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EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome

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Abstract

Several reviews and guidelines on the management of mycosis fungoides and Sézary syndrome (MF/SS) have been published; however, treatment strategies for patients with MF/SS vary from institution to institution and no European consensus has yet been established. There are few phase III trials to support treatment decisions for MF/SS and treatment is often determined by institutional experience. In order to summarise the available evidence and review 'best practices' from each national group, the European Organisation for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Task Force met in September 2004 to establish European guidelines for the treatment of MF/SS.

This article reviews the treatment regimens selected for inclusion in the guidelines and summarises the clinical data for treatments appropriate for each stage of MF/SS. Guideline recommendations are presented according to the quality of supporting data, as defined by the Oxford Centre for Evidence-Based Medicine. Skin-directed therapies are the most appropriate option for early-stage MF/SS and most patients can look forward to a normal life expectancy. Patients with advanced disease should be encouraged to participate in clinical trials and maintenance of quality of life should be paramount.

Keywords: EORTC; Guidelines; Mycosis fungoides; Sézary syndrome; Cutaneous T-cell lymphomas; Evidence-based medicine; Skin-directed therapy; Total skin electron beam therapy; Photochemotherapy; Chemotherapy; Immunotherapy; Biological response modifiers; Retinoids; Corticosteroids

Introduction

Cutaneous lymphomas are a group of disorders characterised by localisation of malignant lymphocytes to the skin. Approximately two-thirds of these lymphomas are of T-cell origin, and the pathogenesis and management of both T- and B-cell cutaneous lymphomas have been recently reviewed [1–6]. The most common form of cutaneous T-cell lymphoma (CTCL) is mycosis fungoides (MF), accounting for around 60% of new cases. Sézary syndrome (SS) is much rarer and accounts for only 5% of CTCL cases [3,7–9]. An analysis of US cancer registries showed that the incidence of MF/SS increased markedly from 1973 to 1984, with the highest incidence reported in the elderly. African-Americans had a two-fold higher incidence than Caucasians: the incidence in men was more than twice than that observed in women [10]. Since 1983 the incidence of MF/SS appears to have stabilised at 0.36 per 10^5 person-years, and the mortality rate has declined [11]. Age-adjusted incidence, relative to Caucasians, is 1.7 for African-Americans and 0.6 for Asians [11].

There are many therapeutic options available for the management of CTCL, including MF/SS [7,12]. The choice of treatment is often determined by physician or patient preference, or institutional experience, particularly as there is a paucity of data from phase III trials and a lack of consensus concerning treatment for later stages of MF/SS [3,13–15]. However, a number of authors have published recommendations or reviews on the management of CTCL [1,3,7,14,16], and guidelines have been published jointly by the British Association of Dermatologists and the UK Cutaneous Lymphoma Group [15]. Nonetheless, treatment choices vary across Europe and there are, as yet, no uniform European guidelines for the management of CTCL.

Development process of recommendations

In September 2004, the European Organisation for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Task Force organised a Workshop meeting to establish a consensus for the development and implementation of European guidelines for the management of MF/SS.* At the meeting, ‘best practices’ from each national group were presented for discussion. Differences between

* EORTC Guidelines Workshop for the management of Mycosis Fungoides/Sézary Syndrome. EORTC Cutaneous Lymphoma Task Force Meeting, Madrid, Spain, 24 September 2004.

the recommendations from each country were discussed, and consensus established. This article reports the outcomes from the meeting and the resulting EORTC recommendations for the management of MF/SS. The recommendations are presented by disease stage and accompanied by 'levels of evidence' to facilitate interpretation.

Classification of CTCL

Primary cutaneous lymphomas often have a different clinical course to histologically similar systemic lymphomas. Therefore, the EORTC classification for primary cutaneous lymphomas was established in 1997: the World Health Organization (WHO) classification for tumours of haematopoietic and lymphoid tissues includes primary cutaneous lymphomas as separate entities. Remaining differences between the two classification systems have resulted in the recent publication of the WHO-EORTC classification of cutaneous lymphomas (Table 1) [6]. This classification is based primarily on distinct disease entities with predictable treatment responses and prognoses.

MF is generally an indolent malignancy, with slow progression over years or even decades [6,7]. Conversely, SS, characterised by erythroderma, lymphadenopathy and the appearance of tumour cells in the peripheral blood, is associated with a median survival of only 32 months from diagnosis [7,15].

Levels of evidence

Much has been written in recent years on the need for clinical guidelines and the criteria they should meet for development and application, as well as evidence and recommendations to be used in their support [17–19]. The levels of evidence used in this article will be as described by the Oxford Centre for Evidence-Based Medicine (Table 2a/b) [19].

Clinical presentation

The onset of MF is often insidious and initial cutaneous symptoms may be difficult to distinguish from other non-malignant pathologies of the skin [7]. The median duration from the initial appearance of skin symptoms to a diagnosis of MF/SS is almost 6 years [7]. Typically, the initial lesions in MF are flat and erythematous skin patches, which evolve over a variable period of time into palpable plaques characterised by well-demarcated edges [7]. Patches and plaques may also exhibit hypopigmentation or hyperpigmentation [1]. Plaques can be followed by tumours, although it is common for patients to have patch, plaque and tumour lesions simultaneously on different parts of the body [7]. The time course of progression from patches to plaques to tumours is variable and unpredictable. Tumours are the presenting stage in about 10% of cases and are characterised by protruding, often ulcerative, lesions and lymphocytic infiltration into the dermis [1,7]. Infection, secondary to ulceration, is a frequent cause of morbidity [3].

Some patients with patch-stage MF will never progress to other forms of the disease, but many will eventually develop advanced disease [7]. Patients in whom erythema extends to 80% or more of the total skin surface are significantly more likely to have leukaemic involvement in the peripheral blood [1]. SS describes patients with generalised erythroderma and so-called Sézary cells in the peripheral blood [1,3]. These are enlarged, atypical lymphocytes with characteristic convoluted nuclei, which can be found in the peripheral blood of approximately 25% and 10% of patients with cutaneous tumours and generalised plaques, respectively [1,7]. The number of circulating Sézary cells required for a diagnosis of SS has been a matter of debate [3,7]. However, the International Society for Cutaneous Lymphomas has proposed the following criteria for diagnosis: a Sézary cell count ≥1000/μL, CD4/CD8 ratio ≥10, an increase in circulating T cells with aberrant marker expression, and evidence of a T-cell clone in the peripheral blood [1,8]. Histopathology of the skin is similar in MF and SS and has been described in other studies [1,3,7,20]. Histopathological diagnosis in early MF may be unreliable unless moderately enlarged lymphocytes with cerebriform nuclei are present [3,20]. Recently, an algorithm for the early diagnosis of MF was proposed, which is based on clinical, histological, and ancillary (immunophenotypic, molecular) criteria [21].

Staging

Staging of MF is based on a tumour–node–metastasis (TNM) system, originally published in 1979 [1,3,7,22]. Numerous studies have shown that prognosis is dependent on the magnitude of the cutaneous tumour burden [1]. Increased skin surface area involvement is also associated with a poorer prognosis, as is lymph node involvement and the appearance of clonal T cells in the peripheral blood [1,7]. Table 3a/b shows the TNM classification, the resulting stages, and the prognostic implications in terms of survival [1,15].

Other findings that might indicate a poorer prognosis are a γδ TCR phenotype, a reduced proportion of CD8-positive lymphocytes in tumour infiltrates, transformation to a large-cell lymphoma, the presence of a T-cell clone in the peripheral blood, follicular mucinosis, and age >60 years at presentation [3,7,15, 23–27].

Treatment modalities considered for inclusion in the consensus recommendations

The aims of treatment for CTCLs include clearance of lesions, that is, remission, in order to maintain or improve quality of life and prolong disease-free survival and overall survival [28,29]. However, assessing response to treatment is not necessarily straightforward. MF is an indolent condition with a long natural history and may not extend beyond the skin for many years [7]. This finding has necessitated the use of surrogate markers, such as the tumour burden measurements described by Heald, which can be used to assess the effects of treatment [28].

Skin-directed therapy

Skin-directed therapy (SDT) comprises one or more of the following: topical corticosteroids, topical nitrogen mustard (HN_2), topical BCNU (carmustine), psoralen plus ultraviolet (UV)A, UVB, total skin electron beam therapy (TSEB), and superficial X-irradiation. These treatment options are described in the following paragraphs.

Topical corticosteroids

This therapy has been successfully used in the treatment of mild, patch-stage MF. Topical corticosteroids target the majority of the tumour burden in the skin by directly inducing apoptosis of malignant T cells, and can induce complete clearance of the disease [4]. This treatment also decreases the number of Langerhans cells, thus interrupting the stimulation of malignant T cells [4]. Topical corticosteroids can be used to treat individual skin lesions and are available as lotions, creams or ointments.

Topical HN_2, mechlorethamine

This medication has no EMEA approval: France and The Netherlands are the only European countries in which it is available. Topical HN_2 has been used for the treatment of MF for almost half a century [30]. HN_2 is applied at 0.01% or 0.02% as either an aqueous or ointment-based formulation; both formulations appear to have equivalent efficacy [15,31,32]. The reported probability of hypersensitivity reactions varies from less than 10% to as much as 67%, although these are less likely with the ointment formulation [14,31–34]. Therapy is usually continued for 6 months after the clearance of skin lesions [14]. HN_2 has also been reported to induce repigmentation in hypopigmented MF lesions [35].

Topical BCNU, carmustine

Topical application is performed with a solution of 10 mg BCNU dissolved in 60 mL 95% alcohol. Alternatively, a 20–40% ointment can be used [15]. Hypersensitivity reactions are less frequent than with HN_2 but regular blood counts should be performed during topical BCNU treatment to monitor for bone marrow suppression [15].

Bexarotene gel

Bexarotene gel is a new topical retinoid (‘rexinoid’) with a unique mechanism of action (see below). In a phase I/II study, 42 of 67 patients with stage IA–IIA disease achieved at least a partial response (PR; ≥50% improvement), and 21% of patients achieved a complete response (CR) based on the Physician’s Global Assessment of skin involvement relative to baseline [36]. Efficacy improved with increases in concentration and frequency of application [36]. Bexarotene gel is generally well tolerated,

with side effects restricted to the site of application. Bexarotene gel was approved by the FDA in June 2000 as therapy for stage IA–IIA CTCL.

Psoralen plus UVA (320–400 nm) phototherapy (PUVA)

Psoralen (methoxsalen) is taken up by epidermal cells and forms bifunctional and monofunctional DNA adducts when photoactivated [37]. The first report of PUVA treatment in MF was published in 1976 [38]. Initial UVA doses can be as low as 0.5 J/cm^2, but are then increased at each treatment session until a CR is achieved or the maximum tolerated dose (MTD) is reached. Treatment regimens vary but, usually, PUVA is administered 2–4 times per week until skin lesions have cleared [14]. Nausea following 8-methoxypsoralen (8MOP) ingestion can be avoided by using 5-methoxypsoralen instead [14]. It has been shown in a large prospective trial in patients with psoriasis that PUVA therapy is associated with an increased risk of non-melanoma skin cancer [15]. A similar study has not been conducted in patients with MF. In this regard, it should be noted that, although patients with relapsed disease can be retreated, maintenance therapy rarely prevents relapse and should be avoided in order to minimize the total dose [15,39].

UVB (broadband 290–320 nm, narrowband 311–312 nm)

In contrast to UVA, use of UVB does not require psoralen ingestion [14]. UVB may also present a lower risk of cutaneous carcinogenesis than PUVA therapy but may be less effective in patients with dark skin [14]. In addition, narrowband UVB produces less irritation and erythema than broadband UVB. A retrospective study of 56 patients with early-stage MF (stage 1A and 1B) suggested that narrowband UVB is at least as effective, if not more so, than PUVA in terms of response and relapse-free interval. Narrowband UVB appears to be an effective treatment for early-stage MF, with advantages over broadband UVB and PUVA [40].

Total skin electron beam therapy

TSEB is a technically challenging treatment modality that requires careful attention to dosimetric techniques to avoid undue toxicity to normal tissues [7,14]. An electron beam is generated in a linear accelerator and the beam is then attenuated so that electrons penetrate the skin to a limited depth [7,14]. Less than 5% of the dose extends beyond 2 cm and, for most patients, the target volume is a skin depth <5 mm: this ensures that toxicity to the internal organs, including the bone marrow, is kept to a minimum [3]. MF cells are radiosensitive and can be effectively killed with low doses of radiation [3,7,15]. Use of TSEB has been extensively reviewed and consensus guidelines for the use of TSEB in MF have been published [41,42]. The total treatment dose is usually 30–36 Gy over 8–10 weeks, and electrons of different energies may be used depending on the required penetration depth [3,7,15]. Patients with MF/SS usually receive TSEB only once, however, repeat treatments following relapse have been reported [15,43,44]. The EORTC consensus guidelines recommend that additional courses of TSEB should be offered only when other appropriate therapies have failed [42].

Superficial X-irradiation

Localised, superficial radiotherapy provides effective palliative treatment for individual lesions. Doses used have ranged from 10– 30 Gy, and may be fractionated [15,29,45].

Systemic therapies

Systemic therapies include the following modalities, which are summarized below: chemotherapy, biological response modifiers (BRMs), immunotherapy, and extra-corporeal photoimmunotherapy (ECP).

Chemotherapy

The chemotherapeutic agents used in MF/SS and discussed in this article include, among others:

- Methotrexate (MTX): a folate antagonist and inhibitor of *de novo* purine and pyrimidine synthesis.

- Gemcitabine: a pyrimidine nucleoside analogue that, after phosphorylation, inhibits ribonucleotide reductase and DNA synthesis.
- The CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) combination [46].
- Chlorambucil: a nitrogen mustard derivative that is a bifunctional alkylating agent.
- Liposome-encapsulated doxorubicin: an anthracycline glycoside antineoplastic antibiotic. The drug's precise mechanism of action is not fully understood but it appears to be a DNA-damaging agent [47].
- Purine analogues (deoxycoformycin, 2-chlorodeoxyadenosine, fludarabine): cytotoxic, immunosuppressive agents [48–51].

Biological response modifiers

BRMs used to treat MF/SS include:

Interferon (IFN)-α

The use of systemic IFN-α in cutaneous lymphomas was first reported by Bunn *et al.* [52]. IFN-α is a type I IFN that binds to the type I IFN receptor, which is expressed in several different tumour cell types [53]. IFN-α appears to act via a number of different mechanisms, including cell cycle regulation, oncogene suppression, and modulation of cell adhesion [53]. Various treatment doses have been used, ranging from 3 million units (MU) three times per week to 36 MU per day, although current practice is to start at 3 MU/day and, if tolerated, increase to approximately 15 MU/day [3,7,15]. Side effects include elevated transaminases, leukopenia, and thrombocytopenia [14]. A dose-related flu-like syndrome is the most common reason for discontinuation, and the cause of dose-limiting toxicity [54,55]. This side effect is observed in most patients but is alleviated by dose reduction [55,56].

Retinoids

Retinoids are derivatives of vitamin A that appear to modulate cell proliferation and differentiation in several different neoplasms [3]. In MF, these effects extend to epithelial cells and possibly immunoregulation of mononuclear skin infiltrates [7]. In *in vitro* studies, 13-cis-retinoic acids induced

cellular differentiation, apoptosis, and DNA fragmentation in sensitive T-cell lines [57]. Retinoids also exhibit immunoadjuvant properties [58]. Commonly used retinoids are acitretin and isotretinoin; typical starting doses are 25–50 mg/day and 1 mg/kg/day, respectively [14]. Acitretin is a metabolite of etretinate, which has also been used as therapy for MF [59,60]. Retinoids are highly teratogenic [58,59]. The most frequently observed side effect is drying of the skin and mucous membranes, although elevated triglyceride levels are also a common occurrence [3].

Rexinoids

Over the last decade, many of the effects of the retinoids have been shown to be mediated by their interaction with a family of nuclear receptors, the retinoic acid receptors (RARs) [61]. The retinoid X receptors (RXRs) are a second family of nuclear receptors that also bind retinoic acid derivatives, although they differ structurally and functionally from the RARs [61]. The ligand specificity of these receptor families is also distinct. Bexarotene is highly selective for the RXRs, and was the first 'rexinoid' to undergo clinical development [62–64]. The drug has received EMEA approval in Europe for the treatment of skin manifestations in advanced CTCL [65]. Although the precise mechanisms are unknown, *in vitro* studies have shown that bexarotene can inhibit growth in tumour cell lines and cause *in vivo* tumour regression in animal models: the drug also stimulates apoptosis [62,66]. Bexarotene is usually administered at 300 mg/m^2/day and treatment is continued indefinitely in patients who respond [14,15,67]. Bexarotene causes severe central hypothyroidism with high frequency, associated with marked reductions in serum concentrations of thyroid-stimulating hormone and thyroxine. During treatment, patients should be monitored for thyroid function and for hypertriglyceridemia [14,15,62]. Most patients will require concomitant treatment with a lipid-lowering agent [15,67]. Gemfibrozil is contraindicated in this regard because it increases plasma concentrations of bexarotene, presumably due to inhibition of cytochrome P450 3A4, which, in turn, results in a paradoxical elevation of triglycerides [14,62,67].

Denileukin diftitox

Denileukin diftitox is a recombinant fusion protein comprising diptheria toxin fragments and interleukin (IL)-2 sequences [14,68]. Denileukin diftitox selectively interacts with the high-affinity IL-2 receptor (IL2R), resulting in internalisation of the diptheria toxin moiety, inhibition of protein synthesis, and cell death [14,68]. The drug is typically administered for 5 consecutive days at 9 or 18 μg/kg/day for up to eight 21-day cycles, but only in patients with neoplastic T cells expressing the high-affinity IL2R [14,68]. In this regard, neoplastic cells from patients should be tested for CD25 (the α subunit of the IL2R) expression prior to initiation of therapy, although CD25-negative tumours may respond through binding of the drug to ßγ-IL2R [68]. Approximately one-quarter of patients in clinical trials developed a 'vascular leak' syndrome characterised by the presence of two or more of the following: hypotension, oedema, hypoalbuminemia [68,69]. Denileukin diftitox should be avoided in patients with poorly controlled hypertension, heart failure, or impaired renal or hepatic function [14]. Furthermore, the prevalence of antibodies to diptheria toxin or denileukin diftitox increased from 40% at baseline to nearly 100% after two cycles. There was no apparent relationship between the presence of antibodies and the likelihood of response [69].Patients who received steroid pretreatment showed an overall decrease in the number of adverse events and a significant reduction in the number of grade 3/4 events [70]. Steroid pretreatment was also correlated with an increase in the overall response rate(ORR): 60% of patients responded to therapy compared with 30% in the original phase III trial [70,71].

Other treatment modalities

Immunotherapy

Alemtuzumab is a humanised recombinant IgG1κ monoclonal antibody with human Fc and V region framework sequences. The complementarity-determining regions are derived from rodent (rat) gene sequences [72]. The antibody is specific for the CD52 cell surface glycoprotein, which is found at densities of up to 5 x 10^5 binding sites/cell on the surface of normal and malignant B and T cells. However, CD52 does not appear to be expressed by granulocytes or myeloid or erythroid bone marrow

cells [72]. Alemtuzumab is usually administered at a dose of 30 mg intravenously three times per week, following an initial dose-escalation phase, for up to 12 weeks [29,73]. In studies in patients with MF/SS to date, the most common adverse events were opportunistic infections and neutropenia, which can be severe [29,73]. Recently, Lenihan *et al*. suggested that severe cardiotoxicity may be a significant complication of alemtuzumab treatment in MF/SS [74].

Extra-corporeal photoimmunotherapy

The use of ECP was first reported in 1987 by Edelson *et al.* [75]. In this procedure, peripheral blood leukocytes are harvested, mixed with 8MOP, exposed to UV radiation, and then returned to the patient [14,76]. In the earlier studies, 8MOP was administered orally, but this practice has now been replaced by *ex vivo* admixture of 8MOP prior to UV administration [14,76]. The procedure has been described in detail by Knobler *et al.* [76]. ECP is usually performed on two successive days every 4 weeks [7,14]. The schedule is generally continued for up to 6 months in order to assess response: maintenance therapy is tailored according to disease course. In general ECP is well tolerated, although patients with a history of heart disease require careful monitoring due to changing fluid volumes [14,76].

Recommendations from the Workshop meeting of the EORTC Cutaneous Lymphoma Task Force

These guideline recommendations are intended for MF/SS and may not be appropriate for other CTCLs. They are laid out by disease stage and subdivided by treatment stage (first- or second-line).

MF: stages IA, IB, and IIA

First-line recommendations

Expectant policy

Patients with stage IA disease have a normal life expectancy [77,78]. For this reason, ‘Expectant Policy’ is a legitimate management option for patients with this early disease stage. However, this

strategy must incorporate careful monitoring. Kim *et al.*, in a retrospective cohort analysis, noted that long-term survival in 122 patients with stage IA disease was similar to that of an age-, sex- and race-matched control population [77]. The median survival of the cohort had not been reached after 32.5 years of follow-up, and only 2% of patients had died within that period [77]. Zackheim *et al.* reviewed survival in 489 patients with CTCL presenting with disease stage I–IV, and noted that the majority of patients with CTCL do not die of their disease [78]. Only 15–20% of patients had died over a 10-year follow-up period. In a multicentre, retrospective cohort analysis, van Doorn *et al.* estimated that the respective risks of disease progression at 5 and 10 years were 4% and 10%, respectively, for stage IA disease, 21% and 39% for stage IB disease, 32% and 60% for patients with skin tumours, and 70% at both 5 and 10 years for patients with stage III disease [27].

Skin-directed therapy

PUVA: There have been numerous studies on the effects of PUVA therapy in MF, most of which have been retrospective analyses. However, Stadler *et al.* reported that IFN-α combined with PUVA was significantly superior to IFN-α plus acitretin [79]. In one of the earlier reports, Hönigsmann *et al.* reported that PUVA could induce CRs in stage IA and IB disease [80]. Fifty-five per cent of patients with stage IA and 39% with stage IB disease remained disease-free over a mean follow-up of 44 months. The authors also reported that 5 of 9 patients with stage IA and 10 of 26 with stage IB disease remained in continuous remission for as long as 79 months following a single PUVA treatment. These results indicate that PUVA can induce long-lasting remissions in early disease without ongoing maintenance therapy. Roupe *et al.* reported follow-up on 24 patients with early and advanced MF treated with PUVA [81]. All patients with T1 disease achieved a CR: half of these patients were still in CR after a follow-up of 3–18 years. Similarly, Herrmann *et al.* reported an ORR of 95% and a CR rate of 65% in a series of 82 patients, of whom 83% had stage IA or IB MF [82]. In addition, Molin *et al.* reported a CR rate of 58% in 51 patients with T1 or T2 disease [83]. Thus, there is good overall evidence that PUVA is an effective treatment in early-stage MF. As noted above, maintenance treatments do not prevent relapse and should therefore be avoided in order to minimise total dose and the ensuing risk of squamous cell carcinoma [15,39]. The most common side effect with methoxsalen

alone is nausea, which occurs in approximately 10% of patients [37]. A mild, transient erythema after PUVA therapy is an expected side effect. The peak erythematous reaction usually occurs about 48 hours after methoxsalen ingestion. Pruritus also occurs in approximately 10% of patients, however systemic adverse reactions have not been reported [37]. As noted above, PUVA therapy was associated with an increased risk of non-melanoma skin cancer in a large prospective trial in patients with psoriasis, although a similar study has not been conducted in patients with MF [15]. Despite the established efficacy of PUVA in early-stage disease, it remains unclear whether PUVA can improve overall survival [15].

UVB: Ramsay *et al.* initially reported a CR rate of 71% in 35 patients with early-stage CTCL treated with UVB [84]. However, although 83% of patients with only patch-stage disease achieved remission, none of the patients with plaque-stage disease attained a remission. Clark *et al.* reported a CR in 6 of 8 patients treated with narrowband UVB [85]. Gathers *et al.* assessed the response of 24 patients with stage IA or IB MF to narrowband UVB phototherapy over a mean follow-up of 29 weeks [86]. Thirteen patients (54%) achieved a CR, with histological clearing in 9 of 10 patients who underwent a repeat biopsy. Seven patients (29%) achieved a PR and there was no response in 4 patients (17%). However, 4 of the patients with a CR experienced relapse following treatment discontinuation. Diederen *et al.* compared narrowband UVB to PUVA therapy in 56 patients with stage IA and IB MF [40]. Twenty-one patients were treated with UVB and 35 with PUVA. CRs were obtained in 81% of patients treated with UVB and in 71% of those treated with PUVA. Corresponding PR rates were 19% and 29%, respectively. Mean PFS was 24.5 months for UVB and 22.8 months for PUVA. The EORTC Workshop meeting recommended that UVB treatment should be used only for patch lesions, and not for plaques, as UVB is known to only reach the superficial layers of the skin.

Topical corticosteroids: Zackheim *et al.* evaluated responses to topical corticosteroids (predominantly class 1) in 51 patients with T1 MF and 28 with T2 MF. Seventy-five patients had patch-stage disease [87]. Topical corticosteroids were applied for 2–3 months and for a further month after the lesions cleared. Patients were followed up for a median of 9 months. CRs and PRs were obtained in 32 (63%)

and 16 (31%) patients with T1 disease, respectively. Comparable results for patients with T2 MF were 7 (25%) CRs and 16 (57%) PRs [78]. Post-treatment biopsies were obtained from 7 of the 39 patients who achieved clinical clearing of their lesions; all 7 biopsies also showed histological clearance. Reversible depression of serum cortisol occurred in 10 patients (13%) and localised, reversible skin atrophy was noted in 1 patient [87]. These data indicate that class 1 corticosteroids can be an effective treatment for patch-stage MF.

Localised radiotherapy: Micaily *et al.* classified 18 of 325 incoming patients with MF as having unilesional MF [88]. Patients received 30.6 Gy in daily fractions of 1.8–2.0 Gy, except for 2 patients treated with 40 Gy or 22 Gy. All treated lesions cleared completely within 4–8 weeks of radiotherapy completion, with a 100% CR rate. Two relapses, confined to the skin, occurred at a median follow-up of 43 months, although at different sites to the original lesions. Relapse-free and overall survival at 10 years were 86% and 100%, respectively [88]. Orthovoltage radiotherapy can also be used at a low dose to treat individual plaques or tumours, with a higher rate of recurrence with doses below 30 Gy [45].

TSEB: As noted earlier, EORTC consensus guidelines for the use of TSEB in MF have been published elsewhere [42]. Jones *et al.* reported a CR rate of 95% in 123 newly diagnosed patients with stage IA MF treated with 31–36 Gy TSEB [41]. PFS was 35% at 15 years, however, PFS in patients with stage IB disease was only 10% at 10 years. In a retrospective review of patients at their centre, Jones *et al.* noted that the overall probability of CR was approximately 90% in early disease and 60% in advanced disease [41]. A meta-analysis of several uncontrolled and retrospective studies has established that CR rates are dependent on disease stage, skin surface dose, and electron beam energy [89]. CR rates are 96% in stages IA, IB, and IIA, 36% in stage IIB, and 60% in stage III. Increased skin surface dose (32–36 Gy) and higher energy beams (4–6 MeV) were significantly associated with higher CR rates [29]. Following administration of TSEB, all patients can be expected to develop complete temporary alopecia and nail stasis, although nail loss is rare [41,42]. Minor erythema may develop in normal skin, although a more severe reaction, perhaps even desquamation, may occur in skin previously exposed

to UV radiation [42]. Approximately 50% of patients experience minor oedema of the hands and feet, which may be exacerbated by physical activity during TSEB therapy or underlying conditions such as diabetes [42]. Long-term effects, including skin infections requiring systemic therapy, are rare, and corneal tears due to internal eye shields occur in <1% of patients [42]. Men may become infertile, so sperm banking should be considered if fertility is a concern. The EORTC Workshop meeting recommended that TSEB should be administered on no more than three occasions to each patient.

Topical HN_2: There have been no randomised clinical trials on the use of topical HN_2 in MF/SS. Hoppe *et al.* reported results from a retrospective series of 123 patients with MF who were treated with topical HN_2 [32]. Response rates depended on the degree of skin involvement. CR rates and ORRs were, respectively, 51% and 88% for T1 disease, and 26% and 69% in T2 disease [32]. In a cohort of 117 patients, Ramsay *et al.* reported that the probability of achieving a remission within 2 years was 76% for patients with stage I disease and 45% for patients with stage II disease [33]. Furthermore, the time to remission was shorter for patients with stage I than stage II disease [33]. Vonderheid *et al.* have reported a 20% CR rate in 331 patients treated with topical HN_2 [90]. The duration of responses was between 4 and 14 years. The Stanford Group has recently updated their retrospective experience with topical HN_2: 203 patients with stage I–III disease received HN_2 as first-line therapy [31]. The ORR was 83% and the CR rate 50%. Median time to CR was 10 months for patients with T1 disease and 19 months for those with T2 disease. Most of the patients achieving an initial CR received only HN_2 throughout the follow-up period [31]. Progression-free survival (PFS) was 92% and 85% at 5 and 10 years, respectively, in patients with T1 disease. The differences between these studies can probably be attributed to the inclusion of different proportions of patients at each disease stage. The treatment was generally well tolerated. In the study by Ramsay *et al.*, 68 patients (58%) developed a delayed hypersensitivity reaction but only 1 patient discontinued therapy as a result [33]. Furthermore, the Stanford Group reported that fewer than 10% of patients experienced contact hypersensitivity, although this appears to be more common with the aqueous preparation than with the ointment [31,32]. The reported incidence of secondary cutaneous malignancies was 4–11%, although this may not be due to topical HN_2 therapy [31,32]. These results indicate that topical HN_2 is an effective first-line treatment for early-stage MF.

Topical BCNU: Most of the studies on the treatment of patients with MF with topical BCNU have been published by the University of California at San Francisco Group [91–93]. No randomised controlled trials have been reported. Zackheim *et al.* retrospectively reported the results of 143 patients treated over a 15-year period [91]. A CR rate of 86% was achieved in patients with T1 disease, and a 48% CR rate was seen in those with T2 disease. In a subsequent report, the same group noted that, at 36 months following initiation of treatment in 172 patients, 92% of patients with stage I and 64% with stage II disease were in CR or PR [92]. The major toxicity is delayed bone marrow suppression, and blood counts should be monitored for at least 6 weeks after BCNU therapy [94]. In addition, bone marrow toxicity is cumulative and dose adjustments should be based on nadir counts after the previous dose [94]. However, bone marrow suppression in the studies described above, was uncommon [92]. Zackheim *et al.*, in their series of 143 patients, reported that mild haematopoietic depression occurred in less than 10% of patients [91]. However, others have reported bone marrow suppression rates of 30% [29]. The most common side effect was an erythematous reaction, although no secondary cutaneous malignancies occurred [91,92]. Gastrointestinal toxicity has been frequently noted, usually within 2 hours of BCNU administration, and renal dysfunction has been reported in patients exposed to large cumulative doses [94]. BCNU appears to be clinically effective, although comparative trials between HN_2 and BCNU are needed [29].

Chemotherapy: Although chemotherapy can induce responses in MF, such responses are usually short-lived and offer no demonstrable improvement in survival [15,95,96]. Kaye *et al.* conducted a randomised trial comparing TSEB combined with chemotherapy (cyclophosphamide, doxorubicin, etoposide, vincristine) with SDT [95]. The combination therapy achieved a significantly higher CR rate but at the expense of considerable toxicity. Importantly, after a median follow-up of 75 months, there was no difference between the treatment groups in terms of PFS or overall survival [95]. Hence, aggressive treatment with radiation and chemotherapy does not improve prognosis in patients with early-stage MF compared with those treated with standard SDT [95]. The EORTC Workshop meeting recommended that systemic chemotherapy should not be used at this disease stage.

Recommendations for first-line treatment of MF (stages IA, IB and IIA) are summarised in Table 4.

Second-line recommendations

Systemic therapies

Oral bexarotene: Oral bexarotene in the treatment of refractory, early-stage CTCL was evaluated in a phase II/III trial, in which 58 patients were treated with doses varying from 6.5–650 mg/m^2 [64]. All but one of the patients had stage IA, IB, or IIA disease. At the optimal dose of 300 mg/m^2, 54% (*n* = 15) of patients responded, with a CR rate of 7% (including clinical CR [CCR]). Response rates were similar across disease stages. At the 300 mg/m^2 dose, the median response duration had not been reached after 73 weeks and only 2 of 15 patients had relapsed disease [64]. In this trial, reversible and treatable adverse events included: hypertriglyceridemia in 46 of 58 patients (79%), hypercholesterolemia in 28 patients (48%), central hypothyroidism in 23 patients (40%), and leukopenia in 16 patients (28%) [64]. No cases of drug-related neutropenic fever, sepsis or death occurred. Pancreatitis occurred in 3 patients taking bexarotene 300 mg/m^2/day who had triglyceride levels >14.7 mmol/L [64]. Bexarotene induces lipid abnormalities in most patients although these can generally be managed with antilipemic therapy [62]. Elevations of liver function tests (LFTs) have been reported in patients receiving an initial dose of 300 mg/m^2, and both LFTs and thyroid function should be monitored during therapy. As previously noted, bexarotene must not be administered to pregnant women as rexinoids are teratogenic [62]. In conclusion, oral bexarotene is an effective alternative for patients with refractory, early-stage CTCL. Bexarotene can also be used topically and is approved for refractory, early-stage disease in the USA.

IFN-α: Monotherapy with IFN-α has been shown to induce significant responses in patients with MF/SS, including responses in previously treated patients [97–100]. Vegna *et al.* administered IFN-α daily to 23 newly diagnosed patients at doses of 3–18 MU over a period of 12 weeks [98]. Responders continued to receive IFN-α at the MTD for 6–9 months. The ORR was 74% and the CR rate was 35%. Olsen *et al.* treated 22 patients with IFN-α and observed CRs in 6 patients, with a CR rate of 27% and

an ORR of 64% [54]. CRs were observed in patients with early (I–IIA) and advanced disease (IVA); all but 3 patients had received prior therapy. Ross *et al.* reviewed the results of IFN-α treatment in 304 patients with CTCL and reported that the ORR, including CRs, PRs and minor responses, was 70% [101]. The authors also noted that fatigue, anorexia, and a flu-like syndrome were common in IFN-treated patients. Leukocyte count declined within hours of drug exposure but stabilised at 40–60% of the normal count. However, recovery occurred rapidly following cessation of IFN-α therapy. Dose reduction was necessary in the majority of patients with CTCL receiving high-dose IFN-α treatment due to flu-like symptoms. At least 1 fatal side effect, severe neutropenic sepsis, has been reported in CTCL, and haematological parameters should be monitored during therapy [101]. Summarising the available evidence, Bunn *et al.* concluded that there is no direct correlation between the dose of IFN-α and response. The authors recommend a schedule of 3 MU three times per week as the optimal regimen [102].

IFN-α plus retinoids: Knobler *et al.* conducted a pilot study, in which 7 patients with CTCL were treated with low-dose IFN-α and 13-cis-retinoic acid: 4 of the patients had received prior treatment [103]. Combination therapy resulted in 2 CRs and 2 PRs, which were maintained for up to 15 months. Dreno *et al.* treated 32 patients with MF with IFN-α for 3 months [60]. Responders continued on IFN-α alone, whereas non-responders were treated with IFN-α and etretinate. Twenty of the 25 patients with stage I–II disease responded; 12 patients with IFN-α alone and 8 with combined therapy. In a study conducted by Stadler *et al*., 38% of patients treated with IFN-α plus acitretin achieved a CR, with an ORR of 60% [79]. Zachariae *et al.* treated 11 patients with MF with IFN-α plus etretinate (*n* = 7) or IFN-α alone (*n* = 4) [97]. Two patients, 1 treated with IFN-α plus etretinate, achieved a CR and 5 a PR. The study showed that IFN-α plus etretinate can induce remission of CTCL. However, it should be noted that response rates observed with IFN-α plus retinoids were similar to IFN-α monotherapy.

Denileukin diftitox: In a phase III trial, of 26 previously treated patients with tumour stage IIA or less were treated with denileukin diftitox 9 (*n* = 14) or 18 μg/kg/day (*n* = 12) [71]. Six of the 14 patients

treated at the lower dose achieved a response, with 3 CRs (either CR or CCR). However, CRs only occurred in patients with stage I disease. At the higher dose, 4 of the 12 patients responded but there was only 1 CR in a patient with stage IB disease. The median duration of response for all patients in the study was 6.9 months (range 2.7–46.1) [71]. In addition, there was no clear indication of any dose response relationship. Routine premedication with systemic corticosteroids was prohibited in this study. As noted above, approximately one-quarter of patients in clinical trials developed a 'vascular leak' syndrome characterised by the presence of two or more of the following: hypotension, oedema, hypoalbuminemia [68,69]. In two clinical trials of 143 patients with lymphoma, including 105 with CTCL, acute hypersensitivity reactions occurred in 98 patients (69%) [68]. Infections occurred in almost half of the patients receiving denileukin diftitox, of which 23% were considered severe. In most of these patients with advanced-stage and/or heavily pretreated CTCL, infections were considered unrelated to treatment. Almost all (91%) patients experienced a flu-like syndrome within hours or days of receiving denileukin diftitox, although in most patients the symptoms were mild-to-moderate and responded to appropriate therapy. Gastrointestinal toxicities included diarrhoea and dehydration. The latter occurred in 9% of patients, usually concurrent with vomiting or anorexia [68]. The above phase III trial was an open, uncontrolled study but, as most of the patients had been heavily pretreated, the level of response suggests a useful role for this drug in patients with resistant, early-stage disease, but the therapy is currently not licensed in Europe [29,71].

Low-dose MTX: There are few published reports on the use of MTX in MF, even though initial reports appeared more than a quarter of a century ago [105]. McDonald *et al.* administered high-dose intravenous MTX to 11 patients with stage II–III MF [106]. Seven patients achieved a CR, which was maintained with weekly low-dose intravenous MTX. More recently, Zackheim *et al.* reported a retrospective study, in which 7 of 60 (12%) patients with patch/plaque MF (T2) attained a CR, and 13 (22%) achieved a PR [104]. Median time to treatment failure (TTF) was 15 months. The incidence and severity of adverse reactions to MTX therapy are related to the dose and frequency of administration [107]. The most common side effects include ulcerative stomatitis, leukopenia, abdominal distress, undue fatigue and decreased resistance to infection. MTX can also suppress haematopoiesis and has been associated with gastrointestinal toxicity, hepatoxicity, and pulmonary symptoms, as well as other

organ toxicities [107]. In the study by Zackheim *et al.* described above the medium weekly dose was 25 mg with maximum doses up to 75 mg; side effects were responsible for treatment failure in 6 (9%) of the total cohort of 69 patients [105].

Systemic therapies combined with SDT

IFN-α plus PUVA: Mostow *et al.* supplemented PUVA treatment with low-dose IFN-α in 5 patients who had previously failed PUVA alone [108]. CRs were achieved in all 5 patients. Kuzel *et al.* reported an ORR of 90%, with 62% CRs, in 39 patients treated with IFN-α plus PUVA [109]. Nineteen of the patients were in MF stage IB or IIA, and 34 had received prior treatment. Stadler *et al.* treated a series of 16 patients with MF with IFN-α (9 MU) plus PUVA, 3 J/cm^2 [110]. IFN-α was continued indefinitely following remission and PUVA was discontinued after a minimum of 2 months. Ten patients achieved a CR and 3 achieved a PR. Over a 10–40-month follow-up period, 4 patients developed progressive disease. A further 3 patients suffered local recurrences but repeat treatment maintained the remission [110]. In a series of 25 patients (19 with stage I disease), Rupoli *et al.* reported final response rates of 76% (CR) and 20% (PR) [111]. PFS was 82% at 12 months and 62% at 24 months. Chiarion-Sileni *et al.* conducted a phase II trial, in which patients with CTCL were given IFN-α (12 MU) three times per week following initial dose escalation [112]. PUVA was then initiated three times per week and continued indefinitely at 2–4-week intervals. Sixty-three patients were enrolled, of whom 46 were in disease stage IIA or earlier. Forty-seven (75%) patients achieved a CR and 10% achieved a PR [112]. Ten of the 63 patients had received prior therapy, although their disease stage was not reported. Nine patients had disease relapse at a median of 12 months, of whom 8 were retreated: 5 of these patients attained a second CR with IFN-α plus PUVA. Collectively, these results indicate that IFN-α plus PUVA can be an effective second-line treatment, although superiority of IFN-α plus PUVA over PUVA alone is not clearly documented.

Retinoids plus PUVA: Thomsen *et al.* reported responses in 69 patients with plaque-stage MF treated with either PUVA or PUVA plus oral retinoids [113]. CRs were obtained in 73% and 72% of patients,

respectively [113]. Furthermore, in the combination treatment group, remissions were obtained with a lower UVA dose.

In one of the few prospective, randomised trials conducted in CTCL, Stadler *et al.* performed a multicentre comparison of IFN-α plus PUVA versus IFN-α plus acitretin [79]. Ninety-eight patients were enrolled, although only 82 were evaluable; 40 for IFN-α plus PUVA, and 42 for IFN-α plus acitretin. In the former group, 35 of the 40 patients had stage IA–IIA disease, whereas in the IFN-α plus acitretin group, the proportion was 39 of 42 patients. Seventy per cent of patients in the IFN-α plus PUVA group achieved a CR compared with 38% in the IFN-α plus acitretin group. Respective ORRs were 80% and 60%. IFN-α plus PUVA resulted in a significantly improved response rate compared with IFN-α plus acitretin. Twenty-four of 40 (60%) patients in the IFN-α plus PUVA group had received prior treatment compared with 34 of 42 (81%) in the IFN-α plus acitretin group, a statistically significant difference that arose from excluding non-evaluable patients after the initial randomisation. However, the superiority of IFN-α plus PUVA was still evident in an intent-to-treat analysis (P<0.05). In short, this trial provided evidence of a marked improvement provided by IFN-α plus PUVA compared with IFN-α plus acitretin, including use as second-line treatment [79].

Bexarotene plus PUVA: Singh *et al.* conducted a retrospective chart review in 8 patients (stage IA–IIB) with CTCL that had recurred following monotherapy with various agents, including TSEB, IFN-α, PUVA and topical steroids: the patients were then treated with PUVA plus bexarotene [114]. A response was achieved in all 8 patients, including 5 CRs [114]. An EORTC-sponsored phase III trial is currently recruiting patients for a comparison between PUVA alone and PUVA plus bexarotene [115].

Recommendations for second-line treatment of MF (stages IA, IB and IIA) are summarised in Table 5.

MF: stage IIB

First-line recommendations

PUVA plus IFN-α: In the prospective, randomised, controlled trial described above, Stadler *et al.* reported that PUVA plus IFN-α resulted in CRs in 2 of 9 patients with stage II disease, and PRs in 3 of 9 patients [79]. Unfortunately, these authors did not discriminate between results obtained in patients with stage IIA and stage IIB disease. Chiarion-Sileni *et al.* included 3 patients with stage IIB MF in their phase II trial, and reported that CRs were obtained in all disease stages, except in patients with SS [112]. However, the investigators did not provide response data by stage. Jumbou *et al.* reported long-term follow-up for a cohort of 51 patients with various stages of MF who were treated with IFN-α [104]. Most (35) patients had not received prior therapy. Of the 30 patients with stage IIB disease, 23 (77%) responded, including 10 (33%) CRs. However, half of the patients in CR had disease relapse within 1 year [104].

TSEB and superficial X-irradiation: As mentioned earlier, a meta-analysis reported CR rates of 36% in patients with stage IIB disease [89]. Superficial irradiation of specific lesions achieves a CR in more than 90% of treated tumours [45]. TSEB has also been combined with total nodal irradiation. Micaily *et al.* reported that this procedure resulted in 100% CRs in 14 patients with stage I–II disease, including 5 with stage IIB disease [116].

PUVA plus acitretin: Early studies include those of Hunziker *et al.* and Serri *et al.* [117,118]. Results from the study by Thomsen *et al.* have been described above [113]. However, in this study, no patients with stage IIB disease were included. Thus, the recommendation for the use of this treatment in this disease stage is based on expert opinion and not on published data.

Recommendations for first-line treatment of MF (stage IIB) are summarised in Table 6.

Second-line recommendations

Bexarotene: In the phase II/III trial of bexarotene in advanced CTCL, the ORR was between 27% and 48%, depending on the criteria used [119]. Forty-one patients with stage IIB disease were treated at 300 mg/m^2/day, and achieved a response rate of 57% for skin lesions.

Chemotherapy: Monotherapy and combination therapy protocols are recommended. A phase II trial of gemcitabine monotherapy achieved an ORR of 70% (10% CR, 60% PR) in 30 previously treated patients with T3 or T4 disease [120]. Kurzrock *et al.* assessed the efficacy of pentostatin (deoxycoformycin) in a study that included 6 patients with tumour-stage MF who had received prior therapy [48]. One patient achieved a CR and 3 attained a PR. Trautinger *et al.* assessed the efficacy of low-dose 2-chlorodeoxyadenosine in 8 patients with > stage IIB MF [49]. Two patients achieved long-lasting PRs (20 and >21 months) and 1 patient had a 14-month period of stable disease [49]. Bunn *et al.* reviewed several studies using chemotherapy in patients with advanced MF and SS (stage IIB onwards) [102]. A total of 331 patients were treated with various combination chemotherapy regimens in these studies. CRs or PRs were obtained in 269 patients (81%), with median response durations ranging from 5–41 months. Response rates (CR + PR) in the individual studies ranged from 57% to >90%, although several of the studies had very low patient numbers [102]. Wollina *et al.* evaluated the efficacy of single-agent pegylated liposomal doxorubicin as second-line chemotherapy in patients with CTCL [121]. Of 34 patients treated with pegylated liposomal doxorubicin, 15 achieved a CR and 15 a PR, with an ORR of 88.2%. Overall survival was 17.8 ± 10.5 months, event-free survival was 12 ± 9.5 months and disease-free survival was 13.3 ± 10.5 months [121].

Denileukin diftitox: The phase III trial described earlier included 19 patients with stage IIB MF who had received a median of 5 prior therapies [71]. One PR was achieved among the 9 patients treated with denileukin diftitox 9 μg/kg, whereas, of the 10 patients treated with 18 μg/kg, 2 achieved a CR and 3 attained a PR. Although these data suggest some dose dependency, the results did not reach statistical significance (P=0.07). Thus, for patients with stage IIB disease, the ORR across both dose levels was 32% (6/19 patients).

Recommendations for second-line treatment of MF (stage IIB) are summarised in Table 7.

MF: stage III

First-line recommendations

PUVA plus IFN-α: Several relevant studies have already been described [108–111]. In the trial conducted by Chiarion-Sileni *et al.*, described above, 12 of 63 patients had stage III disease, and the authors noted that CRs were achieved in all disease stages, except in patients with SS [112]. Unfortunately the response data were not reported by disease stage, or by prior treatment status. Roenigk *et al.* reported results from a phase I trial with PUVA plus IFN-α in 15 patients with MF disease stages IB–IVB. CRs were achieved in 12 of 15 patients, and PRs in 2 patients [122].

IFN-α: In one of the earlier studies, Bunn *et al.* reported results of a phase II trial with IFN-α therapy in 20 patients with refractory MF [55]. Five patients had generalised plaque disease, 10 had cutaneous tumours, and 5 had generalised erythroderma. Nine patients responded (ORR 45%) and 2 patients achieved a CR. In the study by Olsen *et al.*, referred to earlier, responses were observed in 2 of 3 patients with stage III disease [54].

MTX: In a retrospective study of 29 patients with erythrodermic CTCL, Zackheim *et al.* observed a CR rate of 41% and a PR rate of 17%, for a total ORR of 58% following MTX treatment [123]. Median TTF was 31 months. In addition, McDonald *et al.* reported that 7 of the 11 patients with stage II–III MF achieved a CR in their study described above [106].

TSEB: According to guidelines and as discussed above, Jones *et al.* combined TSEB with oral etretinate but, after a median follow-up of 2 years, the relapse-free survival rate in patients who

achieved a CR was similar to that in stage-matched controls [124]. Jones *et al.* have recently reviewed the use of TSEB in combination with other modalities [41].

Topical HN_2: In a retrospective analysis of 117 patients with MF, Ramsay *et al.* reported that the probability of achieving remission within 2 years of initiating HN_2 treatment was 49% in patients with stage III disease. The median time to remission was 39 months [33].

ECP: Since the original publication by Edelson *et al.*, a series of studies have confirmed the efficacy of ECP in treating CTCL [75]. Reported ORRs range from 31–80%, with 0–25% CRs [76]. Suchin *et al.* observed a 75% ORR in a retrospective cohort study, and Gottlieb *et al.* reported a CR rate of 25% and a PR rate of 46% from a retrospective chart review of 28 patients with stage III or IV disease [125,126]. In addition, ECP has minimal side effects [76,127]. Zic *et al.* also reported a CR rate of 25% and PR rate of 25% in a cohort of 20 patients [127]. Long-term follow-up of this cohort showed a median survival of 96 months. In addition, early response after 6–8 months of ECP therapy was predictive of long-term outcome [127].

PUVA plus acitretin or bexarotene: The pertinent literature and the EORTC-sponsored phase III clinical trial have been described above [113,115]. As mentioned above, there is no published evidence as yet for the efficacy of these combination regimens in stage III disease.

Recommendations for first-line treatment of MF (stage III) are summarised in Table 8.

Second-line recommendations

Chemotherapy: Many different chemotherapeutic agents have been assessed in the treatment of CTCL, in both single-agent and combination protocols [14,15,102]. However, response durations are relatively short [15,128]. As mentioned earlier, gemcitabine monotherapy achieved an ORR of 70% in 30 previously treated patients with T3 or T4 disease [120]. Kuzel *et al.* conducted a phase II trial of 2-

chlorodeoxyadenosine in 21 patients with MF disease stage IB–IVB: among the 5 patients with stage III disease, 1 achieved a CR and 1 achieved a PR [50]. One of 8 patients with stage IVA disease achieved a CR; there were no PRs, and neither of the 2 patients with stage IVB disease responded. Tirelli *et al.* treated 16 patients with advanced CTCL (T3, T4 and extra-cutaneous disease) with CVP (cyclophosphamide, vincristine, and prednisone) [129]. A 50% ORR was achieved and 4 patients attained a CR. Fierro *et al.* assessed the efficacy of VICOP-B (idarubicin, etoposide, cyclophosphamide, vincristine, prednisone, bleomycin) in 25 patients with advanced CTCL (stages IIB and IV) [130]. An ORR of 84% was achieved in patients with MF, with a median duration of 8.7 months [130].

Recommendations for second-line treatment of MF (stage III) are summarised in Table 9.

MF: stages IVA–IVB

It should be recognised that treatment at this stage is palliative. Therapy should be chosen to be effective and have a favourable side-effect profile. Treatment options include all of the various modalities previously mentioned. Patients should be entered into clinical trials wherever possible.

Recommendations for treatment of MF (stage IVA–IVB) are summarised in Table 10.

Sézary syndrome

First-line recommendations

ECP: A substantial proportion of patients in the original study by Edelson *et al.* had SS. Following oral administration of methoxsalen, a lymphocyte-enriched fraction of the patient's blood was exposed to 1–2 J/cm^2 *ex vivo* and then returned to the patient [75]. Twenty-seven of 37 patients with resistant CTCL responded to the treatment, with an average decrease in cutaneous involvement of 64% after a mean

period 22 weeks [75]. In the study by Suchin *et al.*, 89% of a consecutive sample of 47 patients had circulating malignant T cells [125]. ECP monotherapy resulted in a 75% ORR and median survival of 66 months. The authors also reported an increase in the ORR and survival duration when ECP was combined with immunostimulatory agents such as IFN-α. Furthermore, Gottlieb *et al.*, reported a CR rate of 25% and a PR rate of 46% from a retrospective chart review of 28 patients with stage III or IV disease [126]. The majority of these patients also had circulating malignant T cells. In a retrospective analysis of data from 23 patients with SS, Evans *et al.* observed an ORR of 57% [133]. The authors noted that responders were more likely to have a higher baseline lymphocyte count and a higher proportion of Sézary cells in the total leukocyte count than non-responders, whereas others have reported optimal responses in patients with a lower CD4/CD8 ratio [133,134]. The use of ECP to treat MF/SS, including ECP combination modalities, has been recently reviewed by Knobler and Jantschitsch [76].

Other recommended treatment options include immunotherapy, BRMs, and chlorambucil plus prednisone [135]. The pertinent studies have been discussed above and are cited in Table 11.

Second-line recommendations

Bexarotene: In the phase II–III trial of bexarotene in patients with advanced MF/SS, the response rate in patients with SS was 24% (4 of 17 patients) [119].

Chemotherapy: In addition to the studies cited earlier, Akpek *et al.* undertook a phase II study to assess the efficacy of the EPOCH (etoposide, vincristine, doxorubicin, bolus cyclophosphamide, oral prednisone) regimen [136]. Fifteen patients with advanced, refractory CTCL were treated, including 6 with SS. The ORR was 80%, with 27% CRs. Two of the 6 patients with SS had complete clearance of circulating Sézary cells. The protocol was deemed to have acceptable toxicity. However, Fierro *et al.* did not observe any responses in patients with SS treated with the VICOP-B regimen [130]. Scarisbrick *et al.* studied the efficacy of fludarabine plus cyclophosphamide in 12 patients with advanced CTCL; 8

patients had SS [51]. Five of 8 patients with SS responded, including 1 CR, but bone marrow toxicity was significant. The authors concluded that, although this protocol might offer clinical benefit, there did not appear to be any evidence of improved survival [51].

Alemtuzumab: Lundin *et al.* conducted a phase II study of alemtuzumab in 22 patients with advanced MF/SS [73]. The ORR was 55%; 32% of patients achieved a CR and 23% a PR. Sézary cells were cleared from the blood in 6 of 7 (86%) patients, and CR in lymph nodes was observed in 6 of 11 (55%) patients [73]. Kennedy *et al*. treated 8 patients with relapsed or refractory advanced-stage CTCL with alemtuzumab [131]. Patients were given alemtuzumab (30 mg) intravenously three times per week for 12 weeks or until maximum response. The ORR was 38%, with 3 patients achieving a PR, 2 with stable disease and 3 with progressive disease during treatment. All patients developed progressive disease within 4 months of starting alemtuzumab [131].

MTX: Zackheim *et al.* treated 17 patients with SS with low-dose MTX for up to 5 years (median 22 months) [137]. Seven patients (41%) achieved a CR and the ORR was 76%. The estimated 5-year survival rate was 71%.

Recommendations for second-line treatment of SS are summarised in Table 12.

Summary and conclusion

In early-stage MF, SDT represents the most appropriate therapy. Most patients will be able to achieve a short-term clinical response with recurrent disease for many years and, in the majority of cases, a normal life expectancy. Therefore, potentially toxic and aggressive therapies should be avoided. Patients with more advanced stages of MF and patients with SS have a poor prognosis. In these patients, the absence of randomised, controlled trials results in a lack of sufficient evidence to provide a basis for a consensus. None of the therapies described so far have a documented impact on disease outcome. Thus, all patients with late-stage disease should be entered into appropriate clinical trials. As

treatment of MF/SS is always palliative, maintenance of quality of life should be at the centre of therapeutic strategies.

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Tables

Table 1. WHO-EORTC classification for cutaneous T-cell lymphomas with primary cutaneous manifestations [6]

MF
MF variants and subtypes:
Folliculotropic MF
Pagetoid reticulosis
Granulomatous slack skin
Sézary syndrome
Adult T-cell leukaemia/lymphoma
Primary cutaneous CD30-positive lymphoproliferative disorders:
Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma
Extranodal natural killer/T-cell lymphoma, nasal type
Peripheral cutaneous peripheral T-cell lymphoma, unspecified
Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (provisional)
Cutaneous ã/ä T-cell lymphoma (provisional)
Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (provisional)

Table 2a. Oxford Centre for Evidence-Based Medicine: levels of evidence [19]

1a	Evidence obtained from systematic reviews of multiple, randomised, controlled trials (RCTs), with homogeneity
1b	Evidence from individual RCT with a narrow confidence interval
1c	All patients died prior to introduction of drug but some now survive or Some patients died prior to introduction of drug but all now survive
2a	Evidence obtained from systematic reviews of multiple cohort studies, with homogeneity
2b	Evidence from individual cohort study or poor-quality RCT (<80% follow-up)
2c	Evidence obtained from outcomes research
3a	Evidence obtained from systematic reviews of multiple case-control studies with homogeneity
3b	Evidence from individual case-control study
4	Evidence from a case series, or poor-quality cohort study, or poor-quality case-control studies
5	Evidence based on expert opinion without critical appraisal, or laboratory research, physiology, or 'first principles'

Table 2b. Grades of recommendation [19]

A	Consistent level 1 studies
B	Consistent level 2 or 3 studies, or extrapolations from level 1 studies
C	Level 4 studies, or extrapolations from level 2 or 3 studies
D	Level 5 evidence, or troublingly inconsistent or inconclusive studies of any level

Table 3. Clinical staging for MF [1,3,22]

3a. Classification

T1	Patches, plaques, or both, involving <10% body surface area
T2	Patches, plaques, or both, involving ≥10% body surface area
T3	One or more cutaneous tumours
T4	Generalised erythroderma
N0	Lymph nodes clinically uninvolved
N1	Lymph nodes clinically enlarged but not histologically involved
N2	Lymph nodes clinically non-palpable but histologically involved
N3	Lymph nodes clinically enlarged and histologically involved
M0	No visceral metastases
M1	Visceral metastases
B0	No circulating atypical cells (Sézary cells), <5%
B1	Circulating atypical cells (Sézary cells), ≥5%

3b. Clinical stages

		Expected 5-year survival [15]
IA	T1 N0 M0	96–100%
IB	T2 N0 M0	73–86%
IIA	T1–2 N1 M0	49–73%
IIB	T3 N0–1 M0	40–65%
III	T4 N0–1 M0	40–57%
IVA	T1–4 N2–3 M0	15–40%
IVB	T1–4 N0–3 M1	0–15%

SS is staged as T4 N1 or N3 M0 B1 [15]

Table 4. Recommendations for first-line treatment of MF (stages IA, IB, and IIA)*

Recommended treatments		**Grade of recommendation** **Level of evidence**	**References**
'Expectant Policy'		C 4	[27,77,78]
SDT	PUVA	C 4	[15,39,80–83]
	UVB (patches only)	C 4	[40,84–86]
	Topical corticosteroids	C 4	[87]
	Localised radiotherapy	C 4	[88]
	TSEB (≤3 treatments)	C 4	[29,41,42,89]
	HN_2	C 4	[31,33,90]
	BCNU	C 4	[29,91,92]

* The order of recommended treatments is based on the consensus opinion of the authors. The individual choice of the appropriate therapy can differ and will depend on clinical presentation and treatment availability.

Table 5. Recommendations for second-line treatment of MF (stages IA, IB, and IIA)*

Recommended treatments	Level of evidence	References
Systemic therapies		
Oral bexarotene	B 1b	[64]
IFN-α monotherapy	B 2b	[54,98,99,101,104]
IFN-α + retinoids	B 1b	[60,79,97,103]
Denileukin diftitox	B 1b	[29,71]
Low-dose MTX	C 4	[105]
Systemic therapies + SDT		
IFN-α + PUVA	B 1b	[79,108,109,112]
Retinoids + PUVA	C 4	[113]
Bexarotene + PUVA	C 4	[114]

Table 6. Recommendations for first-line treatment of MF (stage IIB)*

Recommended treatments	Level of evidence	References
PUVA + IFN-α	B 1b	[79,108,109,112]
TSEB and superficial X-irradiation	C 4	[89,45,116]
Retinoids + IFN-α	B 1b	[60,79,97,103]
PUVA + retinoids	D 5	[113]

Table 7. Recommendations for second-line treatment of MF (stage IIB)*

Recommended treatments	Level of evidence	References
Bexarotene	B 2b	[119]
Chemotherapy	C 4	[48,49,102,120]
Denileukin diftitox	B 1b	[71]

Table 8. Recommendations for first-line treatment of MF (stage III)*

Recommended treatments	Level of evidence	References
PUVA + IFN-α	B 1b	[108–112,122]
IFN-α	B 2b	[54,55,98,101]
MTX	C 4	[122]
TSEB/ X-irradiation	C 4	[41]
HN_2 or BCNU	C 4	[34]
ECP	C 4	[75,76,125–127]
PUVA + retinoids	D 5	[113]

Table 9. Recommendations for second-line treatment of MF (stage III)*

Recommended treatments	Level of evidence	References
Chemotherapy	C 4	[14,15,120,102,50,129]

Table 10. Recommendations for treatment of MF (stages IVA–IVB)*

Recommended treatments	Level of evidence	References
Chemotherapy	C 4	[14,15,120,102,50,129,130,132]
TSEB and/or X-irradiation	C 4	[29,41,42,89]
Bexarotene	B 2b	[119]
Denileukin diftitox	B 1b	[71]
IFN-α	C 2b	[54,55,98,1001]
Alemtuzumab	C 2b	[73,131]
Low-dose MTX	C 4	[123]

Table 11. Recommendations for first-line treatment of SS*

Recommended treatments	Level of evidence	References
ECP	C 2b	[75,76,125,126,133,134]
IFN-α	C 2b	[54,55,98,100,101]
Denileukin diftitox	B 1b	[71]
Chlorambucil + prednisone	C 4	[135]

Table 12. Recommendations for second-line treatment of SS*

Recommended treatments	Level of evidence	References
Bexarotene	B 2b	[119]
Chemotherapy	C 4	[51,129,136]
Alemtuzumab	C 2b	[66,134]
MTX	C 4	[137]

SOP for creation of European Dermatology Guidelines

Step	Responsible	Task	Months duration
1	EDF Guidelines Committee (EDF-GC)	Decision of topic of specific guideline	∅
2	EDF Board	Confirmation of the choice and level of guideline (S1, S2 or S3) plus suggestion to the Guideline Committee of potential chairmen and subcommittee members.	0,5
3	EDF Guidelines Committee	Foundation of subcommittee for specific guidelines. Nomination of EDF members (50 %) as well as identification of possible EADV members (25 % of members for the subcommittee) who could work within the subcommittee. Chairman of EDF guideline committee asks EADV president for approval. Finally nomination of a chairperson of the subcommittee by the group.	at EDF Meeting
4	EDF-GSubC	Development of a business plan (see attachment)	1
5	EDF Board	Confirmation of business plan and signature of the contract for financial support of guideline	1
6	EDF Guidelines Subcommittee (EDF-GSubC)	Identify all existing guidelines for the specific guideline (active process: literature survey plus contact to Dermatological Societies)	1
7	EDF Guidelines Subcommittee	Select the guidelines with highest quality. Criteria for selection: 1. Availability of strength of evidence 2. Availability of strength of recommendation 3. Evidence of mechanics of literature review (adhere to the recommendations of the Cochrane collaboration. These standards should assure high quality for the systematic literature search as well as for the critical appraisal of the papers. For further information see http://www.cochrane.org/crgprocedures/chapter4/1.htm and documents available at EDF Guidelines Secretariat (Mrs. Janine Schweiger, janine.schweiger@charite.de)	1
8	EDF Guidelines Subcommittee	Identification/nomination of additional 50 % EDF members for the EDF-GSubC from amongst the authors of the best guidelines	0,5
9	Chairperson of Subcommittee	Consider involvement of other disciplines and patients´ organisations	1
10	EDF Guidelines Subcommittee	Meet 1. to decide the author of the first draft (normally the chairperson of the subcommittee) and to discuss the present guidelines, their strengths and weaknesses 2. 6 months later to discuss the draft (consensus conference)	6
11	Chairperson of Subcommittee	Circulate the guideline draft to national dermatological societies for comments	2
12	Guidelines Subcommittee	Circulate final version for approval among members of the guideline subcommittee	1
13	Chairperson of Subcommittee	Deliver final version for comments to EDF guideline committee chairperson, who forwards it to EADV Board and to UEMS	2
14	EDF Guidelines Committee	Review and comment guideline	1
15	EDF Guidelines Committee chairperson	Send guideline for official approval to UEMS (formal approval)	2
16	EDF secretary	Distribute guideline for in advance information to EDF members and National Dermatological Societies	1
17	EDF	Publication 1. on EDF homepage 2. in European dermatological journals 3. If publication in other national and international journals is requested by the respective society, this will be encouraged by the EDF	6