Therapy for Mycosis Fungoides

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Opinion statement

Treatment of mycosis fungoides (MF) is indicated to reduce symptoms, improve clinical appearance, prevent secondary complications, and prevent progression of disease, all of which may have an impact on survival. Treatment of MF includes topical and systemic therapies, which can be administered alone or in combination. Psoralen and ultraviolet A radiation is effective in early-stage MF, inducing complete remissions in most patients. Psoralen and ultraviolet A radiation may also be combined with low doses of interferon (IFN)-a to treat stage I/II disease. However, early aggressive therapy with radiation and chemotherapy does not improve the prognosis. Local radiotherapy or total skin electron beam irradiation has been used with success to control advanced skin disease. Extracorporeal photopheresis may also be used successfully, but it is not generally available. Once the disease becomes refractory to topical therapy, IFN-a single-agent or combination chemotherapy may be administered, but the duration of response is often less than 1 year and ultimately all patients will relapse and become refractory. Among chemotherapeutic agents, pentostatin, gemcitabine, and liposomal doxorubicin seem to be particularly effective. Response rates after combined modality therapy with total skin electron beam irradiation and chemotherapy/IFN-a appear similar to response rates of chemotherapy alone. Therefore, there is a great need for the further development of novel emerging treatment modalities, such as retinoids (*ie*, bexarotene) and immunotherapeutic agents (*ie*, cytokines, tumor vaccines, and monoclonal antibodies), all of which appear to have significant therapeutic potential in patients with MF. Biologically based therapies may reduce the need for genotoxic therapies, such as cytostatics and radiotherapy.

Introduction

Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of T-cell malignancies mainly affecting the skin. The major subgroups are mycosis fungoides (MF) with or without Sezary syndrome (SS), $CD30^+$ anaplastic large cell lymphoma and lymphomatoid papulosis, indolent human T-lymphotropic virus type-1–associated T-cell lymphoma, and rare nonepidermotropic peripheral T or T-like natural killer lymphomas diagnosed as subcutaneous panniculitic or angiocentric lesions. MF is the most common form of CTCL and represents 70% of all cases of CTCL. The incidence of MF is approximately 0.4 per 100,000 per year, with most patients 40 to 60 years of age at diagnosis.

PATHOGENESIS AND ETIOLOGY

Mycosis fungoides are a clonal neoplasm of mature $CD4^+$ T cells ($CD8^+$ MF is rare). One of the histopathologic features of MF is the predilection for the neoplastic T cells to infiltrate into the epidermis, particularly in early phases of the disease (epidermotropism) [1]. Recent studies have implicated interferon (IFN)-g–inducible chemokines (IP-10) and thymus and activation-regulated chemokine (TARC/CLL17) as soluble factors released by keratinocytes that probably mediate the epidermotropism of neoplastic T cells [2,3]. Possibly as a consequence of the loss of IFN-g activity that occurs with the switch from a TH1 to a TH2 cytokine profile

during disease progression, epidermotropism is often lost in advanced phases of MF [4]. These observations indicate that a variety of externally applied therapies delivered to the skin (*ie*, topical therapies) would be particularly effective in early MF when neoplastic cells are preferentially confined to the epidermis and dependent on epidermal factors for tumor cell proliferation and survival.

CLINICAL PRESENTATION

The classic MF diagnosis progresses through the following four distinct phases: a premycotic phase with an asymptomatic scaling erythematous macular eruption, often in sun-shielded areas (*ie*, bathing trunk distribution), which lasts for months to years during which the diagnosis may be suspected but cannot be confirmed by standard clinical or histopathologic means; a patch phase with thin barely palpable erythematous and eczematous lesions the histologic features of which are at least consistent with the diagnosis of MF; a plaque phase with more readily palpable erythematous lesions; and a tumor phase in which the neoplastic infiltrate extends below the upper dermis and may infiltrate other organs [5].

Painful erythroderma may arise de novo or during any of the earlier described phases and is not always associated with the presence of leukemic T cells (SS). Occasionally, MF is diagnosed with cutaneous tumor nodules in the absence of patches of plaques. Patients may also be diagnosed with involvement of internal organs. Palpable lymphadenopathy has been noted in 60% of patients at diagnosis. Light microscopic study of these nodes frequently shows dermatopathic lymphadenopathy, thought to be a reactive lymphoid hyperplasia associated with intranodal deposition of melanin released from areas of severe cutaneous damage. More sophisticated immunophenotypic, chromosomal, and molecular studies have detected involvement by neoplastic cells in up to 85% of these nodes.

Visceral involvement is generally associated with short survival times. The liver, spleen, and lung are most commonly involved. There appears to be a predilection for other epithelial surfaces, such as surfaces of the oral cavity, airway, gastrointestinal tract, or genitourinary tract. Bone marrow involvement appears to be relatively uncommon.

STAGING AND PROGNOSTIC FACTORS

The most important clinical prognostic variables related to MF are the type of lesion and the percentage of the total skin surface involved, lymph node involvement, dissemination of visceral sites, and the presence of lymphoma cells in the circulation. These parameters have been codified in the modified TNM staging classification proposed by the Cutaneous T-cell Lymphoma Workshop in 1979 (Table 1) [6].

van Doorn *et al*. [7•] showed among 309 patients with various stages of MF that the overall and disease-specific survival was 80% and 89% at 5 years and 57% and 75% at 10 years, respectively. The actuarial 5-year disease-specific survival of patients with $T_1N_0M_0$, $T_2N_0M_0$, and $T_3N_0M_0$ disease was 100%, 96%, and 80%, respectively, and only 40% for patients with T_1–$T_4N_3M_0$ disease. Using multivariate analysis, the presence of extracutaneous disease, the type and extent of skin involvement, the response to initial treatment, and the presence of follicular mucinosis were independent prognostic factors [7•]. Sex and duration of skin lesions before diagnosis were not significantly related to survival.

Patients with $T_1N_0M_0$ and $T_2N_0M_0$ MF had significantly better survival rates compared to patients with $T_3N_0M_0$ MF ($P < 0.001$); however, no significant difference in survival was found between patients with $T_1N_0M_0$ and $T_2N_0M_0$ disease. Patients with histologically documented lymph node involvement and patients with enlarged but histologically uninvolved lymph nodes had a significantly worse survival rate compared to patients without lymphadenopathy [7•]. Overall survival at 5 years in patients with enlarged but histologically uninvolved lymph node involvement was 49% compared to 0% in patients with pathology-positive lymph node involvement [7•].

Treatment

Topical therapies

- Agents, such as carmustine, mechlorethamine, bexarotene gel, and corticosteroids, are externally applied skin therapies and particularly effective in early-stage MF [8–11,12••].

Ultraviolet irradiation

- In MF/SS, photochemotherapy has been proven to be superior to single ultraviolet (UV) irradiation using UVB or UVA. However, psoralen and ultraviolet A (PUVA) therapy is used most frequently. Extracorporeal photopheresis (ECP) is also highly effective, although it is not generally available [13]. Both treatments

Table 1. TNM classification of mycosis fungoides

Skin*			
Tumor (T)			
T_0	Clinically or histopathologically suspicious lesions		
T_1	Limited plaques, papules, or eczematous patches covering < 10% of the skin surface		
T_2	Generalized plaques, papules, or erythematous patches covering ≥ 10% of the skin surface		
T_3	Tumors		
T_4	Generalized erythroderma		
Lymph nodes (N)†			
N_0	No clinically abnormal peripheral lymph nodes; pathology negative for MF		
N_1	Clinically abnormal peripheral lymph nodes; pathology negative for MF		
N_2	No clinically abnormal peripheral lymph nodes; pathology positive for MF		
N_3	Clinically abnormal peripheral lymph nodes; pathology positive for MF		
Visceral organs			
Metastases (M)			
M_0	No visceral organ involvement		
M_1	Visceral involvement (must have pathology confirmation and the organ involved should be specified)		
Stage grouping			
IA	T_1	N_0	M_0
IB	T_2	N_0	M_0
IIA	T_1–T_2	N_1	M_0
IIB	T_3	N_1	M_0
III	T_4	N_0–N_1	M_0
IVA	T_1–T_4	N_2–N_3	M_0
IVB	T_1–T_4	N_0–N_3	M_1

*Pathology of T_1 to T_4 is diagnostic of MF. When more than one T stage exists, both are recorded, and the highest is used for staging (*eg*, cervical [left and right]).
†Record number of sites of abnormal nodes (*eg*, cervical [left and right]).
MF—mycosis fungoides.

involve the therapeutic use of UVA irradiation after photosensitization using 8-methoxypsoralen. In PUVA therapy, the patient is UVA irradiated after systemic or topical administration of the photosensitizer, whereas ECP is based on separation of a leukocyte/lymphocyte-enriched cell fraction from the peripheral blood, extracorporeal treatment of the cells with 8-methoxypsoralen and UVA, and subsequent reinfusion of the cells.

- Psoralen and ultraviolet A therapy has become a standard therapy regimen in early-stage MF. Applied in stage IA/IIA, PUVA induces complete remission (CR) in 80% to 90% of cases. Even in stage IIB, simultaneous administration of PUVA and local electron beam irradiation results in CR rates of approximately 60% [13]. Although long-term remissions have been described, most patients with MF experience a relapse and require repetitive PUVA cycles.
- Extracorporeal photopheresis represents the therapy of choice in erythrodermic MF. In these cases, CR has been observed in up to 80% of treated cases [14].

- Whether the addition of IFN-a to ECP in refractory patients may be beneficial is unclear. Future studies are needed to provide clarity on this issue.
- Similar reports of success in refractory patients treated with a third agent, such as interleukin (IL)-2, also need to be confirmed [15].

Radiotherapy

- Localized radiotherapy by radiology or electron beam is preferentially administered in T_3 (tumor) disease. In combination with other regimens (*ie*, PUVA), local radiotherapy is successfully applied to single-tumor lesions in patients with extended plaque and limited tumor disease. However, locoregional relapses outside the radiation field may be observed. In unilesional MF, actuarial relapse-free and overall survival rates at 10 years were 86% and 100%, respectively, following radiotherapy [16].
- Total skin electron beam irradiation (TSEB) therapy induces long-term remission, particularly in stage IA disease, with CR rates of 90% (50% disease-free survival [DFS] at 10 years). Considerable responses are also observed in stage IB/III disease ($T_4N_0M_0$ only), with CR rates of 71% and 64%, respectively [17]. Significant adverse events, such as total alopecia (transient in which total dose < 25 Gy), loss of perspiration, and severe xerosis cutis, in addition to the limited availability of the treatment, restrict the use of TSEB therapy. Therefore, TSEB therapy should be reserved for stage II/III cases that are refractory to or relapsing after standard regimens. A study by Wilson *et al.* [18] evaluated 163 patients with CTCL who received a complete course of TSEB therapy (36 Gy at 1 Gy/day for 9 weeks and 6 MeV electrons) with curative intent. Patients with a clinical CR or good partial response (PR) to TSEB therapy were subsequently randomized to adjuvant doxorubicin/cyclophosphamide chemotherapy or ECP. The 3-year survival rate was 75% in the group treated with combination chemotherapy and 100% in the ECP group ($P = 0.06$). A retrospective analysis involving 44 patients with erythrodermic (T_4) MF who received ECP concurrently with TSEB therapy or TSEB therapy only revealed that 73% of patients who received TSEB therapy achieved a CR within 2 months of completion [19]. The 3-year DFS in 32 patients with CR was 63%. Within this group, DFS was 49% in the 17 patients who had not received concomitant ECP, whereas the DFS was 81% in the 15 patients who had received TSEB therapy plus ECP. These data indicate that the use of ECP with TSEB therapy warrants further evaluation.
- Total skin electron beam irradiation therapy has recently been the subject of a consensus report between the European Organization for Research and Treatment of Cancer, the Cutaneous Lymphoma Group, and experts from radiotherapy centers in North America [20••]. The main indications remain stages IA, IB, and IIA of newly diagnosed MF, in which a cutaneous remission rate of approximately 95% is achieved. In the other stages of the disease, TSEB therapy has a palliative action and may be part of a combined treatment. TSEB therapy must be practiced in highly specialized centers with the necessary experience.

Interferon-a

- Initial trials with IFN-a used very high doses, which resulted in intolerable flu-like side effects in approximately 90% of patients. In subsequent studies, doses as low as 3 MU three times per week have been used, and have been shown to be as effective as the higher doses.

- As a single agent for initial therapy, IFN-a induces clinical responses in approximately 50% of patients, with a CR rate of approximately 15% and a median relapse-free survival of 4 to 8 months [21]. The effect of IFN-a often becomes evident after 3 to 5 months of treatment, but it may appear later. Maintenance therapy is recommended for patients with continuing PRs, but relapses may not necessarily be dependent on the discontinuation of IFN therapy.
- Combinations with other therapies may improve IFN-a activity. PUVA plus IFN-a is a combination that allows the use of a lower dosage of both therapies, reducing the adverse events associated with each therapy and increasing the response rate [22•].

Conventional chemotherapy

- Oral chemotherapy with single cytostatic drugs, such as methotrexate or chlorambucil, is effective in many patients with MF.
- The administration of chlorambucil combined with prednisone may be recommended in erythrodermic MF, particularly in relapsing cases. Using this regimen, a response rate of 58% has been observed [23].
- Oral methotrexate at a dose of 10 to 30 mg/week results in high response rates in the treatment of erythrodermic MF [24]. At doses of 50 to 100 mg/week, methotrexate is also effective in MF tumor lesions. However, simultaneously existing patch or plaque lesions require the administration of PUVA or combined regimens. Akpek *et al.* [25] treated 15 patients with advanced refractory CTCL with combination chemotherapy including etoposide, vincristine, doxorubicin, bolus cyclophosphamide, and oral prednisone. The overall response (OR) rate was 80% (27% CR and 53% PR). Median progression-free survival time was 8 months. However, the OR rate of various types of combination chemotherapy are not clearly superior to other treatment modalities [26].
- Among novel cytotoxic agents, pegylated liposomal doxorubicin appears to be effective in relapsing or refractory CTCL. Of 10 patients with relapsing or refractory CTCL (MF stage IB–IVB) treated with pegylated liposomal doxorubicin 20 mg/m^2 once a month, five achieved CR and four achieved PR. Response duration was 15 months [27]. These results were recently updated in 34 patients, in which 15 patients (44%) achieved CR, with an OR rate of 88% [28•].

Purine analogs

- The European Organization for Research and Treatment of Cancer conducted a phase II study in advanced CTCL with pentostatin at a dose of 4 mg/m^2 weekly for the first 3 weeks, followed by every other week [29]. Forty-four patients with CTCL were enrolled (21 patients with SS and 23 with MF). Most of the patients had received prior systemic chemotherapy. Sixteen patients (36%; 1 CR and 15 PR) responded and the median response duration was 4.5 months for the patients with SS and 8 months for the patients with MF [29].
- Kurzrock *et al.* [30•] reported results using escalating doses of pentostatin in 28 patients who had relapsed CTCL. The OR rate was 71%. Ten of 14 (71%) patients with SS responded, and four of six patients with tumor-stage CTCL responded. Dose escalation to 6.25 mg/m^2/day was possible during only a few courses. The most common side effects were granulocytopenia, nausea, and non-neutropenic fever. CD4$^+$ counts decreased signif-

icantly in most patients. These studies demonstrate that pentostatin is an effective agent in patients with advanced CTCL and suggest that alternative dosing may be explored in future trials.

- Several studies have demonstrated potential synergy between purine analogs and alkylating therapies. In one recent study, 12 patients with refractory CTCL received fludarabine and cyclophosphamide [31]. Nine patients had erythrodermic CTCL and three patients had tumor-stage MF. The OR rate was 42%, with five responses in the erythrodermic patients and one response in a patient with MF. The mean duration of the response was 10 months.

Gemcitabine

- Gemcitabine has shown promising activity in CTCL. In the study by Zinzani *et al.* [32••], previously treated patients with MF (n = 30) and peripheral T-cell lymphoma unspecified (PTCLU; n = 14) were treated. Of the 44 patients, five (12%) achieved CR and 26 (59%) patients achieved PR. CR and PR rates were the same for patients with MF and PTCLU, and the rates were also the same in relapsed and refractory patients. These results were confirmed by Sallah *et al.* [33], with two patients achieving CR and four patients achieving PR, among 10 patients with CTCL.

Retinoids

- Bexarotene was the first synthetic highly selective retinoid X receptor retinoid to be studied in humans. In-vitro studies have shown that bexarotene treatment at clinically relevant concentrations causes apoptosis of CTCL cell lines with downregulation of its cognate receptor retinoid X receptor-a, retinoic acid receptor-a, and antiapoptotic protein survivin and activation of caspase 3 [34].
- Two phase II/III multicenter open-label trials were conducted in 58 patients with early-stage CTCL and 94 patients with advanced-stage CTCL who had failed or were refractory to other therapies [35•,36••]. At doses of 6.5 mg/m^2/day, 300 mg/m^2/day, and 650 mg/m^2/day, the response rates in early-stage CTCL were 20%, 54%, and 67%, respectively. In patients with advanced-stage disease, the response rate was 45% when receiving 300 mg/m^2/day and 55% when receiving 650 mg/m^2/day, most of which were PRs. Overall, the 300 mg/m^2/day dose level was recommended for clinical use. These data indicate that oral bexarotene is active even in heavily pretreated patients with advanced-stage CTCL whose disease symptoms included tumors with large cell transformation, lymph node enlargement, or erythroderma [37].

Monoclonal antibodies

- Targeted therapy using monoclonal antibodies (mAbs) is well established in B-cell malignancies and is being explored in T-cell lymphomas. CD52 is a glycosylated peptide antigen expressed at high density on most normal and malignant T cells and B cells. A phase II open-label study evaluated the safety and efficacy of the anti-CD52 mAb alemtuzumab in 22 patients with advanced MF who had failed to respond adequately to therapy with at least PUVA and radiotherapy/chemotherapy [38••]. All of the patients had clinical symptoms or signs (*eg*, pruritus, skin ulcers, B-symptoms, symptomatic lymphadenopathy, anemia, or thrombocytopenia) needing treatment. Alemtuzumab was administered intravenously using a rapidly escalating

initial-dose regimen, followed by 30 mg three times a week for up to 12 weeks. Patients received prophylaxis with cotrimoxazole and valaciclovir for a minimum of 2 months after the end of alemtuzumab therapy. Most patients had stage III/IV disease, reduced performance status, and severe itching. The OR rate was 55%, with 32% achieving CR and 23% PR. The effect was greater in patients who had received one to two previous regimens (OR 80%) compared to patients who had received more than three prior regimens (OR 33%). Itching, self-assessed on a zero-to-10 visual analog scale, was significantly reduced from a median score of eight before treatment to two at the end of therapy. The median time to treatment failure was 12 months (range 5–32+). Cytomegalovirus reactivation (causing fever without pneumonia and responding to ganciclovir) occurred in four patients (18%). Six patients had other suspected or confirmed infections (all of these patients had received more than three prior regimens). Similar results were recently reported by Kennedy *et al.* [39].

- Another potential target antigen is CD4, which is expressed on the tumor cells of practically all patients with MF. Promising results were obtained by Knox *et al.* [40] in pilot experiments using a chimeric anti-CD4 mAb.
- Early interim results from an ongoing study on a fully human CD4 mAb revealed that four of 22 patients with MF responded, and additional patients reported a reduced itching. However, CD4 cells were not completely eradicated from blood at the doses used, indicating that higher mAb doses may be required to obtain receptor-site saturation and an improved antitumor effect [41•].
- These results indicate that mAbs are important therapeutic tools that need to be tested early in the disease course of MF.

Interleukin-2 fusion protein

- Denileukin diftitox is a recombinant fusion protein consisting of peptide sequences of diphtheria toxin and human IL-2. Denileukin diftitox has been approved by the US Food and Drug Administration for the treatment of patients with recurrent or refractory CTCL whose malignant cells express the CD25 component of the IL-2 receptor. In a phase III trial, Olsen *et al.* [42] reported a CR rate of 30% (20% PR and 10% CR) in 71 patients with CTCL treated with denileukin diftitox at a dose of 9 mg/kg/day or 18 mg/kg/day for 5 days. This treatment was repeated every 3 weeks for up to eight cycles. Median response duration was 7 months (range 3–46 months). Adverse events consisted of flu-like symptoms and acute infusion-related events, such as hypotension, dyspnea, chest pain, and vascular leak syndrome, in up to 25% of the patients. A significantly improved OR rate of 60% with considerably less side effects was noted with the use of steroid premedication before denileukin diftitox therapy [43••].

Future directions and emerging drugs

- Although allogeneic stem cell transplantation may be successfully used in selected young patients with MF [44,45], this strategy is not feasible for most patients. Pegylated (polyethylenglycol) IFN, currently being studied in other diseases, may prove to be a more active and better tolerated form of IFN. IFN-g has been tested in small series of patients with some clinical activity observed, indicating that further trials are warranted [46]. As mentioned earlier in this paper, liposomal doxorubicin could be a promising cytotoxic agent in the treatment of CTCL. Wider stage- and type-oriented

studies are the current goals of clinical trials. Recent preliminary data indicate that histone deacetylase inhibitors, such as oral suberoylanilide hydroxamic acid, may display clinical activity in MF [47•].

- The ability to stimulate cytotoxic $CD8^+$ T cells through the administration of exogenous IL-12 was considered to be an important factor in the therapy of CTCL [48]. Phase I/II clinical trials have shown an OR rate of approximately 50% [48,49]. Intralesional recombinant human IL-12 injections were administered in some patients and was associated with tumor flattening and complete resolution of the injected tumors. Further studies involving recombinant human IL-12 are indicated at tolerable doses and in combination with other biologic agents.
- Alemtuzumab has promising clinical activity and an acceptable safety profile in patients with advanced MF, particularly in patients with erythroderma and severe itching, and in patients who are not heavily pretreated. These observations need to be studied further, using various dosing schedules and in combination with other drugs with different mechanisms of action. Further evaluation of other therapeutic mAbs, such as anti-CD4, is also highly warranted. Another emerging therapeutic approach is tumor vaccination. In a very interesting pilot study by Maier *et al.* [50••], intranodal injections of autologous tumor-lysate-pulsed dendritic cells resulted in objective clinical responses in 50% of patients, including one patient achieving CR, which persisted for 19+ months.
- These emerging data indicate that biologically based therapies may be of increasing importance in the treatment of MF, thus reducing the need for genotoxic therapies, such as chemotherapeutic drugs and radiotherapy.

Specific drugs

Bexarotene gel (retinoid X receptor)

Standard dosage	1% gel, applying the ointment to lesions 2 to 4 times daily.
Contraindications	Pregnancy and exposure to sun/sun lamps (photosensitivity).
Main drug interactions	Gemfibrozil, erythromycin, and itraconazole (drugs that effect cytochrome P450 3A4) may potentially influence the disposition of bexarotene.
Main side effects	Local irritant reactions (*eg*, erythema, dermatitis, pruritus, and pain), leukocytoclastic vasculitis, vesiculobullous reaction, pruritus, maculopapular/exfoliative dermatitis, headache, hyperlipidemia, leukopenia, and slightly elevated liver enzymes.
Cost effectiveness	Expensive compared to carmustine and mechlorethamine. Topical treatment allows for outpatient treatment.

High-potency corticosteroids (topical)

Standard dosage	Various dosages reported.
Contraindications	None.
Main drug interactions	Rifampicin.
Main side effects	Purpura, mild irritant dermatitis, striae, and atrophy. Percutaneous absorption of corticosteroids can temporarily depress the hypothalamic-pituitary-adrenal axis, although this has no clinical consequence.
Cost effectiveness	Cheap and well tolerated. Outpatient treatment is possible.

Interferon-a

Standard dosage	3 MU subcutaneously three times a week.
Contraindications	Psoriasis, severe heart disease, and severe renal failure.
Main drug interactions	Teofyllin.

Main side effects	Initial flu-like symptoms (*eg*, fever, nausea, vomiting, diarrhea, chills, myalgias, headache, and malaise), hypothyroidism, depression, and fatigue.
Special points	Effective agent as monotherapy in CTCL. Combinations with other therapies, such as photochemotherapy, retinoid compounds, and topical chemotherapy, may improve its activity.

Bexarotene

Standard dosage	75 mg four to 10 capsules once daily. Recommended initial dose: 150 to 300 mg/m^2/day orally.
Contraindications	Pregnancy, pancreatitis, uncontrolled hypercholesterolemia or hypertriglyceridemia, hypervitaminosis A, uncontrolled hyperthyreosis or hypothyreosis, hepatic insufficiency, and ongoing systemic infection.
Main drug interactions	Ketoconazole, itraconazole, protease inhibitors, clarithromycin, erythromycin, rifampicin, phenytoin, dexamethasone, and phenobarbital.
Main side effects	Leukopenia, hypothyroidism, hyperlipidemia, hypercholesterolemia, elevated hepatic enzymes, headache, constipation, vomiting, pruritus, exanthema, exfoliative dermatitis, myalgia, headache, and insomnia.
Special points	Oral medication allows for outpatient treatment and has acceptable toxicity. The response rate is 50%.

Pentostatin

Standard dosage	4 to 8 mg/m^2 daily for 3 days, with cycles repeated every 21 days.
Main side effects	Nausea, vomiting, nephrotoxicity, hematologic toxicity, and infectious complications.

Cladribine

Standard dosage	0.1 mg/kg/day for 5 to 7 days at 28-day intervals.
Contraindications	Severe renal insufficiency.
Main drug interactions	Other myelosuppressive drugs.
Main side effects	Hematologic toxicity, infectious complications, fever, rigor, fatigue, vomiting, and nausea.
Special points	Overall responses to cladribine have been recorded in approximately 30% of patients with CTCL.

Gemcitabine

Standard dosage	1000 to 1200 mg/m^2 on days 1, 8, and 15 every 28 days.
Contraindications	Severe renal or hepatic failure.
Main drug interactions	None.
Main side effects	Flu-like symptoms, hematologic toxicity, nausea, vomiting, diarrhea, constipation, rash, pain, hematuria, and elevated liver enzymes.
Special points	Acceptable toxicity profile and easy schedule of administration.

Liposomal doxorubicin

Standard dosage	20 mg/m^2 once a month.
Contraindications	Other myelotoxic medication.
Main drug interactions	Myelotoxic medication.
Main side effects	Anemia, lymphopenia, and capillary leak syndrome.
Special points	Liposomal doxorubicin can be considered a promising cytotoxic agent in the treatment of CTCL. This agent has mild toxicity.

Alemtuzumab

Standard dosage	Rapidly escalating 3 to 10 mg intravenously, followed by 30 mg three times a week for up to 12 weeks.

Contraindications	Systemic infections, HIV, and pregnancy.
Main drug interactions	None.
Main side effects	Flu-like symptoms, cytomegalovirus reactivation and other opportunistic infections, and hematologic toxicity.
Special points	Promising clinical activity and an acceptable safety profile in patients with advanced MF who are less heavily pretreated.

Denileukin diftitox

Standard dosage	9 mg/kg/day or 18 mg/kg/day administered intravenously for 5 consecutive days every 3 weeks for up to eight cycles.
Contraindications	Known hypersensitivity to denileukin diftitox or any of its components.
Main drug interactions	None.
Main side effects	Flu-like symptoms (*eg*, fever, chills, nausea/vomiting, and myalgia/arthralgia), acute infusion-related events (*eg*, hypotension, dyspnea, chest pain, and back pain), vascular leak syndrome, and transient elevations in hepatic enzymes.
Special points	The response rate is 30%, although there is a risk of vascular leak syndrome. Corticosteroid prophylaxis may reduce the risk of severe side effects and improve clinical effects by improved tolerability.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Smoller BR, Bishop K, Glusac E, *et al.*: **Reassessment of histologic parameters in the diagnosis of mycosis fungoides.** *Am J Surg Pathol* 1995, **19:**1423–1430.
2. Tensen CP, Flier J, Van Der Raaij-Helmer EM, *et al.*: **Human IP-9: a keratinocyte-derived high affinity CXC-chemokine ligand for the IP-10/Mig receptor (CXCR3).** *J Invest Dermatol* 1999, **112:**716–722.
3. Kakinuma T, Sugaya M, Nakamura K, *et al.*: **Thymus and activation-regulated chemokine (TARC/CCL17) in mycosis fungoides: serum TARC levels reflect the disease activity of mycosis fungoides.** *J Am Acad Dermatol* 2003, **48:**23–30.
4. Rook A, Heald P: **The immunopathogenesis of cutaneous T-cell lymphoma.** *Hematol Oncol Clin North Am* 1995, **9:**997–1010.
5. DeVita V, Hellman S, Rosenberg SA: *Cancer: Principles and Practice of Oncology.* Philadelphia: Lippincott Williams & Wilkins; 2001.
6. Bunn PA Jr, Lamberg SI: **Report of the Committee on Staging and Classification of Cutaneous T-Cell Lymphomas.** *Cancer Treat Rep* 1979, **63:**725–728.
7. • van Doorn R, Van Haselen CW, van Voorst Vader PC, *et al.*: **Mycosis fungoides: disease evolution and prognosis of 309 Dutch patients.** *Arch Dermatol* 2000, **136:**504–510.

A multivariate analysis on prognostic factors in MF and survival rates in different stages of MF.

8. Zackheim HS: **Treatment of mycosis fungoides/Sezary syndrome: the University of California, San Francisco (UCSF) approach.** *Int J Dermatol* 2003, **42:**53–56.
9. Esteve E, Bagot M, Joly P, *et al.*: **A prospective study of cutaneous intolerance to topical mechlorethamine therapy in patients with cutaneous T-cell lymphomas. French Study Group of Cutaneous Lymphomas.** *Arch Dermatol* 1999, **135:**1349–1353.
10. Foulc P, Evrard V, Dalac S, *et al.*: **Evaluation of a 1-h exposure time to mechlorethamine in patients undergoing topical treatment.** *Br J Dermatol* 2002, **147:**926–930.
11. Liu HL, Kim YH: **Bexarotene gel: a Food and Drug Administration-approved skin-directed therapy for early-stage cutaneous T-cell lymphoma.** *Arch Dermatol* 2002, **138:**398–399.
12. •• Heald P, Mehlmauer M, Martin AG, *et al.*: **Topical bexarotene therapy for patients with refractory or persistent early-stage cutaneous T-cell lymphoma: results of the phase III clinical trial.** *J Am Acad Dermatol* 2003, **49:**801–815.

A large phase III trial on topical bexarotene therapy in MF.

13. Herrmann JJ, Roenigk HH Jr, Hurria A, *et al.*: **Treatment of mycosis fungoides with photochemotherapy (PUVA): long-term follow-up.** *J Am Acad Dermatol* 1995, **33:**234–242.
14. Edelson R, Berger C, Gasparro F, *et al.*: **Treatment of cutaneous T-cell lymphoma by extracorporeal photochemotherapy: preliminary results.** *N Engl J Med* 1987, **316:**297–303.
15. Fritz TM, Kleinhans M, Nestle FO, *et al.*: **Combination treatment with extracorporeal photopheresis, interferon alfa and interleukin-2 in a patient with the Sezary syndrome.** *Br J Dermatol* 1999, **140:**1144–1147.
16. Micaily B, Miyamoto C, Kantor G, *et al.*: **Radiotherapy for unilesional mycosis fungoides.** *Int J Radiat Oncol Biol Phys* 1998, **42:**361–364.

17. Hoppe RT, Cox RS, Fuks Z, *et al.*: **Electron-beam therapy for mycosis fungoides: the Stanford University experience.** *Cancer Treat Rep* 1979, **63:**691–700.

18. Wilson LD, Licata AL, Braverman IM, *et al.*: **Systemic chemotherapy and extracorporeal photochemotherapy for T3 and T4 cutaneous T-cell lymphoma patients who have achieved a complete response to total skin electron beam therapy.** *Int J Radiat Oncol Biol Phys* 1995, **32:**987–995.

19. Wilson LD, Jones GW, Kim D, *et al.*: **Experience with total skin electron beam therapy in combination with extracorporeal photopheresis in the management of patients with erythrodermic (T4) mycosis fungoides.** *J Am Acad Dermatol* 2000, **43:**54–60.

20.•• Jones GW, Kacinski BM, Wilson LD, *et al.*: **Total skin electron radiation in the management of mycosis fungoides: Consensus of the European Organization for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Project Group.** *J Am Acad Dermatol* 2002, **47:**364–370.

A consensus report on electron radiation in MF.

21. Olsen EA, Bunn PA: **Interferon in the treatment of cutaneous T-cell lymphoma.** *Hematol Oncol Clin North Am* 1995, **9:**1089–1107.

22.• Stadler R, Otte HG, Luger T, *et al.*: **Prospective randomized multicenter clinical trial on the use of interferon-2a plus acitretin versus interferon-2a plus PUVA in patients with cutaneous T-cell lymphoma stages I and II.** *Blood* 1998, **92:**3578–3581.

An important randomized trial involving IFN and PUVA in combination that allows the use of a lower dosage of both therapies, reducing the adverse events associated with each and increasing the response rate.

23. Winkelmann RK, Diaz-Perez JL, Buechner SA: **The treatment of Sezary syndrome.** *J Am Acad Dermatol* 1984, **10:**1000–1004.

24. Zackheim HS, Kashani-Sabet M, Hwang ST: **Low-dose methotrexate to treat erythrodermic cutaneous T-cell lymphoma: results in twenty-nine patients.** *J Am Acad Dermatol* 1996, **34:**626–631.

25. Akpek G, Koh HK, Bogen S, *et al.*: **Chemotherapy with etoposide, vincristine, doxorubicin, bolus cyclophosphamide, and oral prednisone in patients with refractory cutaneous T-cell lymphoma.** *Cancer* 1999, **86:**1368–1376.

26. Muche JM, Gellrich S, Sterry W: **Treatment of cutaneous T-cell lymphomas.** *Semin Cutan Med Surg* 2000, **19:**142–148.

27. Wollina U, Graefe T, Karte K: **Treatment of relapsing or recalcitrant cutaneous T-cell lymphoma with pegylated liposomal doxorubicin.** *J Am Acad Dermatol* 2000, **42:**40–46.

28.• Wollina U, Dummer R, Brockmeyer NH, *et al.*: **Multicenter study of pegylated liposomal doxorubicin in patients with cutaneous T-cell lymphoma.** *Cancer* 2003, **98:**993–1001.

An important study on pegylated liposomal doxorubicin, which is a new drug for MF.

29. Ho AD, Suciu S, Stryckmans P, *et al.*: **Pentostatin in T-cell malignancies: a phase II trial of the EORTC. Leukemia Cooperative Group.** *Ann Oncol* 1999, **10:**1493–1498.

30.• Kurzrock R, Pilat S, Duvic M: **Pentostatin therapy of T-cell lymphomas with cutaneous manifestations.** *J Clin Oncol* 1999, **17:**3117–3121.

In this trial, escalating doses of pentostatin were used in patients with relapsed CTCL, with an OR rate of 71%.

31. Scarisbrick JJ, Child FJ, Clift A, *et al.*: **A trial of fludarabine and cyclophosphamide combination chemotherapy in the treatment of advanced refractory primary cutaneous T-cell lymphoma.** *Br J Dermatol* 2001, **144:**1010–1015.

32.•• Zinzani PL, Baliva G, Magagnoli M, *et al.*: **Gemcitabine treatment in pretreated cutaneous T-cell lymphoma: experience in 44 patients.** *J Clin Oncol* 2000, **18:**2603–2606.

A major trial regarding gemcitabine, which has promising activity and is well tolerated in CTCL.

33. Sallah S, Wan JY, Nguyen NP: **Treatment of refractory T-cell malignancies using gemcitabine.** *Br J Haematol* 2001, **113:**185–187.

34. Zhang C, Hazarika P, Ni X, *et al.*: **Induction of apoptosis by bexarotene in cutaneous T-cell lymphoma cells: relevance to mechanism of therapeutic action.** *Clin Cancer Res* 2002, **8:**1234–1240.

35.• Duvic M, Martin AG, Kim Y, *et al.*: **Phase II and III clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma.** *Arch Dermatol* 2001, **137:**581–593.

An important trial regarding bexarotene in early-stage CTCL.

36.•• Duvic M, Hymes K, Heald P, *et al.*: **Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II/III trial results.** *J Clin Oncol* 2001, **19:**2456–2471.

A large phase II/III trial regarding bexarotene in advanced-stage CTCL.

37. Talpur R, Ward S, Apisarnthanarax N, *et al.*: **Optimizing bexarotene therapy for cutaneous T-cell lymphoma.** *J Am Acad Dermatol* 2002, **47:**672–684.

38.•• Lundin J, Hagberg H, Repp R, *et al.*: **Phase II study of alemtuzumab (anti-CD52 monoclonal antibody) in patients with advanced mycosis fungoides/Sezary syndrome.** *Blood* 2003, **101:**4267–4272.

This study verifies that alemtuzumab is highly active in CTCL.

39. Kennedy GA, Seymour JF, Wolf M, *et al.*: **Treatment of patients with advanced mycosis fungoides and Sezary syndrome with alemtuzumab.** *Eur J Haematol* 2003, **71:**250–256.

40. Knox S, Hoppe RT, Maloney D, *et al.*: **Treatment of cutaneous T-cell lymphoma with chimeric anti-CD4 monoclonal antibody.** *Blood* 1996, **87:**893–899.

41.• Obitz E, Kim H, Iversen L, *et al.*: **HuMaX-CD4, A fully human monoclonal antibody: early results of an ongoing phase II trial in cutaneous T-cell lymphoma (CTCL) [abstract].** *Blood* 2003, **102:**645a

This paper involves a potential emerging drug in CTCL.

42. Olsen E, Duvic M, Frankel A, *et al.*: **Pivotal phase III trial of two dose levels of denileukin diftitox for the treatment of cutaneous T-cell lymphoma.** *J Clin Oncol* 2001, **19:**376–388.

43.•• Foss FM, Bacha P, Osann KE, *et al.*: **Biological correlates of acute hypersensitivity events with DAB(389)IL-2 (denileukin diftitox, ONTAK) in cutaneous T-cell lymphoma: decreased frequency and severity with steroid premedication.** *Clin Lymphoma* 2001, **1:**298–302.

Steroids improved response and reduced toxicity in patients with MF who were treated with denileukin diftitox.

44. Donato M, Kurzrock R, Champlin R, *et al.*: **Complete remission at late-stage mycosis fungoides/Sezary syndrome following allogeneic transplantation.** *Blood* 2003, **102:**731a.

45. Molina A, Zain J, Arber D, *et al.*: **Is allogeneic hematopoietic stem cell transplantation (AHSCT) potentially curative in a group of refractory cutaneous T-cell lymphomas (CTCLs)? Durable clinical, cytogenetic and molecular remissions after AHSCT for refractory Sezary syndrome and mycosis fungoides.** *Blood* 2003, **102:**476a.

46. Kaplan EH, Rosen ST, Norris DB, *et al.*: **Phase II study of recombinant human interferon gamma for treatment of cutaneous T-cell lymphoma.** *J Natl Cancer Inst* 1990, **82:**208–212.

47.• Duvic M, Talpur R, Chiao N, Chiao J: **Phase II trial of oral suberoylanilide hydroxamic acid (SAHA) for cutaneous T-cell lymphoma (CTCL) and peripheral T-cell lymphoma (PTCL).** *Blood* 2003, **102:**179a.

This paper involves a potential future agent in CTCL.

48. Rook AH, Wood GS, Yoo EK, *et al.*: **Interleukin-12 therapy of cutaneous T-cell lymphoma induces lesion regression and cytotoxic T-cell responses.** *Blood* 1999, **94:**902–908.

49. Rook AH, Zaki MH, Wysocka M, *et al.*: **The role for interleukin-12 therapy of cutaneous T-cell lymphoma.** *Ann N Y Acad Sci* 2001, **941:**177–184.

50.•• Maier T, Tun-Kyi A, Tassis A, *et al.*: **Vaccination of patients with cutaneous T-cell lymphoma using intranodal injection of autologous tumor-lysate-pulsed dendritic cells.** *Blood* 2003, **102:**2338–2344.

This paper describes an entirely new therapeutic principle in CTCL.