Mycosis Fungoides and the Sézary Syndrome Treatment (PDQ®): Treatment - Health Professional Information [NCI]

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General Information About Mycosis Fungoides and the Sézary Syndrome

Clinical Presentation

Mycosis fungoides and the Sézary syndrome (MF/SS) are neoplasias of malignant T lymphocytes that usually possess the helper/inducer cell surface phenotype. These kinds of neoplasms initially present as skin involvement and, as such, have been classified as cutaneous T-cell lymphomas.[1] These types of lymphomas are included in the Revised European-American Lymphoma classification as low-grade T-cell lymphomas, which should be distinguished from other T-cell lymphomas that involve the skin, such as anaplastic large cell lymphoma (CD30 positive), peripheral T-cell lymphoma (CD30 negative, with no epidermal involvement), adult T-cell leukemia/lymphoma (usually with systemic involvement), or subcutaneous panniculitic T-cell lymphoma.[2,3] These histologic types of T-cell lymphomas are discussed in another PDQ summary. (Refer to the PDQ summary on Adult Non-Hodgkin Lymphoma Treatment for more information.) In addition, a number of benign or very indolent conditions can be confused with mycosis fungoides. Consultation with a pathologist who has expertise in distinguishing these conditions is important.[4]

Prognosis and Survival

The prognosis of patients with MF/SS is based on the extent of disease at presentation (stage).[5] The presence of lymphadenopathy and involvement of peripheral blood and viscera increase in likelihood with worsening cutaneous involvement and define poor prognostic groups.[5,6,7] The median survival following diagnosis varies according to stage. Patients with stage IA disease have a median survival of 20 or more years. Most deaths for this group are not caused by, nor are they related to, MF.[8] In contrast, more than 50% of patients with stage III through stage IV disease die of MF, with a median survival of less than 5 years.[7,9,10] A report on 1,798 patients from the National Cancer
Institute's Surveillance, Epidemiology, and End Results Program (SEER) database found an increase in second malignancies (standardized incidence ratio of 1.32; 95% confidence interval, 1.15-1.52), especially for Hodgkin lymphoma, non-Hodgkin lymphoma, and myeloma.[11]

Typically, the natural history of MF is indolent.[12] Symptoms of the disease may present for long periods, an average of 2 to 10 years, as waxing and waning cutaneous eruptions before biopsy confirmation. MF/SS is treatable with available topical and/or systemic therapies. Curative modalities, however, have thus far proven elusive, with the possible exception of patients with minimal disease confined to the skin.

Cutaneous disease typically progresses from an eczematous patch/plaque stage covering less than 10% of the body surface (T1) to plaque stage covering 10% or more of the body surface (T2), and finally to tumors (T3) that frequently undergo necrotic ulceration.[4,13] A retrospective study with a median follow-up of 14.5 years showed that 20% of the 1,422 patients progressed from stage I or II disease to stage III or IV disease.[14] SS presents with generalized erythroderma (T4) and peripheral blood involvement. However, there is some disagreement about whether the MF and SS are actually variants of the same disease.[15] The same retrospective study with a median follow-up of 14.5 years found that only 3% of 1,422 patients progressed from MF to SS.[14] There is consensus that patients with SS have a poor prognosis (median survival of 4 years).[16] Cytologic transformation from a low-grade lymphoma to a high-grade lymphoma (large-cell transformation) occurs rarely (<5%) during the course of these diseases and is associated with a poor prognosis.[17,18,19] A retrospective analysis of 100 cases with large-cell transformation found reduced disease-specific survival with extracutaneous transformation, increased extent of skin lesions, and CD30 negativity.[20] A common cause of death during the tumor phase is sepsis from Pseudomonas aeruginosa or Staphylococcus aureus caused by chronic skin infection with staph species and subsequent systemic infections.[13]

References:

5. Agar NS, Wedgeworth E, Crichton S, et al.: Survival outcomes and prognostic factors in mycosis fungoides/Sézary syndrome: validation of the revised


Cellular Classification of Mycosis Fungoides and the Sézary Syndrome

The histologic diagnosis of mycosis fungoides and the Sézary syndrome (MF/SS) is usually difficult to determine in the initial stages of the disease and may require the review of multiple biopsies by an experienced pathologist.

A definitive diagnosis from a skin biopsy requires the presence of MF/SS cells (convoluted lymphocytes), a band-like upper dermal infiltrate, and epidermal infiltrations with Pautrier abscesses (collections of neoplastic lymphocytes). A definitive diagnosis of SS may be made from a peripheral blood evaluation when skin biopsies are consistent with the diagnosis. Supportive evidence for circulating Sézary cells is provided by T-cell receptor gene analysis, identification of the atypical lymphocytes with hyper-convoluted or cerebriform nuclei, and flow cytometry with the characteristic deletion of cell surface markers such as CD7 and CD26. However, none of these is individually pathognomonic for lymphoma.[1,2]

References:

Stage Information for Mycosis Fungoides and the Sézary Syndrome

The stages that follow are defined by TNM classification. Peripheral blood involvement with mycosis fungoides or Sézary syndrome (MF/SS) cells is correlated with more advanced skin stage, lymph node and visceral involvement, and shortened survival.

MF/SS have a formal staging system proposed by the International Society for Cutaneous Lymphomas (ISCL) and the European Organization of Research and Treatment of Cancer (EORTC).[1,2]

Definitions of TNM

The American Joint Committee on Cancer (AJCC) has designated staging by TNM classification to define MF.[3]
<table>
<thead>
<tr>
<th>Skin</th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>T1</strong></td>
<td>Limited patches,(^b) papules, and/or plaques(^c) covering &lt;10% of the skin surface. May further stratify into T1a (patch only) vs. T1b (plaque ± patch).</td>
</tr>
<tr>
<td><strong>T2</strong></td>
<td>Patches, papules, or plaques covering ≥10% of the skin surface. May further stratify into T2a (patch only) vs. T2b (plaque ± patch).</td>
</tr>
<tr>
<td><strong>T3</strong></td>
<td>≥1 tumor(^d)(≥1 cm diameter).</td>
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</tbody>
</table>

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\(^b\) For skin, patch indicates any size skin lesion without significant elevation or induration. Presence/absence of hypo- or hyperpigmentation, scale, crusting, and/or poikiloderma should be noted.

\(^c\) For skin, plaque indicates any size skin lesion that is elevated or indurated. Presence or absence of scale, crusting, and/or poikiloderma should be noted. Histologic features such as folliculotropism or large-cell transformation (>25% large cells), CD30+ or CD30-, and clinical features, such as ulceration, are important to document.

\(^d\) For skin, tumor indicates at least 1 cm diameter solid or nodular lesion with evidence of depth and/or vertical growth. Note total number of lesions, total volume of lesions, largest size lesion, and region of body involved. Also, note if histologic evidence of large cell transformation has occurred. Phenotyping for CD30 is encouraged.

\(^e\) For node, abnormal peripheral lymph node(s) indicates any palpable peripheral node that on physical examination is firm, irregular, clustered, fixed, or ≥1.5 cm in diameter. Node groups examined on physical examination include: cervical, supraclavicular, epitrochlear, axillary, and inguinal. Central nodes, which are not generally amenable to pathologic assessment, are not currently considered in the nodal classification unless used to establish N3 histopathologically.

\(^f\) A T-cell clone is defined by polymerase chain reaction or Southern blot analysis of the T-cell receptor (TCR) gene.

\(^g\) For viscera, spleen and liver may be diagnosed by imaging criteria.

\(^h\) For blood, Sézary cells are defined as lymphocytes with hyper-convoluted cerebriform nuclei. If Sézary cells are not able to be used to determine tumor burden for B2, then one of the following modified ISCL criteria along with a positive clonal rearrangement of the TCR may be used instead: (1) expanded CD4+ or CD3+ cells with CD4/CD8 ratio of ≥10; and (2) expanded CD4+ cells with abnormal immunophenotype, including loss of CD7 or CD26.
<table>
<thead>
<tr>
<th><strong>Skin</strong></th>
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<tr>
<td><strong>T4</strong></td>
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<table>
<thead>
<tr>
<th><strong>Node</strong></th>
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<tbody>
<tr>
<td><strong>N0</strong></td>
</tr>
<tr>
<td><strong>N1</strong></td>
</tr>
<tr>
<td><strong>N1a</strong></td>
</tr>
</tbody>
</table>

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### Skin

<p>| | |</p>
<table>
<thead>
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</table>
| N1b | Clone positive.  
  f |
| N2  | Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN3. |
| N2a | Clone negative.  
  f |
| N2b | Clone positive.  
  f |

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g For viscera, spleen and liver may be diagnosed by imaging criteria.

h For blood, Sézary cells are defined as lymphocytes with hyper-convoluted cerebriform nuclei. If Sézary cells are not able to be used to determine tumor burden for B2, then one of the following modified ISCL criteria along with a positive clonal rearrangement of the TCR may be used instead: (1) expanded CD4+ or CD3+ cells with CD4/CD8 ratio of ≥10; and (2) expanded CD4+ cells with abnormal immunophenotype, including loss of CD7 or CD26.
### Skin

<table>
<thead>
<tr>
<th>N3</th>
<th>Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3-4 or NCI LN4; clone positive or negative.</th>
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<tbody>
<tr>
<td>Nx</td>
<td>Clinically abnormal peripheral lymph nodes; no histologic confirmation.</td>
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</table>

### Visceral

| M0 | No visceral organ involvement. |

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<table>
<thead>
<tr>
<th><strong>Skin</strong></th>
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<tr>
<td><strong>M1</strong></td>
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</table>

**Peripheral Blood Involvement**

<table>
<thead>
<tr>
<th><strong>B0</strong></th>
<th>Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes are atypical (Sézary) cells.</th>
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<tbody>
<tr>
<td><strong>B0a</strong></td>
<td>Clone negative.</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>B0b</td>
</tr>
<tr>
<td>B1</td>
</tr>
<tr>
<td>B1a</td>
</tr>
<tr>
<td>B1b</td>
</tr>
</tbody>
</table>

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**Skin**

<table>
<thead>
<tr>
<th>B2</th>
<th>High blood-tumor burden: ≥1,000/μL Sézary cells(^h) with positive clone.(^f)</th>
</tr>
</thead>
</table>

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Table 2. Anatomic Stage/Prognostic Groups\textsuperscript{a, b}

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>Peripheral Blood Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0, 1</td>
</tr>
<tr>
<td>IB</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0, 1</td>
</tr>
<tr>
<td>IIA</td>
<td>1, 2</td>
<td>1, 2</td>
<td>0</td>
<td>0, 1</td>
</tr>
<tr>
<td>IIB</td>
<td>3</td>
<td>0-2</td>
<td>0</td>
<td>0, 1</td>
</tr>
<tr>
<td>III</td>
<td>4</td>
<td>0-2</td>
<td>0</td>
<td>0, 1</td>
</tr>
<tr>
<td>IIIA</td>
<td>4</td>
<td>0-2</td>
<td>0</td>
<td>0</td>
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<tr>
<td>IIIB</td>
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<td>0-2</td>
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<td>1</td>
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<td>IVA2</td>
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<td>0</td>
<td>0-2</td>
</tr>
<tr>
<td>IVB</td>
<td>1-4</td>
<td>0-3</td>
<td>1</td>
<td>0-2</td>
</tr>
</tbody>
</table>

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\textsuperscript{b} Adapted from Olsen et al.[1]

Clinical trials have assessed the extent of skin involvement using detailed scoring systems such as the modified Severity-Weighted Assessment Tool (mSWAT).[4]

References:


Treatment Option Overview

Treatment options for patients with mycosis fungoides and the Sézary syndrome (MF/SS) include the following:[1,2,3]

1. Topical corticosteroids.
2. Topical chemotherapy with mechlorethamine (nitrogen mustard) or carmustine (BCNU).
3. Psoralen and ultraviolet A radiation (PUVA).
4. Ultraviolet B radiation (UVB).
5. Total-skin electron-beam radiation (TSEB).
6. Radiation of symptomatic skin lesions.
7. Interferon alpha or interferon gamma alone or in combination with topical therapy.
9. Bexarotene (topical gel or oral); retinoids.
10. Denileukin diftitox (recombinant fusion protein of diphtheria toxin fragments and interleukin-2 sequences).
11. Vorinostat or romidepsin or other histone deacetylase inhibitors.
12. Pralatrexate (folate analog).[4]
13. Alemtuzumab (a humanized monoclonal antibody targeting the CD52 antigen).

These types of treatments produce remissions, but long-term remissions are uncommon. Treatment, therefore, is considered palliative for most patients, although major symptomatic improvement is regularly achieved. Survival in excess of 8 years, however, is common for patients with early stages of disease. All patients with MF/SS are candidates for clinical trials evaluating new approaches to treatment.

Current areas of interest in clinical trials for MF confined to the skin include combined-modality therapies containing both topical and systemic agents such as TSEB combined with chemotherapy, topical mechlorethamine or PUVA combined with interferon, or wide-field radiation techniques with PUVA. Reports are available of activity for extracorporeal photochemotherapy using psoralen; interferon gamma or interferon alpha; pentostatin; retinoids; fludarabine; acyclovir; 2-chlorodeoxyadenosine; serotherapy with unlabeled, toxin-labeled, or radiolabeled monoclonal antibodies; cell surface receptor ligand-toxin fusion protein; and, methotrexate.[3,5,6,7,8,9,10,11,12,13,14] Antigen-specific vaccination using dendritic cells [15] and UVB are also under clinical evaluation.

References:


Stage I Mycosis Fungoides

Because several forms of treatment can produce complete resolution of skin lesions in this stage, the choice of therapy is dependent on local expertise and the facilities available. With therapy, the survival of patients with stage IA disease can be expected to be the same as age and gender-matched controls.[1,2]

Treatment options:[3]

1. Psoralen and ultraviolet A radiation (PUVA). Therapeutic trials with PUVA have shown a 62% to 90% complete remission rate with early cutaneous stages achieving the best responses. Continued maintenance therapy with PUVA at more protracted intervals is generally required to prolong remission duration.[4,5,6] PUVA combined with interferon alpha-2a is associated with a high response rate.[7]

2. Total-skin electron-beam radiation. Electron radiation of appropriate energies will penetrate only to the dermis, and thus the skin alone can be treated without systemic effects. This therapy requires considerable technical expertise to deliver, can result in short- and long-term cutaneous toxic effects, and is not widely available. Based on the long-term survival of these early-stage patients, electron-beam radiation therapy is sometimes used with curative intent.[8,9,10,11] Long-term disease-free survival (DFS) can be achieved in patients with unilesional mycosis fungoides treated with local radiation therapy.[12]

3. Ultraviolet B radiation.[13]

4. Symptomatic management with topical corticosteroids.

5. Topical mechlorethamine (nitrogen mustard). Topical application of mechlorethamine has produced regression of cutaneous lesions, with particular efficacy in early stages of disease. The overall complete remission rate is related to skin stage; 50% to 80% of TNM classification T1, and 25% to 75% of T2 patients have complete responses. Treatments are usually continued for 2 to 3 years. Continuous 5-year DFS may be possible in as many as 33% of T1 patients.[8,14,15]

6. Local electron-beam radiation or orthovoltage radiation therapy may be used to palliate areas of bulky or symptomatic skin disease.[16]

7. Interferon alpha alone or in combination with other agents, such as topical therapy.[17] A retrospective review of 198 patients with mycosis fungoides and the Sézary syndrome (MF/SS) compared time to next treatment (TTNT) between interferon alpha and conventional chemotherapy. Interferon alpha provided a longer TTNT of 8.7 months (95% confidence interval [CI], 6.0-18.0) than did chemotherapy, with a TTNT of 3.9 months (95% CI, 3.2-5.1) and \( P < .0001 \).[18][Level of evidence: 3iiiDiv]

8. Bexarotene, an oral or topical retinoid (NCT00255801).[19,20]

9. Oral methotrexate (NCT00425555).[21]

10. Pegylated liposomal doxorubicin.[22]

11. Vorinostat or romidepsin or other histone deacetylase inhibitors (HDACi).[23,24,25] A retrospective review of 198 patients with MF/SS compared TTNT between HDACi and conventional chemotherapy. HDACi provided a longer TTNT of 4.5 months (95% CI, 4.0-6.1) than did chemotherapy with a TTNT of 3.9 months (95% CI, 3.2-5.1) and \( P = .01 \).[18][Level of evidence: 3iiiDiv]
12. Pralatrexate (folate analog).[26,27]
13. Lenalidomide.[28]

Current Clinical Trials

Check the list of NCI-supported cancer clinical trials that are now accepting patients with stage I mycosis fungoides/Sezary syndrome. The list of clinical trials can be further narrowed by location, drug, intervention, and other criteria.

General information about clinical trials is also available from the NCI website.

References:


Stage II Mycosis Fungoides

No curative therapy exists for patients with stage II disease. Therefore, the choice of initial palliative therapy is dependent on the patient's symptoms and the local expertise with each modality.

A randomized study of 103 patients compared combined total-skin electron-beam radiation (TSEB) plus combination chemotherapy with conservation therapy consisting of sequential topical therapies.[1] In the latter group, combination chemotherapy was reserved for symptomatic extracutaneous disease or for disease refractory to topical therapies. Patients with any stage were eligible. Although the complete response rate was higher with combined therapy, toxic effects were considerably greater, and no difference was seen in disease-free or overall survival between the two groups.[1][Level of evidence: 1iiA]

Treatment options:[2]

1. Psoralen and ultraviolet A radiation (PUVA). Therapeutic trials with PUVA have shown a 62% to 90% complete remission rate with early cutaneous stages achieving the best responses. Maintenance therapy with PUVA is generally required to prolong remission duration.[3,4] PUVA combined with interferon alpha-2a is associated with a high response rate.[5]

2. TSEB. Electron radiation of appropriate energies will penetrate only to the dermis, and the skin alone can be treated without systemic effects. This therapy requires a radiation therapy facility with physics support, considerable technical expertise, and precise dosimetry. The therapy can provide excellent palliation, with complete response rates of as much as 80%.[6,7,8,9]

3. Ultraviolet B radiation.[10]

4. Symptomatic management with topical corticosteroids.

5. Topical mechlorethamine (nitrogen mustard). Topical application of mechlorethamine has produced regression of cutaneous lesions with particular efficacy in early stages of the disease. The overall complete remission rate is related to skin stage; 25% to 75% of TNM classification T2, and as many as 50% of T3 patients have complete responses. Treatments are usually continued for 2 to 3 years.[6,11,12]

6. Local electron-beam radiation or orthovoltage radiation therapy may also be used to palliate areas of bulky or symptomatic disease.[13]

7. Interferon alpha alone or in combination with other agents, such as topical therapy.[14] A retrospective review of 198 patients with mycosis fungoides and the Sézary syndrome (MF/SS) compared time to next treatment (TTNT) between interferon alpha and conventional chemotherapy. Interferon alpha provided a longer TTNT of 8.7 months (95% confidence interval [CI], 6.0-18.0) than did chemotherapy, with a TTNT of 3.9 months (95% CI, 3.2-5.1) and \( P < .00001 \).[15][Level of evidence: 3iiiDiv]

8. Bexarotene, an oral or topical retinoid.[16,17]

9. Oral methotrexate (NCT00425555).[18]

10. Pegylated liposomal doxorubicin.[19,20,21]
11. Vorinostat or romidepsin or other histone deacetylase inhibitors (HDACi).[22,23,24] A retrospective review of 198 patients with MF/SS compared TTNT between HDACi and conventional chemotherapy. HDACi provided a longer TTNT of 4.5 months (95% CI, 4.0-6.1) than did chemotherapy with, a TTNT of 3.9 months (95% CI, 3.2-5.1) and \( P = .01 \).[15][Level of evidence: 3iiiDiv]

12. Pralatrexate (folate analog).[25,26]

13. Lenalidomide.[27]

**Current Clinical Trials**

Check the list of NCI-supported cancer clinical trials that are now accepting patients with stage II mycosis fungoides/Sezary syndrome. The list of clinical trials can be further narrowed by location, drug, intervention, and other criteria.

General information about clinical trials is also available from the NCI website.

**References:**

Stage III Mycosis Fungoides

No curative treatment exists for patients with stage III disease. Therefore, the initial choice of palliative therapy is dependent on the local expertise with each modality.

A randomized study of 103 patients compared combined total-skin electron-beam radiation (TSEB) plus combination chemotherapy with conservation therapy consisting of sequential topical therapies.[1] In the latter group, combination chemotherapy was reserved for symptomatic extracutaneous disease or for disease refractory to topical therapies. Patients with any stage were eligible. Although the complete response rate was higher with combined therapy, toxic effects were considerably greater, and no difference was seen in disease-free or overall survival between the two groups.[1][Level of evidence: 1iiA]

Treatment options (note that in this clinical setting, the skin is easily injured; any of the topical therapies must be administered with extreme caution):[2,3]

1. Psoralen and ultraviolet A radiation (PUVA). Therapeutic trials with PUVA have shown a 62% to 90% complete remission rate, with early cutaneous stages achieving the best responses. PUVA may be used in conjunction with systemic treatment. Maintenance therapy with PUVA is generally required to prolong remission duration.[4] PUVA combined with interferon alpha-2a is associated with a high response rate.[5]

2. TSEB. Electron radiation of appropriate energies will penetrate only to the dermis, and thus the skin alone can be treated without systemic effects. This therapy requires an excellent radiation therapy facility with physics support, considerable technical expertise, and precise dosimetry. The therapy can produce excellent palliation, with complete response rates of as much as 80%.[6,7]

3. Ultraviolet B radiation.[8]

4. Symptomatic management with topical corticosteroids.

5. Local electron-beam radiation or orthovoltage radiation therapy may also be used to palliate areas of bulky or symptomatic disease.[9]

6. Fludarabine, 2-chlorodeoxyadenosine, and pentostatin are active agents for mycosis fungoides and the Sézary syndrome (MF/SS).[10,11,12,13] Chemotherapeutic agents generally demonstrate short durations of response. In a retrospective review of 198 patients with advanced-stage disease, the median time before patients required new therapy was 4 months.[14] However, these comparisons may be confounded by the order in which the agents were introduced.

7. Interferon alpha alone or in combination with other agents, such as topical therapy.[11,15] A retrospective review of 198 patients with MF/SS compared time to next treatment (TTNT) between interferon alpha and conventional chemotherapy. Interferon alpha provided a longer TTNT of 8.7 months (95% confidence interval
Systemic chemotherapy (single agent or combination) often combined with treatment directed at the skin.[1,16,17] Chemotherapeutic agents generally demonstrate short durations of response. In a retrospective review of 198 patients with advanced-stage disease, the median time before patients required new therapy was 4 months.[14] However, these comparisons may be confounded by the order in which the agents were introduced.

Extracorporeal photochemotherapy.[18,19,20]

10. Topical mechlorethamine (nitrogen mustard). This form of treatment may be used palliatively or to supplement therapeutic approaches directed against nodal or visceral disease. The overall complete remission rate of TNM classification T4 patients is 20% to 40%. Treatments are usually continued for 2 to 3 years.[21,22]

11. Bexarotene, an oral or topical retinoid.[23,24]

12. Oral methotrexate (NCT00425555).[25]

13. Pegylated liposomal doxorubicin.[26,27,28]

14. Vorinostat or romidepsin or other HDACi.[3,29,30,31] A retrospective review of 198 patients with MF/SS compared TTNT between HDACi and conventional chemotherapy. HDACi provided a longer TTNT of 4.5 months (95% CI, 4.0-6.1) than did chemotherapy with a TTNT of 3.9 months (95% CI, 3.2-5.1) and \( P = .01 \).[14][Level of evidence: 3iiiDiv]

15. Pralatrexate (folate analog).[32,33] Chemotherapeutic agents generally demonstrate short durations of response. In a retrospective review of 198 patients with advanced-stage disease, the median time before patients required new therapy was 4 months.[14]

16. Alemtuzumab (a humanized monoclonal antibody targeting the CD52 antigen).[3,34]

17. Lenalidomide.[35]

Current Clinical Trials

Check the list of NCI-supported cancer clinical trials that are now accepting patients with stage III mycosis fungoides/Sezary syndrome. The list of clinical trials can be further narrowed by location, drug, intervention, and other criteria.

General information about clinical trials is also available from the NCI website.

References:


Stage IV Mycosis Fungoides and the Sézary Syndrome

The use of single alkylating agents has produced objective responses in 60% of patients, with a duration of less than 6 months. One of the alkylating agents (e.g., mechlorethamine, cyclophosphamide, or chlorambucil), or the antimetabolite methotrexate is the most frequently used. Single agents have not been shown to cure any patients, and insufficient data exist to determine whether these agents prolong survival. Combination chemotherapy is not definitely superior to single agents. Even in stage IV disease, treatments directed at the skin may provide significant palliation.

A randomized study of 103 patients compared combined total-skin electron-beam radiation (TSEB) plus combination chemotherapy with conservation therapy consisting of sequential topical therapies.[1] In the latter group, combination chemotherapy was reserved for symptomatic extracutaneous disease or for disease refractory to topical therapies. Patients with any stage were eligible. Although the complete response rate was higher with combined therapy, toxic effects were considerably greater, and no difference was seen in disease-free survival or overall survival between the two groups.[1][Level of evidence: 1iiA]

Treatment options:[2,3]

1. Psoralen and ultraviolet A radiation (PUVA). Therapeutic trials with PUVA have shown a 62% to 90% complete remission rate, with early cutaneous stages achieving the best responses. PUVA may be used in conjunction with systemic treatment. Maintenance therapy with PUVA is generally required to prolong remission duration.[4] PUVA combined with interferon alpha-2a is associated with a high response rate.[5]

2. TSEB. Electron radiation of appropriate energies will penetrate only to the dermis, and the skin alone can be treated without systemic effects. This therapy requires an excellent radiation therapy facility with physics support, considerable technical expertise, and precise dosimetry. This therapy can produce excellent palliation and may be combined with systemic treatment.[6,7]

3. Ultraviolet B radiation.[8]

4. Symptomatic management with topical corticosteroids.

5. Local electron-beam radiation or orthovoltage radiation therapy may also be used to palliate areas of bulky or symptomatic disease.[9]

6. Fludarabine, 2-chlorodeoxyadenosine, and pentostatin are active agents for mycosis fungoides and Sézary syndrome (MF/SS).[10,11,12] Chemotherapeutic agents generally demonstrate short durations of response. In a retrospective review of 198 patients with advanced-stage disease, the median time before patients required new therapy was 4 months.[13] However, these comparisons may be confounded by the order in which the agents were introduced.

7. Interferon alpha alone or in combination with other agents, such as topical therapy.[11,14] A retrospective review of 198 patients with MF/SS compared time to
next treatment (TTNT) between interferon alpha and conventional chemotherapy. Interferon alpha provided a longer TTNT of 8.7 months (95% confidence interval [CI], 6.0-18.0) than did chemotherapy, with a TTNT of 3.9 months (95% CI, 3.2-5.1) and \( P < .00001 \).\[13\][Level of evidence: 3iiDiv]

8. Systemic chemotherapy: chlorambucil plus prednisone, mechlorethamine, cyclophosphamide, methotrexate, and combination chemotherapy.\[1,15,16\] Chemotherapeutic agents generally demonstrate short durations of response. In a retrospective review of 198 patients with advanced-stage disease, the median time before patients required new therapy was 4 months.\[13\] However, these comparisons may be confounded by the order in which the agents were introduced.

9. Topical mechlorethamine (nitrogen mustard). This form of treatment may be used palliatively or to supplement therapeutic approaches directed against nodal or visceral disease. The overall complete remission rate in 243 patients was 64% and was related to stage; as many as 35% of stage IV patients had complete responses. Treatments are usually continued for 2 to 3 years.\[17,18\]

10. Extracorporeal photochemotherapy alone [19,20,21,22] or in combination with TSEB.\[23\]

11. Bexarotene, an oral or topical retinoid.\[24,25\]

12. Oral methotrexate (NCT00425555).\[26\]

13. Pegylated liposomal doxorubicin.\[27,28,29\] A retrospective review of 198 patients with MF/SS compared TTNT between histone deacetylase inhibitors (HDACi) and conventional chemotherapy. HDACi provided a longer TTNT of 4.5 months (95% CI, 4.0-6.1) than did chemotherapy, with a TTNT of 3.9 months (95% CI, 3.2-5.1) and \( P = .01 \).\[13\][Level of evidence: 3iiDiv]

14. Vorinostat or romidepsin or other HDACi.\[30,31,32\] A retrospective review of 198 patients with MF/SS compared TTNT between HDACi and conventional chemotherapy. HDACi provided a longer TTNT of 4.5 months (95% CI, 4.0-6.1) than did chemotherapy with a TTNT of 3.9 months (95% CI, 3.2-5.1) and \( P = .01 \).\[13\][Level of evidence: 3iiDiv]

15. Pralatrexate (folate analog).\[33,34\] Chemotherapeutic agents generally demonstrate short durations of response. In a retrospective review of 198 patients with advanced-stage disease, the median time before patients required new therapy was 4 months.\[13\]

16. Alemtuzumab (a humanized monoclonal antibody targeting the CD52 antigen).\[35,36\]

17. Lenalidomide.\[37\]

**Current Clinical Trials**

Check the list of NCI-supported cancer clinical trials that are now accepting patients with stage IV mycosis fungoides/Sezary syndrome. The list of clinical trials can be further narrowed by location, drug, intervention, and other criteria.

General information about clinical trials is also available from the NCI website.

**References:**

Recurrent Mycosis Fungoides and the Sézary Syndrome

The treatment of relapsed patients with cutaneous T-cell lymphomas involves the joint decisions of the dermatologist, medical oncologist, and radiation oncologist. It may be possible to re-treat localized areas of relapse in the skin with additional electron-beam radiation or possibly to repeat total-skin electron-beam radiation therapy (TSEB).[1] Photon radiation to bulky skin or nodal masses may prove beneficial. If these options are not possible, then continued topical treatment with other modalities such as mechlorethamine or psoralen and ultraviolet A radiation (PUVA) may be warranted to relieve cutaneous symptoms.

Clinical trials, if possible, should be considered as the next therapeutic option.

Options under clinical evaluation for recurrent mycosis fungoides and the Sézary syndrome (MF/SS) include the following:[2,3]

1. Additional electron-beam radiation or a repeat of TSEB.
2. Photon radiation to bulky skin or nodal masses.[4]
3. Topical treatment with mechlorethamine or PUVA.
4. PUVA combined with interferon alpha-2a is associated with a high response rate.[5]
5. Ultraviolet B radiation.[6]
7. Extracorporeal photochemotherapy has produced tumor regression in patients resistant to other therapies.[7,8]
8. Bexarotene is a retinoid available in an oral or topical form.[9,10]
9. Interferon alpha alone or in combination with other agents, such as topical therapy.[11,12] A retrospective review of 198 patients with MF/SS compared time to next treatment (TTNT) between interferon alpha and conventional chemotherapy. Interferon alpha provided a longer TTNT of 8.7 months (95% confidence interval [CI], 6.0-18.0) than did chemotherapy, with a TTNT of 3.9 months (95% CI, 3.2-5.1) and $P < .00001$.[13][Level of evidence: 3iiiDiv]
10. Allogeneic or autologous bone marrow transplantation.[14,15,16,17,18]
11. Vorinostat or romidepsin or other histone deacetylase inhibitors (HDACi).[19,20,21] A retrospective review of 198 patients with MF/SS compared TTNT between HDACi and conventional chemotherapy. HDACi provided a longer TTNT of 4.5 months (95% confidence interval [CI], 4.0-6.1) than did chemotherapy with a TTNT of 3.9 months (95% CI, 3.2-5.1) and $P = .01$.[13][Level of evidence: 3iiiDiv]
12. Pralatrexate (folate analog).[22,23] Chemotherapeutic agents generally demonstrate short durations of response. In a retrospective review of 198 patients with advance-stage disease, the median time before patients required new therapy was 4 months.[13]

13. Lenalidomide.[24]

14. Pegylated liposomal doxorubicin.[25,26,27] A retrospective review of 198 patients with MF/SS compared TTNT between HDACi and conventional chemotherapy. HDACi provided a longer TTNT of 4.5 months (95% CI, 4.0-6.1) than did chemotherapy with a TTNT of 3.9 months (95% CI, 3.2-5.1) and \( P = .01.\)[13][Level of evidence: 3iiiDiv]

15. Systemic chemotherapy: chlorambucil plus prednisone, mechlorethamine, cyclophosphamide, methotrexate, and combination chemotherapy.[28,29,30] Chemotherapeutic agents generally demonstrate short durations of response. In a retrospective review of 198 patients with advanced-stage disease, the median time before patients required new therapy was 4 months.[13]

**Current Clinical Trials**

Check the list of NCI-supported cancer clinical trials that are now accepting patients with recurrent mycosis fungoides/Sezary syndrome. The list of clinical trials can be further narrowed by location, drug, intervention, and other criteria.

General information about clinical trials is also available from the NCI website.

**References:**


Key References for Mycosis Fungoides and the Sézary Syndrome Treatment

These references have been identified by members of the PDQ Adult Treatment Editorial Board as significant in the field of mycosis fungoides and the Sézary syndrome treatment. This list is provided to inform users of important studies that have helped shape the current understanding of and treatment options for mycosis fungoides and the Sézary syndrome. Listed after each reference are the sections within this summary where the reference is cited.

  Cited in:
  - General Information About Mycosis Fungoides and the Sézary Syndrome
  - Stage Information for Mycosis Fungoides and the Sézary Syndrome
  Cited in:
  - Stage I Mycosis Fungoides
  - Stage II Mycosis Fungoides
  - Stage III Mycosis Fungoides
  - Stage IV Mycosis Fungoides and the Sézary Syndrome
  - Recurrent Mycosis Fungoides and the Sézary Syndrome
Cited in:

- General Information About Mycosis Fungoides and the Sézary Syndrome


Cited in:

- General Information About Mycosis Fungoides and the Sézary Syndrome


Cited in:

- General Information About Mycosis Fungoides and the Sézary Syndrome

Changes to This Summary (03 / 03 / 2016)

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

Key References for Mycosis Fungoides and the Sézary Syndrome Treatment

Added this new section.

This summary is written and maintained by the PDQ Adult Treatment Editorial Board, which is editorially independent of NCI. The summary reflects an independent review of the literature and does not represent a policy statement of NCI or NIH. More information about summary policies and the role of the PDQ Editorial Boards in maintaining the PDQ summaries can be found on the About This PDQ Summary and PDQ® - NCI's Comprehensive Cancer Database pages.

About This PDQ Summary

Purpose of This Summary

This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the treatment of mycosis fungoides and the Sézary Syndrome. It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions.

Reviewers and Updates
This summary is reviewed regularly and updated as necessary by the PDQ Adult Treatment Editorial Board, which is editorially independent of the National Cancer Institute (NCI). The summary reflects an independent review of the literature and does not represent a policy statement of NCI or the National Institutes of Health (NIH).

Board members review recently published articles each month to determine whether an article should:

• be discussed at a meeting,
• be cited with text, or
• replace or update an existing article that is already cited.

Changes to the summaries are made through a consensus process in which Board members evaluate the strength of the evidence in the published articles and determine how the article should be included in the summary.

The lead reviewer for Mycosis Fungoides and the Sézary Syndrome Treatment is:

• Eric J. Seifter, MD (Johns Hopkins University)

Any comments or questions about the summary content should be submitted to Cancer.gov through the NCI website's Email Us. Do not contact the individual Board Members with questions or comments about the summaries. Board members will not respond to individual inquiries.

Levels of Evidence

Some of the reference citations in this summary are accompanied by a level-of-evidence designation. These designations are intended to help readers assess the strength of the evidence supporting the use of specific interventions or approaches. The PDQ Adult Treatment Editorial Board uses a formal evidence ranking system in developing its level-of-evidence designations.

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Disclaimer

Based on the strength of the available evidence, treatment options may be described as either "standard" or "under clinical evaluation." These classifications should not be used as a basis for insurance reimbursement determinations. More information on insurance coverage is available on Cancer.gov on the Managing Cancer Care page.

Contact Us

More information about contacting us or receiving help with the Cancer.gov website can be found on our Contact Us for Help page. Questions can also be submitted to Cancer.gov through the website's Email Us.

Last Revised: 2016-03-03

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