Primary cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome)

Part II. Prognosis, management, and future directions

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After completing this learning activity, participants should be able to identify topical and skin-directed therapy for patch, plaque, and tumor stage MF; demonstrate a fundamental understanding of systemic treatment options in tumor stage MF/ erythrodermic MF and SS; and identify treatment options for alleviation of patient symptoms in advanced stage MF/SS.

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Both mycosis fungoides (MF) and Sézary syndrome (SS) have a chronic, relapsing course, with patients frequently undergoing multiple, consecutive therapies. Treatment is aimed at the clearance of skin disease, the minimization of recurrence, the prevention of disease progression, and the preservation of quality of life. Other important considerations are symptom severity, including pruritus and patient age/comorbidities. In general, for limited patch and plaque disease, patients have excellent prognosis on ≥ 1 topical formulations, including topical corticosteroids and nitrogen mustard, with widespread patch/plaque disease often requiring phototherapy. In refractory early stage MF, transformed MF, and folliculotropic MF, a combination of skin-directed therapy plus low-dose immunomodulators (eg, interferon or bexarotene) may be effective. Patients with advanced and erythrodermic MF/SS can have profound immunosuppression, with treatments targeting tumor cells aimed for immune reconstitution. Biologic agents or targeted therapies either alone or in combination—including immunomodulators and histone-deacetylase inhibitors—are tried first, with more immunosuppressive therapies, such as alemtuzumab or chemotherapy, being generally reserved for refractory or rapidly progressive disease or extensive lymph node and metastatic involvement. Recently, an increased understanding of the pathogenesis of MF and SS with identification of important molecular markers has led to the development of new targeted therapies that are currently being explored in clinical trials in advanced MF and SS. (J Am Acad Dermatol 2014;70:223.e1-17.)

Key words: cutaneous T-cell lymphoma; immunomodulators; mycosis fungoides; phototherapy; prognosis; Sézary syndrome; skin-directed treatment; staging; systemic treatment; targeted therapies; topical corticosteroids; topical nitrogen mustard; topical retinoids/rexinoids.

The treatment of mycosis fungoides (MF) and Sézary syndrome (SS) is primarily determined by disease extent and the impact on quality of life, prognostic factors (eg, folliculotropic MF and large cell transformation), and patient age/comorbidities. Early stage MF (stages IA-IIA), with disease primarily confined to the skin, has a favorable prognosis, with skin-directed therapies as first-line treatment. Prolonged complete remissions have been obtained, although disease cure is unclear.

Advanced stage MF/SS (stages IIB-IVB) is often treatment refractory and results in an unfavorable prognosis; treatment is aimed at reducing the tumor burden, delaying disease progression, and preserving quality of life. Current approaches include immunobiologic and targeted therapies, but the duration of clinical response is often short. Single/multiagent chemotherapy should be reserved for cases that are refractory to treatment. The revised guidelines by the International Society for Cutaneous Lymphomas (ISCL), the United States Cutaneous Lymphoma Consortium (USCLC), and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC) include treatment options for MF/SS that match the National Comprehensive

Abbreviations used:

BSA:	body surface area
CR:	complete response
CRR:	complete response rate
CTCL:	cutaneous T-cell lymphoma
ECP:	extracorporeal photopheresis
EORTC:	European Organization of Research and Treatment of Cancer
HDACi:	histone deacetylase inhibitor
IFNα:	interferon-alfa
ISCL:	International Society for Cutaneous Lymphoma
MF:	mycosis fungoides
mSWAT:	modified severity-weighted assessment tool
NBUVB:	narrowband ultraviolet B light
NCCN:	National Comprehensive Cancer Network
NK:	natural killer
NM:	nitrogen mustard
NMSC:	nonmelanoma skin cancer
ORR:	overall response rate
PUVA:	psoralen plus ultraviolet A light phototherapy
RAR:	retinoic acid receptor
RXR:	retinoid X receptor
SS:	Sézary syndrome
TNMB:	tumor, node, metastasis, blood
TSEBT:	total skin electron beam therapy
USCLC:	United States Cutaneous Lymphoma Consortium
UVB:	ultraviolet B light

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Cancer Network (NCCN) guidelines for MF/SS in 2010.[1] This review focuses on the staging, prognosis, and management of MF/SS, with an emphasis on the development of new treatment strategies. Of note, the response rate and duration data come from a range of studies with variable inclusion criteria, making it difficult to compare the efficacy of different treatments. Therefore, efforts have been made by the ISCL, USCLC, and EORTC to standardize both clinical end points and response criteria.[2]

EVALUATION OF A PATIENT, STAGING, PROGNOSIS

Key points

- **Patient evaluation requires a multidisciplinary team approach with dermatologists, oncologists, dermatopathologists, and radiation oncologists**
- **Staging of a patient requires an assessment of skin, lymph node, viscera, and blood involvement**
- **The prognosis of mycosis fungoides in most patients with limited patch/plaque disease is favorable and similar to that of an age-, sex-, and race-matched control population**

Initial work-up

MF/SS patients should ideally be assessed by a multidisciplinary cutaneous T-cell lymphoma (CTCL) team of dermatologists and oncologists, with support from radiation oncologists, pathologists, and clinical psychologists. A routine evaluation includes a complete physical examination with a formal estimation of skin tumor burden using a modified severity-weighted assessment tool (mSWAT), measuring the total body surface area (BSA) by using the patient's palm and fingers to represent 1% BSA. Patch, plaque, and tumor BSA are determined separately and multiplied by a factor (1, 2, and 4, respectively) to generate the standardized mSWAT score[2] (Fig 1).

Diagnostic tests, including a complete blood cell count with differential, chemistry panel, lactate dehydrogenase, and a skin biopsy specimen for histology, immunophenotyping, and T cell receptor gene rearrangement studies should be performed at a CTCL referral center. Sézary cell count, circulating T cell subsets and clonality, positron emission tomography/computed tomography scans, and/or lymph node biopsy specimens should be obtained in cases suggestive of lymphadenopathy and/or systemic disease to establish staging, with HIV and human T-lymphotrophic virus type 1 serology testing in select patients.[3]

Staging and prognosis

Accurate staging in MF/SS is essential to determine treatment and prognosis. MF/SS staging relies on the tumor, node, metastasis, blood (TNMB) classification proposed by the Mycosis Fungoides Cooperative Group and revised by the ISCL/EORTC, which considers the extent of skin involvement (T), presence of lymph node (N), visceral disease (M), and detection of Sézary cells in the peripheral blood (B); this information is translated into a clinical stage[4,5] (Tables I and II).

Most MF patients (~70%) have early stage disease (stage IA-IIA) at the time of the initial diagnosis.[6] The extent of cutaneous involvement (ranging from T1-T4) is significantly associated with a prognosis with decreased overall survival, and progression-free survival in advanced T-stage. One large study found that that the risk for disease progression at 5 years was 10% in T1, 22% in T2, and 48% to 56% in T3 to T4 levels of cutaneous involvement.[7]

Patients with stage-IA MF have a similar life expectancy as age-, sex-, and race-matched control populations.[8] Inferior survival has been shown in plaque over patch disease for both limited (T1) and extensive (T2) skin disease.[9] Other prognostic factors include advanced age at diagnosis, elevated lactate dehydrogenase and beta-2-microglobulin levels, large cell transformation, and folliculotropic MF.[6,7,9-11] A high Sézary cell count, the loss of T cell markers (eg, CD5 and CD7), and chromosomal abnormalities in circulating T cells are also independently associated with a poor outcome.[2] The presence of a T cell clone in the peripheral blood in B0 patients (<5% Sézary cells) and identical clones in blood and skin portend a poorer prognosis.[9,12]

SKIN-DIRECTED THERAPIES

Key points

- **Topical corticosteroids are the most common treatment used in early mycosis fungoides and serve as an adjunct to other topical and systemic therapies at all stages**
- **Topical nitrogen mustard and phototherapy have similar efficacy in early stage mycosis fungoides with maintenance therapy needed for prolonged complete remissions**
- **Total skin electron beam therapy at a standard dose (30 Gy) is an effective treatment in refractory/relapsed extensive plaque and tumor mycosis fungoides associated with significant skin toxicity**
- **Low-dose local radiation therapy may be useful in selected lesions**

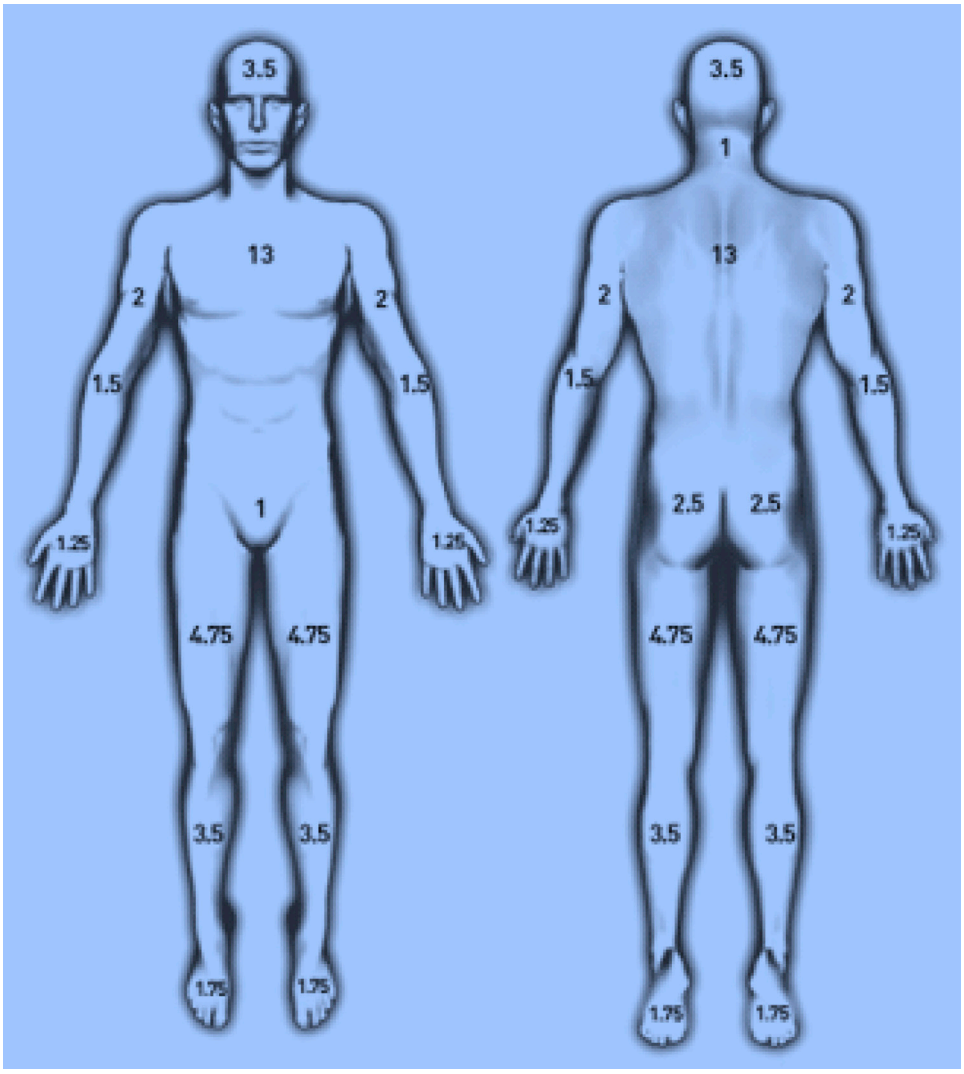

Fig 1. Modified severity-weighted assessment tool (mSWAT) adapted from Levenson and Lund.[211]

Topical corticosteroids

Corticosteroids are frequently used in early MF and as adjunctive therapy in more advanced stages of the disease (Table III). Their multiple effects include induction of apoptosis, impact on lymphocyte adhesion to endothelium, and the downregulation of transcription factors (nuclear factor-κB and activator protein-1) with decreased cytokine, adhesion molecule, and growth factor production.[13-16] Early studies found overall response rates (ORRs) between 80% and 90%[17-20]; a large prospective study of 79 patients with patch disease (stage T1/T2) on daily topical class I to III steroids (median observation time, 9 months) found that 32 (63%) of T1 patients and 7 (25%) of T2 patients achieved a complete response (CR).[21] A sustained response was not seen after steroid discontinuation.[21] Topical steroids also decrease erythema, scaling, and pruritus in erythrodermic CTCL.[16] Side effects associated with long-term use include skin atrophy, hypopigmentation, striae, and potential systemic absorption. The latter was observed in 13% of patients in 1 study without adrenal suppressive effects.[21]

Topical nitrogen mustard (mechlorethamine hydrochloride)

Nitrogen mustard (NM) is an alkylating agent. Topical NM applications are commonly used for early stage MF. NM-induced DNA damage results in its systemic anticancer effects, but the topical formulation may work via immune mechanisms affecting keratinocyte—Langerhans cell—T cell interactions.[22]

Efficacy at concentrations of 0.01% to 0.02% in an aqueous solution or ointment base has been well reported, with a CR in up to 72% of early stage MF patients and occasional long-term remissions

Table I. Revisions to the tumor, node, metastasis, blood classification of mycosis fungoides/Sézary syndrome proposed by the International Society for Cutaneous Lymphomas and the European Organization of Research and Treatment of Cancer*

TNMB stages	Stage description
Skin (T)	
T1	Limited patches, papules, and/or plaques (<10% BSA)
T1a	Patches only
T1b	Presence of plaques with or without patches
T2	Patches, papules, or plaques covering ≥ 10% BSA
T2a	Patch only
T2b	Presence of plaques with or without patches
T3	≥ 1 tumors (≥ 1 cm in diameter)
T4	Generalized erythroderma (≥ 80% BSA)
Node (N)	
N0	No clinically abnormal (palpable; ≥ 1.5 cm diameter) peripheral LNs
N1	Clinically abnormal LNs; histopathology Dutch grade 1 or NCI LN_{0-2}
N1a	Clone positive
N1b	Clone negative
N2	Clinically abnormal LNs; histopathology Dutch grade 2 or NCI LN_3
N2a	Clone negative
N2b	Clone positive
N3	Clinically abnormal LNs; histopathology Dutch grade 3-4 of NCI LN_4; clone positive OR negative
Visceral (M)	
M0	No visceral organ involvement
M1	Visceral involvement (pathology confirmation of specific organ involved)
Blood (B)	
B0	Absence of significant blood involvement (≤ 5% of peripheral blood lymphocytes are atypical/Sézary cells)
B0a	Clone negative
B0b	Clone positive (same clone as in skin)
B1	Low blood tumor burden (>5% of peripheral blood lymphocytes are atypical/Sézary cells but does not meet criteria of B2
B1a	Clone negative
B1b	Clone positive
B2	High blood tumor burden defined as one of the following: ≥ 1000 Sézary cells/μL with positive clonal rearrangement of TCR; CD4:CD8 ratio ≥ 10 with positive clone; or $CD4^+CD7^-$ cells ≥ 40% or $CD4^+CD26^-$ cells ≥ 30% with positive clone

BSA, Body surface area; *LN*, lymph node; *NCI*, National Cancer Institute; *TCR*, T-cell receptor; *TNMB*, tumor, node, metastasis, blood.
*Adapted with permission from Olsen et al.[5]

(>8 years).[23-28] A recent multicenter trial of a 0.02% gel formulation resulted in similar efficacy that has led to the approval in 2013 by the US Food and Drug Administration for the treatment of stage IA/IB MF patients with previous skin-directed therapy.[29] However, only 11% maintained a CR after 10 years.[26,27] In 1 study on 203 stage I to III MF patients, CR rates (CRRs) of 76% to 80% in stage IA and 35% to 68% for stage IB patients were observed.[22] Skin clearance may require ≥ 6 months and is usually followed by maintenance therapy, although there is no evidence that prolonged maintenance reduces recurrence.[30]

Cutaneous side effects are common, including burning, pruritus, and irritant or allergic contact dermatitis, the latter being much more common in aqueous formulations; topical corticosteroids may be helpful.[31] There is a small increased risk (1-5%) of developing nonmelanoma skin cancers (NMSCs), especially with concomitant radiation and psoralen plus ultraviolet A light phototherapy (PUVA).[22,30]

Topical retinoids

Bexarotene is a synthetic retinoid (rexinoid) with the oral form selectively binding retinoid X receptor (RXR) isoforms, affecting cell differentiation and inducing apoptosis.[32,33] The mechanism of action of topical bexarotene 1% gel, which is approved by the US Food and Drug Administration for the treatment of early stage MF (up to 4 times daily), is less clear. Topical bexarotene is recommended twice daily; high rates of irritation are seen with 4 times/day application. Responses were seen in most patients (stage IA-IIA) after a median of 20 weeks of treatment (ORR, 63%; CR, 21%).[34] Tazarotene is a

Table II. Revisions to the staging of mycosis fungoides and Sézary syndrome based on International Society for Cutaneous Lymphomas and the European Organization of Research and Treatment of Cancer revisions to the tumor, node, metastasis, blood classification[5]

Stage	T	N	M	B
IA	1	0	0	0 or 1
IB	2	0	0	0 or 1
IIA	1 or 2	1 or 2	0	0 or 1
IIB	3	0-2	0	0 or 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

B, Blood; *M*, metastasis; *N*, node; *T*, tumor.

topical retinoid that acts at the retinoic acid receptor (RAR). It was found to induce response in 58% of patients with limited (<20% skin involvement) or stable/refractory patch or plaque disease. Both topical bexarotene and 0.1% tazarotene gel cause local irritation.[35]

Phototherapy

PUVA has an established benefit in early stage MF and involves oral 8-methoxypsoralen, which sensitizes the skin to ultraviolet A light radiation (320-400 nm), inducing tumor cell apoptosis and DNA damage, suppressing keratinocyte cytokine production, and depleting Langerhans cells.[36-38]

The initial ultraviolet A light dosage is approximately 0.5 J/cm^2, increasing as tolerated, and given 3 times weekly until CR is achieved. Proper eye protection is needed for 12 to 24 hours after treatment sessions for cataract prevention. Maintenance therapy can be gradually reduced to once every 4 to 6 weeks to maintain remission. CR has been reported in up to 71.4% of patients with early stage MF, including long-term remissions of $\geq$10 years.[39-46]

PUVA is less effective in tumor stage/erythrodermic and folliculotropic MF; however, a combination with low-dose systemic agents (eg, interferon-alfa [IFNα]) may be considered.[47-49] Common PUVA side effects include erythema, photodermatitis, pruritus, and nausea, managed with dose reduction/interruption.[39-46]

Ultraviolet B light (UVB) suppresses neoplastic T cell function and proliferation through antigen-presenting cell inhibition and increased keratinocyte cytokine production.[50-52] Narrowband UVB (NBUVB; 311 nm) is used more frequently than PUVA in early stage MF because of its similar efficacy; there are also increased rates of skin cancer with PUVA. In stage IA/IB MF and parapsoriasis, CRR ranged from 54.2% to 91%,[53-62] with a higher efficacy in patch compared to plaque disease.[53] NBUVB is

Table III. Summary of treatments for patients with mycosis fungoides and Sézary syndrome

Therapy type	Treatment
Early stage MF (stage IA-IIA)	
Topical/skin-directed therapy	Steroids
	Phototherapy
	Nitrogen mustard
	Bexarotene
	Local radiation
	TSEBT
Refractory early stage MF (stage IA-IIA)	
Combination therapy	PUVA or NBUVB and IFNα (low-dose)
	PUVA or NBUVB and bexarotene (low-dose)
Advanced MF/SS (stage IIB-IVB)	
Skin-directed therapy	TSEBT
Immunomodulators	Interferons (IFNα and IFNγ)
	Retinoid/rexinoid (bexarotene)
	ECP
Biologic/targeted therapies	Alemtuzumab
	HDACis (eg, romidepsin and vorinostat)
	Antifolates (eg, methotrexate and pralatrexate)
Combined therapy	IFNα and phototherapy
	IFNα and retinoids/rexinoids
	Retinoid and phototherapy
	ECP and IFNα
	ECP and retinoids/rexinoids
Systemic chemotherapy	
Single-agent	Pegylated doxorubicin
	Purine/pyrimidine analogues (eg, gemcitabine)
Multiagent	CHOP and CHOP-like
Stem cell transplant	Autologous
	Allogeneic
	Nonmyeloablative allogeneic

Continued

Table III. Cont'd

Therapy type	Treatment
Investigational therapy	Lenalidomide Bortezomib CCR4 antibody TLR agonists Interleukins Anti–PD-1 agents Protein kinase C inhibitors Phosphoinositide 3-kinase inhibitors brentuxmab-vedotin

CHOP, Cyclophosphamide, doxorubicin, vincristine, and prednisone; *ECP*, extracorporeal photopheresis; *HDACi*, histone deactetylase inhibitors; *IFNα*, interferon-alfa; *IFNγ*, interferon-gamma; *MF*, mycosis fungoides; *NBUVB*, narrowband ultraviolet B light phototherapy *PD*-1, Programmed-Death-1; *PUVA*, psoralen plus ultraviolet A light phototherapy; *SS*, Sézary syndrome; *TLR*, Toll-like receptor; *TSEBT*, total skin electron beam therapy.

especially useful in hypopigmented MF.[63] UVB is generally well tolerated, with acute side effects of pruritus, burning, and erythema resolving with or without dose reductions. Photoaging and photocarcinogenesis are long-term risks of NBUVB, although less than with PUVA.[64-66] Low-dose bexarotene (75-150 mg) may be combined with lower cumulative NBUVB to achieve a CR.[67]

Radiation

Total skin electron beam therapy (TSEBT) involves the administration of ionizing radiation to the entire surface of the skin, with deeper penetration than both NM and phototherapy.[68,69] With the advent of effective systemic therapies, TSEBT is reserved for rapidly progressive, refractory/relapsed, and extensive plaque (T2) or tumor (T3) disease. TSEBT decreases the burden of circulating malignant T cells that pass through the dermal vasculature and are highly radiosensitive; however, there are conflicting reports of its effectiveness in erythrodermic MF with blood involvement.[70-72]

Conventional TSEBT (30-36 Gy ionizing radiation over 8-10 weeks) may induce a CR,[72-76] leading to 75% and 47% CRRs in T2 and T3 MF, respectively.[75] The duration of the response is limited (a median of 29 and 9 months for T2 and T3 disease, respectively, with a median follow-up time of 77 months).[75] Potential skin toxicity/necrosis limits repeat radiation courses. Subsequent skin-directed/systemic agents (eg, NM, PUVA, oral retinoids, IFNα, and extracorporeal photopheresis [ECP]) have shown mixed results.[76-80] A second TSEBT course at a lower dose may be considered in select populations, depending upon the initial dose, tolerance, and the amount of time that has passed since the administration of the first course.[75]

TSEBT toxicity is dose-dependent and includes erythema, xerosis, and desquamation, with long-term effects of alopecia, nail loss/dystrophy, xerosis, anhidrosis, and skin atrophy/necrosis.[70,81,82] Low-dose radiation (10 Gy) may significantly decrease side effects and enable repeat radiation for disease control/palliation,[81] although lower CRRs and response durations are seen with reduced doses (at 5-10 Gy, 16%; 10-20 Gy, 35%; 20-30 Gy, 34%; and >30 Gy, 62%).[81]

Local radiation therapy is effective for isolated/localized cutaneous tumors, or chronic, painful/ulcerated lesions, with a CRR of >90%.[83-85] Multifractionated doses are standard, but single/few fractions of low-dose radiation may be sufficient: a single or 2 fractions of 7 to 8 Gy provides a CR in 95% of lesions.[85,86] Lower responses are common in transformed MF and lower extremity lesions associated with poor circulation and wound healing. Radiosensitizing agents, such as histone deacetylase inhibitors, may work synergistically with low-dose local radiation therapy.[87,88]

SYSTEMIC THERAPIES

Key points

- **Single-agent systemic therapy (eg, bexarotene) is often used after skin-directed therapy is inadequate or in cases of advanced disease**
- **Immunomodulators, such as interferons and retinoids, are commonly used as first-line monotherapy in advanced mycosis fungoides and are also used in low-dose combination with topical agents**
- **Histone deactylase inhibitors (vorinostat or romidepsin) are also effective single agents in skin, nodal, and blood disease**
- **Alemtuzumab is particularly active in erythrodermic mycosis fungoides/Sézary syndrome, with depletion of the central memory T-cell subset**
- **Chemotherapy is generally reserved for treatment refractory or rapidly progressive advanced mycosis fungoides**
- **Allogeneic stem cell transplantation, also reserved for advanced disease, may have curative potential in mycosis fungoides**

Retinoids/bexarotene

Retinoids are immunomodulating agents that are structurally similar to vitamin A, with the first retinoids (eg, isotretinoin, acitretin, and etretinate) targeting RARs and leading to 44% to 67% ORRs in CTCL with variable response durations (range, 1-25

months).[32,89-95] Oral bexarotene, which was been approved by the US Food and Drug Administration for refractory CTCL in all stages, has effects on cell differentiation and apoptosis and also downregulates CCR4 and E-selectin expression, affecting malignant T-cell trafficking to the skin.[96]

In phase II and III trials of 94 patients with advanced stage MF (stages IIB-IVB) refractory to ≥ 2 standard therapies, ORRs of 45% and 55% were observed with daily doses of 300 or 650 mg/m^2, respectively.[97,98] Decreased skin erythema/scaling and pruritus with temporary blood improvement was seen in erythrodermic MF and SS.[99,100] The median response duration was 7 to 9 months.[97-100] A daily dose regimen of 300 mg/m^2 was recommended based on the safety profile. Bexarotene has been safely combined at lower doses with IFNα, ECP, radiation, and phototherapy in treatment refractory or advanced disease[67,101-106] but has not been shown to be better than bexarotene monotherapy.[99-104]

The most common side effects include hypertriglyceridemia, hypercholesterolemia, and central hypothyroidism, requiring dose adjustments, lipid-lowering, and thyroid medications.[101] Other side effects include skin peeling, headache, arthralgias/myalgias, neutropenia/leukopenia, pancreatitis, and hepatitis.[97-100]

Interferons

IFNs have shown a wide range of biologic effects, and IFNα enhances T_H1 cell—mediated responses to malignant T-lymphocytes.[107,108] IFNα is generally administered long-term, although the optimal dose and duration in MF/SS have not been established. Therapy should start at low doses (ie, 1-3 million units [MUs] 3 times weekly with gradual escalation [9-12 MUs daily as tolerated]).[108]

IFNα monotherapy has shown efficacy in all stages, with 29% to 80% ORRs and 4% to 41% CRRs[107-110] (eg, 51 patients taking a mean daily low dose [2.7 MU] had 21 [41%] CRs, with 57% having disease-free survival of 7.5 months).[111] Greater efficacy is seen in earlier stages.[111] Maintenance IFNα therapy is continued for ≥ 3 months followed by slow tapering over 6 to 12 months if there is no recurrence.[108]

Combination with retinoids does not appear to yield a higher response than IFNα alone[104,107,108] and appears inferior to IFNα plus PUVA (38% CR with nonbexarotene retinoids vs 70% CR with IFN plus PUVA).[112] Combination with ECP results in decreased Sézary cell counts, although no studies have compared this to IFNα monotherapy.[113-117] IFN-gamma may be effective in refractory MF/SS cases, even those refractory to IFNα.[118]

Neutralizing antibodies may decrease IFN efficacy, are dose-related,[107] and occur less frequently with combination therapies.[48] Most common side effects are also dose-related, including headaches, flu-like symptoms, fatigue, anorexia, weight loss, depression, peripheral neuropathy, and dysgeusia.[108]

Extracorporeal photopheresis

ECP involves separating circulating mononuclear cells using a leukapheresis-based method, mixing with 8-methoxypsoralen, exposure to ultraviolet A light (1-2 J/cm^2), and reinfusion into the patient, with possible apoptosis induction of malignant T cells and the subsequent release of tumor antigens, leading to a systemic antitumor response.[119] ECP was approved by the US Food and Drug Administration for the palliative treatment of CTCL in 1988 and is empirically given on 2 consecutive days every 2 to 4 weeks over >6 months.[119,120]

ECP is primarily effective in erythrodermic CTCL, with 1 multicenter study of 37 patients showing a 73% ORR, including 24 patients with erythrodermic MF/SS.[121] Later studies yielded a 35% to 71% ORR and a 14% to 26% CRR.[122-126] Parameters associated with favorable response include short disease duration, clinical improvement in <6 months, normal CD8$^+$ T cell count and CD4:CD8 ratio, low percentage of Sézary cells, and the absence of extracutaneous disease.[122-127] Bexarotene or IFNα may be added for synergy.[126,128-131] ECP may also be beneficial in a subset of limited disease (stage T1/T2) with abnormal flow cytometry (stage B1/B2).[132] The few adverse events of ECP include catheter-related infection, hypotension caused by volume shifts, headache, fever, chills, and nausea secondary to 8-methoxypsoralen.[131]

Targeted therapies

Alemtuzumab. Alemtuzumab is a humanized monoclonal antibody against the CD52 surface antigen on immune cells, including T/B cells, resulting in their depletion from the blood via neutrophil-mediated, antibody dependent cellular cytotoxicity and complement activation.[133-135] CD52 expression is greater on CD4$^+$ than CD8$^+$ T cells.[136] Alemtuzumab was initially approved by the US Food and Drug Administration for the treatment of chronic lymphocytic leukemia, but is often effective in erythrodermic MF/SS, with ORRs of 86% to 100% (because of its depletion of central memory T cells that predominate in SS[133,137-143]). Original studies recommended subcutaneous/intravenous doses of 30 mg 3 times weekly, but lower doses (10 mg 3 times/week) may be equally efficacious.[144]

Alemtuzumab is associated with infusion reactions and prolonged immunosuppression, with earlier studies reporting opportunistic infections (eg, cytomegalovirus reactivation). Recent infectious prophylaxis has likely decreased this risk.[141-143]

Histone deacetylase inhibitors

Histone deacetylase inhibitors (HDACis) may restore the expression of tumor suppressor and/or cell cycle regulatory genes by increasing histone acetylation with resultant growth inhibition and apoptosis. Vorinostat—approved by the US Food and Drug Administration for CTCL that has progressed beyond stage IB that is also refractory to 2 systemic therapies—is an oral HDAC class I and II inhibitor that also inactivates STAT3, which is constitutively expressed in CTCL, and enhances retinoid effects of RAR/RXR activation and gene transcription in vitro.[145,146] A phase II trial showed a partial response in 22 of 74 patients (29.7%) with only 1 CR.[147] All patients received 400 mg of vorinostat once daily, with reductions to 300 mg daily for toxicity. Another phase II trial of 33 heavily pretreated CTCL patients found that sustained 400-mg daily dosing is more effective and less toxic than intermittent dosing (twice-daily 300-mg regimens).[148] A similar ORR of 24.2% was noted.

Romidepsin, which is approved by the US Food and Drug Administration for advanced CTCL that is refractory to ≥ 1 systemic therapy, inhibits class I and II HDACs and is intravenously administered at a weekly dose of 14 mg/m^2 for 3 weeks, 1 week off, and continued until intolerance or disease progression. Two phase II trials have evaluated romidepsin in advanced-stage MF, with 1 showing a 36% response rate (26/68), including 5 patients with CR.[149,150] Significant pruritus reduction was reported in patients; however, this did not correlate with clinical response.[151]

The most common side effects were gastrointestinal disturbances (ie, nausea and anorexia), fatigue, hematologic abnormalities (ie, thrombocytopenia, anemia, lymphopenia, and neutropenia), and infectious complications.[149,150,152] Electrocardiography assessments showed T wave flattening in 71% of patients, less common ST depression, and rare QTc prolongations (2%).[149,150] A new oral pan-deactylase (class I-IV) inhibitor panobinostat, which has a longer half-life, is currently being studied.[153]

Denileukin diftitox. The IL-2-alfa receptor or CD25 is a target for denileukin diftitox, a fusion toxin (IL-2 linked with diphtheria toxin) that was approved by the US Food and Drug Administration in 1999 for recurrent/persistent CTCL with $\geq 20\%$ expression of CD25 on malignant T cells, but it is currently unavailable by manufacturer.[154] After interleukin-2 receptor binding, denileukin diftitox is internalized, inducing apoptosis by blocking protein synthesis.[155,156] Phase III studies found RRs of 23% and 38% at low dose (9 mg/kg/day) and 36% and 49% at 18 mg/kg/day, respectively (median duration, 7 months).[157-159] Response may be seen in patients with <20% CD25 expression.[160] Adverse effects include acute infusion-related events (eg, fever, rash, chills, dyspnea, or hypotension), myalgias, elevated serum transaminase levels, and vascular leak syndrome.[157,159]

CHEMOTHERAPY

Antifolates

The reduced folate carrier type 1, an oncofetoprotein that is predominantly expressed in the membranes of fetal and tumor cells, mediates the cellular uptake of folates and antifolate drugs, including methotrexate and a newer agent, pralatrexate (which is approved by the US Food and Drug Administration for relapsed/refractory peripheral T-cell lymphoma).[161,162] Both antifolates are substrates for folylpolyglutamate synthetase and potently inhibit dihydrofolate reductase.[163]

Low-dose methotrexate (median weekly dose, 25 mg) has an ORR of 33% and 58% in plaque (T2) MF and erythrodermic MF, respectively, with an increased ORR (82%) at higher doses (60-240 mg/m^2 intravenously).[164-166] In a study on relapsed/refractory CTCL, an optimal intravenous dose of pralatrexate of 15 mg/m^2 weekly for 3 to 4 weeks was identified with an ORR of 45%, including patients previously treated with methotrexate.[167] Common side effects include gastrointestinal (eg, nausea/vomiting, mucositis, and ulcers), hematologic (eg, leukopenia, anemia, and thrombocytopenia), and hepatic toxicities.[167,168]

Single and multiagent chemotherapy. Both single and multiagent chemotherapy have been used in refractory/relapsed CTCL. Gemcitabine and pegylated liposomal doxorubicin are relatively new effective monotherapies with ORRs of 68% and 75% for gemcitabine[169,170] and 40.8% and 88% for doxorubicin.[171,172] Multiagent chemotherapy regimens including cyclophosphamide, doxorubicine, vincristine, and prednisone–based regimens have shown comparable efficacy, but with greater toxicity.[1]

Hematopoietic stem cell transplantation. Hematopoietic stem cell transplantation—specifically allogeneic stem cell transplantation—may have a curative potential in advanced MF/SS, although no large series exist and conditioning regimens are largely driven by institutional preference.[173-175] Despite reported CRRs in most patients treated by autologous stem cell transplantation, relapses are frequent, occurring within 6 months posttransplant.[176-180] Allogeneic transplants achieve

more durable CRRs, which are largely attributed to the donor T/natural killer (NK) cell–mediated graft versus lymphoma effect. Donor lymphocyte infusions in the early posttransplant period or in relapsed disease may enhance this effect.[181,182] Response durations of 6 years posttransplant have been reported.[183,184] Treatment-related mortality (ie, life-threatening infections and graft versus host disease) occurs in approximately 30% of cases. Reduced-intensity nonmyeloablative (mini) allogeneic stem cell transplantation potentially offers a graft versus lymphoma effect with decreased conditioning regimen–related toxicity.[183,185-187]

Other investigational therapies

Lenalidomide, a thalidomide analog that has been approved by the US Food and Drug Administration for the treatment of myelodysplastic syndrome and relapsed/refractory multiple myeloma and mantle cell lymphoma, increases T_H1-cytokine production and enhances T and NK cell–mediated killing.[188] A phase II trial of 32 patients with advanced/refractory CTCL showed an ORR of 29%.[189] Side effects include temporary flares of skin disease and circulating Sézary cells, cytopenias, and fatigue/malaise.

Toll-like receptor agonists, which mimic bacterial antigens and stimulate the innate immune response, have been used in CTCL patients,[190,191] as have interleukins-12 and -2.[192-195] In 2 phase II studies of zanolimumab, a monoclonal antibody with specificity for CD4 receptors on T cells, a 56% ORR at 560 to 980 mg was observed, with early (8-week) durable response, and side effects similar to other T cell–targeted therapies.[196] T-cell receptor CCR4, which is involved in the skin-homing of malignant T cells, is another potential therapeutic target in CTCL.[197-201]

Proteasomes function in nonlysosomal degradation of intracellular proteins, regulating cell survival; bortezomib, a proteasome inhibitor, which also downregulates the transcription factor nuclear factor-κB, has shown efficacy in relapsed/refractory CTCL (67% ORR) with side effects of myelosuppression and sensory neuropathy.[202,203] Other targeted therapies currently in clinical trials include antibody-drug conjugate directed to CD30 surface protein (brentuximab-vedotin), anti–PD-1 therapies, phosphoinositide 3-kinase inhibitors, and protein kinase C inhibitors.[204-209]

GENERAL HEALTH CARE

Key points

- **Important quality of life considerations include pruritus, xerosis, and the prevention of skin infections**
- **Treatment-related toxicities may require dose adjustments, particularly in the elderly, patients with advanced disease, and patients with multiple comorbidities**

Many patients are disabled by their pruritus and skin appearance. Emollients should be used for dryness and scaling, and the application of midpotency steroids, particularly triamcinolone 0.1% ointment once or twice daily, is especially useful in SS. A short-term course with systemic steroids often gives immediate symptomatic relief. Oral antihistamines, gabapentin, aprepitant, and/or mirtazapine may be of benefit for pruritus. Patients with more widespread cutaneous disease or generalized erythroderma need screening for secondary infections (eg, staphylococcus, streptococcus, dermatophytes, and herpesviruses) and appropriate systemic treatment. Bleach baths, as given in children with severe atopic dermatitis, can minimize colonization of *Staphylococcus aureus*.[210] Patients with advanced disease are particularly at increased risk for infections and sepsis given their immunosuppressed state.

In summary, while there is no cure for MF and SS, treatment is directed at clearing cutaneous and extracutaneous disease, minimizing disease recurrence, and preventing disease progression. Treatment-associated toxicities can be problematic, particularly in elderly patients. Dose adjustments are often required in those patients, because treatment is palliative and must be balanced against the increased risk for toxicities.

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