen/pelvis computed tomography (CT) scan or whole body FDG-PET/CT, is appropriate. The usefulness of added functional information with FDG-PET (positron emission tomography) has been demonstrated in

Table 10.1 TNMB classification and Staging of mycosis fungoides/Sézary syndrome according to ISCL/EORTC

TNMB stages	Description
Skin (T)	
T1	Limited patches, papules, plaques covering <10% of the skin surface
T2	Patches, papules, plaques covering ≥10% of the skin surface
T3	One or more tumors
T4	Confluent erythema covering >80% BSA
Node (N)	
N0	No abnormal nodes; biopsy not required
N1	Abnormal lymph nodes; histopathology Dutch grade I or NCI LN0-2
N1a	Clone negative
N1b	Clone positive
N2	Abnormal lymph nodes; histopathology Dutch grade 2 or NCI LN3
N2a	Clone negative
N2b	Clone positive
N3	Abnormal lymph nodes; histopathology Dutch grades 3–4 or NCI LN4; clone positive or negative
Nx	Abnormal lymph nodes; no histologic confirmation
Visceral (M)	
M0	No visceral organ involvement
M1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
Blood (B)	
B0	Absence of significant blood involvement: <5% of peripheral blood lymphocytes are atypical (Sézary cells)
B0a	Clone negative
B0b	Clone positive
B1	Low blood tumor burden: >5% of peripheral blood lymphocytes are atypical (Sézary cells) but do not meet the criteria of B2
B1a	Clone negative
B1b	Clone positive
B2	High blood tumor burden: >1,000/μL Sézary cells on ≥ 407.$CD4^+/CD7^-$ or ≥ 307.$CD4^+$ /$CD26^-$ cells with positive clone

Table 10.2 Clinical Staging of mycosis fungoides/Sézary syndrome according to ISCL/EORTC

Stage	T	N	M	B
IA	1	0	0	0, 1
IB	2	0	0	0, 1
IIA	1, 2	1, 2	0	0, 1
IIB	3	0–2	0	0, 1
IIIA	4	0–2	0	0
IIIB	4	0–2	0	1
IVA_1	1–4	0–2	0	2
IVA_2	1–4	3	0	0–2
IVB	1–4	0–3	1	0–2

mycosis fungoides and SS [23]. Lymph node biopsies should be obtained if lymphadenopathy is present. Suspected sites of visceral involvement should be confirmed by appropriate biopsy. Bone marrow involvement may often be detected in patients who meet the clinical criteria for SS but is extremely uncommon in classic mycosis fungoides [24]. Therefore, a bone marrow biopsy is not routinely used as part of the initial staging.

The updated classification also eliminated the need for biopsy of lymph nodes that are not enlarged on physical examination or imaging for staging purposes. A clinically abnormal peripheral node is now defined as measuring 1.5 cm in the longest transverse diameter, or any size of palpable peripheral node that is firm, irregular, clustered, or fixed on physical examination [5]. The revision also further specified histopathologic grading systems for lymph nodes.

The ISCL/EORTC revision also considers visceral involvement to include splenomegaly on physical examination and by imaging that shows either enlargement or focal defects that are not cystic or vascular, even without biopsy confirmation. On the other hand, liver disease should be confirmed with biopsy. However, hepatic enlargement or focal defects that are not cystic or vascular on at least two imaging techniques may be considered to show tumor involvement. Any abnormalities found on imaging of the lungs or visceral organs other than the above would still warrant pathological evaluation, since they could be secondary to another malignancy or infectious disease [5].

Prognostic Factors

The T classification and presence of extracutaneous disease are the most important predictors of survival in patients with mycosis fungoides [4, 25]. Among patients with T4 disease (erythroderma), age older than 60 years, peripheral blood involvement, and extracutaneous disease are independent adverse predictive factors for survival [26]. Other worse prognostic factors include folliculotropic or large cell transformed disease [22, 27]. Mycosis fungoides may be associated with follicular involvement with or without mucin deposit. In these cases, involvement of the hair follicles is clinically prominent, and biopsy shows a heavy infiltration of the hair follicle epithelium by atypical cerebriform lymphocytes with sparing of the interfollicular epidermis [7].

Histologically, transformation to large-cell lymphoma is defined on the basis of either an infiltrate of large atypical lymphocytes that comprise greater than 25% of the dermal infiltrate, or nodular expansile aggregates of atypical large lymphocytes [28, 29]. This large cell transformation is associated with worse clinical outcome [27]. In the majority of cases, increased mitotic activity is readily observed, and the Ki-67 proliferation rate by immunohistochemistry is greater than 25% [28]. Immunophenotypically, the transformed large lymphocytes can exhibit variable loss of one or more T-cell–associated antigens such as CD3, CD5, CD4, CD8, CD45RO, or CD43. Also, the large cells may express lymphocyte activation markers such as CD30 and CD25 [28]. In some cases, there are intermixed aggregates of small, medium, or large-sized B lymphocytes, which are presumably reactive and should not be erroneously interpreted as a secondary B-cell lymphoproliferative disorder [28]. When CD30 expression is prominent among the transformed large lymphocytes, $CD30^+$ lymphoproliferative disorders (especially $CD30^+$ anaplastic large-cell lymphoma) must be considered in the differential diagnosis. Histologic findings that favor a diagnosis of transformed mycosis fungoides include an accompanying infiltrate of smaller-sized lymphocytes that exhibit epidermotropism (as seen in earlier-stage mycosis fungoides lesions), epidermotropism by $CD30^+$ lymphocytes (which is usually not a feature of anaplastic large-cell lymphoma), and a relatively low percentage of $CD30^+$ lymphocytes (as compared to cases of anaplastic large-cell lymphoma in which $CD30^+$ large lymphocytes are greater than 75%). In many cases, correlation with the clinical findings is essential for a definitive diagnosis.

General Principles of Therapy

While there are multiple therapeutic options for MF and SS, there is a lack of well-designed, prospective, controlled clinical trials comparing the efficacy and safety of various therapies. Many studies use skin response as the primary endpoint only while others used composite or global responses as the primary endpoint. As a result, caution is needed when interpreting efficacy data such as duration of response and time to response. The most important factor in designing a treatment plan is the clinical stage (Figs. 10.3, 10.4, 10.5, 10.6, 10.7, and 10.8). Selection of a specific treatment plan is based on the clinical stage, additional prognostic factors (e.g., folliculotropism or large cell transformation), toxicities associated with the treatment options, the patient's age, and other social and medical problems. The NCCN as well as the European Organisation for the Research and Treatment of Cancer (EORTC)

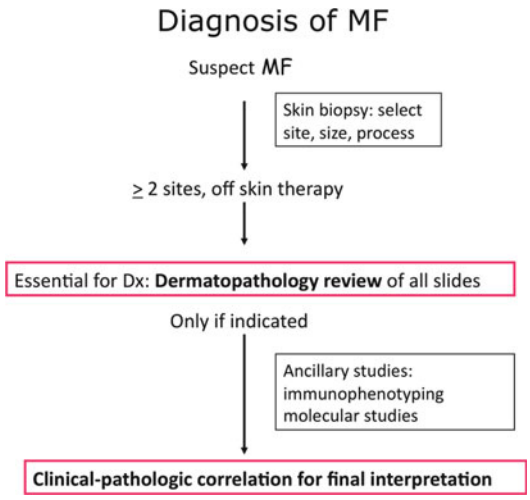

Fig. 10.3 Diagnosis of MF

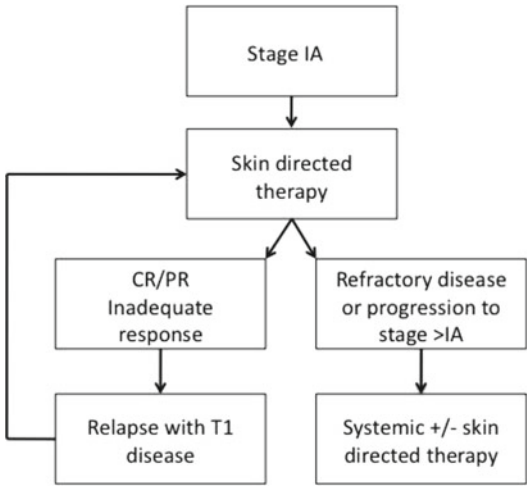

Fig. 10.4 Therapy schematic for mycosis fungoides, IA

outline the treatment guidelines for MF and SS according to stage of disease [30]. In considering all possible therapeutic options for a given stage of disease, retrospective cohort as well prospective studies were reviewed. Subsequently, the studies were evaluated using the U.S. Preventive Services Task Force: Hierarchy of Evidence [31].

In general, the treatment options in MF/SS are categorized into skin-directed treatments, systemic biologic/non-cytotoxic therapies, and systemic cytotoxic chemotherapies. For patients with T1 and T2 disease without extracutaneous involvement, stages IA–IIA, the primary treatment plan will usually be limited to skin-directed therapies. However, if these fail or there is histologic evidence of either large cell transformation or folliculotropism, a more intensive regimen is usually indicated. With respect to tumor disease, stage IIB, the treatment plan depends on the extent of the tumor lesions. If the tumor lesions are few in number, the skin-directed treatment options for stage IA-IIA are indicated, and the tumor lesions should be treated with local radiation. In cases with extensive tumor involvement, total skin electron beam therapy (TSEBT) or systemic therapies are considered. The affected skin in patients with erythroderma (T4) is very sensitive and may not tolerate skin-directed treatment. Hence, primary therapy for patients with erythroderma consists of the use of systemic biologic response modifiers (e.g., photopheresis, and oral retinoids/rexinoids, interferons [IFNs]), histone deacetylase inhibitors (HDAC-i), denileukin diftitox (fusion toxin), or low-dose methotrexate monotherapy or in combination. When biologic therapies fail in patients with refractory stage IIB to IV disease, single-agent chemotherapy such as gemcitabine, liposomal doxorubicin or Pralatrexate is considered.

Effective supportive care is critical in the management of patients with T4 disease. Increased susceptibility to bacterial and viral infection is a considerable source of morbidity and mortality. Patients with this type of compromise to the skin barrier should have diligent surveillance for skin infections, especially *Staphylococcus aureus* and herpes simplex virus. There is a low threshold for beginning systemic and skin-directed antibacterial agents with the appropriate susceptibilities.

Mycosis Fungoides and SS are associated with severe pruritus, which can be a serious detriment to patient quality of life. The measurement of this very subjective symptom is important to assess improvements in itching. It is important to attempt to quantify the severity of pruritus using a tool such as a visual analog scale. The Visual Analog Scale is a line with the numbers one (representing minimal itch) through ten (representing the worst itch), and it is the most common assessment tool utilized in the assessment of pruritus in clinical trials. However,

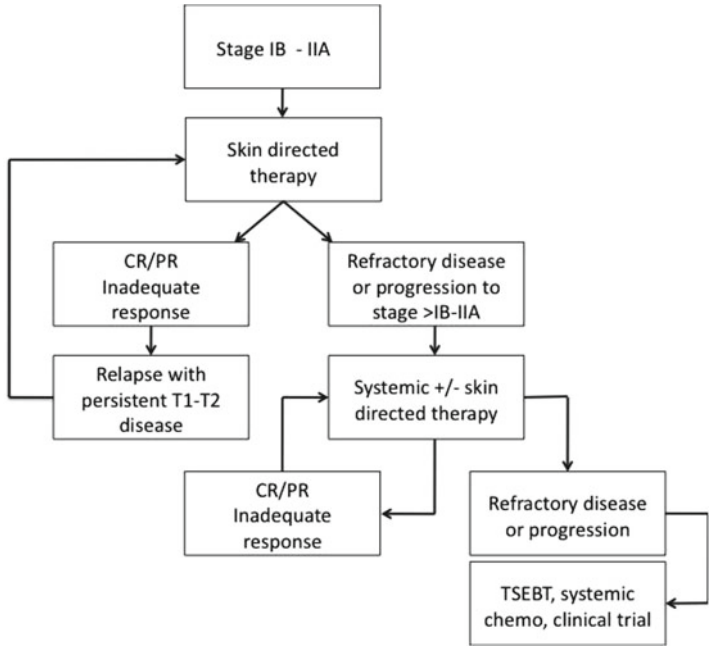

Fig. 10.5 Therapy schematic for mycosis fungoides, IB-IIA

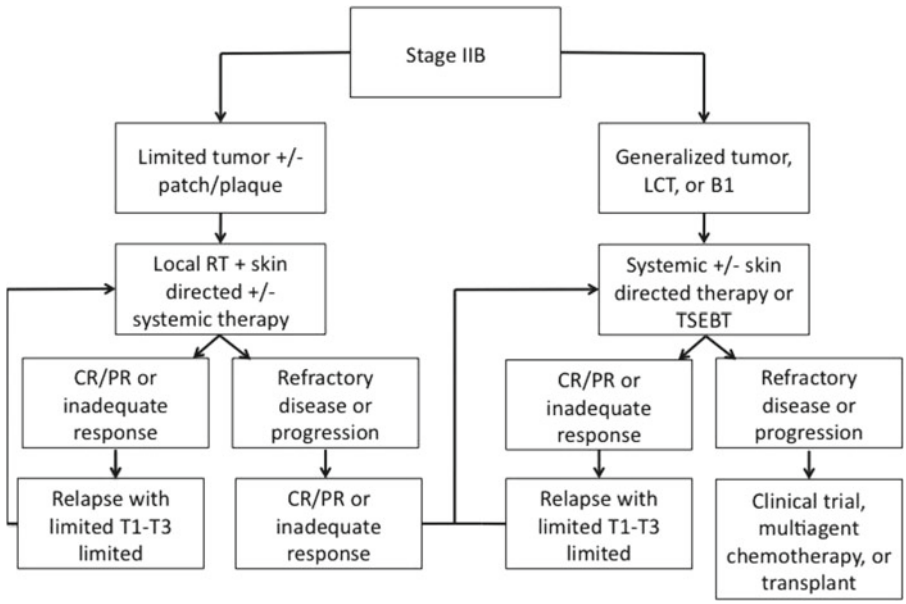

Fig. 10.6 Therapy schematic for mycosis fungoides, IIB

a more rigorous validated tool is needed for clinical trials. The effective symptomatic treatment of pruritus is of utmost importance, especially in SS. Most often, occlusive medium potency topical steroids and oral anti-itch measures such as gabapentin and mirtazapine are used [32].

Combination chemotherapy is generally reserved for patients with refractory lymph node

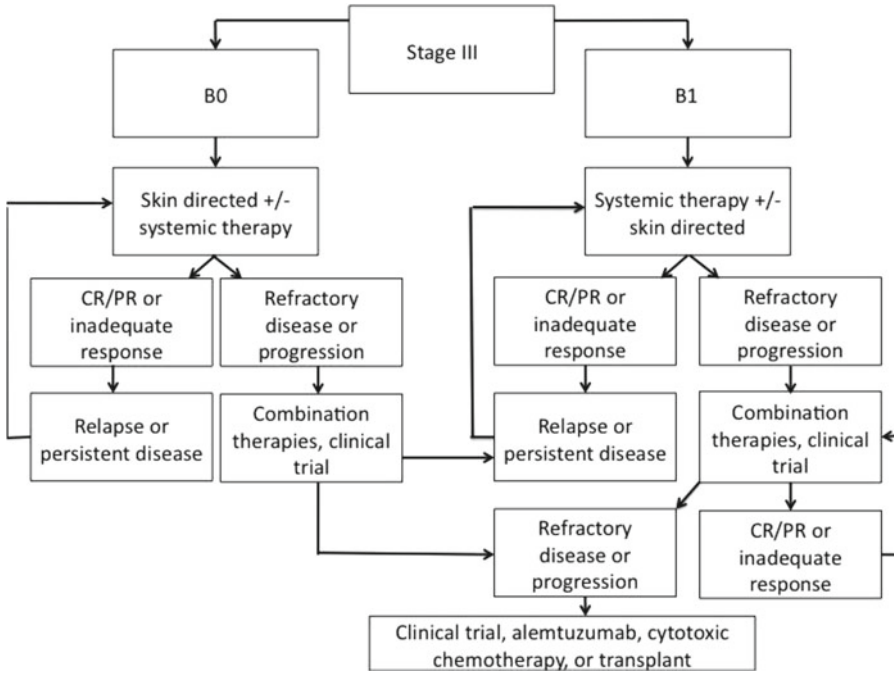

Fig. 10.7 Therapy schematic for mycosis fungoides, III

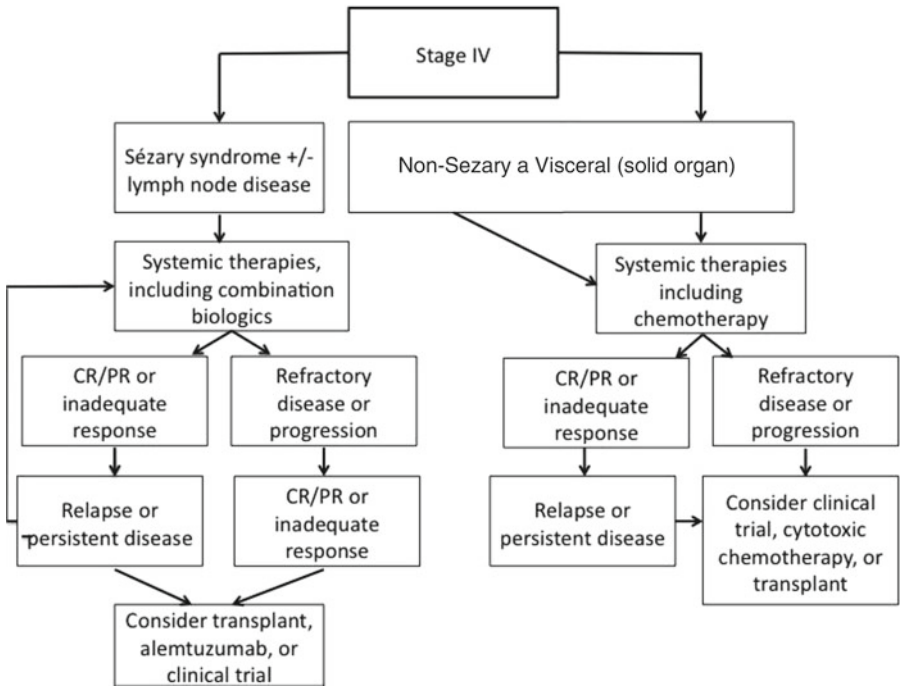

Fig. 10.8 Therapy schematic for mycosis fungoides, IV

or visceral (solid organ) disease. Patients with advanced disease in whom primary treatment fails are candidates for potential allogeneic stem cell transplantation. There is no evidence that early aggressive systemic therapy is better than conservative therapy in the management of limited disease. There is a definite need for more reliably effective therapies, especially in advanced cases of the disease. As a result, participation in clinical trials is critical for patients with advanced disease who have failed primary systemic therapies. It is important to consider allogenic stem cell transplant in patients with advanced disease as this may offer a long-lasting remission or possible cure.

Skin-Directed Therapies

Despite advances in treatment for MF and SS, traditional skin-directed therapies are still used as the primary therapeutic modality in the majority of patients with stage I–IIA disease. In patients where initial skin-directed therapy has failed or in those with severely symptomatic disease, skin-directed therapies can be combined with systemic treatments, or the patients may be referred for experimental therapy.

Topical Corticosteroid Therapy

Topical steroids can be used either as primary treatment in patients with limited patch or thin plaque disease, or they can be combined with other skin-directed treatments for added symptomatic control. The rationale for use of corticosteroids in MF is that they inhibit lymphocyte binding to endothelium and intercellular adhesion [33]. In addition, they also induce apoptosis of neoplastic lymphoid cells [34].

For patients with very limited skin involvement, topical corticosteroids can be a very cost-effective option for disease control. Application of topical steroids as treatment is generally performed once to twice a day to affected areas [35]. The percentage of complete clearance in patients with T1 disease is 63% and in T2 disease is 25% [35]. However, all patients with complete clearance had patch disease only [35]. The efficacy of topical steroids it not diminished over time and can be used again in the event of disease relapse. The benefit is that topical steroids can be used again for relapse of disease. However, long-term use of topical corticosteroids in any disease may lead to epidermal atrophy, striae, dyspigmentation, and steroid addiction. In particular clinical morphologic subsets of MF, such as the poikilodermatous MF, it may be difficult to interpret resolution of disease when topical steroids are used. In this variant, the clinical findings of telangiectasias and atrophy are the same as the side effects induced by prolonged use of topical corticosteroids. Hence, caution should be used in interpretation of disease vs. side effect of therapy.

Topical Chemotherapy

Topical nitrogen mustard (mechlorethamine hydrochloride) is the major form of topical chemotherapy used for MF and SS [36]. Topical carmustine (BCNU) has also been used [37].

Nitrogen mustard is the most widely utilized topical chemotherapeutic agent for MF because of its well-demonstrated efficacy, safety, and ease of application. The mechanism of action of nitrogen mustard in MF is unclear but may be mediated by immune mechanisms (e.g., immune stimulation) or by interaction with the epidermal Langerhans cell [36].

Topical nitrogen mustard preparation is applied to the skin once daily as initial therapy. If the disease is localized, the application field may be limited to the regional area of involvement or to the entire skin surface for those patients with generalized skin involvement. The initial concentration used is usually 20 mg%. Other areas of disease activity may become evident secondary to the inflammatory reaction provoked by the nitrogen mustard. After a period of several weeks, treatment may be limited to the affected region. Alternatively, if the disease is initially limited in distribution, the nitrogen mustard may be applied only to the affected anatomic region or regions, with careful follow-up to detect any new areas of involvement. Treatment is continued on a daily basis until skin clearance is complete. This may require 6 months or longer and is then followed by a variable duration of maintenance therapy

(3–6 months). If response is particularly slow, the concentration of the topical nitrogen mustard may be increased to 30 or 40 mg%. In addition, the frequency of application may be increased. The complete response rate for topical nitrogen mustard for limited patch or plaque (T1) disease is 70–80%. The median time to skin clearance is 6–8 months. When treatment is discontinued, more than one-half of patients will relapse in the skin, but most will respond to a resumption of therapy. The proportion of patients treated with topical nitrogen mustard who have a durable complete response (longer than 10 years) is 20–25%. In patients with a discrete number of refractory lesions, treatment may be supplemented with local irradiation. Once complete skin clearance is achieved with topical nitrogen mustard, a maintenance regimen of some kind is usually instituted, but there is no evidence that more prolonged maintenance is beneficial [36, 38, 39].

Both acute and chronic complications have been associated with topical nitrogen mustard therapy. The most frequent acute complication is an immediate or delayed cutaneous hypersensitivity reaction. It occurs in less than 10% of patients treated with the ointment-based preparation of nitrogen mustard. However, patients can be desensitized with a variety of topical or systemic desensitizing regimens [36, 39].

Chronic use of topical nitrogen mustard is not associated with increased risk of secondary cutaneous malignancies [36]. However, in patients who have used topical nitrogen mustard in combination or sequentially with other skin-damaging therapies (e.g., ultraviolet [UV] phototherapy, radiation therapy), there is an increased risk for non-melanoma skin cancers [40, 41]. Application of nitrogen mustard in the genital areas should be strictly avoided since genital application has been linked with development of secondary skin cancers. Topical Nitrogen Mustard can be used safely in pediatric patients, and studies have not shown worse adverse effects in children [36]. There is no evidence of significant systemic absorption of the medication.

Another topical chemotherapeutic agent that has been used for patients with limited disease is carmustine (BCNU). The efficacy of topical BCNU is similar to topical nitrogen mustard. BCNU can be used in solution or ointment form [37, 38]. Similar to nitrogen mustard, it can be applied to regional areas for localized disease or to the entire skin surface for generalized disease. 86% of patients with T1 were completely clear after a median of 9 weeks of use, while 47% with T2 disease were clear after a median of 11.5 weeks [42]. Contact should be avoided with the eyes or orifices [42]. There are both cutaneous and hematologic side effects. The majority of patients experience a degree of erythema accompanied by a burning sensation. This tends to localize to the intertriginous areas. It usually subsides with the use of topical corticosteroids and cool compresses. More severe erythematous reactions can lead to the development of telangiectasias that can persist for several years. Because of the systemic absorption of BCNU, the potential hematologic complications are greater, and the maximum duration of treatment is limited. Five percent of patients treating the general body surface had mild leukopenia. Other adverse hematological side effects have not been observed [42].

Topical corticosteroids, nitrogen mustard, and BCNU are indicated as initial primary therapy for patients with stage IA or IB disease. Topical chemotherapy should be considered as an alternative for those patients who are candidates for phototherapy but prefer the convenience of home application or already have a significant amount of photodamage.

Phototherapy

Phototherapy involves using UV radiation in the form of UVA or UVB wavelengths. It can be used alone or in combination with psoralen, a photosensitizing agent. Psoralen used with UVA (PUVA) is also referred to as photochemotherapy. PUVA therapy is widely used in dermatology for various dermatoses such as psoriasis. Psoralens intercalate between pyrimidines within DNA and, upon exposure to UVA, form photoadducts and DNA crosslinks [43]. This process results in cytotoxic, antiproliferative, and immunomodulatory effects. The long-wave UVA has an advantage over UVB because of its greater depth of penetration. This is useful in that while MF is

defined as an epidermotropic process, a considerable amount of neoplastic infiltrate is still in the dermis.

PUVA is indicated as primary therapy in generalized plaque and erythrodermic MF without evidence of extracutaneous disease. It is also used as palliative therapy in combination with another treatment in patients with advanced disease. Initially, PUVA treatments are given 2–3 times per week, with a minimum of 48 h between treatments to monitor the delayed erythema reaction [44]. The initial dose of UVA and the rate at which the dose is increased are generally dependent upon the skin type. Erythrodermic patients tend to require very low starting doses with very small dose increments. After maximal response, the frequency of PUVA treatments is decreased.

Both acute and chronic adverse effects have been observed with PUVA therapy [44]. Nausea from psoralen ingestion is observed in 10–20% of patients and can be managed by ingesting the drug with food or milk, or with appropriate antiemetics [43]. Phototoxic reactions can range from erythema to the development of bullae. Ultraviolet-opaque goggles must be worn during the UVA irradiation. Long-term PUVA therapy with high cumulative doses has been linked to an increased risk for the development of squamous cell carcinomas [45, 46], pigmented macules [47], and cataract formation [45]. Up to one-third of patients treated with PUVA develop signs of chronic photodamage and secondary cutaneous malignancies. After each PUVA treatment, appropriate photoprotection, including application of sunscreens, protective clothing, and UV-shielding glasses, should be used for a minimum of 24 h.

UVB therapy is a widely used alternative to PUVA. While broadband has been used, it has been supplanted with light limited to the 311 nm wavelength known as narrowband UVB (NBUVB). The use of NBUVB does not require the ingestion of psoralen prior to therapy, which is advantageous in patients that have problems tolerating the medication. Similar to PUVA, it is performed 2–3 times per week with 24 h between treatments. NBUVB is considered to have less toxicity than broadband UVB or PUVA since the penetration of UVB is reduced. The clearance rate of NBUVB is T1 and T2 disease is 70–80% and is the same with PUVA [48].

Topical Retinoid and Rexinoid Therapy

Retinoids modulate gene expression by activating nuclear retinoic acid receptors (RARs) and retinoid X receptors (RXRs). This leads to alterations in cell differentiation, proliferation, and apoptosis [49]. These properties have prompted investigation into their use as antineoplastic agents. Broad-spectrum retinoids have an affinity for RARs but exhibit poor tissue specificity and low activity. There is a derivative category of agents, known as rexinoids, which specifically activate the RXR receptors and have a lower affinity for RAR receptors. A rexinoid agent commonly used in MF is bexarotene. Although the molecular basis of bexarotene has not been clearly elucidated, it has been shown to induce apoptosis in CTCL lines [50].

Bexarotene 1% gel, a rexinoid, is the most commonly used topical retinoid for treating MF. The medication is typically applied as a thin film to the patches or plaques. It is most effective and best tolerated when used twice daily [51]. The reported overall response rate is 63%, with a complete response rate of 21% [52]. Due to the irritant effect of the rexinoids, it is only feasible to use this agent when there is limited number of patches or plaques. It is not intended for generalized application. The most common toxicity of bexarotene gel is irritation at the sites of application and occurs in the majority of patients [51]. The irritation commonly occurs in flexural areas affected by MF. Because of the erythema from the irritant reaction, it may be necessary to withhold therapy for a few weeks to assess disease activity.

Tazarotene 0.1% gel, a RAR agonist, has also been evaluated in a pilot study [53]. The gel was applied daily to discrete lesions only. Use of the gel to lesions resulted in a 35% clearance rate [53]. Mild to moderate local irritation was the most common adverse event in the majority of patients (84%). Any associated irritation was relieved by decreasing the frequency to every other day application or the use of a mid-potency steroid [53].

Imiquimod

Imiquimod is a topical immunomodulator that has been approved by the Food and Drug Administration (FDA) for the treatment of genital warts. The drug is believed to function in part through the induction of local IFN production [54]. Because systemic IFN is effective in the treatment of MF, it has been hypothesized that topical imiquimod might also be effective while sparing patients the systemic side effects of IFN treatment. An open-label, pilot study used 5% imiquimod cream to localized patches and plaques of MF. Of the six patients, three had complete histologic clearance [55]. Imiquimod was generally well-tolerated, and skin irritation was limited to lesions, which ultimately cleared with treatment.

Radiation Therapy

Mycosis fungoides is an extremely radiosensitive neoplasm. Individual plaques or tumors can be treated with local electron beam therapy (EBT) to total doses of 12–36 Gy, with a high complete response rates. The widespread use of total-skin EBT (TSEBT) was facilitated by the development of the modern medical linear accelerator. TSEBT has been developed to treat patients with extensive cutaneous disease [56]. Radiation is administered four times a week to a total dose of 30–36 Gy. A full "cycle" of treatment is administered over a 2-day period. The dose administered with each cycle is 1.5–2.0 Gy. Most patients will tolerate 2.0 Gy per cycle, but lower doses are used for patients with erythroderma, atrophic skin, or a previous course of EBT.

The treatment course is 8–10 weeks in duration. During each treatment session, patients assume multiple positions to ensure that the entire skin surface is irradiated. Supplementary treatment is required for the soles of the feet, perineum, and inframammary areas. Also, some patients with a discrete number of tumorous lesions will receive boost treatment to these tumors at the outset of EBT to reduce their thickness and permit better penetration by the electrons. The eyes are shielded routinely, but other areas may be protected over the course of the treatment to help control localized skin reactions.

TSEBT should be considered as initial therapy for patients with generalized very thickened plaque or tumorous disease, because the effective depth of treatment of EBT is more substantial than either topical nitrogen mustard or phototherapy. It is also appropriate palliative therapy for patients with a recent history of rapid progression of disease and for those patients for whom topical nitrogen mustard, bexarotene gel, or phototherapy was not effective. Although the curative potential of this treatment remains disputed, there is no doubt that it provides an important palliative benefit, especially for patients with extensive disease. Often, when disease recurs, it is in a more limited distribution and may be controlled more readily with localized topical therapies. Generally, after completion of TSEBT, adjuvant treatment with topical nitrogen mustard with or without systemic adjuvant (e.g., oral bexarotene, photopheresis) is indicated and may be continued for up to 6–12 months. Several centers have developed expertise in the use of TSEBT [56]. Overall response rates are nearly 100%, with complete response rates ranging from 40 to 98% depending on the extent of skin involvement. As many as 50% of patients with limited plaque disease and 25% of patients with generalized plaque disease may remain free of disease for longer than 5 years after completion of a single course of EBT [1, 56, 57]. Up to two courses of TSEBT may be administered over the course of a lifetime, which can limit its use in long-term management of the disease [58].

In patients who have lymph node involvement or in some situations of localized visceral disease, megavoltage (4–15 MeV) photon irradiation may be helpful in providing important additional palliation. Doses of 24–36 Gy in 3–4 weeks are often sufficient to achieve local control of lymph nodes or other extracutaneous sites of disease. This is often combined with systemic chemotherapy or biologic therapy (IFN-α or bexarotene), depending on the extent of the extracutaneous involvement.

Short-term side effects associated with TSEBT include acute erythema, desquamation, temporary nail and hair loss, and an impaired ability to perspire properly for up to 12 months. Long term,

there is an increased risk of secondary squamous cell and basal cell carcinomas of the skin. The risk of secondary malignancies is greatest in those who have received long courses of therapy with other skin-damaging therapies such as phototherapy [43].

Systemic Therapies

Systemic therapies are indicated when skin-directed primary therapies fail or in aggressive or advanced MF cases. Patients with significant numbers of circulating Sézary cells should also be placed on a systemic therapy as part of their treatment regimen. Therapeutic efforts are focused on targeted biologic agents that promote apoptosis and manipulate the host immune response. The combination of either a biologic agent with a skin-directed therapy or the combination of multiple biologic agents results in improved disease control by acting in a synergistic manner. Toxicity can also be reduced in combination regimens as lower doses are required for each therapeutic modality.

Biologic Therapies

Extracorporeal Photopheresis

Extracorporeal photopheresis (ECP) is considered first line therapy for patients with Sézary cell blood involvement. ECP delivers psoralen and UVA radiation systemically by utilizing an extracorporeal technique [59]. White blood cells are collected in a clear container (leukapheresis) and exposed to psoralen. The cells are then irradiated with UVA (PUVA). The irradiated cells are returned to the patient in a closed system. The ECP instrument performs the leukapheresis and delivers the UVA. The mechanism of action of ECP involves induction of malignant T cell apoptosis with PUVA, which is accompanied by the enhancement of a tumor-specific immune response. ECP also induces monocytes to differentiate into dendritic cells capable of phagocytosing and processing the apoptotic tumor cell antigens [9, 60].

A standard complete ECP regimen for CTCL consists of 2 consecutive days of therapy repeated at 2–4-week intervals. The frequency of administration is adjusted according to disease severity and/or clinical response. After a maximal, stable response has been achieved, the frequency of treatments is gradually decreased, and then stopped completely, unless the disease relapses or flares during the weaning process, or when maintenance therapy is given. Maintenance therapy is given every 4–6 weeks; a repeat attempt at weaning can be made at a later time. If an adequate response is not attained with ECP monotherapy, or if patients have a significant level of circulating Sézary cells, additional biologic agents should be added. These can include IFN or systemic retinoid. A minimum of 4–6 months of treatment should be given before ECP is considered a failure. The overall response rate is 70–80% [61, 62].

An advantage of ECP is its limited side effect profile. One of the greatest advantages of ECP is that the adverse effects are minimal [59]. Common side effects include mild fatigue associated with leukapheresis and fluid shifts. Peripheral intravenous access for treatment is preferable to central access to minimize complications. There are no significant side effects in terms of laboratory parameters. Patients receive psoralen, and need to protect their eyes and skin from UV exposure for 24 h after treatment. ECP has been shown to be most effective in patients with blood involvement, particularly those with SS [61, 63].

Interferon-Alpha

IFN therapy is indicated for refractory or advanced disease and is often combined with other skin-directed or systemic therapies. IFN was originally discovered by Isaacs and Lindenmann [64]. It is a protein expressing virus non-specific antiviral activity [65]. Based on antigenic proteins, IFNs are divided into three main groups: IFN-alpha, IFN-beta, and IFN-gamma. IFN-alpha and beta bind to IFN type I receptor while IFN-gamma binds to the IFN type II receptor. IFN-alpha preparations are primarily used in the treatment of CTCL [66]. IFN-gamma has been used rarely as an alternative in patients who have developed resistance to IFN-alpha [66].

IFN-alpha induces a variety of immunologic effects that may lead to clinical response [9]. It directly enhances cell-mediated cytotoxicity by $CD8^+$ T cells and NK cells which augments the antitumor response. It also suppresses TH2 cytokine production by malignant T cells, which can lead to enhanced immunomodulation.

IFNs are administered intramuscularly or subcutaneously with a maximum plasma concentration 6–8 h after administration [66]. There are multiple regimens used. Traditionally, IFN-alpha is started at lower doses, such as 1–3 MU three times per week subcutaneously and titrated up as tolerated. However, because of the numerous associated side effects, it is typically not used as monotherapy. Rather, it is used in combination with ECP, systemic retinoids, methotrexate, and phototherapy in an effort to limit side effects. When used in combination, it is a first line therapy for advanced MF and SS.

The dosage of IFN-a for mycosis fungoides is usually initiated at 3–5 million units daily or three times per week and is gradually increased, depending on the clinical response and the severity of adverse effects. Reported overall response rates when used as monotherapy are 53–74%, with complete response rates of 21–35% [67, 68].

The adverse effects of IFN can prohibit its use in some patient populations such as the elderly. The most common side effects include fevers, chills, tachycardia, malaise, myalgias, and headaches that are part of the general flu-like syndrome [69]. The flu-like syndrome seems to decrease in intensity with time [68]. However, in patients on low-dose intermittent therapy, acetaminophen is able to control the symptoms. Hematological side effects primarily involve leukocytes, platelets and erythrocytes. Leukopenia occurs within hours of exposure, and often stabilizes around 40–60% of the normal leukocyte count. The recovery of granulocyte and lymphocyte counts is rather rapid after discontinuation of IFN therapy [69]. Prolonged IFN therapy often results in normocytic normochromic anemia, which in contrast to the IFN-induced leukopenia, has a slow recovery. Thrombocytopenia is also an observed side effect especially in patients with hematological malignancies [69].

Retinoids

Systemic retinoids are indicated primarily in patients with advanced disease and can be used as monotherapy or as part of combination regimens with skin-directed or other biologic therapies. They are also used in early stage, refractory disease.

The most commonly used systemic retinoid is a RXR agonist, bexarotene; however, RAR agonists, such as isotretinoin, acitretin, or all-*trans* retinoic acid, are available as alternative agents [70]. Much of the molecular basis of the mechanism of action of bexarotene is unknown. However, it has been shown to induce apoptosis in CTCL lines and T lymphocytes from Sézary patients [50, 71]. In addition, patients who have responded to bexarotene had higher $CD8^+$ cell counts after therapy [72]. The initial dose of oral bexarotene is 300 mg/m^2/day, which can be adjusted according to the clinical response, patients; comorbidity risk, and the severity of adverse effects.

The reported response rate is approximately 45–55%, with a 10–20% complete response rate depending on the dose of bexarotene and the severity of disease [52, 73].

There is a common toxicity profile for the different forms of retinoids, and many of these adverse effects are dose dependent. Most commonly, patients experience photosensitivity and dryness of the skin and mucous membranes. Other adverse effects include myalgia, arthralgia, hyperlipidemic, and fatigue, and less commonly, headaches. On rare occasions, headaches can be caused by pseudotumor cerebri. The well-known teratogenic effects of retinoids must be carefully addressed in female patients of childbearing age. Potential long-term, cumulative toxicity of retinoids includes the development of bony changes such as hyperostosis. Bexarotene also has unique effects on the pituitary-thyroid axis, which results in hypothyroidism with low free thyroxine (FT4) and low thyroid-stimulating hormone (TSH) levels.

Bexarotene is a selective agonist for RXR receptors. The receptors can form homodimers and heterodimers with RARs as well as with other nuclear receptors such as vitamin D receptors and thyroid receptors. Due to the formation of heterodimers, the use of bexarotene affects the thyroid receptors leading to central hypothyroidism.

Because of their potential hepatotoxic and hyperlipidemic effects, liver function and serum lipid levels (triglycerides/cholesterol) should be monitored during treatment. Bexarotene also has more profound effects on serum lipid levels, especially triglycerides, than any other retinoid. Thus, it is conventional to have patients on lipid-lowering agents and thyroid supplements during bexarotene therapy. These are ideally started in the week prior to beginning bexarotene therapy. Gemfibrizol is contraindicated with bexarotene due to increased plasma levels of bexarotene and higher triglyceride levels. In addition, several patients were known to develop pancreatitis in early clinical trials [73]. The preferred lipid-lowering drugs are of the statin or fenofibrate class of agents [74]. Toxicities associated with systemic retinoids are usually reversible upon cessation of therapy.

Retinoids can be combined with skin-directed such as PUVA or with other systemic agents including IFN-alpha, ECP, or denileukin diftitox therapy. Combination therapies often have better efficacy and safety profiles when compared to the use of individual biologic agents alone [9].

Recombinant Fusion Proteins

Denileukin difitox is a recombinant cytotoxic fusion protein that targets the IL-2 receptor on T-cells. It is indicated for use in patients with advanced, persistent and recurrent MF and SS [75–77]. This recombinant fusion protein combines the receptor-binding domain of IL-2 with diphtheria toxin. Once the molecule is bound to the IL-2 receptor, it is taken up by endocytosis, and the diphtheria toxin is cleaved. This leads to inhibition of protein synthesis and results in killing of defined neoplastic cell populations [78].

Denileukin difitox is administered intravenously for 5 consecutive days and repeated every 3 weeks at daily doses of 9 or 18 μg/kg over 1 h. Ontak has undergone a multicenter phase III trial in patients with IL-2 receptor ($CD25^+$)-expressing mycosis fungoides [75]. Patients with intermediate or advanced stages of disease were included in the phase III trial. The overall response rate was 30%, with complete-response and partial-response rates of 10% and 20%, respectively. Toxicities include fever, chills, nausea, a "capillary leak" syndrome, which may be ameliorated by pre- and post-treatment hydration, and a hypersensitivity reaction, which can be countered with premedication with corticosteroids [77, 78].

Bexarotene upregulates IL-2 receptors expression on T-cells. Hence, the use of bexarotene may lead to more enhanced binding of denileukin difitox and greater effectiveness [79].

Histone Deacetylase Inhibitors

HDAC-i are a novel class of agents. HDAC inhibition results in acetylation of histone and non-histone proteins leading to a transcriptionally active chromatin and activation of gene expression [80]. Defective histone-acetylation enzymes have been identified in malignant cells [81, 82]; hence, HDAC-i may have anticancer properties through the restoration of normal acetylation.

There are two HDAC-i used in advanced, refractory, and relapsed MF and SS. The first is vorinostat. It is generally used as monotherapy, but it can be used in combination with other skin directed and systemic agents. However, there is no data for the use of combination therapy involving HDAC-i, and caution is needed with regards to safety and efficacy. Vorinostat is an oral agent that is dosed orally at 400 mg daily. The clinical efficacy and safety was studied in a multicenter trial followed by United States FDA approval for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients with refractory disease [83, 84]. The overall response rate was 30% with no complete responses.

The most common side effects are gastrointestinal (nausea, vomiting, diarrhea), constitutional, hematologic, and taste disorders [83]. HDAC-i can potentially prolong QTc; thus, any electrolyte abnormalities should be corrected to minimize complications. This is especially relevant in patients with a history of heart disease. Other serious side effects to monitor include thromboembolic events, gastrointestinal hemorrhage, ischemic stroke, and thrombocytopenia [83].

A second HDAC-i, romidepsin, is FDA-approved for use in CTCL. It is an intravenous drug used which is primarily used as monotherapy. It is given on days 1, 8, and 15 of a 28-day cycle at

a dose of 14 mg/m^2. Toxicities are similar to those in seen in vorinostat [85]. The same monitoring recommendations are applicable to vorinostat and romidepsin. A clinically meaningful response is seen in up to one-third of patients. In advanced disease, global response rates were higher with romidepsin than vorinostat [83, 84, 86].

Monoclonal Antibody Therapy

One of the most effective monoclonal antibodies used in the treatment of advanced disease such as erythrodermic (T4) MF and SS is alemtuzumab. It is reserved for those patients with advanced disease in whom other traditional therapies have failed. It is a humanized IgG antibody directed against CD52 [78]. CD52 is expressed on T-lymphocytes, B-lymphocytes, natural killer cells, monocyte, and malignant T-cells in CTCL [87, 88]. The mechanism through which alemtuzumab exerts its clinical effect is not well known, but likely includes apoptosis [89], antibody-dependent cellular cytotoxicity [90, 91], and complement mediated cell lysis [92, 93].

In the standard therapeutic schedule used in other lymphomas, such as chronic lymphocytic leukemia, T-cell prolymphocytic leukemia, and peripheral T-cell lymphoma, escalating doses from 3 to 10 mg and then to 30 mg are administered on alternating days followed by 30 mg three times per week for 12 weeks [94–97]. However, evidence suggests that low dose intermittent alemtuzumab (3 mg on day 1 with 10 mg on days administered subcutaneously thereafter), has equal efficacy and durable remissions with less toxicity [98]. Alemtuzumab is more efficacious in patients with SS. One of the goals of therapy is to keep the Sézary cell count <1,000 mm^3. The overall response rate for advanced disease is 28% and the duration of response is less than 3 months [99].

Complications of alemtuzumab include serious infections such as cytomegalovirus, generalized herpes simplex virus, fatal fungal and mycobacterial infections. Thus, prophylactic regimen of antivirals, antifungals, and antibacterials are typically utilized with alemtuzumab therapy [99]. In addition, other hematologic toxicities occur, such as severe neutropenia, thrombocytopenia, and anemia [99].

Systemic Cytotoxic Therapy (Chemotherapy)

Systemic chemotherapy is appropriate for patients with large cell transformed stage IIB MF and stage IV MF with extracutaneous involvement. Most chemotherapeutic regimens, however, result in only temporary palliative responses. Multiple single-agent and combination chemotherapies have been tried in advanced MF and SS. For single-agent chemotherapy, no particular drug has been shown to be superior and no large, randomized studies comparing agents have been reported. Single agent chemotherapy is more widely utilized in MF/SS. Combination regimens are largely reserved as salvage after single agent therapy has failed or if there is solid organ involvement.

While typically used in advanced MF and SS, methotrexate has been used in lower doses for extensive stage IB disease. Methotrexate inhibits dihydrofolate reductase (DHFR), leading to the subsequent inhibition of DNA synthesis [100]. Multiple dose ranges and schedules have been used as therapy in erythrodermic MF (T4) and SS. No clear benefit has been demonstrated for higher doses compared to lower doses of methotrexate. Side effects observed with the use of methotrexate include elevated serum aminotransferase levels (which are usually reversible after dose reduction or withdrawal), oral mucositis, pharyngeal mucositis, gastrointestinal complications such as nausea and diarrhea, interstitial pulmonary fibrosis, and uncommonly, reversible leucopenia [101]. More recently, newer antifolate prolatrexate has been shown to have clinical activity is relapsed on refractory MF or SS with less intensive dose regimen than systemic peripheral T- cell lymphoma.

Gemcitabine, a novel nucleoside analog, is activated by deoxycytidine kinase to its triphosphate form, gemcitabine triphosphate, which is then incorporated into RNA and DNA. The latter causes chain termination and inhibition of DNA repair, which is responsible for antitumor effect of the medication. Response rates as high as 70% have been reported, but the complete remission rate is low with a median duration of complete remission of 10 months (range 4–22 months) [102]. Recently this agent has been used as frontline therapy for patients in whom control is

needed of massive lymph node disease. Gemcitabine is generally well tolerated, even in the elderly population. Myelosuppression with resulting anemia, thrombocytopenia, or leukopenia are the most common adverse events [102]. Cutaneous adverse events include flares of lesional erythema within 1 week of treatment as well as generalized hyperpigmentation [102]. Serious adverse events are rare.

Doxorubicin is an anthracycline agent used in advanced stages of MF and SS. Pegylated liposomal doxorubicin is a formulation of doxorubicin that is encapsulated into liposomes. The liposomes serve as stable, long-circulating carriers useful for delivering doxorubicin to tumor sites with a lower toxicity than the free drug. The most frequent side effects are mild anemia and lymphopenia. Another significant toxicity with this class of drugs is palmoplantar erythrodysesthesia [103].

Another cytotoxic agent is temozolomide, which has shown encouraging activity in advanced MF. It is an imidazotetrazine derivative and oral alkylating agent that has excellent oral bioavailability [104]. Its mechanism of action is similar to that of other alkylating agents, which induce DNA damage by cross-linking. Resistance has been associated with high levels of the scavenger protein O6-alkylguanine-DNA alkyltransferase in tumor cells. Response rates of 30% have been reported in stage IIB and III patients. In a phase II study, the most frequent adverse effects were nausea, vomiting, neutropenia, and thrombocytopenia [104].

In addition, other mechanisms to inhibit growth and encourage apoptosis of tumor cells are being developed. Bortezomib, which inhibits the proteasome, leads to the down-regulation of NF-KB activation and induction of CTCL cell apoptosis [105]. In a phase II trial, the response rate was 67% in all stages; however, the complete response rate was much lower at 10% [106]. With regard to hematologic adverse effects, neutropenia and thrombocytopenia were observed. The most significant non-hematologic toxicity was sensory neuropathy [106].

The purine analogs are a class of drugs that have demonstrated activity in MF and a variety of other NHL. T-cells have a high level of adenosine deaminase (ADA), a key enzyme in the purine degradation pathway. The purine analogs pentostatin, fludarabine, and 2-chloro-deoxyadenosine are a group of structurally similar agents, which were developed to target ADA. They have different interactions with ADA, but all result in DNA damage. Hematologic toxicity and opportunistic infections are the most common complications associated with this class of drugs. Prophylactic antibiotics against *Pneumocystis carinii* and antivirals to prevent herpes virus infection are routinely indicated [107].

Most of the patients treated with combination chemotherapy have failed single agent chemotherapy or have solid organ involvement (IIB to IV). There are no randomized trials comparing combination chemotherapy with single-agent regimens. The largest experience is with combinations such as cyclophosphamide, vincristine, and prednisone, with or without doxorubicin [108, 109]. Complete response rates are generally about 25% (range 11–57%) and response duration is 3–20 months.

Hematopoietic Stem Cell Transplantation

There has been recent interest in using hematopoietic stem cell transplantation (HSCT) in MF. Given the small number of patients treated thus far, there are no well-defined prognostic factors to identify patients suitable for this therapy. Bigler and associates reported that five of six patients achieved a complete response with an autologous transplant [110]. In another study, eight of nine patients achieved a complete response [111]. However, all of the patients in these studies ultimately relapsed, suggesting that autologous transplantation is not a curative approach.

The concept of allogeneic HSCT is promising. Even in the absence of a complete response, an allogeneic graft-versus-tumor effect may provide an immune mechanism to control the malignant T-cell process associated with mycosis fungoides. Molina and associates reported a complete response in all eight patients transplanted for refractory MF or SS. With a median follow-up of 56 months, six patients remained alive and without evidence of lymphoma [112]. Mild acute and

chronic GVHD developed in all patients who survived. A non-myeloablative approach has also been reported in which all three patients who achieved a durable complete response [113].

It appears that compared to autologous HSCT, allogeneic HSCT may result in durable long-term remissions [114]. With better understanding of the disease biology, it may be possible to develop prognostic factors so that these aggressive approaches can be offered to suitable patients. Larger studies will be required to identify the best conditioning regimen, efficacy, safety, and impact on quality of life.

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