Review

Treatment Algorithms for Mycosis Fungoides and Sézary Syndrome

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Abstract

Mycosis fungoides (MF) is the most prevalent form of cutaneous T-cell lymphoma (CTCL). Tumor, lymph nodes, metastasis, and blood (TNMB) staging serves as the primary prognostic factor that significantly influences treatment strategies. The objectives of MF therapy are tailored to each patient, focusing on achieving adequate responses to alleviate symptoms and reducing the risk of progression. Continuing or maintenance therapies with low adverse effects are preferred to sustain disease control and enhance quality of life. This review is based on the latest international treatment guidelines from the European Organization for Research and Treatment of Cancer (EORTC), the National Comprehensive Cancer Network, and the British Association of Dermatologists in the United Kingdom Cutaneous Lymphoma Group. In early-stage MF, skin-directed treatments are effective, whereas systemic agents are required for early-stage refractory MF and advanced cases, including Sézary syndrome (SS). Biological and targeted therapies, as well as immunosuppressive treatments, are utilized in more severe cases, with new therapies for advanced disease currently under investigation in clinical trials. This review provides a comprehensive overview of the current treatment options for MF/SS by examining their mechanisms of action, efficacy, and side effects, thereby guiding clinicians in optimizing patient care.

Keywords: Cutaneous lymphoma, mycosis fungoides, Sézary syndrome, T-cell lymphoma, treatment

Introduction

Mycosis fungoides (MF) is the most common cutaneous T-cell lymphoma (CTCL), and many clinicopathologic variants of MF have been described. Tumor, lymph nodes, metastasis, blood (TNMB) staging remains the most important prognostic factor in CTCL, forming the basis of the treatment approach. In addition to clinical stage, histological evidence of folliculotropic and large cell transformation can be associated with poorer prognosis, which may warrant more aggressive treatment. The objectives of MF therapy should be tailored to the individual patient, but frequently include achieving an adequate response to reduce and control symptoms and minimize the risk of progression. Therapies with a low incidence of adverse effects and an absence of cumulative toxicity are frequently administered on an ongoing or maintenance basis to enhance and sustain disease control and quality of life.[1]

In CTCL, the decision to continue or modify treatment is based on clinical observations. Relapsed diseases may respond to prior therapies. Unlike other non-Hodgkin lymphomas, treatment responses can differ across compartments (skin, blood, lymph nodes), necessitating careful consideration in advanced-stage patients. The treatment of MF/Sézary syndrome (SS) requires a multidisciplinary approach involving dermatology, hematology, medical oncology, and radiation oncology. In patients with early-stage disease, skin-directed treatments

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(SDT) may be an effective option. However, patients with early-stage refractory MF or advanced MF and SS may require treatment with systemic agents. In this case, biological or targeted therapies, such as extracorporeal photochemotherapy, interferons (IFN), bexarotene, and histone deacetylase (HDAC) inhibitors, are employed as monotherapy or in combination with SDT. Immunosuppressive therapies, either as monotherapy (e.g., prelatrexate and methotrexate (MTX), gemcitabine, liposomal doxorubicin) or in combination with other chemotherapeutics, are employed in refractory or rapidly progressive cases with diffuse involvement, lymph node involvement, and/or metastasis. New treatments for advanced diseases are currently being developed through clinical trials. Patients with a resistant or progressive course should be enrolled in clinical trials at every stage of the disease.[2]

This review will provide an overview of the treatment options available for MF/SS, including an analysis of the mechanisms of action, efficacy, and side effects.

Methods

The treatment algorithms were based on the international guidelines for the treatment of MF, namely the European Organization for Research and Treatment of Cancer (EORTC), 2023 (1); the National Comprehensive Cancer Network (NCCN), version 3.2024 (2); and the British Association of Dermatologists and the United Kingdom Cutaneous Lymphoma Group guidelines (BAD-UKCLG), 2018.[3] Common and divergent aspects of these guidelines have been subjected to detailed analysis and summary to facilitate treatment planning.

The text includes information about whether the treatments mentioned have received approval from the US. The Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Although not currently included in the guidelines, this review also addresses the nuances of treatment for clinicopathological MF variants and specific patient populations.

Results

Accurate diagnosis and appropriate staging of patients with MF/SS are fundamental aspects in selecting the optimal therapeutic approach. MF and SS are both treatable, yet not curable, with conventional systemic therapy. The aforementioned principle does not apply to allogeneic stem cell transplantation (alloSCT) in cases of advanced disease and to a small number of patients with prolonged remission following SDT in localized early stages, where the primary objective of treatment is to achieve a cure.

Treatment of MF/SS should be performed in a stepwise and stage-adapted manner, with a primary focus on maintaining quality of life. In the absence of larger randomized controlled trials, the evidence base for decision making is limited. However, guidelines developed by various national and international groups can provide valuable assistance in this context. In general, the NCCN guidelines encompass a broader treatment spectrum, incorporating therapies that have shown benefits in small case series. In contrast, the EORTC guidelines focus on therapies approved in Europe that have more definitive evidence of efficacy.

The EORTC guidelines recommend that second-line options be reserved for patients who are refractory (showing no or only minimal response to treatment and experiencing progression during therapy) or who have contraindications to first-line treatment. In cases of relapse after successful first-line treatment, patients should not be considered refractory, and therapy can typically be reinitiated. The individual choice of appropriate therapy may vary according to clinical presentation and treatment availability (Table 1).[1]

The BAD-UKCLG guidelines recommend the establishment of supranetwork multidisciplinary teams (MDTs) that include dermatologists, clinical oncologists, hemato-oncologists, dermatopathologist, and hematopathologist. All patients with early-stage MF refractory to SDT and late-stage MF and SS should be reviewed by supranetwork MDTs to agree on a management plan and provide the opportunity for consideration in appropriate clinical trials. Additionally, the MDT is responsible for overseeing patients requiring specialized treatments, such as total skin electron beam therapy (TSEB), extracorporeal photopheresis (ECP), and stem cell transplantation (Figure 1).[3]

Watch and Wait (Expectant Policy)

Patients with stage IA disease have a low risk of progression and a life expectancy comparable to that of the general population. Therefore, the "watch and wait" approach remains a valid option for these patients, particularly those classified as T1a (with patches covering < 10% of the body surface area). However, careful monitoring is essential because some patients will eventually progress; over a 10-year period, approximately 10% of patients with early-stage disease experience progression.[1] The expectant policy has been recommended by the EORTC, but it is not included in the NCCN and BAD-UKCLG guidelines.

Skin-Directed Treatment

SDT is a recommended first-line intervention in the early stages of MF. In advanced stages, they may also be used in

combination with systemic options to control symptoms such as pain and pruritus and to improve skin tumor burden.

Topical Therapies

Topical therapies have demonstrated clinical efficacy for patches and thin plaques; however, the paucity of well-controlled studies limits the quality of evidence. A significant proportion of topical therapies have not been granted a license for use in MF.

Topical corticosteroids, nitrogen mustard, topical retinoids, carmustine, imiquimod, and topical calcineurin inhibitors (TCI) are discussed in detail in the context of topical therapies. However, topical MTX, 5-fluorouracil, and peldesine (a potent, competitive, reversible, and orally active purine nucleoside phosphorylase inhibitor) are not included in any of the three guidelines.

Table 1. EORTC recommendations according to clinical stage[1]

Recommendations for the treatment of MF stages IA, IB, and IIA	
First-line	**Second-line**
Expectant policy (mainly T1a) SDT - Topical corticosteroids (mainly T1a and T2a) - Topical chlormethine - nbUVB (mainly T1a and T2a) - PUVA - Localized RT (for localized MF including pagetoid reticulosis)	Systemic therapies - Retinoids - IFN-α TSEB (mainly T2b) Brentuximab vedotin Mogamulizumab Low-dose MTX
Recommendations for treatment of MF stage IIB	
First-line	**Second-line**
Systemic therapies - Retinoids - IFN-α TSEB Brentuximab vedotin Mogamulizumab Monochemotherapy (pegylated liposomal doxorubicin, gemcitabine) Low-dose MTX Localized RT	(Poly-)chemotherapy Brentuximab vedotin Mogamulizumab AlloSCT
Recommendations for the treatment of MF stages IIIA and IIIB	
First-line	**Second-line**
Systemic therapies - Retinoids - IFN-α ECP Brentuximab vedotin Mogamulizumab Low-dose MTX TSEB	Monochemotherapy (gemcitabine, pegylated liposomal doxorubicine) Brentuximab vedotin Mogamulizumab AlloSCT
Recommendations for the treatment of MF stages IVA and IVB	
Chemotherapy (gemcitabine, pegylated liposomal doxorubicine, CHOP and CHOP-like polychemotherapy) Radiotherapy (TSEB and localized) Brentuximab vedotin Mogamulizumab Alemtuzumab (mainly in B2) AlloSCT	
Recommendations for the treatment of SS	
First-line	**Second-line**
ECP Systemic therapies in combination with ECP or PUVA - Retinoids - IFN-α Chlorambucil + prednisone Low-dose MTX	Mogamulizumab Brentuximab vedotin Alemtuzumab Chemotherapy (gemcitabine, pegylated liposomal doxorubicine, CHOP and CHOP-like polychemotherapy) AlloSCT

AlloSCT: Allogeneic stem cell transplantation, CHOP: Cyclophosphamide doxorubicin vincristin prednisone, ECP: Extracorporeal photopheresis, IFN-α: Interferon alpha, MF: Mycosis fungoides, MTX: Methotrexate, nbUVB: Narrowband ultraviolet-B, PUVA: Psoralen plus ultraviolet-A, RT: Radiotherapy, SDT: Skin-directed treatment, SS: Sézary syndrome, TSEB: Total skin electron beam therapy, *For stage IV disease, no distinction is made between first- and second-line options because of insufficient evidence to justify such separation

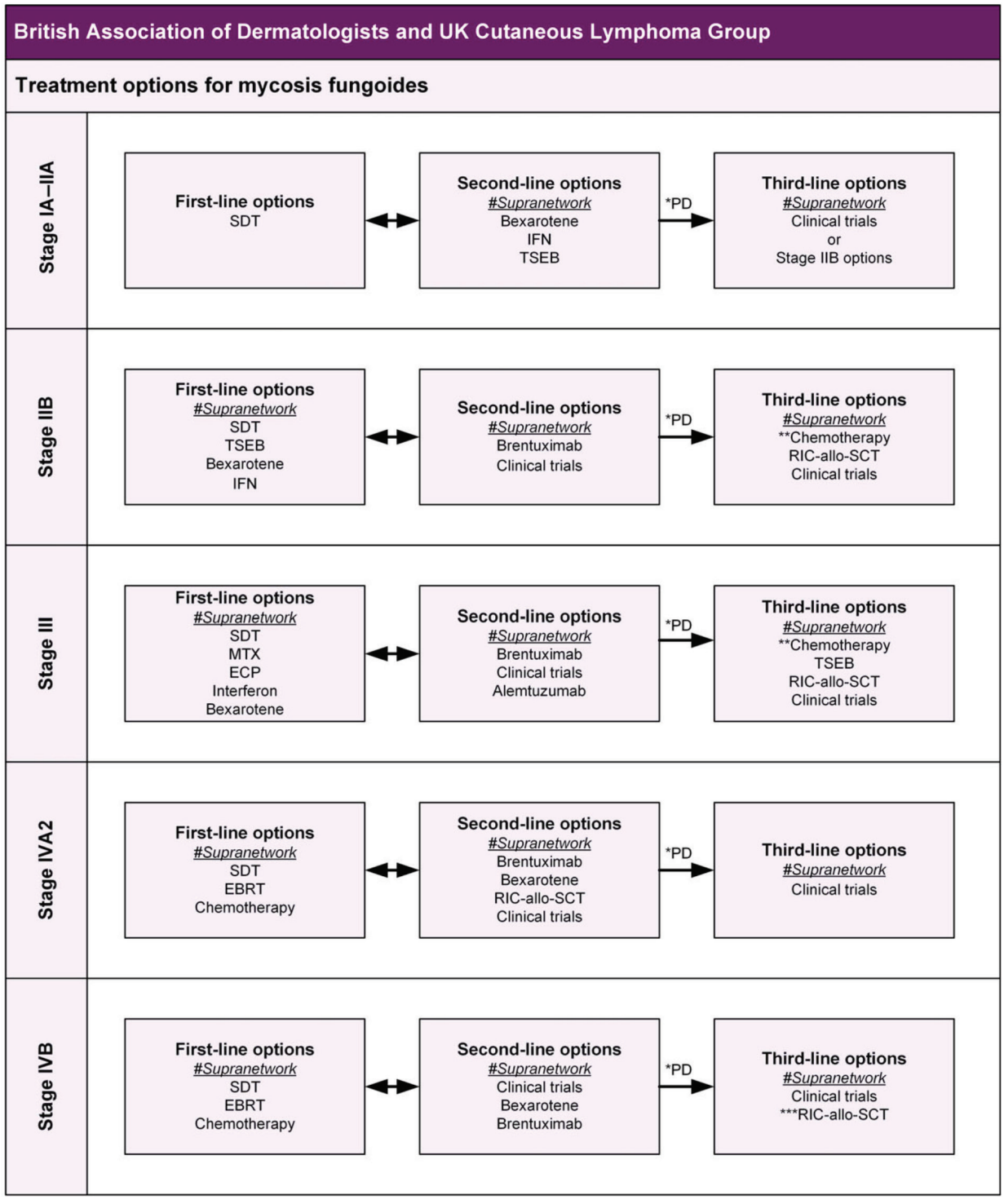

Figure 1. British Association of Dermatologists and the United Kingdom Cutaneous Lymphoma Group guidelines for the treatment of mycosis fungoides.[3] *EBRT: External beam radiotherapy with photons or electrons for lymph node, soft tissue or visceral lymphoma, ECP: Extracorporeal photopheresis, IFN: Interferon, MTX: Methotrexate, PD: Progressive disease, RIC-allo-SCT: Reduced intensity allogeneic stem cell transplantation, SDT: Skin-directed therapy (topical steroids, ultraviolet B, psoralen-ultraviolet A, skin radiotherapy, topical nitrogen mustard), TSEB: Total skin electron beam radiotherapy. Skin radiotherapy indicates superficial radiotherapy or EBRT to skin patches, plaques and tumours. #Supranetwork: refers to the supranetwork multidisciplinary team (MDT) meeting for treatment decision. *PD and exhausted first- and second-line options. **Chemotherapy as recommended by the supranetwork MDT. ***Consider only if the patient has durable complete response. ↔ indicates that after treatment, patients may respond to treatments included in earlier "line" options. Patients can move between first- and second-line options.*

Topical Corticosteroids

Topical corticosteroids induce lymphocyte apoptosis and inhibit the adhesion of lymphocytes to endothelial and intracellular areas. Since the early 1960s, these agents have been widely used in the treatment of MF owing to their accessibility, ease of application, and minimal adverse effects. However, the efficacy of these agents in the treatment of MF remains inconclusively supported by experimental evidence.[1]

In 2003, Zackheim[4] employed high-potency, class I topical steroids (predominantly clobetasol) as a primary therapeutic modality in approximately 200 patients with patch and early plaque stage MF and documented overall response rates (ORR) exceeding 90% in stage T1 patients and over 80% in stage T2 patients. They reported that contrary to the recommendations for the use of topical corticosteroids (maximum dosage of 50 g/week for two consecutive weeks, with careful application in sensitive areas such as the face, axilla, and groin), applying them without regard to the total dose and using occlusion in intertriginous areas, as well as in widespread body lesions, is an effective treatment for early-stage MF. It is noteworthy that cutaneous side effects (such as purpura, atrophy, and striae) that would necessitate the discontinuation of treatment are rare. Furthermore, they suggested that individuals using high-dose topical corticosteroids for an extended period do not routinely need to be tested for adrenal insufficiency unless significant clinical findings are present.[4]

In a recent single-center retrospective study, Kartan et al.[5] confirmed the efficacy and safety of topical clobetasol propionate monotherapy in 37 patients with MF, demonstrating a high response rate (81%) in early-stage MF (stages IA/IB).

All three guidelines recommend the use of topical corticosteroids for the treatment of MF.

Topical Chlormethine/Mechlorethamine (Nitrogen Mustard)

Mechlorethamine is an alkylating agent that impedes the processes of DNA replication and RNA transcription by forming crosslinks in DNA strands, ultimately resulting in apoptosis. There are solution, ointment, and gel formulations. In a randomized, controlled, multicenter trial involving 260 patients, the gel preparation demonstrated non-inferiority to the ointment, with response rates of 58.5% (gel) and 47.7% (ointment).[6]

The 0.016% gel preparation was approved by the FDA in 2013 for the topical treatment of stage IA and IB MF in patients who have received prior SDT. Subsequently, in 2017, the EMA granted it a broader indication for the topical treatment of MF in adult patients.[1]

The product should be applied once daily to all affected skin areas. Widespread disease can be applied to the whole body and safely. No evidence of systemic absorption after topical application was found, and no systemic toxicity was observed.[7] The side effect of contact dermatitis, which occurs in approximately 50% of patients, can be managed by treatment interruption and reintroduction with longer intervals between applications and by combination therapy with topical corticosteroids.[8] All three guidelines recommend the use of topical mechlorethamine for the treatment of early-stage MF.

Topical Retinoids

Bexarotene is a retinoid X receptor (RXR) antagonist. The gel formulation has been approved by the FDA for topical treatment of cutaneous lesions in patients with CTCL (stage IA and IB) who have refractory or persistent disease after other therapies or who have not tolerated other therapies.

In the phase I-II trial involving 67 patients with early-stage MF, the ORR was 63%, with 21% achieving complete response (CR). The estimated median response duration from the start of therapy was 99 weeks. Patients who had not received prior therapy for MF had a higher response rate (75%) than those who had previously undergone topical treatments (67%).[9]

In a phase III multicenter study involving 50 patients with early-stage refractory MF treated with topical bexarotene gel 1%, the ORR was 44%, with a complete remission rate of 8%. The most common adverse events (AE) likely associated with the drug were mild to moderate irritant dermatitis, pruritus and pain (primarily burning at the application site).[10]

A case report describes a patient with folliculotropic mycosis fungoides (FMF) who was refractory to intralesional and subcutaneous IFN-α-2a but achieved successful treatment with topical bexarotene gel, resulting in complete remission by the fifth month. This suggests that bexarotene gel is an effective option for localized early-stage FMF, even in cases resistant to systemic therapies.[11]

Bexarotene gel is not licensed in Europe. Thus, the current EORTC guidelines do not include any recommendations regarding the use of bexarotene gel.

Tazarotene, another topical retinoid, exerts antiproliferative and anti-inflammatory effects on the skin by binding to retinoic acid receptors (RAR)-β and RAR-γ. The efficacy and safety of tazarotene 0.1% topical gel/cream have been demonstrated in two small trials involving patients with early patch or plaque MF lesions.[12,13] Nevertheless, these results have not been followed up, the product has been discontinued in Europe, and it is not included as a treatment option in the current EORTC guideline.

Topical Carmustine (BCNU)

Carmustine is an alkylating agent that forms DNA crosslinks, leading to apoptosis.

Topical carmustine is an effective treatment for early-stage MF, with high response rates of 92% and 64% observed in patients with T1 and T2 disease, respectively, at 36 months. However, greater absorption increases the risk of bone marrow suppression, thereby making the use of topical carmustine in maintenance therapy inadvisable. In contrast, the incidence of irritant contact dermatitis is lower (10%) than that of topical mechlorethamine.[14] Topical carmustine has been recommended by the NCCN (category 2B) guidelines, but it is not included in the EORTC guidelines.

Topical Imiquimod

The toll-like receptor agonist imiquimod induces the production of local IFN-α, tumor necrosis factor-α, interleukin-1 (IL-1), and IL-6 and suppresses anti-apoptotic BCL-2. It is efficacious in a limited number of patients with early-stage MF refractory to other therapies.[15,16] Shipman and Scarisbrick[17] reported a total response rate of 80%, with a CR rate of 45%, and a partial response rate of 35% in 20 patients with stage IA-IIB MF treated with 5% imiquimod. The duration of topical imiquimod use among patients varied from 3 weeks to 7 months, employing different protocols, including application three nights a week or daily use. Although rare, some patients experience flu-like symptoms and fatigue; the side effects were primarily localized to the skin, and commonly include pain, erythema, local irritation, ulceration, and pruritus.[17]

Imiquimod may be used for areas with few lesions that are unresponsive to treatment or those located on sun-damaged skin, such as the forearms, scalp, and face.[2]

Topical imiquimod is recommended under the SDT section of the NCCN guidelines for patients with limited or localized skin involvement. Additionally, the EORTC and BAD-UKCLG guidelines include brief statements in case reports suggesting the potential benefit of imiquimod in the treatment of MF.

Topical Calcineurin Inhibitors

In a phase II multicenter study of 39 patients with stage IA-IIA MF, topical pimecrolimus (1% cream) resulted in an ORR of 56% (one CR, 21 partial responses). It was well tolerated, and no patient required dose reduction or treatment discontinuation due to drug-related toxicity.[18] There is only one case report of the successful use of 0.1% tacrolimus ointment for the treatment of MF.[19] The NCCN guidelines suggest that TCI should be considered as a steroid-sparing treatment for perioral and periorbital lesions in patients with early-stage MF.[2] In contrast, the EORTC guidelines acknowledge that while the results are promising, they should be interpreted with caution, and no recommendation can currently be made regarding the use of TCI in MF.[1]

Phototherapy

Psoralen plus ultraviolet-A (PUVA) and narrowband UVB (nbUVB) have a longstanding history in the treatment of MF and continue to be a mainstay in disease management, with high response rates in early-stage disease. Although some retrospective studies have indicated that PUVA is associated with superior outcomes and longer relapse-free intervals,[20] other studies have shown that UVB is as efficacious as PUVA for the management of early-stage MF.[21] However, these approaches have not been compared in randomized clinical trials.

A limited number of case series have demonstrated the efficacy of UVA1 phototherapy and excimer laser in the treatment of MF. However, only PUVA and nbUVB were considered in the EORTC guideline given that only these therapies have a sufficient body of evidence together with broad accessibility is available.[1]

Psoralen-Ultraviolet A Photochemotherapy

A substantial body of evidence from extensive, non-randomized and retrospective case studies has demonstrated that PUVA is an effective treatment option for patients with early-stage disease, with high rates of CR.[3]

A retrospective study of long-term outcomes following complete remission from PUVA monotherapy reported that 30-50% of patients exhibited durable remission (10-year disease-free survival), but maintenance PUVA was given to almost all responding patients. One-third of patients presented with chronic photodamage and secondary skin cancers.[22]

The potential risks and benefits of phototherapy should be carefully considered in patients with a history of immunosuppressive medication use, basal cell carcinoma, squamous cell carcinoma, or melanoma.[2]

In cases where clinical necessity arises, a combination of phototherapy with systemic treatments (most commonly retinoids or IFN-α) may be considered.[1]

A study assessing the efficacy of PUVA and low-dose IFN-α-2a combination therapy in 68 patients with both early and advanced MF found that CR was achieved in 45.6% of patients, resulting in an ORR of 60.3%. The authors reported that CR was significantly higher in early-stage patients. However,

despite achieving CR, 80% of the patients experienced relapse, and no significant difference in disease-free survival was observed between early and advanced stages.[23]

The combination of PUVA and acitretin has been demonstrated to result in a reduction in the cumulative UVA dose required to achieve the best response, while exhibiting no difference in response rates when compared with PUVA alone. The duration of remission was found to be prolonged when retinoids were administered as maintenance therapy.[24]

The combination of PUVA and bexarotene is also safe, with similar response rates and durations to those observed with PUVA alone.[25]

The results of a prospective cohort study indicate that maintenance therapy does not prevent future relapse.[26] For maintenance PUVA, the risks may outweigh the benefits.

The pivotal questions regarding the impact of PUVA on progression and disease-specific survival remain unresolved.[3]

Ultraviolet-B Phototherapy

The BAD-UKCLG guideline asserted that both nbUVB and broadband UVB (bbUVB) phototherapy can result in high CR rates, with a greater likelihood of responses in patients who have only patches.[3] However, the EORTC guidelines do not recommend bbUVB because of its disadvantages compared with nbUVB.[1]

NbUVB has antiproliferative, anti-inflammatory, and immunosuppressive properties. Some studies have demonstrated that nbUVB is as efficacious as PUVA for the management of early-stage MF, as previously mentioned. Additionally, a pediatric case series revealed high response rates (> 80%), including a number of CR in children with the hypopigmented variant of MF.[27]

Compared with PUVA, it has several significant advantages, including a lower risk of photocarcinogenesis, suitability for use in pregnant women and children, absence of gastrointestinal, hepatic, and other side effects associated with psoralene, and no need for eye protection after treatment. Maintenance treatment with nbUVB is still controversial.

Photodynamic Therapy

Photodynamic therapy (PDT) is a treatment option for solitary plaques that do not respond to topical treatment. The efficacy of MF treatment has been demonstrated in numerous case studies, as recently reviewed by Hooper et al.[28] CR was achieved in 67.3%, partial response in 13.5%, and no response in 3.8% of all included cases. The mean number of treatments in this analysis was 9.5, indicating that serial PDT is likely necessary for the successful treatment of MF.[28]

Further trials are necessary to optimize PDT protocols in terms of lesion type, thickness, and location. In addition, PDT is not a viable option for the treatment of large areas of the body surface or total skin exposure. Consequently, the EORTC and NCCN guidelines do not recommend the use of PDT for the treatment of MF.

Radiation Therapy

MF is a highly radiosensitive malignancy, and localized radiotherapy represents an efficacious treatment option for patients at all stages of the disease. Photons and electrons can be used, and the dose ranges from 0.7 to 35 Gy.[1]

Local radiation therapy (RT) alone (without adjuvant therapy) has an ORR of 97-100% for unilateral or stage IA MF.[2,29]

In a study involving 31 patients with MF, the CR rate was 30% when low-dose RT (4 Gy in 2 fractions) was used, whereas increasing the dose to 8 Gy in two fractions yielded a CR rate of 92%. Patients who did not respond to low-dose RT were re-treated with 20 Gy administered in eight fractions. The study also concluded that higher radiation doses during disease progression are safe and feasible.[30]

The optimal management of individual plaque and tumor lesions is with external beam radiotherapy (EBRT), typically administered at a dose of 8-12 Gy. An 8 Gy dose may be given in a single fraction, whereas 24-30 Gy is recommended for achieving a more durable response or for unilateral presentations.[31]

Localized, peripheral nodal disease and visceral metastases can also be treated with EBRT. Central nervous system disease in patients with MF has a very poor prognosis. In patients who are suitable for treatment and have good performance status, palliative low-dose whole-brain RT may be an option.[3] Combinations of RT with other SDT and systemic therapies are possible.

Total Skin Electron Beam Therapy

TSEB has a long history of treating MF. Conventional-dose (30-36 Gy) or low dose (< 30 Gy) TSEBT, either alone or in combination with adjuvant therapy, has been shown to be effective for all stages. To minimize the dose-dependent toxicity of TSEB, including erythema, desquamation, anhydrosis, alopecia, and xerosis, low-dose regimens (8-12 Gy) have been increasingly reported.

In a retrospective study that evaluated low-dose TSEBT in 102 patients with T2-T4 disease (excluding those with extracutaneous involvement), the ORRs were 98% and 97% for TSEBT doses of 10 Gy to less than 20 Gy and 20 Gy to less than 30 Gy, respectively. The overall survival (OS) and progression-free survival (PFS) rates were not significantly different between dose groups and were comparable to those observed with standard-dose TSEBT (≥ 30 Gy).[32] In a prospective study conducted in the UK, 103 patients received a low-dose TSEB schedule of 12 Gy administered in 8 fractions over a 2-week period. Of these patients, 54 had stage IB disease, 33 had stage IIB, 12 had stage III, and 4 had stage IV. The ORR was 87% (18% CR and 69% partial response). The median response duration was 11.8 months, and the median time to relapse after CR was 7.3 months. The treatment was well tolerated with lower toxicity than higher-dose schedules.[33]

It is common practice to follow TSEBT with systemic therapies, such as IFN or bexarotene, to maintain response in patients with stage IB-IIA disease and higher skin disease burden. Adjuvant systemic therapy may be a viable option for enhancing response rates in patients with tumorigenic stage. TSEBT may not be well tolerated in patients with erythrodermic disease, and should be used with caution. In these patients, it may be used at lower doses and with slower fractionation.[2]

Systemic Biological Therapies

Systemic therapies are recommended for early-stage disease refractory to SDT and for advanced-stage MF and SS. The choice of systemic therapy regimens is dependent on a number of factors, including the clinical features of the patient (such as extent of patch or plaques, the burden of disease in the skin, lymph nodes and blood, previous therapies, and comorbidities), the pathological features (like presence of large cell transformation or FMF), and the immunohistochemical data (e.g., CD30 positivity).[2] Generally, systemic therapy regimens that are better tolerated for longer durations, exhibit lower rates of cumulative toxicity, and/or demonstrate higher efficacy are preferred in earlier lines of treatment. For patients requiring chemotherapy, single agents are favored over combination chemotherapy due to the higher toxicity profiles associated with multi-agent regimens and the short-lived responses observed with time-limited combination therapies. Multi-agent chemotherapy regimens are generally reserved only for disease refractory to multiple prior therapies, bulky lymph node, or solid organ disease, and/or as a bridge to alloSCT.[1,2]

Bexarotene, brentuximab vedotin (BV), mogamulizumab, vorinostat, romidepsin, and denileukin diftitox have been approved by the FDA for the treatment of MF and SS. The efficacy of BV and mogamulizumab compared with standard therapies has been demonstrated in phase III randomized trials (ALCANZA and MAVORIC, respectively). Bexarotene, vorinostat, romidepsin, and other systemic therapies, such as pralatrexate, alemtuzumab, and pembrolizumab, have only been assessed in phase II studies. Although IFNs and MTX provide clinical benefits, they have not been evaluated in phase II studies within the context of modern staging for MF and SS.[2]

Retinoids

Bexarotene, a substrate of RXR (thus termed a "rexinoid"), is the only retinoid specifically developed for the treatment of CTCL. In 1999, the FDA and EMA approved bexarotene for use in patients with advanced-stage (IIB-IVB) CTCL who failed to respond to at least one prior systemic therapy. A Japanese study assessed the safety and efficacy of bexarotene in 139 patients with MF and reported an objective response rate of 46.8%. Patients starting treatment at 300 mg/m^2 showed significantly higher response rates (61.6%) compared to those on lower doses (22.6%). Additionally, among the 92 patients treated with bexarotene combined with photo(chemo)therapy, the response rate was 57.6%, which was significantly higher than the 25.5% seen in those treated with bexarotene alone. The findings of this study indicate that higher doses of bexarotene and combination therapy may enhance the treatment efficacy for MF. Common treatment-related AE were hypothyroidism (85.8%), hypertriglyceridemia (68.5%), hypercholesterolemia (43.8%), and neutropenia (21.3%). Among these, hypertriglyceridemia, hypercholesterolemia, and neutropenia were reported more frequently in patients starting treatment with bexarotene at a dose of 300 mg/m^2 compared to those starting at doses below 300 mg/m^2.[34] Laboratory monitoring of triglycerides and free thyroxine (T4) levels is essential and often necessitates additional management. Due to its favorable tolerability profile and lack of significant cumulative toxicity, the NCCN guidelines recommend bexarotene for patients with early-stage MF who do not achieve adequate disease control with SDT. It is also utilized in combination with phototherapy or ECP for early-stage disease that does not respond sufficiently to single-agent therapy, as well as for patients with advanced-stage disease.[2]

RAR agonists, such as acitretin and isotretinoin, are effective in treating early-stage MF. In a small cohort of 35 patients with early-stage MF, acitretin and isotretinoin yielded ORR of 64% and 80%, respectively, although the CR rates were low at 4% and 8%, respectively. Side effect profiles were as

previously reported for retinoids (most notably teratogenicity, dryness of skin and mucous membranes, hyperlipidemia).[35] Only moderate response rates can be achieved with retinoid monotherapy in patients with MF/SS. Therefore, these agents are often used in combination with other treatments or for maintenance therapy.[1]

Interferon-Alpha

IFN-α exerts an immunomodulatory effect by activating $CD8^+$ T lymphocytes and natural killer cells and suppressing Th2 cytokine production in malignant T lymphocytes. IFN enhances cytotoxic effects by increasing MHC class I molecule expression in lymphocytes and inhibiting excessive production of IL-5, thereby reducing eosinophil proliferation. IFN gained prominence as a treatment modality for CTCL in 1984 and has since been incorporated into CTCL treatment guidelines worldwide.[36]

Numerous relatively small, non-randomized studies of IFN-α have been conducted in pretreated patients with MF/SS across all stages, utilizing variable dosing schedules (3-9 megaunits, three to seven times weekly). ORR > 50% and CR > 20% have been reported. Response rates are higher in the early stages and with increased IFN doses.[37]

A prospective, randomized study evaluated the efficacy of IFN combined with PUVA versus IFN combined with retinoids in patients with stage I or II CTCL. The combination of IFN and PUVA resulted in significantly higher CR rates in this patient population (70% vs. 38%).[38]

Both previously available formulations of recombinant IFN (IFN-α 2a and IFN-α 2b) have been withdrawn from the market since 2019. Given the essential role of IFN-α in the treatment of MF and SS, it is imperative that the withdrawn preparations be replaced with the sole remaining available pharmacological variant, namely pegylated IFN-α 2a (peg-IFN-α 2a).[1]

The safety, tolerability, and efficacy of peg-IFN-α 2a were prospectively evaluated by Schiller et al.[39] in an open-label, multicenter, dose-escalation study involving patients with MF stages IB-III. Patients received subcutaneous peg-IFN-α 2a at doses of 180 µg (n = 4), 270 µg (n = 6), or 360 µg (n = 3) once weekly for 12 weeks. The treatment was generally well tolerated, and the most common AE being fatigue, acute flu-like symptoms, and hepatotoxicity. Dose reductions or withholding due to AE were infrequent (n = 1 for 180 µg, n = 4 for 270 µg, and n = 0 for 360 µg). Response rates (complete or partial response) ranged from 50% to 66%, with no clear dose–response relationship observed.[39]

Targeted Immunotherapy

Brentuximab Vedotin

BV is an antibody-drug conjugate consisting of an anti-CD30 immunoglobulin G1 (IgG1) antibody linked to monomethyl auristatin E, a microtubule-disrupting agent, which is released upon internalization into CD30-expressing tumor cells. The standard therapeutic regimen is an intravenous infusion of 1.8 mg/kg every 3 weeks for 16 cycles or until unacceptable toxicity or disease progression occurs.[40]

Based on the results of the international, open-label, randomized phase 3 ALCANZA trial, BV has been approved for the treatment of adult patients with $CD30^+$ CTCL following at least one prior systemic therapy in Europe and the US. In this trial, BV was more effective than MTX or bexarotene in patients with ≥ stage IB MF.[41] The final analysis confirmed that BV significantly improved the ORR lasting at least 4 months (ORR4: 55% vs. 13%), as well as the median PFS (17 months vs. 4 months), and reduced patient-reported symptom burden compared with MTX or bexarotene in patients with CD30-positive MF. Peripheral neuropathy was the most common AE, reported in 44 patients (69%).[42]

In the ALCANZA trial, CD30 positivity was defined as CD30 expression in ≥ 10% of total lymphoid cells in at least one skin biopsy. The results of an exploratory analysis showed that BV resulted in higher ORR4 and improved PFS in patients with ≥ 10% CD30 expression, regardless of the large cell transformation status.[43] When addressing the practical challenge of selecting suitable patients for BV treatment, it is important to recognize that the cut-off value used in the ALCANZA trial (10% positivity) was established arbitrarily. The evidence suggests that significant responses can be observed at low positivity levels. Furthermore, CD30 expression can vary among individuals. A retrospective analysis of 135 biopsy specimens from 95 patients with MF was performed to evaluate CD30 expression by immunohistochemistry. The authors found that CD30 was detectable in 90% of the samples, with ≥ 10% positivity observed in 60%. In patients with multiple biopsies, considerable variability in CD30 expression was noted, particularly in samples obtained at different time points. The authors concluded that examining multiple tissue samples enhances the evaluation of CD30 expression in MF, potentially reducing the risk of inappropriate treatment assignment.[44]

Mogamulizumab

Mogamulizumab is a humanized monoclonal antibody that targets CCR4, a chemokine receptor expressed on T-cells that is involved in the cell trafficking of lymphocytes to the skin.[45]

The drug received FDA and EMA approval in 2018 for relapsed/refractory MF and SS.

The safety and efficacy of mogamulizumab were demonstrated in a large open-label, randomized, controlled phase 3 (MAVORIC) trial involving 372 patients (204 with MF and 168 with SS). Patients were randomly assigned to receive either mogamulizumab (n = 186) or vorinostat (n = 186). The trial showed a PFS of 7.7 months for mogamulizumab and 3.1 months for vorinostat, with ORRs of 28% and 4.8%, respectively. The most common drug-related AEs were infusion-related reactions, drug rash, diarrhea, and fatigue.[46] Post-hoc analyses assessing the efficacy of mogamulizumab based on blood tumor burden showed that blood involvement was correlated with improved ORRs, PFS, and time to next treatment (TTNT) among patients receiving mogamulizumab. The ORRs were 26% and 37% for patients with B1 and B2 blood involvement, respectively, and 16% for those with B0 blood involvement. The median PFS was 11 months for B2 and 8 months for B1, whereas it was only 5 months for patients with B0 involvement. The TTNT was 20 months for patients with B2 involvement, 12 months for B1, and 7 months for B0. Additionally, mogamulizumab was linked to rapid and sustained reductions in $CD4^+$ $CD26^-$ cell counts and CD4/CD8 ratios across all blood involvement categories.[47,48]

The most common AE leading to the discontinuation of mogamulizumab was drug-induced skin eruptions, which can mimic MF/SS. However, mogamulizumab-associated skin rash may serve as a potential marker of tumor response.[49] It is recommended that skin biopsies, including appropriate immunohistochemical staining and clonality assessments, be performed to rule out disease progression in patients experiencing these skin eruptions.[50]

Alemtuzumab

Alemtuzumab is a humanized recombinant IgG1 monoclonal antibody targeting CD52.

This treatment demonstrates significant clinical activity in patients with previously treated advanced MF and SS, showing a higher ORR in patients with erythroderma or SS compared to those with advanced MF. However, it is associated with myelotoxicity and infectious complications. The subcutaneous administration of reduced-dose alemtuzumab (3-15 mg) over a shorter duration was equally effective with fewer infectious complications in patients with SS.[51] Although alemtuzumab is no longer commercially available, it can still be administered to patients with CTCL and other hematologic malignancies.[2]

Other Immunotherapies

Immune checkpoint inhibitors, particularly anti-programmed cell death protein 1 (PD-1) and anti-PD-L1 antibodies, have transformed the treatment landscape for metastatic melanoma and other solid cancers by inducing durable responses in a significant proportion of patients with manageable immune-mediated toxicity.[1] In a phase II trial, pembrolizumab, an immune checkpoint inhibitor, demonstrated durable responses in both MF and SS, achieving an ORR of 38% with a median duration of response not reached at a median follow-up of 58 weeks. Notably, pembrolizumab was associated with a skin flare reaction, which occurred exclusively in patients with SS and correlated with high PD-1 expression in Sézary cells; this reaction must be differentiated from disease progression.[52]

KIR3DL2, a member of the KIR family of natural killer cell Ig-like receptors, is aberrantly expressed in tumor cells of most patients with SS and other CTCLs. In addition to its use in diagnosis, follow-up, and as a prognostic biomarker, targeting KIR3DL2 with IPH4102, a therapeutic monoclonal antibody, was reported to be safe and clinically active in a first-in-human phase 1 study in CTCL. A confirmed global overall response was achieved in 16 (36.4%) of 44 patients, of which 15 responses were observed in 35 patients with SS (43%).[53] A subsequent, multi-cohort, and multi-center phase II study (TELLOMAK) will evaluate the clinical activity and safety of IPH4102 alone or in combination with chemotherapy in patients with advanced T-cell lymphoma is ongoing.[1]

Histone Deacetylase Inhibitors

HDAC inhibitors enhance the acetylation of histones and non-histone proteins, influencing gene transcription and leading to cell cycle arrest and apoptosis.

Vorinostat was the first HDAC inhibitor approved by the FDA in 2006 for the treatment of progressive, persistent, or recurrent MF/SS. In the initial phase IIB registration study, oral vorinostat (400 mg) achieved an ORR of 30%.[54] Long-term evaluation of patients on vorinostat for > 2 years indicates its safety and tolerability in patients with heavily pretreated MF/SS, with rare cumulative toxicities. However, patients should be monitored for gastrointestinal side effects, including nausea, diarrhea, and possible dehydration.[55]

Romidepsin, another HDAC inhibitor, has shown clinical efficacy across all disease compartments in treating MF/SS. The median duration of response to romidepsin ranged from 13 to 15 months. Notably, it significantly alleviated pruritus scores regardless of the clinical objective response. The ORRs were 40% for skin involvement, 35% for erythroderma, 32% for blood involvement, and 27% for lymphadenopathy.[56] When administering romidepsin, monitoring for QTc prolongation is

essential, especially when used with antiemetics, which can also affect QTc. Romidepsin is recommended as the preferred treatment for patients with SS exhibiting a great burden of Sézary cells.[2]

None of the HDAC inhibitors have received authorization for use in Europe, and they are not included in the EORTC guidelines.

Denileukin Diftitox

Denileukin diftitox is a recombinant human IL-2 diphtheria toxin fusion protein that targets the IL-2 receptor (CD25). It was initially approved in the US for relapsed/refractory CTCL but was withdrawn from the market in 2014 due to manufacturing issues.[2] It has not been approved by the EMA for MF/SS and is therefore not included in the EORTC guidelines.[1]

A reformulated version was assessed in a study that included 69 patients with relapsed or refractory MF/SS, predominantly with stage IB-IIA (n = 25) or stage IIB (n = 24) disease. The ORR was 36%, with a median response duration of 6.5 months. Higher ORRs were observed in stage IIB patients (46%) compared with stage IA-IIA (37%) and stage III (20%). No correlation was observed between CD25 expression and treatment efficacy. The skin disease burden decreased in 84% of evaluable patients (54 out of 64). Treatment-related AE, mainly grade 1-2, included capillary leak syndrome, infusion-related reactions, visual impairment, and hepatotoxicity, with no cumulative toxicity observed.[57,58]

Denileukin diftitox is recommended in the NCCN guideline as a preferred systemic therapy for stage IIB (generalized tumor disease) and as a useful option in certain circumstances for stage IB-IIA, limited stage IIB, and stage III disease.[2]

Chemotherapy

Liposomal Doxorubicin

Pegylated liposomal doxorubicin exhibits single-agent activity in patients with pretreated, advanced, or refractory MF and SS. In a phase II EORTC multicenter trial involving 49 patients with relapsed/refractory advanced MF after at least two prior systemic therapies, the drug achieved an ORR of 41% (with 6% CR) and a median duration of response and median time to progression of 6 and 7 months, respectively. It was well tolerated, with no grade 3 or 4 hematologic toxicities; the most common grade 3 or 4 adverse effects were dermatologic toxicity (6%), constitutional symptoms (4%), gastrointestinal issues (4%), and infections (4%).[59]

Another real-life cohort study of 36 patients (34 with MF and 2 with SS) further confirmed the efficacy of doxorubicin, particularly in patients with tumor stage disease.[60]

Gemcitabine

Gemcitabine, another cytostatic drug, is an effective treatment option for patients with heavily pretreated advanced-stage MF and SS. In a retrospective observational study involving 25 patients with advanced MF and SS, long-term follow-up over 15 years revealed estimated OS, PFS, and disease-free survival rates of 47%, 9%, and 40%, respectively.[61]

A single-center study of 14 heavily pretreated patients (12 with MF and 2 with SS) showed an ORR of 57%, with a median TTNT of 12 months.[62] Moreover, retrospective studies have shown favorable clinical outcomes with low-dose gemcitabine (1000 mg every 15 days), accompanied by tolerable and manageable adverse effects.[63]

Other Chemotherapeutic Agents

The other chemotherapeutic agents included in the EORTC recommendations are chlorambucil and MTX. The recommended MTX doses range from 5 to 25 mg once weekly. Chlorambucil is used in SS in combination with low-dose prednisone. Prolonged exposure is associated with a risk of leukemia, and thus, exposure should be avoided. Due to the high efficacy of mogamulizumab in the treatment of SS, the use of chlorambucil is limited to individual patients and resource-poor settings.[1]

The NCCN guidelines recommend the use of pralatrexate in patients with heavily pretreated MF and SS. In a multicenter dose-finding study involving 54 patients with relapsed or refractory MF and SS, pralatrexate was administered at doses ranging from 10 to 30 mg/m^2 weekly for 2 of 3 weeks or 3 of 4 weeks, resulting in an ORR of 41% (with 6% CR). Among the 29 patients receiving the recommended dose of 15 mg/m^2 weekly for 3 weeks in a 4-week cycle, the ORR was 45% (with 3% CR). The most common grade 3 AE was mucositis (17%); the only grade 4 AE was leukopenia (3%).[64]

In the subgroup of patients with transformed MF treated in the PROPEL trial, pralatrexate at 30 mg/m^2 yielded an objective response of 25% per independent central review and 58% per investigator assessment, with median PFS and OS rates of 5 and 13 months, respectively.[65]

Extracorporeal Photopheresis

ECP is an immunomodulating procedure that has been used for treating CTCL since 1987. The procedure is administered

over two consecutive days and is typically repeated every four weeks although it can be performed more frequently in patients with a high blood tumor burden. Responses to ECP may take up to six months to manifest, and therapy should continue until there is a loss of response.[3]

ECP can be safely applied alone or in combination with other systemic (e.g., IFN-α, retinoids) and skin-directed therapies.[66]

In a meta-analysis of over 400 patients with MF and SS, ECP as a monotherapy achieved a combined ORR of 55.7% across all stages of CTCL, with a 17.6% CR rate.[67]

A retrospective study involving 50 patients with MF reported an ORR of 42% (21 out of 50), with a median time to response of 11 months (ranging from 3 to 48 months). The OS was 72 months, showing no statistically significant differences between early-stage (77 months) and late-stage disease (69 months; $P = 0.077$). The authors concluded that the low incidence of side effects and the improved OS observed with combination therapy make ECP a viable treatment option for MF.[68] There may be an emerging role for ECP in early-stage MF; however, the available data are limited, and current guidelines do not provide recommendations in this regard.[1,69]

The degree of blood involvement, CD4/CD8 ratio, and circulating $CD3^+CD8^+$ cells or $CD4^+CD7^-$ lymphocytes have been identified as predictors of clinical response to ECP.[70,71] ECP is particularly well-suited as a systemic therapy for patients at risk of blood involvement (B1 or B2), including those with erythrodermic stage III MF or stage IVA with SS. However, there is currently no strong evidence to suggest that one combination therapy is superior to another or that ECP alone.[1]

Hematopoietic Stem Cell Transplantation

Autologous stem cell transplantation has been abandoned in patients with MF/SS because of the invariable occurrence of relapse in all patients, despite associated toxicity. On the other hand, alloSCT is the only curative option for MF/SS in patients with advanced disease. Allogeneic transplantation is successful in part because of the graft-versus-lymphoma effect of the donor graft, but this benefit must be carefully balanced against the potential risks associated with chronic graft-versus-host disease (GVHD). A significant concern following allogeneic transplantation is the potential for disease relapse. Although some patients can be successfully treated with donor lymphocyte infusion, this can also result in severe GVHD.[3]

In a single-center retrospective study of 19 patients with advanced MF/SS who underwent autologous hematopoietic stem cell transplantation (AHSCT) (the majority of whom had progressive disease prior to the transplant), non-relapse mortality was observed to be 35.9% at 1 year and 26.9% at 3 years and beyond. The probability of OS was 48.5% and 32.3% at 1 and 5 years after transplantation, respectively. The authors noted that considering the poor prognosis for patients not receiving transplants and the absence of curative non-transplant therapies, AHSCT successfully rescued 32.3% of the transplant-eligible, heavily treated patient population within 5 years.[72]

In a systematic review and meta-analysis focusing on alloSCT in CTCL, five studies involving 266 patients were analyzed. Reduced intensity and non-myeloablative regimens were most commonly used, accounting for 76% of cases, whereas mobilized peripheral blood stem cells were the preferred graft source in 78% of patients. The pooled OS rate was 59%, and the PFS rate was 36%. The pooled relapse rate was 47%, with a non-relapse mortality rate of 19%. The findings indicate that allo-SCT provides promising OS and PFS rates; however, relapse remains a significant challenge and common cause of treatment failure. Future strategies should focus on administering allo-SCT before the onset of resistant disease and incorporating post-transplant maintenance therapies to mitigate relapse rates.[73]

In a prospective, controlled trial on alloSCT in patients with advanced MF/SS, 99 patients were enrolled, with 55 receiving alloSCT and 44 undergoing non-allogeneic therapy (patients without a compatible donor). The primary endpoint was PFS, which was significantly better in the alloSCT group (median PFS of 9.0 months after alloSCT versus 3.0 months in the matched control group). At the time of publication, the median OS was 26.9 months in the control group and was not reached in the alloSCT group. Serious AE were more common in the alloSCT group, with infections being the most common. The study concluded that alloSCT significantly improves PFS in patients with high-risk advanced-stage MF or SS who achieve remission before transplantation.[74] The decision to proceed with transplantation requires thorough counseling to weigh the significant risks against the potential long-term benefits and the options for alternative treatments.[2]

Maintenance

Maintenance therapy refers to the ongoing administration of either skin-directed or systemic treatment after remission, with the goal of sustaining the response and preventing relapse or progression. Treatments that are deemed appropriate for maintenance should be effective, palliative, available, and simple to administer. Furthermore, they must have an excellent safety profile and exert minimal impact on the patient's quality of life.[75]

The EORTC guidelines list several agents that can be used for maintenance therapy after MF and SS. These include topical corticosteroids, chlormethine, nbUVB, PUVA, ECP, IFN-α, low-dose MTX, and oral retinoids.[1]

Currently, there is a paucity of evidence-based guidelines for the maintenance therapy of CTCL. The question of how initial remission or stable disease can be maintained is one of the most significant challenges in the management of CTCL.[76]

In practice, maintenance therapy often involves tapering the treatment that induces remission (such as phototherapy, retinoids, IFN-α, or ECP) or introducing a maintenance agent after achieving remission using a method that has dose-limiting toxicity, such as TSEB or systemic chemotherapy.[77] Overall, no definitive evidence has been available to guide the indications and selection of maintenance therapy for MF/SS. The EORTC guidelines recommend maintenance therapy for patients with a clinical stage of ≥ IB (T2b) who are at high risk of relapse and/or progression, following careful consideration and counseling.[1] In contrast, the NCCN guidelines suggest that all patients (stage IA-IV) who experience clinical benefits or have shown a response to primary treatment should be considered for maintenance therapy or tapering of their treatment regimens to enhance the duration of their response.[2]

Supportive Care

Management of Pruritus

Pruritus affects a large proportion of patients (nearly 90%) with CTCL and is significantly more severe in late- than in early-stage disease and in SS than in MF.[78]

The treatment of pruritus requires optimization of both SDT and systemic therapies. Daily use of moisturizers and emollients is beneficial for maintaining and protecting skin barrier. In early-stage disease, topical steroids can effectively manage both the disease and associated pruritus.[79] First-line treatment options include H1 antihistamines and gabapentin.[80] In the second-line setting, aprepitant, mirtazapine, or selective serotonin reuptake inhibitors may be considered.[81,82] If pruritus does not resolve with these agents, treatment with naltrexone may be an option.[2,83]

Prevention and Treatment of Infections

Bacteremia/sepsis and bacterial pneumonia were identified as the primary causes of death due to infections in a retrospective cohort study of patients with MF and SS.[84] Several preventive measures can be implemented to minimize infectious complications, including maintaining and protecting the skin barrier, using bleach baths or soaks, avoiding central lines, and employing prophylactic mupirocin in cases of Staphylococcus aureus colonization. Additionally, HSV prophylaxis with acyclovir or an equivalent should be considered for patients with frequent recurrences of HSV infection.[2]

Clinicopathological Variants of Mycosis fungoides

Clinicopathologic presentations of MF extend beyond the conventional form and include various subtypes, such as folliculotropic, erythrodermic, granulomatous, poikilodermic, hypopigmented, hyperpigmented, pagetoid reticulosis, pigmented purpura-like, bullous/vesicular, palmoplantar, hyperkeratotic/verrucous, vegetating/papillomatous, ichthyosiform, and invisible forms.[85] According to the latest World Health Organization classification of cutaneous lymphomas, only three MF variants are recognized as distinct entities with unique presentations, clinical behaviors, and treatment responses compared with classical MF. These recognized variants are FMF, pagetoid reticulosis (localized Woringer-Kolopp type), and granulomatous slack skin syndrome (GSSS).[86]

Currently, there are no guidelines specifically designed for the treatment of clinicopathological MF variants. However, information from the literature is summarized below in order to provide guidance for clinicians.

Folliculotropic Mycosis Fungoides

FMF is the most common non-classical variant in adults. In the absence of specific guidelines, a considerable number of treatments are employed in clinical practice, with variable results. Phototherapy, in all its forms, particularly PUVA, shows the greatest initial therapeutic efficacy. In a study analyzing the treatment outcomes of 203 patients with FMF, topical steroids and UVB or PUVA phototherapy for early-stage FMF showed high efficacy, achieving an ORR of 83% (28% CR) for topical steroids and 83% and 88% for UVB and PUVA, respectively. Local RT, TSEBT, and PUVA combined with RT were more effective in patients with advanced-stage FMF, resulting in ORRs of 100% (63% CR), 100% (59% CR), and 75% (5% CR), respectively.[87] Despite their widespread use, retinoids, particularly acitretin, appear to be relatively ineffective when used together. Combination treatment with phototherapy may be advisable.[88] Patients with generalized FMF should initially be considered for single-agent systemic therapy before switching to multi-agent chemotherapy.[2]

Pagetoid Reticulosis

Pagetoid reticulosis is characterized by an indolent clinical behavior. However, recurrence and relapse are common,

occurring at the original site or at a separate site. The minimal propensity for dissemination or extracutaneous involvement. The treatment options include TCS, topical nitrogen mustard, PUVA, nbUVB, RT, and surgery.[85]

Granulomatous Slack Skin Syndrome

There is no specific therapeutic regimen, and the selection of a particular therapy depends entirely on the stage. Treatment options include topical nitrogen mustard, PUVA, retinoids, RT, systemic steroids, IFN-α, chemotherapy, and some combination therapies. The surgical excision of redundant skin for esthetic and functional improvement has a high relapse rate. GSSS has a slowly progressive course, with rare cases developing nodal involvement. Although the 5-year disease-specific survival of GSSS is close to 100%, its association with lymphoproliferative disorders necessitates lifelong close monitoring.[89]

Hypopigmented Mycosis Fungoides

It is typically more prevalent in younger individuals with darker skin and a better prognosis than other types of MF. The lesions tend to persist for a long time, but respond well to TCS, TCI, nitrogen mustard, or phototherapy. In patients who present with widespread lesions at diagnosis or show rapid recent progression, the addition of IFN to the initial treatment regimen may be considered.[90]

Bullous Mycosis Fungoides

Bullous/vesicular MF primarily affects elderly individuals and is characterized by the appearance of flaccid or tense bullae, which can develop on normal skin or within typical MF lesions. The presence of bullous lesions in MF is associated with an aggressive course and poor prognosis, as mortality within 1 year of bullous lesion development approaches 50% in reported cases.[91,92]

Granulomatous Mycosis Fungoides

The impact of granulomatous inflammation on the prognosis of cutaneous lymphoma remains a topic of debate, as both favorable and unfavorable outcomes have been documented. In a multicenter study involving 15 patients with granulomatous mycosis fungoides (GMF), the most commonly used treatment modalities were PUVA and/or IFN-α in addition to RT. Other treatment options included TCS, imiquimod, systemic retinoids, single-agent chemotherapy, and CHOP. A disease-specific 5-year survival rate of 66% was previously identified for GMF.[93]

A systematic review of 116 cases of GMF revealed that 30% of patients developed organ metastasis, indicating that GMF is an aggressive form of MF.[94]

Treatment in Special Patient Populations

There are currently no specific guidelines for the treatment of MF in special patient populations. However, a table has been prepared that summarizes the treatment considerations for pregnant women, pediatric and geriatric patients, and patients with renal or hepatic failure (Table 2).

Pediatric Cases

In contrast to adults, most children with MF present with non-classic variants of the disease, which include hypopigmented, hyperpigmented, and folliculotropic forms.

In a review of 248 patients with pediatric MF, phototherapy represents the most common treatment modality. Despite the increased overall response and durability of treatment for patients receiving PUVA compared with UVB therapy, nbUVB is commonly regarded as the primary treatment modality for pediatric MF because of its more favorable side effect profile.[95] The British Phototherapy Group does not recommend the use of oral psoralen in children aged 10 years given the difficulty in ensuring adequate eye protection.[96]

TCS was frequently combined with phototherapy. Other topical agents, such as retinoids, nitrogen mustard, imiquimod, and TCI, were occasionally used in pediatric patients. Oral retinoids and MTX, as well as combinations of systemic therapies with SDTs, have been applied as advanced treatment in a small number of patients and have shown variable efficacy. In selecting an appropriate therapy for pediatric patients, it is of paramount importance to consider the risk-benefit ratio.[97]

Pregnancy

The impact of pregnancy on MF is controversial, with some reports suggesting that pregnancy negatively influences disease progression,[87] while others indicate no effect on early MF.[98] Treatment options for pregnant patients diagnosed with malignancy present unique ethical challenges because of the competing responsibilities toward both the mother and fetus. The ethical dilemma becomes more pronounced in advanced CTCL cases.

While uncomplicated pregnancies and healthy births can occur during treatment for early-stage disease, the systemic therapies recommended for advanced MF carry heightened risks for the fetus. The effects of radiation on the fetus depend on gestational age and include an increased risk of congenital

Table 2. Treatment in special patient populations*

	Pregnancy category	Pediatric use	Geriatric use	Kidney failure	Liver failure
Potent TCS (clobetasol cream)	Not assigned (use on the smallest area of skin, for the shortest duration possible)	NR (due to potential HPA axis suppression)	Start with the low end of the dosing range	NS	NS
Topical mechlorethamine	Category D (can cause fetal harm)	ND	Cutaneous adverse reactions and discontinuation of treatment more common	NS	NS
Topical retiroids	Category X (contraindicated)	Tazarotene-safety and efficacy have been established in patients ≥ 9 years old Bexarotene-ND	NS	NS	NS
Topical imiquimod	Category C (used only if the potential benefit justifies the potential risk to the fetus)	NR for patients < 12 years of age	NS	NS	NS
TCI	Category C	Not indicated for < 2 years of age	NS	NS	NS
Methoxsalen (for PUVA)	Category D	ND but should not be used in children < 12 years of age	NS	NS but should not be used in patients with severe renal impairment	NS but should not be used in patients with severe hepatic impairment
Oral retiroids	Category X	ND	Start with the low end of the dosing range	Contraindicated in patients with severely impaired kidney function	Contraindicated in patients with severely impaired liver function
Pegylated IFN-α	Category C	Safety and efficacy in patients < 5 years old have not been established	Neuropsychiatric, cardiac, and systemic (flu-like) adverse reactions may be more severe	Dose should be reduced in patients with CLcr < 30 mL/min	Hepatic function should be closely monitored
Brentuximab vedotin	Category D	ND	NS	Avoid the use in patients with severe renal impairment (CLcr < 30 mL/min)	Avoid the use in patients with moderate or severe hepatic impairment
Mogamulizumab	Not assigned	ND	Similar effectiveness but higher risk of side effects	NS	NS
Pembrolizumab	Category D	ND	NS	NS	No dose adjustment is needed for mild hepatic impairment, ND for moderate or severe impairment
Histone deacetylase inhibitors	Category D	ND	NS	Patients with end-stage renal disease should be treated with caution	Use with caution in moderate to severe hepatic impairment
Denileukin diftitox	Not assigned No human or animal data Use only if clearly needed	ND	ND	NS	NS
Doxorubicin	Category D	ND	NS	ND	Dosage should be reduced in patients with impaired hepatic function
Gemcitabine	Not assigned but can cause fetal harm when administered to a pregnant woman	ND	NS	ND	ND
Methorexate	Category X for non-neoplastic diseases like psoriasis and rheumatoid arthritis Not assigned for all other conditions	Safety and efficacy have been established for treatment of ALL and pJIA but not for other indications	ND	Closely monitor patients with renal impairment (CLcr < 90 mL/min) Reduce the dosage or discontinue as appropriate	Closely monitor patients with hepatic impairment for adverse reactions Reduce the dosage or discontinue as appropriate

TCS: Topical cortocosteroids, NR: Not recommended, HPA: Hypothalamic-pituitary-adrenal, NS: Not specified, ND: No data (safety and effectiveness have not been established), TCI: Topical calcineurin inhibitors, PUVA: Psoralen plus ultraviolet-A, IFN-α: Interferon alpha, ALL: Acute lymphoblastic leukemia, CLcr: Creatinine clearance, pJIA: Polyarticular juvenile idiopathic arthritis, *The data presented in the table were sourced from the FDA website (accessdata.fda.gov)

malformations and future childhood cancer. Chemotherapy may increase the risk of teratogenesis, spontaneous abortion, congenital malformation, and fetal death.

Teratogenesis has been demonstrated in animal models using conventional systemic cytotoxic agents (alkylating agents, antimetabolites, and mitotic inhibitors).[99]

The data on fetal risk are based on the standard FDA pregnancy categories (A, B, C, D and X) and are presented in Table 2.

Organ Transplant Recipients

A rare complication of transplantation is the development of post-transplant lymphoproliferative diseases (PTLD). Most cases originate from B-cells, whereas those arising from the T-cell lineage are less common. The incidence of PTLD varies depending on the organ type, with multiorgan/intestinal transplantation being the most common.[100] Managing PTLD is challenging because it requires carefully balanced therapies that minimize the risk of graft rejection while avoiding excessive lymphoproliferation. The initial treatment approach often involves the reduction, modification, or discontinuation of immunosuppressive drugs. In addition, classical MF is frequently treated with SDTs, such as topical corticosteroids or PUVA. Systemic retinoids are also preferred due to the absence of immunosuppressive effects.[101] The safety and efficacy of pegylated IFN treatment in patients undergoing organ transplantation have not been established. As with other alpha INFs, liver and renal graft rejections have been reported for pegylated IFN.[102]

Limitations and Future Research Needs

Many of the recommendations for the treatment of MF/SS are based on relatively low-quality evidence. The majority of studies included fewer than 50 participants, none evaluated expectant management as a control, and few assessed quality of life. In addition, when assessing treatment efficacy, it remains difficult to identify and record measures of therapeutic success that accurately reflect the benefit to the patient. The paucity of participants in existing studies on this rare disease presents a significant challenge in conducting research on a diverse and individualized range of treatment options. For effective research to be conducted in the future, it is essential that standardized measures of disease response, clearly defined meaningful endpoints and uniformly reported prognostic markers are in place.[103]

Conclusion

The most recent evidence-based recommendations for the treatment of MF and SS have been extracted from international guidelines. Generally, patients with early-stage disease should undergo SDT as their initial treatment. In the event of relapse, patients should receive additional courses of the same SDT or consider alternative treatment options. Systemic therapy should primarily be considered for patients with advanced-stage refractory cutaneous disease. Currently, there is no established treatment for refractory disease that can consistently produce reliable, durable remissions, or curative results. All patients with refractory disease should participate in multicenter clinical trials. Furthermore, maintaining quality of life should be a primary objective of therapeutic strategies and should be evaluated in clinical trials along with response rates.

Footnotes

Authorship Contributions

Concept: H.Ş., H.M.E.M., Design: H.Ş., H.M.E.M., Data Collection or Processing: H.Ş., H.M.E.M., Analysis or Interpretation: H.Ş., H.M.E.M., Literature Search: H.Ş., H.M.E.M., Writing: H.Ş., H.M.E.M.

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