

# Review of the Treatment of Mycosis Fungoides and Sézary Syndrome: A Stage-Based Approach

Steven M. Horwitz, MD;<sup>a</sup> Elise A. Olsen, MD;<sup>b</sup> Madeleine Duvic, MD;<sup>c</sup> Pierluigi Porcu, MD;<sup>d</sup> and Youn H. Kim, MD,<sup>e</sup>  
New York, New York; Durham, North Carolina; Houston, Texas; Columbus, Ohio; and Stanford, California

## Key Words

Mycosis fungoides, Sézary syndrome, cutaneous T-cell lymphoma

## Abstract

The NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Disease were recently revised to include recommendations for treating mycosis fungoides and Sézary syndrome. These uncommon lymphomas require a specialized evaluation and use a unique TNMB staging system. Unlike the other forms of non-Hodgkin's lymphomas, stage overwhelmingly determines prognosis and defines radically different treatment approaches. For patients with early-stage disease, initial treatment with skin-directed therapies is preferred, and many patients never require systemic therapy. For patients with refractory or advanced-stage disease, biologic therapies are often the first choices, whereas chemotherapies are reserved for later in the disease course. Many milder therapies may be repeated several times in the disease course, and maintenance and tapering strategies are common. This article also discusses the emerging role of allogeneic stem cell transplantation. (*JNCCN* 2008;6:436–442)

**M**ycosis fungoides (MF), and its leukemic variant Sézary syndrome (SS), are the most common forms of cutaneous T-cell lymphoma (CTCL). The annual incidence of CTCL (more broadly defined than MF/SS) is reportedly increasing and currently estimated at 9.6 cases per 1 million person-years.<sup>1</sup> The long-term survival of most pa-

tients results in a much higher overall prevalence. In 2007, the NCCN created its first guidelines on MF/SS. There are not sufficient randomized studies to recommend a preferred treatment strategy for MF/SS, nor do universally accepted standard treatments exist. The chronicity of the disease results in many patients being treated with multiple therapies in their lifetime, including: skin-directed therapies, such as ultraviolet light, topicals, and radiation; an increasing armamentarium of systemic agents ranging from retinoids to other biologics to chemotherapy; and an emerging role for allogeneic stem cell transplantation. Thus, the algorithms of these guidelines are complex. This article overviews the approach to diagnosis and discusses the critical importance of stage-based prognosis and its logical sequelae, stage-based therapy. It does not provide a detailed review of the data behind all therapies or choices of therapies presented in the guidelines.

## Clinical Features and Diagnosis

Patients with MF/SS present with patch, plaque, tumor, or erythrodermic involvement on their skin<sup>2,3</sup> (Figure 1). The most classic presentation involves poikilodermatous (epidermal atrophy often with telangiectasia, pigment alteration) patches in the “bathing trunk” distribution. However, many clinical and histologic variants or subtypes have atypical or unique clinical presentations, such as hypopigmented/vitiliginous MF, Woringer-Kolopp disease (pagetoid reticulosis), folliculocentric (+/- follicular mucinosis) MF, granulomatous MF, pigmented purpuric eruption-like MF, interstitial MF, and papular MF.<sup>2</sup> Patients often present with more than 1 type of skin involvement (e.g., patches and plaques or patches, plaques, and tumor lesions). This polymorphic skin involvement is important to acknowledge when determining the

From <sup>a</sup>Memorial Sloan-Kettering Cancer Center, New York, New York; <sup>b</sup>Duke University, Durham, North Carolina; <sup>c</sup>M. D. Anderson Cancer Center, Houston, Texas; <sup>d</sup>Ohio State University, Columbus, Ohio; and <sup>e</sup>Stanford University, Stanford, California.

Submitted December 23, 2007; accepted for publication February 13, 2008.

Dr. Horwitz serves as a consultant for and receives honoraria from Merck & Co., Inc., THERAKOS, Inc., and Eisai Pharmaceuticals. Drs. Olsen, Duvic, Porcu, and Kim have no financial interest, arrangement, or affiliation with the manufacturers of any products discussed in the article or their competitors.

Correspondence: Steven M. Horwitz, MD, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.  
E-mail: horwitzs@mskcc.org

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**Figure 1** Representative photographs of presenting skin lesions in patients with mycosis fungoides. All lesions are categorized as patch, plaque, tumor, or erythroderma. The type of skin lesions present are important in determining stage and planning therapy.

optimal treatment strategy. For example, patients who have primary patch/plaque disease with limited skin tumors are often managed with treatment options used for the patch/plaque disease combined with local radiation therapy to the tumor lesions. Patients may undergo changes in their primary type of skin involvement (e.g., present with tumor disease but have mostly patches/plaques after treatment [or visa-versa]) or progress to extracutaneous involvement; thus, the management strategy should be modified accordingly.

SS is a leukemic form of CTCL in which patients have significant blood involvement with Sézary cells and diffuse skin erythema (erythroderma). Lymphadenopathy is a frequent finding in patients with SS, and can range from reactive dermatopathic changes to frank lymphoma on histopathologic examination. Additional clinical findings commonly seen in SS include keratoderma, nail dystrophy, alopecia, ectropion, and skin edema (especially in the legs). These patients often experience intractable itching (pruritus), which can be the most significant life-altering symptom, and therefore treatments that can successfully reduce pruritus even without measurable objective response may still be a valuable option.

MF is suspected in patients who present with years of refractory or recurrent skin eruption with

a poikilodermatous or polymorphic skin involvement in typical distribution. SS should be suspected in patients with unexplained erythroderma associated with atypical lymphocytes in their blood. In MF or SS, clinicians must rule out drug reactions that can mimic the clinical or histologic appearance (lymphomatoid drug eruptions). As specified in the NCCN guidelines on non-Hodgkin's lymphomas (NHL; in this issue; to view the most recent version, please visit [www.nccn.org](http://www.nccn.org)), some diagnostic evaluations are considered essential and some useful under certain circumstances.<sup>4,5</sup> The key element of diagnosis is the skin biopsy reviewed by a dermatopathologist. However, skin biopsies of patients with erythrodermic skin involvement often do not have well-established diagnostic features; thus, assessment of other sites of potential involvement, such as blood or lymph nodes, may help confirm the clinical diagnosis. In MF and SS, it is important to know when to obtain ancillary immunohistochemical or molecular studies (because of false-positive and -negative cases) and to learn how to interpret and incorporate the information for optimal clinical pathologic diagnosis.<sup>6</sup> Ancillary tests should be performed when routine histology is not diagnostic but a high clinical suspicion of MF or SS exists.

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## Staging and Prognosis

After the diagnosis is established, appropriate staging workup should be obtained before treatment options are considered. Accurate staging is important because therapeutic strategies in MF are primarily based on the clinical stage of the disease. Most staging studies described in the NCCN guidelines are essential, including comprehensive skin examination, peripheral blood evaluation for Sézary cells, and appropriate imaging studies.<sup>4,5</sup> The bone marrow biopsy nonessential evaluation which can be considered in patients believed to have marrow involvement, including those with SS. The staging workup recommended by NCCN institutions is consistent with the guidelines in the consensus document of the revised staging in MF/SS proposed by the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the EORTC.<sup>5</sup> In the revised staging system (Tables 1 and 2), blood involvement (B classification) is incorporated into the overall clinical stage because cumulative prognostic data show that SS level of blood tumor burden (B2) is associated with compromised survival equivalent to frank nodal lymphoma.<sup>3,7,8</sup>

Several large studies have shown that the most significant prognostic factors in MF include type and extent of skin involvement (T classification) and presence or absence of extracutaneous disease (NMB classifications), which determine overall clinical stage (Figures 2 and 3).<sup>3,9-11</sup> Patients with limited patch and/or plaque disease (stage IA) have a very favorable long-term outcome; life expectancy is not altered compared with matched control population involvement. Patients with disease limited to generalized patch and/or plaque involvement (stage IB/IIA) have a median survival of 11 to 12 years, with fewer than 20% experiencing progression to a worse TNMB stage. Patients diagnosed with tumor disease (T3) or erythroderma (T4) have a worse overall outcome, with median survivals of 4 to 5 years. The actual survivals of patients with T3/T4 disease also depend on other prognostic variables, such as large-cell transformation or blood involvement. These patients are also at a greater risk for developing extracutaneous disease. Those who either present with or develop extracutaneous disease have the

**Table 1 Revised Components and Definitions of TNM Staging for Mycosis Fungoides/Sézary Syndrome**

<b>T (Skin)</b>		<b>N (Nodes)</b>	
T1	Limited patch/plaque (< 10% of total skin surface)	N0	No clinically abnormal LNs
T2	Generalized patch/plaque (≥ 10% of total skin surface)	N1	Clinically abnormal LNs; histopathology Dutch grade 1 or NCI LN0-2 (clone +/-)
T3	Tumors	N2	Clinically abnormal LNs; histopathology Dutch grade 2 or NCI LN3 (clone +/-)
T4	Generalized erythroderma	N3	Clinically abnormal LNs; histopathology Dutch grade 3-4 or NCI LN4 (clone +/-)
		Nx	Clinically abnormal LNs, no histopathology info
<b>M (Viscera)</b>		<b>B (Blood)</b>	
M0	No visceral involvement	B0*	No significant blood involvement
M1	Visceral involvement	B1†	Low blood tumor burden
		B2‡	High blood tumor burden

• CD4/CD8 ratio ≥ 10 (setting of an expanded CD4), or CD4+CD7- cells ≥ 40% or CD4+CD26- ≥ 30% of lymphocytes, or other aberrant expression of pan T-cell markers

\*Sézary cells ≤ 5% lymphs.

†Sézary cells > 5% lymphs, but < 1000 /mm<sup>3</sup> by morphology, lack of other B2 parameters.

‡Sézary syndrome, ≥ 1 of following parameters: morphology, positive relevant clone and Sézary cells ≥ 1000 /mm<sup>3</sup>, relevant clone+, or Immunophenotypic abnormalities (flow cytometry)

Abbreviations: LN, lymph node; NCI, National Cancer Institute.

This research was originally published in Blood. Olsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the staging and classification of mycosis fungoides and Sézary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110: 1713-1722. ©the American Society of Hematology.

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**Table 2 Revised TNM Staging for Mycosis Fungoides/Sézary Syndrome**

Clinical Stages		TNM Classification			
IA	T1	N0	M0	B0-1	
IB	T2	N0	M0	B0-1	
IIA	T1-2	N1-2	M0	B0-1	
IIB	T3	N0-2	M0	B0-1	
IIIA	T4	N0-2	M0	B0	
IIIB	T4	N0-2	M0	B1	
IVA	T1-4	N0-3	M0	B0-2	
IVB	T1-4	N0-3	M1	B0-2	

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worst outcome, with median survivals of 1.5 to 3 years.<sup>3,5</sup>

In addition to the unfavorable prognostic association of blood involvement, the proposed revised staging system<sup>5</sup> recognizes additional prognostic factors, including histologic subtypes that have been associated with a worse outcome, namely folliculocentric

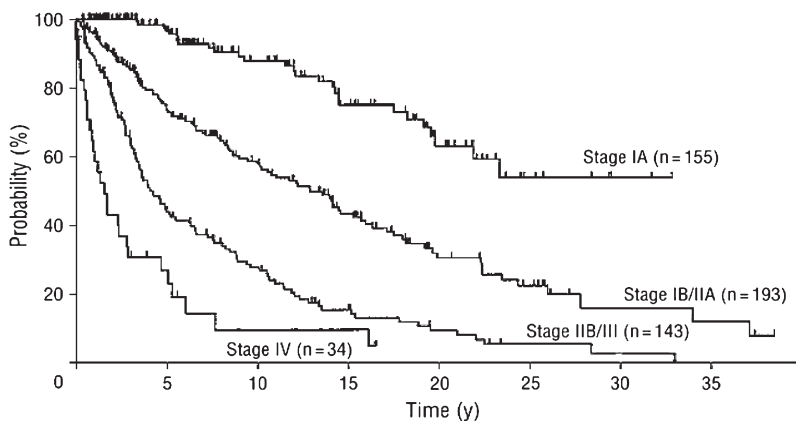
and transformed MF (> 25% large cells, +/- CD30+).<sup>12-14</sup> These additional prognostic variables should be considered when deciding appropriate management, as shown in the NCCN guidelines.

### Treatment Selection Factors

Choosing appropriate treatment is based primarily on major prognostic factors, TMNB classification, and overall clinical stage.<sup>4</sup> However, other prognostic variables, such as folliculocentric involvement or large cell transformation, should also be considered. Additional factors in treatment selection include acuity or severity of associated symptoms (e.g., pruritus, tumor ulceration), data on efficacy (response rate), time to and duration of treatment response, comorbidities and data on treatment-related toxicities, and accessibility or cost-benefit features of treatments.

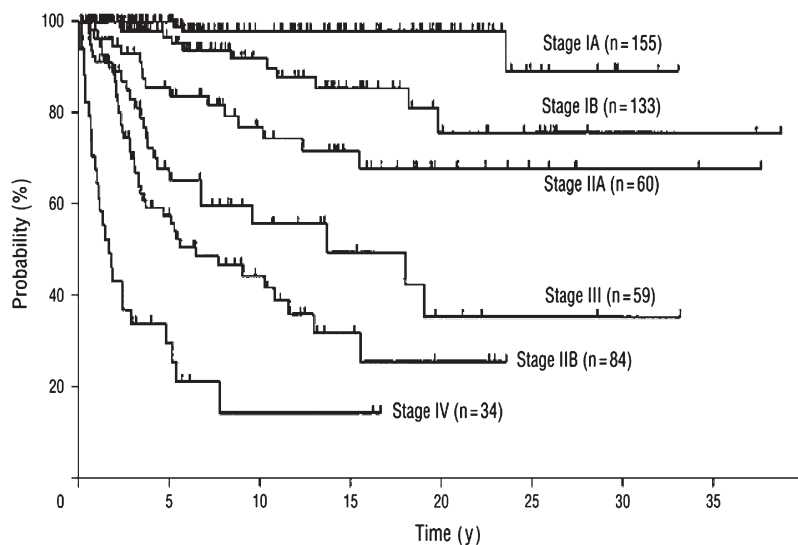
Patients with stage I (patch/plaque) disease, who constitute two thirds of the newly diagnosed with excellent prognosis, require only skin-directed therapy options as primary treatment, and many will never require systemic therapy. For these patients who have additional poor prognostic factors (e.g., folliculocentric MF, large-cell transformation, B1 blood involvement), treatment may be intensified with the combination of skin-directed therapies or skin-directed plus systemic therapy.<sup>4</sup> Patients with stage IIB (tumor) disease may require total skin electron beam therapy, a combination of skin-directed plus systemic therapy, or systemic therapy alone, depending on symptom severity and other prognostic factors. Because those with erythrodermic skin (T4, stage III) can be sensitive to most skin-directed therapies other than topical steroids, these should be used with caution. A systemic therapy option is indicated for patients who have any blood involvement.

Patients with SS (T4B2, stage IVA) require intensive systemic therapy because of associated poor prognosis. Single or a combination of biologic treatment with agents, denileukin diftitox, histone deacetylase inhibitor, or methotrexate may be considered as a primary treatment option. Because these patients may have severe, intractable



**Figure 2** Actuarial overall survival of 525 patients with mycosis fungoides/Sézary syndrome according to TNM stage at diagnosis (stages IA–IV). Clinical stage and T score, which are the primary determinants of stage, are the most important factors in determining prognosis. Choice of therapy is heavily determined by stage. From Kim YH, Liu HL, Mraz-Gernhard S, et al. Long-term outcome of 525 patients with mycosis fungoides and Sézary syndrome: clinical prognostic risk factors for disease progression. *Arch Dermatol* 2003;139:857–866. Copyright © 2003, American Medical Association. All Rights reserved.

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**Figure 3** Disease-specific survival of 525 patients with mycosis fungoides/Sézary syndrome according to TNM stage. Patients with early-stage disease have excellent disease-specific survival, with most dying of causes other than mycosis fungoides/Sézary syndrome. Patients with advanced-stage disease usually die of their lymphoma. From Kim YH, Liu HL, Mraz-Gernhard S, et al. Long-term outcome of 525 patients with mycosis fungoides and Sézary syndrome: clinical prognostic risk factors for disease progression. *Arch Dermatol* 2003;139:857–866. Copyright © 2003, American Medical Association. All Rights reserved.

pruritus, supportive anti-itch treatments such as antihistamines, gabapentin, or mirtazapine may be helpful. Aggressive topical steroid treatment (+/- occlusive wraps or suits) can often significantly improve symptoms. Secondary skin infections are common because of frequent scratching and compromised skin. Patients may benefit from long-term oral antibiotics and periodic cultures to rule out methicillin-resistant *Staphylococcus aureus* or other atypical microbes if symptoms are not controlled.

Chemotherapy regimens are most appropriate in patients with bulky lymph node or visceral disease or as salvage therapy when other options have failed. Single agents are often attempted before combination regimens. After tumor reduction with combination chemotherapy, maintenance with biologic therapy (e.g., bexarotene, interferon) may be considered to optimize response duration.

Several management concepts unique in MF/SS must be emphasized. Patients who experience complete response with a primary therapy may undergo the same treatment if they experience disease relapse; patients who respond well to an initial primary therapy tend to respond well again to the same therapy. Unmaintained remissions in MF/SS are uncommon, particularly in patients requiring systemic therapy. In patients experiencing clinical response, maintenance

and/or tapering schedules should be incorporated to optimize response duration, balancing long-term toxicity and cost issues. No studies show that one particular therapy can positively impact survival in MF/SS. Thus, as a general guideline, less-toxic therapies, such as skin-directed therapies or biologics, usually yield longer disease control and less risk to the patient than more active agents such as chemotherapy, which cannot be maintained because of cumulative side effects.

### Skin-Directed Therapy

A list of the most commonly used skin-directed therapies are included in the NCCN guidelines (in this issue; to view the most recent version, please visit [www.nccn.org](http://www.nccn.org)).<sup>4</sup> If patients have limited patch/plaque (T1) disease, topical

steroids are commonly used as initial therapy. However, if one primary treatment fails, other options in the primary therapy list should be tried, including topical nitrogen mustard, topical retinoids, and phototherapy. Local radiation therapy may be used in patients with unilesional presentation or those with recalcitrant or aggressive local disease. Narrow-band UVB (nbUVB) can be highly effective for patients with patch or thin plaque disease. Psoralen plus UVA (PUVA) may be more effective in patients with thicker plaques, although it has a greater long-term phototoxicity and risk for secondary UV-associated skin cancer than nbUVB. Total skin electron beam therapy, considered the most intensive skin-directed therapy, is reserved for patients with extensive generalized disease and severe skin symptoms. Although the reliability of clinical response is greater with more intensive skin-directed treatments, no data show that more aggressive therapies are associated with improved progression-free or overall survival.

Combinations of skin-directed therapies (either alone or in combination with systemic therapy) are indicated when monotherapy fails, with severe skin symptoms, or in the presence of other unfavorable prognostic factors. In patients with advanced clinical stage ( $\geq$  IIB), most skin-directed therapies are used as combination strategy or adjuvant support. After

maximal response, maintenance or taper regimen can be initiated, tailored for the patient and specific therapy.

### Systemic Therapy: Category A

When managing patients with MF/SS, initial systemic therapies are most commonly mild immunomodulating agents (biologics) broadly defined as category A. These therapies have a slow time to response and generally provide partial response rates no greater than 50%.<sup>15-17</sup> Their prime advantages are little to no immunosuppression and lack of cumulative toxicity, allowing them to be used to maintain remissions for long periods, unlike combination chemotherapies. These systemic therapies are most commonly used when skin-directed therapies do not provide adequate control in patients with stage IB or IIA disease, or as primary therapy (often in combination with skin-directed therapy or other biologics) for those with more advanced disease (stage IIB-IV). No comparative studies guide initial choice of systemic therapy, and many patients are managed with a combination approach.<sup>18,19</sup> For example, patients who start on bexarotene may frequently have interferon added if the response is suboptimal, or vice versa. Extracorporeal photopheresis is most commonly used for patients with SS, and frequently in combination with interferon or bexarotene or both.<sup>20-22</sup> Choice of initial therapy involves factors such as side effect profile, route of administration, accessibility, and cost. Most patients will undergo multiple category A therapies in sequence or combination before proceeding to more traditional cytotoxic chemotherapy.

### Systemic Therapy: Category B

Many chemotherapeutics show good activity in patients with MF/SS. Compared with biologics, they have the advantage of shorter times to response and higher response rates.<sup>23,24</sup> However, frequent immunosuppression and subsequent toxicity and cumulative toxicities that prevent a maintenance strategy have relegated combination chemotherapy to use only in patients with the most advanced stage or refractory disease. Several single agents, such as liposomal doxorubicin and gemcitabine,<sup>25,26</sup> have recently been used as common initial chemotherapeutic choices. These agents, along with older chemotherapies such as chlorambucil, can be used in low enough doses to minimize the risks for myelosuppression and can often be con-

tinued for extended periods. Patients often move from one single agent to another before proceeding to combination chemotherapies or referral for transplantation.

### Systemic Therapy: Other

Alemtuzumab recently showed activity, particularly in patients with SS. The first reports described significant infectious toxicity, which appeared to limit its use.<sup>27</sup> More recent reports, including those using lower doses, suggest that alemtuzumab can be used safely, although the authors generally reserve this drug for patients with advanced SS who have experienced progression after biologic therapies.<sup>28,29</sup> Emerging data on allogeneic hematopoietic stem cell transplant (HSCT), particularly using nonmyeloablative conditioning, suggest the existence of a graft-versus-T-cell lymphoma effect.<sup>30</sup> Allogeneic HSCT may be considered for patients with advanced disease ( $\geq$  stage IIB) whose disease fails to respond to all primary therapy options or who do not experience durable responses with any primary or salvage therapies. Long-term remission and potential curative outcomes have been shown in selected patients.<sup>30</sup> The timing of the allogeneic HSCT remains controversial, because some patients whose disease progresses rapidly to severely recalcitrant disease become ineligible. However, early exposure of patients to this high-risk procedure is not advisable. Finally, all patients whose disease fails to respond to primary treatment options should be considered for clinical trials.

### Conclusions

Patients with MF/SS are increasingly managed by oncologists, and therefore how approaches for these lymphomas differ from those of other NHLs is important to understand. Unlike other NHLs, which use the Ann Arbor staging system, MF/SS uses a TNM staging that is critical to understand, because prognosis varies widely according to stage. Accordingly, treatment is also staged-based, and many patients with early-stage disease experience lifelong control with skin-directed therapies and never require systemic therapy. Compared with other NHLs, unmaintained remissions are uncommon and milder biologic therapies, often in combination, are frequently used chronically. These agents are often different than those used for other NHLs and several are unique to

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MF/SS. Conventional chemotherapies are reserved for patients whose disease is more advanced and refractory.

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