

How We Treat Mycosis Fungoides and Sézary Syndrome

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Overview

- Mycosis fungoides/Sézary syndrome is managed as a chronic disease.
- Skin-directed therapy is most effective for early-stage disease.
- Sequential single-agent therapy is more effective than combination chemotherapy for advanced-stage disease.

Introduction

Cutaneous T-cell lymphomas (CTCLs) are non-Hodgkin lymphomas that present with skin lesions and variable blood and lymph node involvement. The 2 main subtypes of CTCL are mycosis fungoides (MF) and Sézary syndrome (SS). Both MF and SS can be symptomatic and disfiguring, with pruritus reported in 62% to 82% of patients, and they have been shown to have a significantly negative effect on quality of life.^{1,2} Given the cutaneous and sometimes extracutaneous involvement characteristic of CTCL, these patients are often best managed in a multidisciplinary setting by dermatologists and oncologists in consultation with radiation oncologists.

The initial approach to a patient with MF or SS involves a physical examination to assess the type and extent of skin disease, as well as a lymph node examination. Diagnostic testing includes skin biopsy for histology, immunophenotyping, and T-cell receptor gene rearrangement studies; laboratory workup (Sézary cell count, circulating T-cell subsets, and clonality); and in some cases imaging via positron emission tomography/computed tomography. Disease is staged according to the International Society of Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer (ISCL/EORTC) classification system, which takes into account the extent of skin involvement (T), lymph node disease (N), visceral disease (M), and blood

involvement (B; Table 1).³ The current treatment paradigm includes a combination of skin-directed therapies (topical agents/phototherapy), radiation therapy, and systemic therapies to control disease, improve quality of life, and minimize infectious complications, which can be a source of morbidity.⁴

Here, we present a case of early-stage MF (stages IA-IIA) and one of advanced-stage MF (stages IIB-IVB), and we discuss our overall approach to treatment.

Case No. 1

A 47-year-old woman presented for the evaluation of pruritic patches on her trunk that had appeared over the past year. Eczema had previously been diagnosed and treated with a topical corticosteroid cream that was not effective. She was referred to Memorial Sloan Kettering Cancer Center after an outside biopsy had been suggestive of MF. On presentation, she had hyperpigmented scaly patches on both flanks that involved less than 10% of her body surface area. She had no constitutional symptoms, and the physical examination was negative for any palpable lymphadenopathy. The results of a second skin biopsy with histology, immunophenotyping, and T-cell receptor gene rearrangement studies were supportive of the MF diagnosis. The flow cytometry result was negative, and stage IA MF was diagnosed. She was started on narrow-band ultraviolet B phototherapy (NB-UVB), which was initiated at 3 times per week, with a slow upward titration of the dose. Initially, her response was good, but a few thicker plaques developed after 6 months of phototherapy (Figure 1). Oral bexarotene (titrated up to 300 mg daily) was started, with a good clinical response, while the NB-UVB was continued 2 times per week.

Treatment Approach for Early-Stage Disease

Early-stage MF with primarily skin involvement (patches or plaques) is initially approached with skin-directed

Table 1. Proposed Revisions to the TNMB Classification of Mycosis Fungoides/Sézary Syndrome

A. TNMB Stage	Description			
Skin (T)				
T1	Limited patches or plaques <10% of BSA			
T1A	Patches only			
T1B	Plaques with or without patches			
T2	Patches or plaques covering ≥10% of BSA			
T2A	Patches only			
T2B	Plaques with or without patches			
T3	Presence of ≥1 tumors			
T4	Generalized erythroderma (≥80% BSA)			
Node (N)				
N0	No clinically abnormal peripheral LNs			
N1	Clinically abnormal LNs; histopathology Dutch grade 1 or NCI LN0-2			
N1A	Clone positive			
N1B	Clone negative			
N2	Clinically abnormal LNs; histopathology Dutch grade 2 or NCI LN3			
N2A	Clone negative			
N2B	Clone positive			
N3	Clinically abnormal LNs; histopathology Dutch grade 3-4 or NCI LN4 (clone positive <i>or</i> negative)			
Viscera (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 Sézary cells)			
B0A	Clone negative			
B0B	Clone positive			
B1	Low blood tumor burden (>5% of peripheral blood lymphocytes are Sézary cells but criteria for B2 not met)			
B1A	Clone negative			
B1B	Clone positive			
B2	High blood tumor burden, defined as (1) ≥1000 Sézary cells/μL with positive T-cell clone; <i>or</i> (2) CD4:CD8 ratio ≥10 with positive clone; <i>or</i> CD4+/CD7- cells ≥40% <i>or</i> CD4+/CD26- cells ≥30% with positive clone			
B. TNMB Stage	Components			
	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
IVA₁	1-4	0-2	0	2
IVA₂	1-4	3	0	0-2
IVB	1-4	0-3	1	0-2

BSA, body surface area; LN, lymph node; NCI, National Cancer Institute; TNMB, tumor, node, metastasis, blood classification.

Revisions proposed by the International Society for Cutaneous Lymphomas and the European Organization for Research and Treatment of Cancer. Adapted from Olsen et al. *Blood*. 2007;110(6):1713-1722.³



Figure 1. A 47-year-old woman with stage IA mycosis fungoides who was started on narrow-band ultraviolet B phototherapy. She initially had a good response, but a few thicker plaques developed after 6 months of phototherapy.

therapies (including topical agents and phototherapy), with the goals of disease control and symptom relief. The choice of skin-directed therapy is based on the type of skin lesion, extent of the body surface area involved, therapy side effect profile, provider experience, and patient tolerance of/adherence to the recommended regimen.

T1: Patch/Plaque Involving Less Than 10% of Body Surface Area

In patients with a solitary patch or a few patches, our typical approach is to start with topical therapy. The most commonly used topical agents include corticosteroids, nitrogen mustard (NM), and bexarotene. Both topical bexarotene and topical NM are approved by the US Food and Drug Administration (FDA) for stages IA and IB disease. Our preference is to start with topical corticosteroids owing to good response, wide availability, and favorable side effect profile. Topical corticosteroids have multiple anti-inflammatory effects, including decreased lymphocyte adhesion to endothelium, induction of apoptosis, downregulation of proinflammatory transcription factors, and decreased production of cytokines and growth factors.² In a prospective study of 79 patients (51 T1 and 28 T2) with primarily MF patches who were treated with topical corticosteroids twice daily (with a median follow-up of 9 months), clinical clearing was achieved in 32 of the patients with T1 disease (63%), and partial remission in 16 (31%).⁵ Patients with T2 disease (patch/plaque

involving $\geq 10\%$ of body surface area) had an overall response rate (ORR) of 82%, with complete remission achieved in 25%. The responses were rarely prolonged, however; on topical steroid discontinuation, only 37% of the T1 patients and 18% of the T2 patients remained in complete remission.⁵

Our preference is to use a potent, class 1 topical corticosteroid (eg, clobetasol propionate at 0.05%) for initial rapid control of the disease. Other factors to consider when choosing a topical corticosteroid include the vehicle (ointments are more occlusive than creams), anatomic site (better topical corticosteroid absorption in areas of thin epidermis, such as the eyelids, than in the thicker skin of the palms and soles), and disease state (generally increased penetration in states of cutaneous inflammation/desquamation).⁶ Some studies have suggested that applying a topical corticosteroid under occlusion or applying it to damp skin can improve absorption. Side effects associated with long-term use include skin atrophy (which is typically reversible), hypopigmentation, and striae formation.⁷ Systemic absorption has been reported, although without adrenal suppression.⁵

Topical mechlorethamine hydrochloride, also known as nitrogen mustard, is a cytotoxic alkylating agent with systemic effects attributed to direct DNA damage due to crosslinking. The mechanism of action of topical NM is unknown, and the agent may have immunogenic effects in MF.^{4,8,9} Its efficacy in early-stage MF has ranged from

complete response (CR) rates of 51% to 84% in patients with T1 disease to CR rates of 31% to 62% in those with T2 disease, with varying dose formulations and vehicles used in earlier studies.⁸ Mechlorethamine 0.016% gel (Valchlor, Helsinn) is commercially available in the United States. In the phase 2 clinical trial that led to FDA approval, 260 patients (the majority with stage IA or IB disease) applied mechlorethamine 0.02% gel or ointment once daily for 12 months. In the gel arm, the ORR was 58.5%, the CR rate was 13.8%, and the average time to response was 26 weeks (6.5 months).¹⁰

Common side effects include skin irritation, erythema, and pruritus; true allergic contact dermatitis is less common with the gel formulation than with the ointment (15% of patients in the phase 2 trial).¹⁰ In clinical practice, this irritation can be minimized through an incremental increase in frequency during initial application and treatment with topical corticosteroids if a reaction develops, and/or a decreased frequency of topical application. Initial studies showed a possible increased risk for secondary cutaneous malignancies (this association was confounded by patient risk factors and the concurrent use of treatments known to increase risk); however, a 30-year population-based cohort study published in 2014 found no increased risk for melanoma and nonmelanoma skin cancers.¹¹ Studies have also found no evidence of systemic absorption with topical NM use.¹⁰ Although topical mechlorethamine is now more commonly used than carmustine, topical carmustine is a similar alkylating agent that was previously used to treat early MF¹² and more recently has been shown to be effective as monotherapy or in combination with other agents to treat folliculotropic MF.¹³

Bexarotene is a synthetic retinoid that binds to retinoid X receptors (RXRs). A topical 1% gel formulation is approved in the United States for early-stage MF. Whereas the oral form has known effects on cell differentiation and apoptosis and downregulates cell adhesion molecules, thereby decreasing malignant T-cell trafficking to the skin, the mechanism of action of topical bexarotene is less clear.⁴ In phase 1 and 2 trials of bexarotene 1% gel, the ORR was 63% (the CR rate was 21%) after a median of 20 weeks of treatment.¹⁴ As with topical NM, the main side effects are mild to moderate irritation at the application site, particularly when topical bexarotene is used 4 times per day. Irritation can be minimized by gradually increasing the application frequency (eg, once every other day for the first week, then increased gradually to twice per day).

Other topical agents that have been used in case reports or small series include other topical retinoids (tazarotene 0.1%), topical imiquimod 5%, topical 5-fluorouracil, and tacrolimus.¹⁵ Monochromatic excimer light (wavelength of 308 nm) has demonstrated efficacy

in the treatment of patch/plaque MF (median of 24 twice-weekly treatments), with an unclear duration of response.¹⁶ It may be useful in treating sites not easily accessible by phototherapy, including the palms/soles and intertriginous areas.

T2: Patch/Plaque Involving 10% or More of Body Surface Area

Although the use of topical agents is our primary approach in patients with a solitary patch or a few patches, our initial treatment in patients with T2 disease (primarily patches) is to use phototherapy, specifically NB-UVB (wavelength of 311 nm) phototherapy. UVB suppresses neoplastic T cells by inhibiting antigen-presenting cells and is thought to increase keratinocyte cytokine production.⁴ CR rates for NB-UVB in patients with early-stage disease have ranged from 54% to 90% (average of 84%) with the recommended regimen of 3 times weekly.⁴ Studies have shown better responses in primarily patch vs plaque disease and in patients with lighter skin types, although a hypopigmented variant of MF that is seen in patients with darker skin types responds well to phototherapy.^{17,18}

Relapse occurs after cessation of phototherapy in 29% to 100% of patients, with a mean relapse-free interval ranging from 5.9 to 14.5 months.¹⁸ Although reported maintenance therapy regimens have varied, a prolonged maintenance period may be of some benefit.¹⁷ In our clinical practice, we recommend more frequent phototherapy during periods of active skin disease, alternating with less frequent maintenance regimens or intermittent breaks during periods of skin quiescence. Initially, we recommend thrice-weekly phototherapy with upward dose titration until skin clearing or remission. Once clinical remission occurs, we often recommend a maintenance regimen of the same dose at decreased frequency (eg, twice weekly for 1-2 months and then once weekly for 1-2 months). If no skin worsening occurs with the regimen of less frequent phototherapy, it is reasonable to trial a period without phototherapy because clinical remission is possible while a patient is off active treatment. Patients who experience a quick skin recurrence while off phototherapy may benefit from prolonged maintenance.

Although NB-UVB phototherapy is the most commonly used type of phototherapy, psoralen plus UVA (PUVA) phototherapy is also used. This phototherapy modality involves the administration of oral psoralen, which sensitizes the skin to UVA radiation. It has the advantage of deeper penetration than that of UVB, and it is more effective in patients with plaques. However, the adverse event profile of PUVA limits its long-term use; acute nausea and photosensitivity, as well as long-term side effects of photoaging, increased risk for cataracts, and increased risk for nonmelanoma skin cancers, have been

reported.^{3,4} Given its side effect profile and the availability of low-dose systemic agents (bexarotene, methotrexate, and interferon, discussed in detail in Case No. 2) that can be added to increase the efficacy of NB-UVB phototherapy, as in our example case, we do not use PUVA frequently at our institution.

Total skin electron beam (TSEB) therapy, which involves the administration of superficially penetrant ionizing radiation to the entire skin surface, can provide rapid skin clearing and symptomatic benefit for patients with diffuse skin involvement.¹⁹ Conventional TSEB doses (30-36 Gy) may induce a CR in approximately 60% of patients, but skin toxicity limits repeated courses.¹⁹ In addition, the response duration with TSEB is short and maintenance treatment is required, often with systemic agents. Modern efforts have focused on TSEB dose reduction, with recent studies suggesting that 10 to 12 Gy is sufficient, with an ORR higher than 85% and a CR rate of approximately 50%.²⁰⁻²² Side effects are dose-dependent and include acute erythema and desquamation with chronic skin changes of xerosis, anhidrosis, nail loss/dystrophy, and alopecia.⁴

Case No. 2

A 65-year-old woman presented for continued management of her MF. She had initially received NB-UVB phototherapy at diagnosis, but then new plaques and tumors developed over her left elbow, right forearm, and left ankle. She responded to focal radiation to the tumors, then started oral methotrexate at 15 mg weekly for 2 to 3 cycles without further improvement. Romidepsin was started, which led to partial regression of her skin lymphoma. She remained on this treatment for 9 months, with concurrent use of topical corticosteroids as needed.

After 9 months of romidepsin, another skin plaque developed (Figure 2). Biopsy showed an atypical epidermotropic CD4-positive lymphoid infiltrate with large cells partly coexpressing CD30 (25%-30%). This finding was compatible with a plaque lesion of MF with large cell transformation. The result of peripheral flow cytometry was negative.

The patient was started on brentuximab vedotin (Adcetris, Seagen) at 1.8 mg/m² every 3 weeks. After the first 3 cycles of therapy, the patient noted partial regression in the patches and plaques, without any new spots. Owing to grade 1 neuropathy, the dose of brentuximab vedotin was reduced to 1.2 mg/m² every 3 weeks after 6 cycles. The patient's neuropathy resolved, and she continued on this schedule for an additional 12 cycles. At this point, grade 1 neuropathy again developed. Treatment was spaced to 1.2 mg/m² every 4 weeks, which led to lessening of the neuropathy.



Figure 2. A 65-year-old woman with mycosis fungoides who received treatment with narrow-band ultraviolet B phototherapy, focal radiation to the tumors, oral methotrexate, and romidepsin. After 9 months of romidepsin, another skin plaque developed.

Treatment Approach for Advanced-Stage Disease

Advanced MF with tumors or blood involvement (stages IIB-IVB) is best treated with systemic agents, often in combination with skin-directed therapy or radiation therapy (RT). Table 2 presents some options for systemic therapy in MF. The ORR for most agents is between 30% and 45%, with the exception of newly approved agents such as brentuximab vedotin. Additionally, many systemic agents lead to a partial response (PR) rather than a CR of disease. The goal of treatment is to achieve disease control and minimize the effect on quality of life. We generally start with the mildest and best-tolerated systemic therapy options (ie, bexarotene, methotrexate) and treat in an ongoing or maintenance fashion until disease progression. We also recommend an interdisciplinary approach to treatment, with the incorporation of skin-directed therapy to maintain or improve the response to systemic treatment and with the involvement of both oncologists and dermatologists in patient care.

Staging for advanced-stage MF includes a complete skin examination, laboratory tests including peripheral flow cytometry to rule out SS (including CD4, CD7, and CD26), and imaging with computed tomography or positron emission tomography. Clinically, progression includes both the onset of new skin disease (typically plaques or tumors) and the development of extracutaneous

Table 2. Selected Systemic Therapies Used for Cutaneous T-Cell Lymphomas

Medication	Authors	N	ORR, %	DOR
Bexarotene	Duvic et al ²⁴	56	45 (300 mg/m ²)	299 d
Vorinostat	Olsen et al ³⁵	74	30	≥185 d (estimated median DOR NR)
Romidepsin	Whittaker et al ³³ Piekarz et al ³⁴	96 71	34 34	15 mo 13.7 mo
Pralatrexate	Horwitz et al ⁴²	54	45	NR
Brentuximab vedotin vs physician's choice (methotrexate or bexarotene)	Prince et al ³⁶	128 (64 vs 64)	67 vs 20	15.1 vs 18.3 mo
Mogamulizumab vs vorinostat	Kim et al ³⁷	372 (186 vs 186)	28 vs 5	14.1 vs 9.1 mo

d, days; DOR, duration of response; mo, months; NR, not reached; ORR, overall response rate.

disease (eg, new lymph node involvement). We generally recommend additional skin biopsies at the time of skin progression. Workup of the repeat biopsy should include immunophenotyping (including CD2, CD3, CD4, CD5, CD7, CD8, CD20, and CD30) and molecular analysis to detect clonal T-cell receptor gene rearrangements.

Immunomodulatory Treatments

First-line systemic therapy includes immunomodulatory agents, which are relatively well tolerated, in conjunction with skin-directed therapy, such as topical corticosteroids. Oral bexarotene is a synthetic, selective retinoid agonist that has been demonstrated to have antiproliferative activity against tumor cells²³ and is an FDA-approved agent for refractory CTCL.²⁴ In a phase 2/3 trial of stage IIB to IVB refractory CTCL, 94 patients were treated with bexarotene (56 patients at 300 mg/m² daily and 38 patients at >300 mg/m² daily). The median duration of response was 7 to 9 months, and a regimen of 300 mg/m² daily was ultimately recommended. Major side effects include hypertriglyceridemia, hypercholesterolemia, and central hypothyroidism, which can be managed with supportive medications and are reversible once the drug is stopped or the dose is adjusted.²⁵ Bexarotene can be combined with radiation, phototherapy, or extracorporeal photopheresis (ECP).²⁶ ECP is particularly effective in patients with SS. In this process, leukocytes are taken from the patient, exposed to psoralen and UVA, and then reinfused to promote the apoptosis of malignant T-cell clones.^{27,28} Other available immunomodulatory agents are interferon alfa and interferon gamma, which lead to upregulation of the Th1 T-cell phenotype²⁹ and also can be combined with phototherapy or ECP. However, both agents are associated with side effects such as fever, flulike symptoms, weight loss, and fatigue. Additionally, neither

interferon has been studied for the treatment of CTCL in a phase 2 trial.

Low-dose methotrexate, an oral antifolate agent (<50 mg/wk orally), is also a treatment option for those with patch/plaque MF. In retrospective studies, methotrexate has shown a 33% ORR in 60 patients with stage T2 disease. Time to treatment failure was approximately 15 months (95% CI, 9-20).³⁰ The ORR was 58% in another, similar retrospective study of 29 patients who had erythrodermic CTCL, with 12 CRs (41%) and 5 PRs (17%). The median time of freedom from treatment failure was 31 months.³¹ Of note, the initial trials for bexarotene and methotrexate were conducted before implementation of the global response criteria. These consensus criteria for disease assessment incorporate a detailed assessment of the CTCL burden in lymph nodes and blood, as well as in skin, and provide a uniform method for staging disease response in clinical trials.³² When bexarotene and methotrexate were used as controls in prospective randomized trials, response rates were lower than previously reported, as detailed below and in Table 2.

Targeted Therapies

When disease progresses after first-line treatments, we often consider the use of targeted treatments. These include romidepsin, a class 1 histone deacetylase (HDAC) inhibitor that is FDA-approved for patients with refractory CTCL after 1 line of therapy. In the pivotal phase 2 trial, the ORR among 96 patients was 34%, including a CR rate of 6% (6/96), and the median duration of response was 15 months.³³ A second phase 2 trial in 84 patients showed an ORR of 33% (95% CI, 23%-46%), with a CR rate of 6% (5/84) and a median duration of response of 13.8 months.³⁴ Major adverse effects include gastrointestinal side effects, such as nausea (56%) and

dysgeusia (11%), and low blood cell counts, including thrombocytopenia (11%). Romidepsin can also prolong the corrected QT (QTc) interval. Correction of electrolyte abnormalities (eg, potassium and magnesium) during treatment is recommended. Another agent is vorinostat (Zolinza, Merck), an oral pan-class HDAC inhibitor, which is approved for the treatment of patients with refractory CTCL after 2 or more lines of therapy. This agent produced an ORR of 30% in 74 patients with MF/SS in the initial phase 2 study.³⁵

In recent years, 2 major antibody-based therapies have been effective in CTCL. Brentuximab vedotin is an antibody-drug conjugate that targets CD30, which is expressed on many MF cells and anaplastic large cell lymphomas. In the phase 3 ALCANZA study, patients with previously treated CD30-positive MF or primary cutaneous anaplastic large cell lymphoma were randomized to either brentuximab vedotin or physician's choice (methotrexate or bexarotene). ORRs were 67% (43/64) in the brentuximab vedotin arm and 20% (13/20) in the physician's choice arm.³⁶ Median progression-free survival (PFS) with brentuximab vedotin was also superior to PFS with physician's choice (16.7 vs 3.5 months; $P < .0001$). Although brentuximab vedotin was well tolerated overall, peripheral sensory neuropathy was reported in 67% of patients (44/66: 17 with grade 1 neuropathy, 21 with grade 2 neuropathy, and 6 with grade 3 neuropathy). Peripheral neuropathy developed in a total of 6% of patients (4/62) in the physician's choice arm. In most cases, this toxicity resolves with discontinuation of therapy. A total of 82% of patients (36/44) with neuropathy in the brentuximab vedotin group had a decrease of at least one grade or resolution of their symptoms. However, this toxicity is an important consideration when brentuximab vedotin is selected as a treatment for patients with existing risk factors for neuropathy and ultimately limits treatment duration in many cases.

Mogamulizumab (Poteligeo, Kyowa Kirin) is a humanized monoclonal antibody against C-C chemokine receptor 4 (CCR4), which is expressed on the surface of malignant T lymphocytes. In the phase 3 MAVORIC study, patients with previously treated MF or SS were randomized to either mogamulizumab or vorinostat.³⁷ The primary endpoint was PFS. Median PFS was 7.7 months (95% CI, 5.7-10.3) in the patients treated with mogamulizumab vs 3.1 months (95% CI, 2.9-4.1) in those receiving vorinostat. The ORR was also superior in the patients who received mogamulizumab: 21% (22/105) in the patients with MF treated with mogamulizumab vs 7% (7/99) in those with MF receiving vorinostat, and 37% (30/81) in those with SS receiving mogamulizumab vs 2% (2/87) in patients with SS who received vorinostat. The common adverse events associated with mogamuli-

zumab included infusion-related reactions (37%), skin eruptions (25%), and diarrhea (14%).

Both the ALCANZA and MAVORIC clinical trials used the global response criteria to assess the CTCL response to treatment.³² Earlier trials of first-line agents typically used skin assessments alone or other nonstandardized means of response assessment. Therefore, when the global response criteria were used for assessment, the response rates for some first-line agents used as controls (eg, vorinostat in MAVORIC and bexarotene and methotrexate in ALCANZA) were lower than previously reported.

Additional Options

Immunotherapy is a potential treatment strategy. In a phase 1 study of the anti-programmed death 1 (PD-1) monoclonal antibody nivolumab (Opdivo, Bristol Myers Squibb), including 13 patients with MF, the ORR was 15% (2/13).³⁸ The anti-PD-1 antibody pembrolizumab (Keytruda, Merck) demonstrated an ORR of 38% (9/24 patients) as a single agent in a phase 2 study. Toxicities were similar to those demonstrated in other studies of PD-1 inhibitors. One notable toxicity was an acute flare or worsening of erythema and pruritus in patients with SS.³⁹ Clinical trials are ongoing to evaluate immunotherapy in combination with other single agents.

Large cell transformation, defined as the presence of large cells in more than 25% of a biopsy specimen, can be seen in some subgroups of patients with MF and may represent more aggressive disease.⁴⁰ CD30 expression is associated with large cell transformation in 30% to 50% of cases, suggesting a role for brentuximab vedotin. Other targeted agents that may be beneficial include romidepsin and pralatrexate (Folotyn, Acrotech Biopharma), a folate analogue. In a trial of patients with peripheral T-cell lymphoma, 12 patients with MF were treated with pralatrexate at 30 mg/m² for 6 weeks, followed by 1 week off, in a 7-week cycle. The ORR in this trial was 25% by independent review and 58% by investigator assessment. The median duration of response was 4 months.⁴¹ In a subsequent trial, patients with refractory or relapsed CTCL who received pralatrexate at 15 mg/m² according to a schedule of 3 of every 4 weeks had an ORR of 45%, including patients previously treated with methotrexate.⁴²

Finally, although our preference is to use targeted therapy, single-agent chemotherapy also may be effective in patients with large cell transformation. Gemcitabine has shown ORRs of 68% (17/25 patients) and 75% (24/32 patients) in phase 2 studies of patients with CTCL.^{43,44} Liposomal doxorubicin had an ORR of 41% (20/49) in patients with advanced MF in a phase 2 trial, with a time to progression of 7 months.⁴⁵ Another prospective

study reported an ORR of 56% in 25 patients receiving pegylated liposomal doxorubicin.⁴⁶

Conclusion

Despite recent advances and the development of new drugs, MF and SS often remain indolent yet incurable diseases. Appropriate treatment should be directed at producing the most effective and durable response while minimizing treatment-associated toxicities and maintaining quality of life. Trials are under way to determine appropriate combinations of targeted, immune, and antibody-based therapies, along with skin-directed therapy. For patients with refractory cases of CTCL, we recommend enrollment in clinical trials whenever possible. Ultimately, an interdisciplinary approach is essential that involves medical oncologists, dermatologists, radiation oncologists, and pathologists, and that incorporates multiple treatment modalities.

Disclosures

Dr Khan has received research funding from Seagen. Dr Noor has served on the medical advisory board for Kyowa Kirin. Dr Horwitz has consulted for, received honoraria from, or participated in advisory boards for Acrotech Biopharma, C4 Therapeutics, Kyowa Kirin, Myeloid Therapeutics, ONO Pharmaceuticals, Seagen, SecuraBio, Shoreline Biosciences, Takeda, Trillium Therapeutics, Tubulis, and Vividion Therapeutics. In addition, Dr Horwitz has received research support for clinical trials from ADC Therapeutics, Affimed, Celgene, Daiichi Sankyo, Kyowa Kirin, Millennium/Takeda, Seagen, and Verastem/SecuraBio.

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