Review of the treatment of mycosis fungoides and Sézary syndrome: A stage-based approach

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Abstract

Mycosis fungoides (MF) and Sézary Syndrome (SS) are the most common subtypes of cutaneous T-cell lymphomas. Most of patients have indolent and incurable course of disease. Therefore, treatment should be reaching the optimal benefit with minimizing the toxicity as much as possible. To achieve this aim, the management should follow a -stage-based- approach.

Treatment of early-stage MF (IA-IIA) involves skin-directed therapy (SDT) including topical corticosteroids, phototherapy, topical chemotherapy, topical retinoids and radiotherapy.

For aggressive/recalcitrant early-stage MF or advanced-stage MF, systemic therapy should be considered including interferone-alpha, oral retinoids including bexarotine and more recently acitretin, histone deacetylase inhibitors (HDACi), fusion toxin denileukin diftitox and chemotherapy drugs. Combined drug regimens can be considered in some situations to get the synergistic effect while lowering the individual drug's doses on the other hand. By exception of aggressive stages, chemotherapy should always come after other systemic drugs have been tried or contraindicated. Novel drugs should be considered in situations when all systemic drugs have failed.

Key words:

Ctaneous T-cell lymphoma, Mycosis fungoides, Sézary Syndrome

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Introduction

Primary cutaneous lymphomas are composed of both T-cell (75%+) and B-cell lymphomas and are rare conditions representing 2% of all lymphomas with an annual incidence of 0.3 to 1 per 100 000. [1,2] There are a variety of different types of cutaneous T-cell lymphomas (CTCL); and until relatively recently, there were 2 classifications for CTCL, the World Health Organization (WHO) [3] and the European Organization for Research and Treatment of Cancer (EORTC)' [4] the latter characterized by dividing the entities into aggressive or indolent conditions based on clinicopathologic criteria. In 2005, the 2 classification systems were combined (Table 1). [1]

Mycosis fungoides (MF), and its leukemic variant Sézary syndrome (SS), are the most common forms of cutaneous T-cell lymphoma (CTCL). The annual incidence of CTCL (more broadly defined than MF/SS) is reportedly increasing and currently estimated at 9.6 cases per 1 million person-years. [5] Long-term survival of most patients results in a much higher overall prevalence. The chronicity of the disease results in many patients being treated with multiple therapies in their lifetime, including: skin-directed therapies, such as ultraviolet light, topicals, and radiation; an increasing armamentarium of systemic agents ranging from retinoids to other biologics to chemotherapy; and an emerging role for allogeneic stem cell transplantation. This indeed makes the algorithms of these guidelines complex. In 2007, the National Comprehensive Cancer Network NCCN created its first guidelines on MF/SS. There are no sufficient randomized studies to recommend a preferred treatment strategy for MF/SS and no universally accepted standard treatments exist. This article overviews the stage-based treatment of MF/SS and of its significant importance.

Etiology

The etiology of mycosis fungoides remains unknown. However, various theories implicate occupational or environmental exposures (e.g. Agent Orange), cytokines, oncogenes, other forms of chronic antigenic stimulation, or viral exposure.

MF variants

The classical type of MF has 4 stages: patch, plaque, tumoral and erythroderma or Sézary syndrome. [6,7] Of them, the most common is the patch/plaque MF, initially described by Alibert, which presents with extremely pruritic, erythematous macules and patches with telangiectasias and atrophy in the “bathing trunk” distribution. However, many clinical and histologic variants have atypical or unique clinical presentations, such as erythrodermic, follicular, syringotropic, bullous/vesicular, granulomatous, hypopigmented, hyperpigmented, poikilodermic, hyperkeratotic, papillomatous, ichthyosiform, palmoplantar, unilateral, pigmented purpura-like eruption, pustular, pagetoid reticulosis and extracutaneous.

SS is a distinctive (leukemic) form of CTCL in which patients have significant blood involvement with Sézary cells, erythroderma and lymphadenopathy. Additional clinical findings commonly seen in SS include keratoderma, nail dystrophy, alopecia, ectropion, and skin edema (especially in the legs). These patients often experience intractable itching (pruritus), which can be the most significant life-altering symptom, and therefore treatments that can successfully reduce pruritus even without measurable objective response may still be a valuable option.

Natural history and diagnosis

MF is suspected when patient present with long year’s history of intractable, recurrent, pruritic kin eruption with poikilodermatous or polymorphic skin involvement in a typical distribution. Thus it's not uncommon for the diagnosis of MF to remain elusive for many years requiring observation and repeated biopsies with clinicopathological

correlation. SS should be suspected in patient with unexplained pruritic erythroderma associated with atypical lymphocytes in their blood. The approach to diagnosis is summarized in (Table 2) with joining clinical and laboratory assessments.

Staging and prognosis

The management of MF/SS is centered on a "stage-based" approach, and MF is classified into 4 clinical stages based on the TNM classification (Table 3), [9] which then is synthesized into a clinically based staging system broadly divided into early- and advanced-stage disease. [9] (Table 4). Skin patches and plaques occur in stage I, which is divided into IA (< 10% body surface area [BSA]) or IB (>10% BSA). The presence of clinically evident lymphadenopathy without pathologic nodal infiltration represents stage IIA, cutaneous tumors characterize stage IIB, generalized erythroderma characterizes stage III, and pathologically positive lymph nodes (IVA) and visceral disease characterizing stage IVB. Patients with staged IA, IB, and IIA disease are considered to have "limited-stage" disease, while those with stages IIB (tumor), III (erythroderma), and IV (pathologic nodes with or without viscera) have "advanced-stage" disease.

Although MF/SS are generally considered incurable conditions, it is important to recognize that the majority of patients have an indolent form of the disease and will live for many years. Indeed, it is estimated that 65% to 85% of patients with MF have stage IA or IB disease. [10, 11] The most important factor in planning management and determining prognosis is the stage of the disease. Indeed, the majority of patients with early-stage disease (stages IA, IB, and IIA) do not progress to more advanced-stage disease, and patients presenting with isolated patch or plaque disease (T1-T2) have a median survival of more than 12 years. [11,12] Moreover, patients with stage IA disease do not appear to have a decreased survival compared with an age-, sex-, and race-matched population. [13] Patients with advanced-stage disease (stages IIB, III, and IVA) with tumors, erythroderma, and lymph node or blood involvement but no visceral involvement has a median survival of 5 years from time of presentation. Of note, patients with tumors (T3) have an inferior outcome to those with erythroderma (T4). Patients with visceral involvement are rare (stage IVB) and have a median survival of only 2.5 years or less. [10,11,13,14,15]

Within early-stage MF, there is some prognostic heterogeneity. Indeed, we recognize an "intermediate-risk" group between early- and advanced-stage diseases. This includes patients with stage IIA/IB folliculotropic variant of MF and patients with very thick plaques. [16,17] The relatively inferior outcomes in these groups are thought to be the result of its reduced responsiveness to skin-directed therapy (SDT). [18] For advanced-stage disease, patients with stage IIB disease with multiple tumor nodules (a higher tumor burden) and large-cell transformation of MF have a substantially poorer prognosis (see "Transformed disease"). [10] Low numbers of CD8+ T cells in the dermal infiltrate and/or the blood have also been independently associated with reduced survival. [12,19,20]

Investigation

The approach of staging the patient is summarized in (Table 5) and it's based on the recommendations of the International Society for Cutaneous Lymphomas (ISCL). [9] For patients with clinically very limited-stage disease with skin patches and/or plaques with no palpable lymphadenopathy, extensive staging investigations are not generally required. Occasional patients will present with regional lymphadenopathy, which may reflect dermatopathic changes in the node rather than true nodal involvement with MF. Thus, it is not always necessary to biopsy every patient with mildly enlarged nodes. In general, it's recommended to biopsy nodes larger than 1.5 cm as nodal involvement has substantial prognostic impact (Table 3). The relative hesitancy in performing

node biopsies relates to the high incidence of skin colonization with pathogenic organisms in patients with MF/SS, which increases the risk of infection after surgery.

Treatment

Choosing appropriate treatment is based primarily on disease's stage depending on TMNB classification. [21] However, other prognostic variables, such as folliculocentric involvement or large cell transformation, should also be considered. Additional factors in treatment selection include patient age, overall health status, acuity or severity of associated symptoms (e.g., pruritus, tumor ulceration, response rate, time to and duration of treatment response, data on treatment-related toxicities, and accessibility or cost–benefit features of treatments. Generally, treatment is divided into skin-directed therapy [SDT], systemic therapy and combination therapy. For more recent version of National Comprehensive Cancer Network (NCCN) guidelines please visit www.nccn.org.

Treatment of MF/SS.*

SKIN-DIRECTED THERAPIES	SYSTEMATIC THERAPIES
For limited/localized skin involvement • Topical corticosteroidsb • Topical chemotherapy (mechlorethamine [nitrogen mustard], carmustine) • Local radiation (12-36 Gy) • Topical retinoids (bexarotene, tazarotene) • Phototherapy (UVB, NBUVB for patch/thin plaques; PUVA for thicker plaques • Topical imiquimod	Category A (SYST-CAT A) • Retinoids (bexarotene, all-trans retinoic acid, isotretinoin [13-cis-retinoic acid], acitretin) • Interferons (IFN-alpha, IFN-gamma) • HDAC-inhibitors (vorinostat, romidepsin)e • Extracorporeal photopheresisf • Denileukin diftitox • Methotrexate (£ 100 mg q week)
For generalized skin involvement • Topical corticosteroidsb • Topical chemotherapy (mechlorethamine [nitrogen mustard], carmustine) • Phototherapy (UVB, nbUVB, for patch/thin plaques; PUVA for thicker plaques) c • Total skin electron beam therapy (30-36 Gy) d (reserved for those with severe skin symptoms or generalized thick plaque or tumor disease, or poor response to other therapies)	Category B (SYST-CAT B) • First-line therapies Liposomal doxorubicin Gemcitabine • Second-line therapies Chlorambucil Pentostatin Etoposide Cyclophosphamide Temozolomide Methothrexate (>100 mg q week) Bortezomib Low dose pralatrexate

* From the NCCN Guidelines Version **3.2012**

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Managing early-stage (IA-IIA) MF

As mentioned, the majority of patients present with early-stage disease (Table 6). [40] As the use of early application of therapy does not impact on survival,[15] a nonaggressive approach to therapy is

warranted with treatment aimed at improving symptoms and cosmesis while limiting toxicity. As patients with stage IA disease have a long life expectancy, an "Expectant Policy" may be a legitimate management option in selected patients, provided that it incorporates careful monitoring. Given that multiple skin sites are often involved, the initial treatment is primarily Skin-Directed Therapy (SDT) which aims to control skin lesions while minimizing morbidity. The key choices for SDT are topical or intra-lesional corticosteroids or psoralen plus ultraviolet A radiation (PUVA) or ultraviolet B (UVB). Indeed, for patients with limited patch disease, topical steroids often control the disease for many years, and often this is the only form of therapy required for such patients. Class I (potent) topical corticosteroids, such as betamethasone dipropionate 0.05% or mometasone furoate 0.1%, are the most effective at obtaining objective disease regression. Patients with stage T1 disease have an approximately 60% to 65% complete response (CR) rate and a 30% partial response (PR) rate with topical steroids. Patients with T2 disease (generalized patch/plaque with >10% of skin surface involved) have a 25% CR rate and a 57% PR rate. Topical corticosteroids have CR rates similar to other forms of SDTs. [22] Intralesional corticosteroids can be effective in treating thicker MF lesions, such as plaques or tumor deposits. For more widespread disease, phototherapy with PUVA or UVB is recommended. Response rates to PUVA therapy in patients with patch disease are high with CR rates of approximately 58% to 83% and overall response rates of up to 95%. [23,24] Furthermore, remission is often prolonged with a reported mean duration of 43 months. [23] Maintenance treatment with weekly or fortnightly therapy can be effective in maintaining remission. PUVA therapy is generally well tolerated; however, acute side effects include nausea (from the oral psoralens) or photosensitivity. Long-term side effects are acceleration of actinic damage and an increased rate of skin malignancies, including squamous cell carcinoma and melanoma. [25-27]

UVB is also effective for MF, especially for patch and thin plaque disease, specifically narrow band UVB (311 nm) has also been shown to be effective in MF, although remission duration with the latter may be inferior. The advantage of UVB over PUVA is that it is more readily available (more community-based dermatology practices have UVB equipment) and avoids the side effects, albeit modest, of psoralen. The disadvantage of UVB is its somewhat lower response rate and duration of remission and less effective than PUVA with thicker lesions. [28,29] PUVA has been reported to achieve improved response rates when combined with interferon-alpha-2b. [30,31] or retinoids such as acitretin. [32] PUVA therapy has also been used as a salvage or maintenance therapy after total skin electron beam (TSEB) therapy. [33] For even thicker plaques, particularly if localized, radiotherapy is effective as the disease is highly radiosensitive.

Other choices for first-line therapy are topical chemotherapy using mechlorethamine (nitrogen mustard [NM]) or carmustine. However, the use of these agents can be impractical if lesions are extensive.

Adverse reactions to nitrogen mustard include irritant contact dermatitis, *dry*skin, hyperpigmentation, and telangiectasias as well as an increased risk of squamous cell and basal cell skin cancers. When applied in a water vehicle, hypersensitivity to topical nitrogen mustard occurs in up to 40%. Hypersensitivity is less common with the use of an ointment base. [34]

"Second-line" therapy for early-stage disease can be highly effective for disease refractory to topical therapies, and these choices are always considered before the use of chemotherapy. These are retinoids like bexarotene and more recently acitretin is shown in a recent retrospective study to be well tolerated and potentially effective for early-stage CTCL with a comparable result with other oral agents currently approved for this disease, [35] IFN-alpha, low-dose oral

methotrexate (MTX), histone deacetylase inhibitors (HDACi), or denileukin diftitox. Radiotherapy is a highly effective therapy in MF/SS and can be used for both early- and advanced-stage disease, as first-line and relapsed/progressive disease. Partial regression of disease may be observed with single doses as low as 1.0 Gy. [36] Whether this is curable is unknown, but the approach is similar to the management of other low-grade lymphomas: to treat such patients with local radio- therapy with "curative" intent to a dose of approximately 30 Gy. A large proportion of these patients may remain disease-free. [37]

Combinations of skin-directed therapies (either alone or in combination with systemic therapy) are indicated when mono-therapy fails, with severe skin symptoms, or in the presence of other unfavorable prognostic factors. In patients with advanced clinical stage (≥ IIB), most skin-directed therapies are used as combination strategy or adjuvant support. Radiation has been used sequentially with several other treatments: PUVA, UVB, retinoids, and topical or systemic chemotherapy. Occasionally, treatments may be administered concurrently, but doses of radiation will have to be modified if large fields are being treated to minimize the risk for erythema or desquamation. TSEB therapy followed by adjuvant PUVA, NM, photopheresis, or other adjuvants does lead to a significant benefit in disease-free survival, but not in overall survival. [38,39] One combined modality approach for patients with extensive disease that have been found to have promising efficacy is the use of 2 or 3 courses of chemotherapy, e.g. high-dose MTX (>1 g/m2) or liposomal doxorubicin to reduce disease to clinically minimal levels before proceeding with TSEB.

Managing Advanced-stage (IIB-IVB) MF

Treatment of advanced-stage disease, or indeed refractory early stage disease, is more problematic and always requires a multidisciplinary approach. Although systemic multiagent chemotherapy is often considered in patients with advanced-stage disease, the randomized National Cancer Institute study demonstrated that combination chemo-radiotherapy offered no survival benefit over "conservative" sequential therapy. [15] Moreover, relatively rapid relapses are observed after chemotherapy; consequently, SDT or biologic response-modifying agents should be used first where practicable and systemic chemotherapy considered in patients progressing after these treatments.

Thus, the approach is to separately consider treatment options of patients with stage IIB (Table 7), stage III/SS (Table 8), stage IV (Table 9), and transformed disease. In general, IFN-alpha, bexarotene, vorinostat, and the fusion toxin denileukin diftitox are generally considered before embarking on systemic chemotherapy. Conversely, for the relatively rare patient with stage IVB disease of suitable performance status, aggressive chemotherapy, including transplantation strategies, should be considered early. Novel agents within clinical trials should be always considered in these patients. The single-agent or multiagent chemotherapy regimens described in (Table 10) are selected depending on disease characteristics and side-effect profile of the agents. The value of extracorporeal photopheresis (ECP) is generally limited to patients with erythrodermic disease and circulating malignant cells.

Transplantation

Interpretation of the transplantation data are difficult because the number of patients with MF/SS treated to date with stem cell transplantation is very small. It is better that allogeneic transplantation be considered in younger patients with advanced-stage disease if not responding to agents such as IFN-alpha, bexarotene, HDACi, or denileukin diftitox. A review of this subject has been published. [51]

Results with autologous stem cell transplantation have not been particularly promising. [51,52] Clearly, more investigation is required for this group of patients.

Novel agents within clinical trials

Novel agents that are being investigated in the context of clinical trials are listed in (Table 11). These agents should be considered for clinical trials as alternative strategy to systemic chemotherapy when other systemic drugs failed.

Conclusion

The critical step in managing a case of mycosis fungoides is to determine the matched clinical-stage and this requires good clinical-pathological evaluation. This in some times will need regular follow-up and repeated biopsies.

Treatment should be individualized according to the stage of disease and patient's health status in order to avoid overaggressive therapy including chemotherapy. Challenging the novel drugs is reasonable when the known systemic drugs failed.

Table 1. WHO-EORTC Classification of Cutaneous T-Cell Lymphoma

WHO-EORTC Classification	Frequency, %	5-Year Survival Rate, %
Indolent Clinical behavior		
Mycosis fungoides	44	88
Mycosis fungoides subtypes:		
—Folliculotropic mycosis fungoides	4	80
—Pagetoid reticulosis	< 1	100
—Granulomatous slack skin	< 1	100
Primary cutaneous $CD30^+$ lymphoproliferative disorder		
—Primary cutaneous anaplastic large cell lymphoma	8	95
—Lymphomatoid papulosis	12	100
Subcutaneous panniculitis- like T-cell lymphoma (provisional)	1	82
Primary cutaneous $CD4^+$ small/medium-sized pleomorphic T-cell lymphoma (provisional)	2	75
Aggressive Clinical Behavior		
Sézary syndrome	3%	24%
Adult T-cell leukemia/lymphoma	NR	NR
Extranodal NK/T-cell lymphoma, nasal type	NR	NR
Primary cutaneous peripheral T-cell lymphoma, unspecified	2	16
Primary cutaneous aggressive epidermotropic $CD8^+$ T-cell lymphoma (provisional)	< 1	18
Cutaneous gamma/delta T-cell lymphoma (provisional)	< 1	NR
Precursor Hematologic Neoplasm (not a T-cell lymphoma)		
$CD4^+/CD56^+$ hematodermic neoplasm (blastic NK-cell lymphoma)	NR	NR

Source: Adapted from Willemze et al. *Blood*. 2005;105(10):3768-85. [1]EORTC = European Organization of Research and Treatment of Cancer; NR = not reported; NK = natural killer; WHO = World Health Organization.

Table 2. Algorithm of diagnosing early MF developed by the ISCL. [8]

	Criteria			Scoring system	
	Basic	**Additional**	**Other**	**2 points**	**1 point**
Clinical	Persistent and/or progressive patches/thin plaques	(1) Non–sun-exposed location		2 points for basic criteria and 2 additional criteria	1 point for basic criteria and 1 additional criteria
		(2) Size/shape variation			
		(3) Poikiloderma			
Histopathologic	Superficial lymphoid infiltrate	(1) Epidermotropism without spongiosis		2 points for basic criteria and 2 additional criteria	1 point for basic criteria and 1 additional criteria
		(2) Lymphoid atypia*			
Molecular biologic			Clonal T-cell receptor gene rearrangement		1 point for clonality
Immunopathologic			< 50% $CD2^+$, $CD3^+$, and/or $CD5^+$ cells		1 point for 1 or more criteria
			< 10% $CD7^+$ cells		
			Epidermal/dermal discordance of CD2, CD3, CD5, or CD7†		

A total of 4 points is required for the diagnosis of MF based on any combination of points from the clinical, histopathologic, molecular biologic, and immunopathologic criteria.

Lymphoid atypical is defined as cells with enlarged hyperchromatic nuclei and irregular or cerebriform nuclear contours.

† T-cell antigen deficiency confined to the epidermis

Table 3. ISCL/EORTC revision to the classification of MF and SS [9]

TNMB classification	Characteristics
Skin	
T1	Limited patches,* papules, and/or plaques† covering < 10% of the skin surface; may further stratify into T1a (patch only) versus T1b (plaque ± patch)
T2	Patches, papules, or plaques covering ≥ 10% of the skin surface; may further stratify into T2a (patch only) versus T2b (plaque ± patch)
T3	One or more tumors‡ (≥ 1 cm diameter)
T4	Confluence of erythema covering ≥ 80% BSA

Node	
N0	No clinically abnormal peripheral lymph nodes ; biopsy not required
N1	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI LN0-2
N1a	Clone negative
N1b	Clone positive
N2	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN3
N2a	Clone negative
N2b	Clone positive
N3	Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3-4 or NCI LN4; clone positive or negative
Nx	Clinically abnormal peripheral lymph nodes; no histologic confirmation
Visceral	
M0	No visceral organ involvement
M1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
TNMB classification	**Characteristics**
Blood	
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 does not meet the criteria of B2
B1a	Clone negative
B1b	Clone positive
B2	High blood tumor burden: ≥ 1000/µL Sézary cells with positive clone

Table 4. ISCL/EORTC revision to the staging of mycosis fungoides and Sézary syndrome .1

	T	**N**	**M**	**B**
IA	1	0	0	0, 1
IB	2	0	0	0, 1
IIA	1, 2	1, 2	0	0, 1
Advanced-stage disease [9]				
IIB	3	0-2	0	0, 1
III	4	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

Table 5. Recommended evaluation/initial staging of the patient with mycosis fungoides/Sézary syndrome [9]

Evaluation and staging
Complete physical examination, including:
-Determination of type(s) of skin lesions
-If only patch/plaque disease or erythroderma, then estimate percentage of BSA involved and note any ulceration of lesions
-If tumors are present, determine total number of lesions, aggregate volume, largest size lesion, and regions of the body involved
-Identification of any palpable lymph node, especially those ≥ 1.5 cm in largest diameter or firm, irregular, clustered, or fixed
-Identification of any organomegaly
Skin biopsy
-Most indurated area if only one biopsy
-Immunophenotyping to include at least the following markers: CD2, CD3, CD4, CD5, CD7, and CD8, and a B-cell marker, such as CD20; CD30 may also be indicated in cases where lymphomatoid papulosis, anaplastic lymphoma, or large-cell transformation is considered
-Evaluation for clonality of TCR gene rearrangement
Blood tests
-CBC with manual differential, liver function tests, LDH, comprehensive chemistries
-TCR gene rearrangement and relatedness to any clone in skin
-Analysis for abnormal lymphocytes by either SC count with determination absolute number of SCs and/or flow cytometry (including $CD4^+/CD7^-$ or $CD4^+/CD26^-$)
Radiologic tests
-In patients with $T_1N_0B_0$ stage disease who are otherwise healthy and without complaints directed to a specific organ system; and in selected patients with $T_2N_0B_0$ disease with limited skin involvement, radiologic studies may be limited to a chest x-ray or ultrasound of the peripheral nodal groups to corroborate the absence of adenopathy
-In all patients with other than presumed stage IA disease, or selected patients with limited T_2 disease and the absence of adenopathy or blood involvement, CT scans of chest, abdomen, and pelvis alone ± FDG-PET scan are recommended to further evaluate any potential lymphadenopathy, visceral involvement, or abnormal laboratory tests; in patients unable to safely undergo CT scans, MRI may be substituted.
Lymph node biopsy
-Excisional biopsy is indicated in those patients with a node that is either ≥ 1.5 cm in diameter and/or is firm, irregular, clustered, or fixed
-Site of biopsy: preference is given to the largest lymph node draining an involved area of the skin or if FDG-PET scan data are available, the node with highest standardized uptake value; if there is no additional imaging information and multiple nodes are enlarged and otherwise equal in size or consistency, the order of preference is cervical, axillary, and inguinal areas
-Analysis: pathologic assessment by light microscopy, flow cytometry, and TCR gene rearrangement

TCR indicates T-cell receptor; CBC, complete blood count; and FDG-PET, F-fluoro-2-deoxyglucose positron emission tomography.

Table 6. Recommendations for treatment of MF stages IA, IB, and IIA

Treatment	Comments*
First-line	
" Expectant policy"	Usually suitable for those with stage IA disease in conjunction with symptomatic treatment if required; patients with single lesion may be considered for "curative therapy" with radiation therapy
PUVA	For patch/plaque disease; requires regular 2 or 3 times/week treatment; there may be limited availability of PUVA in nonmetropolitan areas; can be combined with retinoids/rexinoids
UVB	For patch stage disease as skin penetration not as deep as PUVA; requires regular 2 or 3 times/week treatment and generally more readily available than PUVA
Topical corticosteroids	Simple therapy; toxicities if extensive skin application for long periods
Topical bexarotene	For limited sites of disease; simple therapy; local reactions may occur
Topical NM	For limited sites of disease or generalized involvement; local reactions occasionally problematic; ointment causes fewer reactions; availability of NM worldwide has been a problem recently
Topical carmustine	Rarely used now; for limited sites of disease; local reactions may occur; causes telangiectasias
Localized radiotherapy	Especially for patients with limited number of lesions and/or thickened plaques; durable remissions achieved
TSEB	Patients with stage IB disease with relatively slow progression; limited availability; can take 6 to 10 weeks to complete
Second-line+	
Oral bexarotene	Generally well tolerated and convenient (oral capsule); some responses can be very durable; most common side effects are hypertriglyceridemia and hypothyroidism that usually require treatment; other relatively common side effects are rash and headache; can be used in conjunction with other therapies
IFN-α monotherapy	Major difficulty is tolerance and compliance; some responses can be very durable; som
Low-dose MTX	Generally well tolerated and convenient (oral weekly); dose-response effect is common and usually starts at 20 to 30

	mg/week (up to 60-70 mg/week); some responses can be very durable; most common side effects are cytopenias and long-term risk of liver disease; very effective in patients with coexistent lymphomatoid papulosis; can be used in conjunction with other therapies, such as steroids, ECP, PUVA, IFN-α
Vorinostat	Only approved HDACi currently; generally well tolerated and convenient (oral daily); there appears to be a dose-response effect in some patients; most common SEs are fatigue, lethargy, mild/moderate thrombocytopenia and elevated creatinine and taste changes; can improve itch even when skin lesions remain; some responses can be very durable; virtually no data on use in combination with other therapies, such as PUVA, IFN-α, MTX, chemotherapy
Denileukin diftitox	Generally considered after trial of bexarotene and/or HDACi; inconvenient administration requiring daily dosing times 5 days every 3 weeks (6-8 courses); patient's tumor must express CD25 (although responses are observed in patients with $CD25^-$ lesions); there can be substantial supportive care requirements for some patients during therapy who develop capillary leak syndrome; some responses can be very durable even in heavily pretreated patients
Novel agents within clinical trials	In patients with stage IA-IIA disease, chemotherapy is not recommended and novel agents within clinical trials are generally recommended before chemotherapy is considered (see Table 11)

* For more details and detailed references, we refer the reader to the EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome. [40]

Table 7. Recommendations for treatment of MF stage IIB

Treatment	Comments*
First-line	
IFN-α	Can be effective even in patients with tumor and/or ulcerated lesions; see Table 6 for other comments; IFN-α can also be combined with PUVA, retinoids, bexarotene, MTX
TSEB and superficial X-irradiation	"Boosts" needed to site of thickened plaques/tumors; limited availability; can take 6 to 10 weeks to complete
PUVA	For patch/plaque disease; requires regular 2 or 3 times/week treatment; there may be limited availability of PUVA in nonmetropolitan areas; can be combined with retinoids/rexinoids, bexarotene, IFN-α
Second-line	
Bexarotene	See Table 6 for comments
Vorinostat	See Table 6 for comments
Denileukin diftitox	See Table 6 for comments
Novel agents within clinical trials	In patients with stage IIB disease, chemotherapy is recommended after bexarotene and/or and HDACi and/or DD; it is very acceptable to consider novel agents within clinical trials before chemotherapy is considered (see Table 11)
Chemotherapy	Choice of chemotherapy regimens is extensive (see Table 10), and choice depends on patient tolerance, risk of infection versus the relatively short duration of remission observed with most chemotherapy regimens; transplantation may be considered in highly selected persons

* For more details and detailed references, we refer the reader to the EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome.[40]

Table 8 Recommendations for treatment of stage III or SS (stages III or IVa)

Treatment	Comments*
First-line	
ECP	Well tolerated with limited toxicities; circulating T-cell clone should be detectable in blood by morphology, flow cytometry, or molecular studies; should not be considered in patients with SS who have extensive nodal (IVa) or visceral (IVb) disease; side effects to methoxsalen is rare; requires good venous

	access with the associated risk of infection; often combined with oral steroids (short-term), IFN-α, bexarotene, or low-dose MTX; improvement with ECP alone can take some weeks and maximum improvement may not be seen for many months; durable responses are not uncommon
IFN-α	Major difficulty is tolerance and compliance; some responses can be very durable; somewhat inconvenient (daily subcutaneous injection); most common side effect is fatigue, particularly in older patients; requires moderately high doses aiming for 3 to 5+ MU/day; monitor FBC and thyroid function; IFN-α can also be combined with PUVA, retinoids, bexarotene, and ECP
PUVA + IFN-α	For stage III disease; would not generally recommend PUVA alone; requires regular 2 or 3 times/week treatment and limited number of sites in nonmetropolitan areas
MTX	See Table 6 for comments
Second-line	
Bexarotene	See Table 6 for comments; can consider adding to ECP or IFN-α
Vorinostat	See Table 6 for comments; no data available of adding to ECP or IFN-α
Denileukin diftitox	See Table 6 for comments
Alemtuzumab	See Table 9 for comments
Novel agents within clinical trials	In patients with SS, chemotherapy is recommended after bexarotene and/or and HDACi and/or DD; it is very acceptable to consider novel agents within clinical trials before chemotherapy is considered (see Table 11)
Chemotherapy	Choice of chemotherapy regimens is extensive (see Table 10), and choice depends on patient tolerance, risk of infection versus the relatively short duration of remission observed with most chemotherapy regimens; transplantation may be considered in highly selected individuals

*****FBC indicates fludarabine, busulphan, and alemtuzumab.

* For more details and detailed references, we refer the reader to the EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome.[40]

Table 9. Recommendations for treatment of MF stages IVA-IVB: first-line

Treatment	Comments*
Chemotherapy	Choice of chemotherapy regimens is extensive (see Table 10), and choice depends on patient tolerance, risk of infection versus the relatively short duration of remission observed with most chemotherapy regimens; autologous or allogeneic transplantation should be considered early in treatment paradigm for selected persons
TSEB and/or X-irradiation	Patients with advanced-stage disease may benefit from TSEB; "boosts" to site of thickened plaques/tumors; TSEB has limited availability; can take 6 to 10 weeks to complete; conventional radiation therapy can be valuable for local control of tumors or localized/bulky nodal disease
Bexarotene	See Table 6 for comments; few patients on clinical trials had stage IVB disease; thus, response rate and response durations are not well described
Denileukin diftitox	See Table 6 for comments; few patients on clinical trials had stage IVB disease; thus, response rate and response durations are not well described
IFN-α	See Table 6 for comments; less used in this stage of disease but may be helpful in patients unable to tolerate chemotherapy
Alemtuzumab	Major toxicity is immune suppression with infection; requires surveillance for cytomegalovirus and antimicrobial prophylaxis; short responses if used in multirelapsed disease so should consider early
Vorinostat	See Table 6 for comments; few patients on clinical trials had stage IVB disease; thus, response rate and response durations are not well described
Novel agents within clinical trials	Given poor prognosis and incurable nature of advanced-stage disease, it is very acceptable to consider novel agents within clinical trials before chemotherapy is considered (see Table 11)
Low-dose MTX	Generally well tolerated and convenient (oral weekly); dose-response effect is common and usually starts at 20 to 30 mg/week (up to 60-70 mg/week); some responses can be very durable; most common side effects are cytopenias and long-term risk of liver disease; very effective in patients with coexistent lymphomatoid papulosis; anecdotal experience that can be very useful in $CD30^+$ MF or $CD30^+$ transformed disease; can be used in conjunction with other therapies, such as steroids, ECP, and PUVA

* For more details and detailed references, we refer the reader to the EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome.[40]

Table 10. Key clinical studies of systemic chemotherapy in cutaneous T-cell lymphoma

Therapy examples	Efficacy	Comments
CHOP-based[49]	ORR stage IIB: 66%	Myelosuppression with risk of infection; very short remission duration
EPOCH[43]	ORR stage IIB-IV: 80%	Myelosuppression with risk of infection; short remission duration
CMED/ABV[41,44]	ORR stage III-IV: 81%	Myelosuppression with risk of infection; median DFS of 7 months and 27% 5-year DFS
Pegylated liposomal doxorubicin[47]	ORR stage IA-IV: 88%	Single agent; well tolerated; infusion-related events; no comparisons with standard anthracyclines
Pentostatin[46]	ORR stage IIB: 75% Stage III: 58% Stage IV: 50%	Numerous trials and regimens used; activity in PTCL; perhaps best activity in SS; prolonged therapy needed in some cases; lymphopenia
Fludarabine plus IFN-α[42]	ORR stage IIA-IVA: 58% stage IVB: 40%	Neutropenia common
Fludarabine plus cyclophosphamide[48]	ORR stage IIB-III: 55%	Appears higher RR to fludarabine-alone; lymphopenia and prolonged myelosuppression in some patients; stem cell collection yields are lower
Gemcitabine[45]	ORR stage IIB-III: 70%	Neutropenia; recent evidence that toxicities (rash, infection) may be higher in patients with CTCL (see "Systemic chemotherapy")
2-Chlorodeoxyadensine[50]	ORR stage IIA-IV: 28%	Median duration or response of 4.5 months; bone marrow suppression and infections in 62%

CR indicates complete response; CRR, complete response rate; EPOCH, etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone; ORR, overall response rate; PR, partial response; PUVA, ultraviolet A light with oral methoxypsoralen; and DFS, disease-free survival.

Table 11. Selected novel drugs being evaluated in current clinical trials for MF/SS

Drug class	Examples	Comments
HDACi	Romidepsin[53] Panobinostat[61] Belinostat[54]	Vorinostat is approved for relapsed, refractory CTCL, which has led to investigation to other HDACi in CTCL and PTCL; a number are undergoing regulatory approval process; response rates and toxicities are similar
Monoclonal antibodies	Zanolimumab[60]	ORR of 50%+ as single agent in early studies but of relatively short duration; well tolerated with little infection risk; combination studies planned
	Alemtuzumab[55-58,59]	Single-agent studies with ORR of 40%+ but short duration; immunosuppressive; combination studies underway
Purine nucleoside phosphorylase inhibitor	Forodesine (BCX-1777)[62]	Single-agent activity of 30%+ with durable remissions observed; well tolerated and convenient (oral)
Proteasome inhibitors	Bortezomib[63]	Single-agent activity observed in heavily pretreated

		patients; generally well tolerated with minimal myelosuppression; combination studies planned
IMiDs	Lenalidomide[64]	Single-agent activity observed in heavily pretreated patients; generally well tolerated, but fatigue appears dose-limiting; maintenance studies being considered
Synthetic oligodeoxynucleotides containing unmethylated CG dinucleotides (CpG-ODN)	PF-3512676	CpG-ODN have potent immunostimulatory effects and activate professional antigen-presenting cells that express the target receptor, Toll-like receptor 9[65]
Retinoids	Tazarotene[66]	Novel synthetic retinoid
Fusion toxins	Anti-Tac(Fv)-PE38 (LMB-2)[67]	Fusion toxins, which combines a target cell binding domain linked to a bacterial toxin
Antifolate	Pralatrexate[68]	Pralatrexate is a novel antifolate designed to have high affinity for the reduced folate carrier type 1

IMiDs indicates immunomodulatory drugs; and CpG-ODN, cytosine-phosphate-guanosine oligodeoxynucleotide.

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