

Cutaneous T-Cell Lymphoma: Current and Emerging Therapies

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ABSTRACT

Cutaneous T-cell lymphomas (CTCLs) are clinically heterogeneous T-cell lymphomas that arise in the skin and are characterized by their clinical and pathological features. This review will focus on mycosis fungoides (MF) and Sézary syndrome (SS), which represent 60% to 80% and less than 10% of CTCL cases, respectively. While most patients with MF present with patches and plaques and can be successfully treated with skin-directed therapies, a minority of patients progress from early to advanced stages or undergo large cell transformation. SS is defined as erythroderma, lymphadenopathy, and more than 1000 circulating atypical T-cells/uL with cerebriform nuclei. It has a poor overall survival of 2.5 years. Given the overall rarity of CTCLs, it is notable that clinical trials of treatments for MF/SS have been successfully completed, resulting in FDA approvals of novel therapies with increasing overall response rates. This review outlines the current multidisciplinary approach to diagnosing and treating MF/SS, with a focus on combining skin-directed therapies with emerging targeted and investigational systemic therapies. Integrating these anticancer therapies with skin care and bacterial decolonization is critical for comprehensive management. Curing patients with MF/SS may be possible by using a personalized medicine approach including novel combination strategies, restoration of T helper 1 cytokines, and avoidance of immunosuppressive regimens.

Introduction

Cutaneous T-cell lymphoma (CTCL) describes a group of clinically heterogeneous T-cell lymphomas that arise in the skin.¹ Mycosis fungoides (MF), the most common CTCL, represents 60% to 80% of all CTCLs whereas Sézary syndrome (SS), the erythrodermic and leukemic variant, affects fewer than 10% of patients with CTCL. Most patients with MF present with stage IA disease, defined as patches and plaques involving less than 10% of the body surface area (**Figure 1**). For most individuals diagnosed with early-stage disease, this is a chronic skin affliction managed with skin-directed therapy (SDT) with acceptable disease control and possible complete remissions. If the disease progresses, the treatment of MF/SS consists of sequential therapies that have increasing toxicity and potential immunosuppression.

When the first randomized study of patients with CTCL was conducted at the National Institutes of Health in 1989, no survival advantage was seen with electron beam radiation therapy (EBT) combined with chemotherapy compared with less aggressive sequential topical therapies.² Thus, the oncologist should be aware of the full toolbox of possible non-immunosuppressive treatments, especially skin-directed therapies and immunotherapies that can prolong the lifespan of patients with MF or SS.

Skin-Directed Therapies

SDTs are the mainstay for treatment of early-stage disease, but they also have an important role in disease palliation in patients with advanced disease. Because MF/SS is a chronic skin disease that likely requires treatment for many years, management should start out as conservatively as possible, with the goals of putting the disease in a prolonged or permanent remission and controlling pruritus.

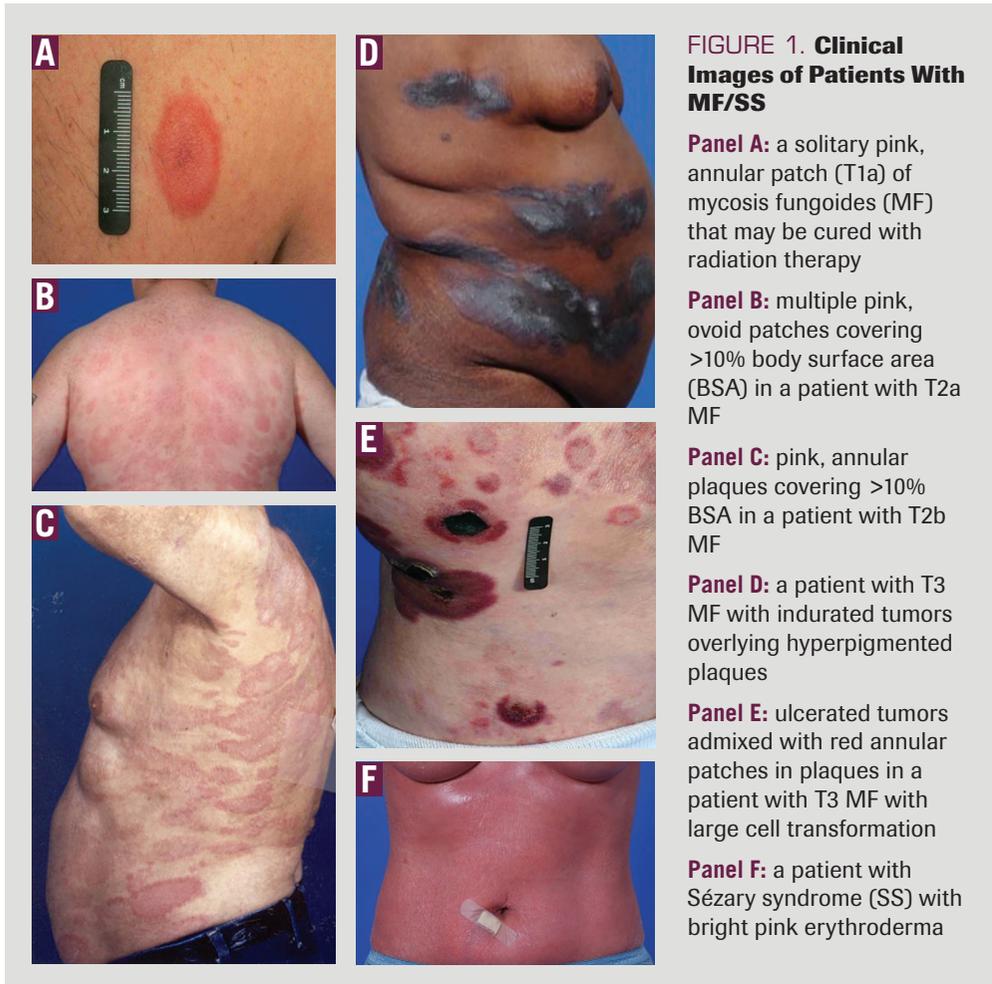


FIGURE 1. Clinical Images of Patients With MF/SS

Panel A: a solitary pink, annular patch (T1a) of mycosis fungoides (MF) that may be cured with radiation therapy

Panel B: multiple pink, ovoid patches covering >10% body surface area (BSA) in a patient with T2a MF

Panel C: pink, annular plaques covering >10% BSA in a patient with T2b MF

Panel D: a patient with T3 MF with indurated tumors overlying hyperpigmented plaques

Panel E: ulcerated tumors admixed with red annular patches in a patient with T3 MF with large cell transformation

Panel F: a patient with Sézary syndrome (SS) with bright pink erythroderma

elicit an inflammatory response that may lead to earlier disease clearance. Topical steroids have been used in conjunction with NM but may limit the contact dermatitis.

Topical retinoids

Vitamin A is a lipid-soluble, essential nutrient that dimerizes and binds to retinoid receptors. Its action depends on the type of retinoid: With retinoic acid receptors (RARs), it can induce T-cell or keratinocyte differentiation, and with retinoid X receptors (RXRs), it can induce apoptosis of tumor cells. Topical bexarotene (Targretin gel) is an RXR retinoid approved for the treatment of MF based on phase 1 and 2 trials.⁴ The RAR retinoid tazarotene is

Topical steroids

We use high-potency topical clobetasol 0.05% twice daily as a first-line SDT. If lesions resolve, the frequency or potency should be slowly tapered. Tapering is desirable because steroids decrease collagen production; this leads to skin atrophy, which can be severe in intertriginous areas and on the face and neck.

For patients with extensive skin involvement or erythroderma, application of topical triamcinolone 0.1% with wet warm towels for 15 minutes (wet wraps) can be helpful for

controlling the itching and skin lesions for a limited period.

Topical nitrogen mustard

Topical nitrogen mustard (NM) has been used off label as a frontline SDT in MF for decades. In 2013, mechlorethamine 0.016% gel (Valchlor gel) was approved by the FDA for use in MF.³ NM may be used as salvage therapy for patients who failed topical steroids or as a maintenance therapy following EBT. The most common adverse effect (AE) seen with NM is contact dermatitis, which is thought to

be used sparingly in these regions. approved for acne and psoriasis and demonstrates efficacy similar to that of bexarotene in patients with MF. Topical retinoids are especially helpful for hypertrophic, psoriatic, acral, or follicular lesions. Retinoids will cause irritation in intertriginous areas and should be used sparingly in these regions.

Topical immunotherapy

Imiquimod 5% cream (Aldara) is a Toll-like receptor (TLR)-7 agonist approved for treatment of genital warts. Several case reports observed that imiquimod 5% cream twice daily

is effective in treating tumors in MF. Topical resiquimod is a more potent TLR-7 and TLR-8 agonist and demonstrated efficacy in patients with MF in a phase 1 trial.⁵ Both imiquimod and resiquimod may cause irritation and may have an abscopal effect, possibly through the generation of γ -interferon, interleukin (IL)-12, and natural killer (NK) cells.

Two steroid-sparing topical calcineurin agents (pimecrolimus and tacrolimus) have been used off label to treat areas at risk for atrophy, such as eyelids or genitalia. In a phase 2 trial evaluating topical pimecrolimus 1% cream twice daily for 16 weeks in early-stage MF, response rates of 54% and 73% were seen in patients with stage IA and IB disease, respectively.⁶

Phototherapy

Phototherapy with narrowband ultraviolet B (nbUVB) or psoralen

plus ultraviolet A (PUVA) are often the first therapies considered after topical therapies have failed.⁷ PUVA is a combination of oral psoralen, a photosensitizing agent, followed by UVA exposure. PUVA is more effective than nbUVB for treating more extensive plaque disease. Choice of phototherapy depends on the patient’s clinical phenotype and access to phototherapy centers. Phototherapy may be used alone or combined with topical steroids as well as topical/oral retinoids; however, adjunctive treatment with NM is not recommended.

Photodynamic therapy

Photodynamic therapy is a novel treatment that combines fluorescent light and a topical photochemical (eg, hypericin) applied prior to light exposure. A phase 2 trial demonstrated safety and efficacy of topical hypericin to individual lesions followed by

visible light exposure.⁸ A phase 3 study of hypericin ointment with photodynamic therapy demonstrated an index lesion response rate (defined as 50% or greater improvement) in 49% of lesions after 3 cycles of therapy.⁹

Electron beam radiation (EBT) therapy

Treatment with EBT has the highest response rates, greater than 90%. Complete response rates are highest in patients with T1 and T2 disease, and early use of low-dose radiation to a solitary lesion may be curative. Low-dose (12 Gy) total skin EBT (TSEBT) can be used for disease control and palliation of symptoms in patients with disseminated skin disease,¹⁰ whereas higher doses (up to 36 Gy) are recommended to debulk skin compartment disease prior to allogeneic hematopoietic stem cell transplantation (alloHSCT).^{11,12}

TABLE 1. Indication for and Efficacy of FDA-approved Therapies for MF/SS

Agent (Class)	Indication	Study	N	ORR	DOR
Romidepsin (HDAC inhibitor)	CTCL with 1 prior systemic therapy	Pivotal Supportive	96 71	34% 35%	15m 11m
Denileukin diftitox, discontinued (Fusion protein)	CTCL with CD25 expression	Pivotal	71	30%	4m
Bexarotene (Retinoid x-receptor activator)	CTCL with 1 prior systemic therapy	Pivotal	62	32%	5m
Vorinostat (HDAC inhibitor)	CTCL with 2 prior systemic therapies	Pivotal Supportive	74 33	30% 24%	6m 4m
Mogamulizumab (CCR4 inhibitor)	MF/SS with 1 prior systemic therapy	Pivotal	186	28%	14m
Brentuximab (CD30 inhibitor)	CTCL with 1 prior systemic therapy	Pivotal	64	55%	17m

CCR4, CC chemokine receptor 4; CTCL, cutaneous T-cell lymphoma; DOR, duration of response; HDAC, histone deacetylase; m, months; MF/SS, mycosis fungoides/Sézary syndrome; N, number; ORR, overall response rate

First-line Systemic Therapies Extracorporeal photopheresis

In patients with erythrodermic MF and SS, the frontline therapy is extracorporeal photopheresis (ECP), which combines phototherapy with leukapheresis.¹³ ECP may be administered for 2 consecutive days every month or, if disease is progressing, every 2 weeks. ECP as monotherapy has been shown to have overall response rates (ORRs) ranging from 33% to 75%.^{14,15} Studies demonstrate that ECP prolongs survival in patients with erythrodermic and advanced MF/SS, and they support the use of ECP as first-line treatment for many patients with stage III and IV disease. Photopheresis may be combined with immunomodulatory agents like oral retinoids and interferon.

Oral retinoids

Oral retinoids are often selected as first-line systemic therapy for patients who have failed SDT (**Table 2**). Two phase 2 trials led to the FDA approval of oral bexarotene based on the ORR of 48% at the optimal dose of 300 mg/m² daily in a combined group of patients with early and advanced-stage MF/SS.^{16,17} In practice, oral bexarotene is started at 75 mg to 150 mg daily with gradual escalation to a goal dose of 300 mg/m² daily. Because bexarotene causes central hypothyroidism leading to hypertriglyceridemia, we initiate patients on low-dose levothyroxine (eg, 25-75 mcg daily) and fenofibrate 145 mg daily. There is a cumulative dose effect of bexarotene, and it may take 6 or more months for a response at the lower dose range. Bexarotene is the only FDA-approved retinoid for MF/SS. However, other retinoids such as acitretin and isotretinoin may be less cost-prohibitive and associated with similar efficacy.¹⁸ Retinoids have been combined with other therapies and used for maintenance after EBT.

Interferons and interleukins

As the immune system of patients with advanced-stage MF/SS is shifted toward T-helper 2 (Th2) cytokines, treatment with interferons (IFNs) may aid in restoring the T-helper 1 (Th1)/Th2 balance.¹⁹ IFN- α and pegylated IFN- α both have demonstrated efficacy of 64%, making them among the more effective therapies used alone or in combination with ECP or retinoids.²⁰ IFN- γ is as effective as IFN- α and tends to be associated with fewer AEs.

IL-12 activates NK cells and cytotoxic CD8⁺ T cells, thereby potentiating the production of IFN- γ and reversing the drift from Th1 to Th2 cytokines. A phase 1 trial of recombinant human IL-12 (rhIL-12) administered intralesionally or subcutaneously twice weekly for up to 24 weeks demonstrated clinical response across multiple disease phenotypes.²¹ Our phase 2 trial of rhIL-12 in patients with early-stage MF found that twice-weekly subcutaneous administration of rhIL-12 showed an ORR of 43%.²² IL-12 is not commercially available, but it is a promising agent that warrants further investigation.

Histone deacetylase inhibitors

Histone deacetylase inhibitors (HDACi) are small molecules that block deacetylation of tumor suppressor genes and cell cycle regulatory pathways. Vorinostat is an oral HDACi that is FDA-approved for the treatment of MF/SS; its ORR is 29%.^{23,24} Vorinostat has been largely replaced by romidepsin, an FDA-approved HDACi that is given intravenously (IV) weekly for 3 consecutive weeks of a 4-week cycle. A phase 2 trial demonstrated an ORR of 34%.²⁵ Responses were seen across all stages and disease subtypes. Multiple clinical trials utilizing these inhibitors in combination with other treatments are under investigation.

Targeted Immunotherapies E7777

Initially known as denileukin diftitox (Ontak), E7777 is emerging as a more stable and less toxic recombinant fusion protein. As Ontak, this agent was initially evaluated in a phase 1 study of patients with hematologic malignancies expressing CD25, and it demonstrated an ORR of 37%, including 5 complete responses.²⁶ A 2-dose randomized study of patients with stage IB-IVA MF/SS showed an ORR of 30%.²⁷ A second randomized study of patients with stage IA-III MF/SS demonstrated an ORR of 44%.²⁸ Patients whose skin biopsy had greater than 25% CD25 expression appeared to perform better (ORR, 78%) than patients having low to undetectable expression (ORR, 20%). These pivotal studies led to the full approval by the FDA in 2008. However, Ontak was withdrawn in 2014 for inconsistencies in the folding of the protein, and the new formulation, E7777, has since been in development. A recent phase 2 registration trial in 71 patients established a dose of 9 ug/kg/day.²⁹ Preliminary results show an ORR of 44%. Potential AEs are infusion reactions and capillary leak syndrome. Guidelines to prevent and manage capillary leak syndrome have been developed.³⁰

Brentuximab vedotin

Brentuximab vedotin (BV) is an antibody-drug conjugate to monomethyl auristatin E that targets CD30. In a phase 2 trial, high response rates were seen in patients with MF (54%), primary cutaneous anaplastic large cell lymphoma (100%), and lymphomatoid papulosis (100%).³¹ Patients with MF demonstrated similar response rates, irrespective of low, medium, or high CD30 expression (50%, 58%, and 50%, respectively). In a parallel phase 2 trial of patients with stage IB-IV MF/SS, ORR was 70%.³² Clinical

TABLE 2. Summary of Select Investigational Trials in Advanced MF/SS

Category	Investigational agent	Clinicaltrials.gov ID	Phase	Status
KIR3DL2				
	IPH4102	NCT02593045	II	Completed
	IPH4102 + chemotherapy (TELLOMAK)	NCT03902184	II	Recruiting
PD1/PDL1				
	Pembro	NCT02243579	II	Completed
	Pembro + RT	NCT03385226	II	Recruiting
	Pembro + decitabine + pralatrexate	NCT03240211	I	Recruiting
	Pembro + pralatrexate	NCT03598998	I/II	Recruiting
	Pembro + romidepsin	NCT03278782	I/II	Recruiting
	Pembro + IFN-gamma	NCT03063632	II	Active, not recruiting
	Pembro + gemcitabine	NCT04960618	II	Recruiting
	Pembro + brentuximab	NCT05313243	II	Not yet recruiting
	Nivolumab + T-VEC	NCT02978625	II	Recruiting
	Nivolumab + duvelisib	NCT04652960	I	Recruiting
	Durvalumab + lenalidomide	NCT03011814	I/II	Recruiting
CD47				
	TTI-621 (SIRPaFc IgG4)	NCT02663518	I	Active, not recruiting
	Intratumoral TTI-621	NCT02890368	I	Terminated
	Hu5F9-G4	NCT02216409	I	Completed
	Hu5F9-G4 + mogamulizumab	NCT04541017	Ib/II	Suspended
CART				
	LB1901 (anti-CD4 CAR T)	NCT04712864	I	Active, not recruiting
	CD4CAR (anti-CD4 lentiviral vector)	NCT03829540	I	Active, not recruiting
	ATLCAR.CD30 and ATLCAR.CD30.CCR4	NCT03602157	I	Recruiting
	CTX130 (CRISPR/Cas9 targeting CD70)	NCT04502446	I	Recruiting
JAK/STAT/SYK				
	Ruxolitinib (JAK1/2)	NCT02974647	II	Recruiting
	Ruxolitinib + duvelisib	NCT05010005	I	Recruiting
	Cerdulatinib (JAK/SYK)	NCT01994382	I/IIa	Completed
PI3K/AKT/mTOR				
	Tenalisib (RP6530, dual PI3K delta/gamma)	NCT02567656	I	Completed
	Tenalisib + romidepsin	NCT03770000	I/II	Completed
	Duvelisib (PI3K) + romidepsin or bortezomib	NCT02783625	II	Active, not recruiting
	Parsaclisib (PI3K) + romidepsin	NCT04774068	I	Recruiting

CAR T, chimeric antigen receptor T-cell therapy; CRISPR, Clustered Regularly Interspaced Short Palindromic Repeats; IFN, interferon; Ig, immunoglobulin; MF/SS, mycosis fungoides/Sézary syndrome; pembro, pembrolizumab; PD1, Programmed Cell Death Protein 1; PI3K, phosphoinositide 3-kinase; RT, radiation therapy; SIRP, signal regulatory protein; T-VEC, talimogene laherparepvec

responses were seen across all levels of CD30 expression, although median CD30_{max} was higher in responders than in nonresponders. The randomized phase 3 ALCANZA trial showed that BV was superior to physician's choice (oral bexarotene or methotrexate) in patients with CD30⁺ CTCL based on an ORR lasting at least 4 months (56.3% vs 12.5%).³³ Longer median progression-free survival (PFS) intervals were observed in patients treated with BV compared with physician's choice (16.7 vs 3.5 months).

Peripheral neuropathy is the major dose-related AE, seen in 67% of patients. After discontinuing treatment, symptoms improve with time in most patients.

Mogamulizumab

Mogamulizumab is a humanized monoclonal antibody that is defucosylated to enhance antibody-dependent cellular cytotoxicity. Its target is the CC chemokine receptor 4 (CCR4), a receptor expressed by malignant cells across multiple clinical phenotypes in MF/SS and also on the surface of Th2 and regulatory T cells (Tregs).

A phase 1/2 trial in 41 patients with MF/SS demonstrated an ORR of 37%, including a response in 18 of 19 (95%) patients with B1 or greater blood involvement.³⁴ In the phase 3 MAVORIC registration trial, 372 patients with MF/SS were randomized to receive either mogamulizumab (1 mg/kg IV weekly for 4 weeks, then every 2 weeks) or vorinostat.³⁵ Global ORR was 28% for patients treated with mogamulizumab, and a higher ORR of 47% in patients with SS was observed.

Mogamulizumab-associated rash (MAR) is seen in 16% to 24% of treated patients. Skin biopsies may aid in distinguishing MAR from disease, as MAR demonstrates features of spongiotic, psoriasiform, or interface der-

matitis with a predominance of CD8⁺ T cells. Given mogamulizumab's profound effect in reducing Tregs, which are integral to successful engraftment, mogamulizumab should not be administered in the months leading up to alloHSCT.

IPH4102

KIR3DL2 (also known as CD158k) is a member of a family of inhibitory killer cell immunoglobulin-like receptors (KIRs) found on NK cells. KIR3DL2 is expressed in more than 85% of patients with SS. It has been proposed as a diagnostic and prognostic marker for SS that is superior to loss of CD26 or CD7. IPH4102, also known as lacutamab, is a fully humanized monoclonal antibody targeting KIR3DL2 that binds to receptors of target cells, inducing NK-cell mediated lysis. A phase 1, international, multicenter trial of 44 patients with MF/SS demonstrated an ORR of 43% in SS patients with minimal AEs.³⁶ A phase 2 trial (TELOMAK; NCT03902184) is ongoing to study the efficacy of IPH4102 alone or in combination with chemotherapy in patients with advanced MF/SS.

Pembrolizumab and nivolumab

The use of immune checkpoint inhibitors, such as the anti-PD-1 agents pembrolizumab and nivolumab, has demonstrated how reinvigorating exhausted tumor-infiltrating lymphocytes may restore the host antitumor response in many cancers. Their role in MF/SS is less defined owing to the expression of these markers on both nonmalignant and malignant T cells. Hence, blocking PD-1 in malignant cells in T-cell lymphomas may theoretically promote tumor growth. Treatment with pembrolizumab resulted in an ORR of 38% in patients with advanced MF/SS in a phase 2 trial.³⁷ A transient disease

flare characterized by erythroderma and pruritus was seen in more than half of patients with SS. The phase 1 study of nivolumab in patients with hematologic malignancy also demonstrated clinical responses in 15% of patients with MF/SS.³⁸ Ongoing trials are studying the use of checkpoint inhibitors in combination with other therapies (Table 2).

Single-Agent Chemotherapy Folate antagonists

Pralatrexate is a dihydrofolate reductase inhibitor with higher activity and greater selectivity for cancer cells than methotrexate. In a dose de-escalation study in CTCL, pralatrexate 15 mg/m²/week for 3 of 4 weeks resulted in an ORR of 45%.³⁹ We found that addition of oral bexarotene at 150-300 mg/m² based on preclinical activity enhanced the efficacy to an ORR of 61%; the safety profile was consistent with that previously seen with individual study drugs.⁴⁰ Durable responses were observed, with a median PFS of 12.8 months. We recommend pretreatment with oral folinic acid (leucovorin) at 25 mg twice daily for 3 days at the start of each pralatrexate cycle and vitamin B12 at 1 mg intramuscularly every 8 to 10 weeks.

Gemcitabine

Gemcitabine is a pyrimidine nucleoside analogue. Its use in patients with CTCL has been studied, utilizing a dose of 1000-1200 mg/m²/week for 3 of 4 weeks.⁴¹ A dose reduction—treatment for 2 weeks rather than 3—has been used in the elderly with good tolerability. In our phase 2 trial of patients with advanced CTCL, we observed an ORR of 68% (17 of 25 patients).⁴² Gemcitabine should be administered carefully in patients with a recent history of radiation given the potential for radiation recall.

Liposomal doxorubicin

Liposomal doxorubicin (Doxil) is an anthracycline with antineoplastic effects. In the first published study of liposomal doxorubicin in patients with MF, treatment of 20 mg/m² once monthly resulted in an ORR of 80% (8 of 10 patients).⁴³

Combination chemotherapy

Patients with advanced MF/SS, especially those with large cell transformation, may develop tumors and bulky lymphadenopathy so severe and extensive that combination chemotherapy may be considered. Several regimens have been used, but no data suggest that one is better than another. Romidepsin and E7777 have been studied in combination with CHOP (cyclophosphamide, vincristine, prednisone, and bleomycin), and studies of mogamulizumab with CHOP in other T-cell lymphomas are ongoing (**Table 2**). Response rates may be high, but responses are often short-lived without increased survival. Subsequent relapsed disease may be even more aggressive, and the risk of immunosuppression associated with chemotherapy may result in high morbidity and mortality from opportunistic infections in patients with whose skin and/or immune system are already compromised.

Other Investigational Agents

Bortezomib

Bortezomib inhibits proteasome-dependent NF- κ B signaling. A phase 2 study of bortezomib in 12 patients with advanced MF or peripheral T-cell lymphoma (PTCL) with isolated skin involvement demonstrated an ORR of 67%.⁴⁴ Patients were treated with a dose of 1.3 mg/m² twice weekly for 2 weeks followed by 1 week off. Treatment was well tolerated and responses were durable, lasting 7 to 14 months.

In vitro studies have suggested that bortezomib may also enhance the activity of HDACi.

Lenalidomide

Lenalidomide is an oral immunomodulatory agent that induces Th1 cytokine production and augments NK cell cytotoxicity. In a phase 2 exploratory trial, lenalidomide was found to be active in patients with advanced MF/SS with an ORR of 28% (9 of 32 patients, all partial responses).⁴⁵ Many patients were unable to tolerate 25 mg daily. Although doses of 10 mg daily were better tolerated, they were not as effective. In a small, sequential phase 1 study, lenalidomide demonstrated efficacy in combination with romidepsin with an ORR of 44% (4 of 9 patients).⁴⁶

JAK-STAT inhibitors

Janus kinase-signal transducer and activator of transcription (JAK-STAT) is a signaling pathway that is critical in mediating inflammatory skin diseases, including atopic dermatitis, psoriasis, alopecia areata, and vitiligo. Mutations in the JAK-STAT pathway have been reported in SS cells by whole genome sequencing. In a phase 2 trial evaluating oral ruxolitinib, a JAK1/2 inhibitor, in patients with T-cell lymphoma with or without activating JAK-STAT mutations, 1 of 7 patients with MF/SS demonstrated a clinical response.⁴⁷

SYK inhibitors

Overexpression of SYK, a protein tyrosine kinase, occurs in T cell lymphomas and is thought to contribute to malignant cell growth and survival. In a phase 2 study of cerdulatinib, a dual SYK/JAK inhibitor, in patients with T-cell lymphoma, ORR was 35% with the highest activity in patients with MF (ORR 45%).⁴⁸ Rapid improvements in pruritus occurred, and several patients experienced a durable response.

PI3K inhibitors

Modulation of phosphatidylinositol 3-kinase (PI3K), a lipid kinase involved in intracellular signal transduction, may contribute to the survival and differentiation of malignant tumor cells. Duvelisib and tenalisib are PI3K inhibitors with activity against the δ and γ isoforms, which are key effectors in the innate and adaptive immune response and in modulating the tumor microenvironment through tumor-associated macrophages. A phase 1 study of duvelisib demonstrated an ORR of 32% in MF/SS.⁴⁹ A phase 1/1b study of tenalisib in patients with T-cell lymphoma showed an ORR of 45% in MF/SS.⁵⁰

Anti-CD47

CD47 has garnered much interest as a macrophage checkpoint (or “do not eat me” signal) that is overexpressed in many cancer types. In a phase 1 study of intralesional TT1-621, a CD47-SIRP α inhibitor, 35 patients with MF/SS were treated in a sequential dose escalation study with intralesional TT1-621 alone or in combination with pembrolizumab or pegylated IFN- α .⁵¹ A response in Composite Assessment of Index Lesion Severity (CAILS) score was seen in 34% (10 of 29 evaluable patients). A phase 1 study of IV TT1-621 reported an ORR of 21% in 29 patients with MF/SS.⁵²

Chimeric Antigen Receptor

Chimeric antigen receptor (CAR T) are an emerging therapy in which the patient’s own CD8⁺ T cells are engineered and expanded in culture to recognize and eliminate tumor-specific antigen, independent of MHC. In 2017, the first CAR T therapy was approved for the treatment of B-cell lymphoma using a CD19 target. However, the use of therapy in patients with T-cell lymphoma may offer unique challenges because sustained

elimination of T-cells would result in severe immunosuppression with infectious complications. To optimize “on-target, off-tumor” selection, CAR T-cells using targets CD30 and CCR4 are being studied in advanced MF/SS (Table 2).

Allogeneic stem cell Transplantation

AlloHSCT may result in long-term remission in a subset of patients with MF/SS and should be considered up-front for younger patients in otherwise good health who are refractory to multiple therapies or who demonstrate a high-risk profile of disease with poor life expectancy. Optimizing timing of alloHSCT when the disease is well controlled is critical, as alloHSCT administered while the patient has clinically active disease or poor immunity due to treatment toxicity may lead to relapse.

Preparatory cyto-reduction with reduced-intensity or nonmyeloablative regimens is preferred as patients with advanced MF/SS are older, and post-transplant infectious complications may contribute to high morbidity and mortality in the setting of immunosuppression and skin barrier breakdown. TSEBT is often an important component because the skin is a frequent site of posttransplant relapse.

The preparatory regimen at The University of Texas MD Anderson Cancer Center incorporates TSEBT and nonmyeloablative conditioning with fludarabine and antithymocyte globulin (ATG).⁵³ We have observed durable remissions in patients with SS after alloHSCT (13/24 patients; 54%).⁵⁴ A Stanford University group has reported on their experience in patients with advanced MF/SS using the conditioning regimen of TSEBT, total lymphoid irradiation, and ATG, citing clinical and molecular remission in 43% of patients and 5-year OS of 56%.¹³

Treatment algorithm in advanced disease

There is no standard treatment or sequence of treatments for patients with advanced MF/SS. Treatment selection is predicated on clinical stage as well as burden of activity within each disease compartment (skin, blood, nodal, and visceral). At MD Anderson Cancer Center, we begin with therapies associated with fewer toxicities that may still offer a high response rate and durability of response. For patients with leukemic disease, treatment with oral bexarotene, ECP, and mogamulizumab are considered to be frontline therapies, with early evaluation for alloHSCT in the appropriate populations. In contrast, patients with tumors or bulky lymph node disease, especially those with large cell transformation, may be preferentially considered for treatment with BV or pralatrexate. In our experience, management with chemotherapy portends worse outcomes. Integration of relevant biomarkers, such as CD30 for BV and other next generation—sequencing mutational panels for investigational agents (eg, CCR4, KIR3DL2, JAK) should be assessed for targetable mutations. Finally, skin-directed treatment with topicals, phototherapy, and radiation (TSEBT or to individual lesions) should be incorporated to augment treatment response and enhance quality of life. Treatment within a multidisciplinary team—including dermatologists, oncologists, radiation oncologists, and bone marrow transplant specialists—is ideal for comprehensive care.

Supportive Care

Patients with erythrodermic MF or SS who are having flares are often colonized with staphylococcus aureus (*S aureus*), which can develop into methicillin-resistant *S aureus*. Colonization must be eliminated for the patient to

improve. Soaking in a bathtub of water mixed with a half-cup of bleach may help decolonize bacteria from the skin. Mupirocin 2% ointment may be useful for decolonization of nares and skin lesions.

We do not favor use of systemic corticosteroids for symptom palliation, as we frequently observe steroid dependence with resistance to subsequent therapies.

Pruritus may profoundly affect quality of life in patients with MF/SS. Effective management will lessen patients' psychological and emotional burden and also minimize secondary skin infection through less frequent manipulation of the skin. Topical steroids may offer temporary relief from pruritus and should be integrated with gentle emollients to optimize the skin barrier. Oral agents, such as gabapentin and aprepitant, may offer additional relief. Although oral antihistamines are generally ineffective for relieving severe pruritus, an evening dose may be considered for its sedating effects. ■

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