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Review of Treatment Algorithms in Mycosis Fungoides and Sezary Syndrome

Şanlı and Erol Mart. Treatment Algorithms in MF and SS

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Abstract
Mycosis fungoides (MF) is the most prevalent form of cutaneous T-cell lymphoma. TNMB (tumor, lymph nodes, metastasis, blood) staging serves as the primary prognostic factor, significantly enfluencing treatment strategies. The objectives of MF therapy are tailored to each patient, focusing on achieving adequate responses to alleviate symptoms and reduce the risk of progression. Ongoing 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 Organisation for Research and Treatment of Cancer, the National Comprehensive Cancer Network, and the British Association of Dermatologists and U.K. Cutaneous Lymphoma Group.
In early-stage MF, SDT are effective, while systemic agents are required for early-stage refractory MF and advanced cases, including Sezary 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, examining their mechanisms of action, efficacy, and side effects, thereby guiding clinicians in optimizing patient care.
Keywords: Cutaneous lymphoma, Mycosis fungoides, Sezary syndrome, T-cell lymphoma, Treatment

1.INTRODUCTİON

Mycosis fungoides (MF) is the most common cutaneous T-cell lymphoma (CTLCL) and many clinicopathologic variants of MF have been described. TNMB (tumor, lymph nodes, metastasis, blood) staging remains the most important prognostic factor in CTCL, forming the basis of the treatment approach. In addition to clinical stage, histological evidence of folliculotropism and large cell transformation can be associated with a 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 in order to reduce and control symptoms and minimise 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 disease 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/ Sezary syndrome (SS) necessitates a multidisciplinary approach involving dermatology, hematology, medical oncology, and radiation oncology. In patients with early-stage disease, skin-directed treatments (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, bexarotene, 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 disease 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 offer an overview of the treatment options available for MF/SS, including an analysis of the mechanisms of action, efficacy and side effects.

2.Methods

Treatment algorithms were based on the international guidelines for the treatment of MF, namely the European Organisation 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 U.K. Cutaneous Lymphoma Group guidelines (BAD-UKCLG), 2018.[3] The common and divergent aspects of these guidelines have been subjected to detailed analysis and summary in order to facilitate treatment planning.

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

3.Results

An accurate diagnosis and appropriate staging of MF/SS patients 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 localised early stages, where the primary objective of treatment is to achieve a cure.

The treatment of MF/SS should be conducted in a stepwise and stage-adapted manner, with a primary focus on the maintenance of quality of life. In the absence of larger randomised 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 guideline encompass a broader treatment spectrum, incorporating therapies that have shown benefits in small case series. In contrast, the EORTC guideline focus on therapies that are approved in Europe and have more definitive evidence of efficacy.

In the EORTC guidelines, it is recommended 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 a successful first-line treatment, patients should not be considered refractory, and therapy can typically be reinitiated. The individual choice of appropriate therapy may vary based on clinical presentation and treatment availability (Table 1).[1]

The British Association of Dermatologists and U.K. Cutaneous Lymphoma Group (BAD-UKCLG) guidelines recommend the establishment of supranetwork multidisciplinary teams (MDTs) that include dermatologists, clinical oncologists, hemato-oncologists, dermatopathologists, and hematopathologists. All patients with early-stage MF refractory to SDT and late-stage MF and SS should be reviewed by supranetwork MDTs to agree 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 TSEB, ECP and stem cell transplantation (Figure 1).[3]

3.1.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, as some patients will eventually progress; over a 10-year period, approximately 10% of patients with early-stage disease experience progression.[1] Expectant policy has been recommended by the EORTC, but it is not included in the NCCN and BAD-UKCLG guidelines.

3.2.Skin-directed treatment

SDT are the recommended first-line intervention in the early stages of MF. They may also be used in combination with systemic options in advanced stages to control symptoms such as pain and pruritus and improve skin tumor burden.

3.2.1.Topical therapies

Topical therapies have demonstrated some clinical efficacy for patches and thin plaques; however, the paucity of well-controlled studies constrains the quality of evidence. A significant proportion of the topical therapies have not been granted a licence for use in MF. Topical corticosteroids, nitrogen mustard, topical retinoids, topical carmustine, imiquimod, and topical calcineurin inhibitors are discussed in detail under 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.

3.2.1.1. Topical corticosteroids

Topical corticosteroids induce apoptosis in lymphocytes 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 due to their accessibility, ease of application and minimal adverse effects. However, the efficacy of these agents in MF remains inconclusively supported by experimental evidence.[1]

In 2003, Zackheim et al.[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 report that, contrary to the recommedations 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 suggest 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.

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

3.2.1.2. Topical chlormethine/mechlorethamine (nitrogen mustard)

Mechlorethamine is an alkylating agent that impedes the processes of DNA replication and RNA transcription by forming cross-links in DNA strands, which ultimately results 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 areas of the skin. For widespread disease application to the whole body is possible and safe. No evidence for systemic absorption after topical application has been found and no systemic toxicity 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 with topical corticosteroids.[8] All three guidelines recommend the use of topical mechlorethamine in the treatment of early-stage MF.

3.2.1.3. Topical retinoids

Bexarotene is a retinoid X receptor (RXR) agonist. The gel formulation is 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% complete response (CR) and the estimated median response duration from the start of therapy was 99 weeks. Patients who had not received prior therapy for MF demonstrated a higher response rate (75%) compared to 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 (AEs) likely associated with the drug included mild to moderate irritant dermatitis, pruritus, pain (primarily burning at the application site), and skin disorders (such as inflammation and excoriation).[10]
A case report described a patient with folliculotropic MF (FMF) who was refractory to intralesional and subcutaneous interferon-alpha-2a but achieved successful treatment with topical bexarotene gel, resulting in complete remission by the fifth month. This suggests that bexarotene gel can be an effective option for localized early-stage folliculotropic MF, even in cases resistant to systemic therapies.[11]
Bexarotene gel is not licensed in Europe. Thus, the current EORTC guideline does not include any recommendation regarding the use of bexarotene gel.
Tazarotene, another topical retinoid, exerts anti-proliferative 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 and the product has been discontinued in Europe, and not included as a treatment option in the current EORTC guideline.

3.2.1.4. Topical carmustine (BCNU)

Carmustine is an alkylating agent that forms cross-links in DNA, leading to apoptosis.

Topical carmustine has been demonstrated to be an efficacious 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 rendering the utilisation of topical carmustine in maintenance therapy inadvisable. In contrast, the incidence of irritant contact dermatitis is lower (10%) compared to topical mechlorethamine.[14] Topical carmustine has been recommended by the NCCN (category 2B) guideline, but it is not included in the EORTC guideline.

3.2.1.5. Topical imiquimod

The toll-like receptor agonist imiquimod induces the production of local interferon (IFN)-α, tumor necrosis factor-α, interleukin (IL)-1, and IL-6, and suppresses the anti-apoptotic Bcl-2. It has been shown to be efficacious in a limited number of patients with early-stage MF refractory to other therapies.[15,16] Shipman et al.[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 experienced flu-like symptoms and fatigue; the side effects were primarily localized to the skin, commonly including pain, erythema, local irritation, ulceration, and pruritus.

Imiquimod may be considered for areas with few lesions that are unresponsive to treatment or located on sun-damaged skin, such as 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 potential benefit of imiquimod in MF treatment.

3.2.1.6. 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 a dose reduction or discontinued treatment due to drug-related toxicity.[18] There is only one case report of the successful use of tacrolimus ointment 0.1% in the treatment of MF.[19] The NCCN guidelines suggest that TCI may be considered as a steroid-sparing treatment for lesions in the perioral and periorbital regions 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]

3.2.2. 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-stages. While 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 modalities 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, since only these therapies have a sufficient body of evidence together with broad accessibility is available.[1]

3.2.2.1. Psoralen–ultraviolet A photochemotherapy

A substantial body of evidence, derived from extensive, non-randomised 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 a durable remission (10-year disease-free survival), but maintenance PUVA was given to almost all responding patients. One third of the patients showed 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 interferon 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 the 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 remissions was found to be prolonged when retinoids were administered as maintenance therapy. [24]
The PUVA and bexarotene combination has also been demonstrated to be 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 inquiries pertaining to the impact of PUVA on time to progression and disease-specific survival remain unresolved.[3]

3.2.2.2. Ultraviolet B phototherapy

In the BAD-UKCLG guideline, the authors 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 guideline does not recommend bbUVB due to its disadvantages compared to 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 CRs in children with the hypopigmented variant of MF.[27]
Compared to PUVA, it presents 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.

3.2.3. Photodynamic therapy

Photodynamic therapy (PDT) is a treatment option for solitary plaques that are unresponsive to topical treatment. Its efficacy in the treatment of MF has been demonstrated in numerous case studies, as recently reviewed by Hooper et al. 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 optimise PDT protocols in relation to lesion type, thickness, and location. Moreover, 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 currently cannot recommend the use of PDT for the treatment of MF.

3.2.4. Radiation Therapy

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

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

In a study comprising 31 patients with MF, the CR rate was 30% when low-dose RT (4 Gy in 2 fractions) was employed, 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 in eight fractions. The study also concluded that applying higher radiation doses during disease progression is 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, while 24-30 Gy is recommended for achieving a more durable response or for unilesional presentations. [31]

Localized, peripheral nodal disease and visceral metastases can also be treated with EBRT. Central nervous system disease in MF has a very poor prognosis. In patients who are fit for treatment and have a 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.

3.2.5. Total skin electron beam therapy

Total skin electron beam therapy (TSEB) has a long history in the treatment of 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 treatment for all stages. In order to minimise the dose-dependent toxicity of TSEB, including erythema, desquamation, anhydrosis, alopecia and xerosis, low-dose regimens (8-12 Gy) have been increasingly reported in the literature.

In a retrospective study that evaluated low-dose TSEBT in 102 patients with T2 to 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 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). Median response duration was 11.8 months and 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 interferon or bexarotene to maintain response, for patients with stage IB–IIA disease with higher skin disease burden. Adjuvant systemic therapy may be a viable option to enhance the response rate in patients with tumoral stage. TSEBT may not be well tolerated in patients with erythrodermic disease and should be employed with caution. In these patients, it may be utilised with lower doses and slower fractionation.[2]

3.3. Systemic biological therapies

Systemic therapies are recommended in early stage disease refractory to SDT and in advanced stages of 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 folliculotropic MF), and the immunohistochemical data (eg, 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 seen with time-limited combination therapies. Multiagent chemotherapy regimens are generally reserved only for refractory disease to multiple prior therapies or 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 are approved by the FDA for the treatment of MF and SS. The efficacy of BV and mogamulizumab compared to 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. While interferons 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]

3.3.1. Retinoids

Bexarotene, a substrate of the 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 have 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, reporting an objective response rate of 46.8%. Patients starting treatment at 300 mg/m² showed significantly higher response rates (61.6%) compared to those on lower doses (22.6%). Additionally, among 92 patients treated with bexarotene combined with photo(chemo)therapy, the response rate was 57.6%, significantly higher than the 25.5% seen in those treated with bexarotene alone. The study indicates that higher doses of bexarotene and combination therapy may enhance treatment efficacy for MF. Common treatment-related AEs included 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 300 mg/m² compared to those starting at doses below 300 mg/m².[34] Laboratory monitoring of triglycerides and free thyroxine (T4) 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, have proven 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, though 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 MF/SS. Therefore, these agents are often used in combination with other treatments or for maintenance therapy. [1]

3.3.2. Interferon-alpha

Interferon-alpha (IFN-α) exerts an immunomodulatory effect by activating CD8 + T lymphocytes and natural killer cells, while suppressing the production of Th2 cytokines from malignant T lymphocytes. IFN enhances cytotoxic effects by increasing MHC class I molecule expression on 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, nonrandomized 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 rates >20% have been reported. Response rates are higher in the early stages and with increased doses of IFN.[37]

A prospective, randomised 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 with 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 to 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, with the most common AEs being fatigue, acute flu-like symptoms, and hepatotoxicity. Dose reductions or withholding due to AEs 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.

3.3.3. Targeted immunotherapy

3.3.1. Brentuximab vedotin

BV is an antibody-drug conjugate consisting of an anti-CD30 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 three 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 in Europe and US for the treatment of adult patients with CD30 + CTCL following at least one prior systemic therapy. 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 four months (ORR4: 55% vs. 13%), as well as median PFS (17 months vs. 4 months), and reduced patient-reported symptom burden compared to m 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 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. Evidence suggests that significant responses can be observed even at lower positivity levels. Furthermore, CD30 expression can vary within the same individual. A retrospective analysis of 135 biopsy specimens from 95 patients with MF evaluated CD30 expression through immunohistochemistry. The authors found that CD30 was detectable in 90% of samples, with ≥10% positivity in 60%. Additionally, in patients with multiple biopsies, considerable variability in CD30 expression was noted, particularly in samples taken at different time points. The authors conclude that examining multiple tissue samples enhances the evaluation

of CD30 expression status in MF, potentially reducing the risk of inappropriate treatment assignment.[44]

3.3.3.2. Mogamulizumab

Mogamulizumab is a humanized monoclonal antibody that targets CCR4, a chemokine receptor expressed on T cells and involved in cell trafficking of lymphocytes to skin. [45]
It 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 compared to 3.1 months for vorinostat, with an ORR of 28% for mogamulizumab and 4.8% for vorinostat. The most common drug related AEs were infusion-related reactions, drug rash, diarrhoea, and fatigue.[46] Post-hoc analyses assessing the efficacy of mogamulizumab based on blood tumor burden indicated that blood involvement correlated with improved ORRs, PFS, and time to next treatment (TTNT) for patients receiving mogamulizumab. The ORRs were 26% and 37% for patients with B1 and B2 blood involvement, respectively, compared to 16% for those with B0 blood involvement. The median PFS was 11 months for B2 and 8 months for B1, while it was only 5 months for patients with B0 involvement. The TTNT was 20 months for patients with B2 involvement, compared to 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 for tumor response. [49] It is advised that skin biopsies be performed, including appropriate immunohistochemical stains and clonality assessments, in order to rule out disease progression in patients experiencing these skin eruptions. [50]

3.3.3.3. Alemtuzumab

Alemtuzumab is a humanized recombinant IgG1 monoclonal antibody targeting CD52.
It 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 myelotoxicities and infectious complications. Subcutaneous administration of reduced-dose alemtuzumab (3–15 mg) over a shorter duration proved equally effective with fewer infectious complications in SS patients [51]. Although alemtuzumab is no longer commercially available, it can still be accessed for compassionate use in patients with CTCL and other hematologic malignancies [2].

3.3.3.4. 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 various 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 on 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, has been found to be aberrantly expressed in tumur cells of most patients with SS and other CTCL. 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, and of those, 15 responses were observed in 35 patients with SS (43%). [53] A subsequent, multi-cohort, and multi-center phase II study (TELLOMAK), evaluating the clinical activity and safety of IPH4102 alone or in combination with chemotherapy in patients with advanced T cell lymphoma is ongoing. [1]

3.3.4. Histone Deacetylase Inhibitors

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

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

Romidepsin, another HDAC inhibitor, has shown clinical efficacy across all disease compartments in treating MF/SS. The median duration of response for patients responding to romidepsin ranges from 13 to 15 months. Notably, it significantly alleviates pruritus scores, irrespective of 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, it is essential to monitor for QTc prolongation, especially when used with antiemetics that can also affect QTc. Romidepsin is recommended as a preferred treatment for patients with SS exhibiting a high 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.

3.3.5. Denileukin Diftitox

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

A reformulated version was assessed in a study, which 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 duration of response of 6.5 months. Higher ORRs were observed in stage IIB patients (46%) compared to stage IA-IIA (37%) and stage III (20%). There was no correlation between CD25 expression and treatment efficacy. Skin disease burden decreased in 84% of evaluable patients (54 out of 64). Treatment-related AEs 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]

3.3.6. Chemotherapy

3.3.6.1. Liposomal doxorubicin

Pegylated liposomal doxorubicin has demonstrated 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% CRs) and a median duration of response and median time to progression of 6 months 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 included 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]

3.3.6.2. 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 time to next treatment 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]

3.3.6.3. Other chemotherapeutic agents

Other chemotherapeutic agents included in the EORTC recommendations are chlorambucil and MTX. Recommended doses of MTX 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 leukaemia and thus should be avoided. Due to the introduction of mogamulizumab with high efficacy in the treatment of SS, the use of chlorambucil is limited to individual patients and resource-poor settings.[1]

The NCCN guidelines address 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/m² 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/m² 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/m² yielded an objective response of 25% per independent central review and 58% per investigator assessment, with median PFS and OS rates of 5 months and 13 months, respectively.[65]

3.3.7. Extracorporeal Photopheresis

Extracorporeal Photopheresis (ECP) is an immunomodulating procedure that has been available for the treatment of CTCL since 1987. The procedure is administered over two consecutive days and typically repeated every four weeks, though it can be done more frequently for 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-a, 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=.077). The authors concluded that the low incidence of side effects, along with the improved OS observed in combination therapy, makes ECP a viable treatment option for MF. [68] There may be an emerging role for ECP in early-stage MF; however, the available data is limited, and current guidelines do not provide recommendations in this regard. [1,69]

The degree of blood involvement, CD4/CD8 ratio, and levels of 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 with or 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 to ECP alone. [1]

3.3.8. Hematopoietic stem cell transplantation (HSCT)

Autologous stem cell transplantation has been abandoned in MF/SS due to invariable occurrence of relapse in all patients, despite associated toxicity. On the other hand, alloSCT is the only option in MF/SS with curative intention in patients with advanced disease. Allogeneic transplant 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 transplant is the potential for disease relapse. While some patients can be treated successfully 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 AHSCT (the majority of whom had progressive disease prior to the transplant), non-relapse mortality was observed to be 35.9% at one year and 26.9% at three years and beyond. The probability of OS was 48.5% and 32.3% at 1 and 5 years post-transplant, 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, while 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 stood at 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 a 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 advanced MF/SS 99 patients were enrolled, with 55 receiving alloSCT and 44 undergoing non-allogeneic therapy (patients without a compatible donor). The primary end-point was PFS with a significant benefit for 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, median OS was 26.9 months in controls and not reached in the alloSCT group. Serious AEs were more common in the alloSCT group, with infections being the most frequent. The study concluded that alloSCT significantly improves PFS for patients with high-risk, advanced-stage MF or SS who achieve remission before transplantation.[74] Deciding 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]

3.4. Maintenance

Maintenance therapy refers to the ongoing administration of either skin-directed or systemic treatment after achieving remission, with the goal of sustaining the response and preventing relapse or progression. For treatments to be deemed appropriate for maintenance, they 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 remission in MF and SS. These include topical corticosteroids, topical chlormethine, nbUVB, PUVA, ECP, IFN-α, low-dose methotrexate, and oral retinoids. [1]

Currently, there is a paucity of evidence-based guidelines for the maintenance therapy in CTCL. The question of how an initial remission or stable disease can be maintained represents one of the most significant challenges in the management of CTCL. [76]
In practice, maintenance therapy often involves tapering the treatment that induced remission (such as phototherapy, retinoids, IFN-α, or ECP) or introducing a maintenance agent after achieving remission with a method that has dose-limiting toxicity, such as TSEB or systemic chemotherapy.[77] Overall, there is still no definitive evidence guiding the indications and selection of maintenance therapy in 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]

3.5. Supportive Care

3.5.1. 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 involves optimizing both SDT and systemic therapies. Daily use of moisturizers and emollients is beneficial for maintaining and protecting the skin barrier. In early-stage disease, topical steroids can effectively manage both the disease and associated pruritus.[79] First-line options include H1 antihistamines or 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]

3.5.2. 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]

4. Treatment in Clinicopathological Variants of MF

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 WHO classification of cutaneous lymphomas, only three MF variants are officially recognized as distinct entities with unique presentations, clinical behaviors, and treatment responses compared to classical MF. These recognized variants are folliculotropic MF, pagetoid reticulosis (localized Woringer-Kolopp type), and granulomatous slack skin syndrome (GSSS). [86]
At present, there are no guidelines that have been specifically designed for the treatment of clinicopathological MF variants. However, information from the literature is summarised below in order to provide guidance for clinicians.

4.1. Folliculotropic MF (FMF)

(FMF) is the most common non-classical MF 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, appears to demonstrate the greatest initial therapeutic efficacy. In a study analyzing the treatment outcomes of 203 FMF

patients, 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 an ORRs of 100% (63% CR), 100% (59% CR) and 75% (5% CR), respectively.[87] Despite their widespread use, retinoids appear to be relatively ineffective when used as a single therapy, particularly acitretin. Combination treatment with phototherapy seems to be advisable. [88] Patients with generalized FMF should initially be considered for single-agent systemic therapies before switching to multi-agent chemotherapy.[2]

4.2. Pagetoid Reticulosis

Pagetoid reticulosis is characterised by an indolent clinical behaviour. However, recurrence and relapses are common, occurring either at the original site or at a separate site. There is minimal propensity for dissemination or extracutaneous involvement. The treatment options include TCS, topical nitrogen mustard, PUVA, nbUVB, RT, and surgery. [85]

4.3. Granulomatous Slack Skin Syndrome (GSSS)

There is no specific therapeutic regimen and the choice of a particular therapy will depend 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 the redundant skin for esthetic and functional improvement has a high relapse rate. GSSS has a slowly progressive course, with rare cases developing nodal involvement. Even though the 5-year disease-specific survival of GSSS is close to 100%, its association with lymphoproliferative disorders necessitates lifelong close monitoring. [89]

4.4. Hypopigmented MF

It is typically more prevalent in younger individuals with darker skin types and has 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 cases where patients present with widespread lesions at diagnosis or show rapid recent progression, the addition of IFN to the initial treatment regimen may be considered. [90]

4.5. Bullous MF

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 one year of development of bullous lesions approaches 50% in reported cases.[91,92]

4.6. Granulomatous MF (GMF)

The impact of granulomatous inflammation on the prognosis of cutaneous lymphoma remains a topic of debate as there have been both favorable and unfavorable outcomes documented. In a multicentre study involving 15 patients with Granulomatous MF (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 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]

5. Treatment in Special Patient Populations

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

5.1. Pediatric cases

In contrast to adults, the majority of 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 in comparison with UVB therapy, nbUVB is commonly regarded as the primary treatment modality for pediatric MF due to a more favorable side effect profile.[95]
The British Phototherapy Group does not recommend the use of oral psoralen in children under the age of 10, given the difficulty in ensuring adequate eye protection. [96]
TCS were frequently combined with phototherapy. Other topical agents, such as retinoids, nitrogen mustard, imiquimod and TCI were occasionally employed in pediatric patients. Oral retinoids and methotrexate, 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]

5.2. Pregnancy

The impact of pregnancy on MF is controversial, with some reports suggesting it negatively enfluences the disease's progression [87], while others indicate no effect on early MF. [98]
Treatment options for a pregnant patient diagnosed with malignancy present unique ethical challenges due to the competing responsibilities toward both the mother and fetus. The ethical dilemma becomes more pronounced in advanced cases of CTCL.
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. Effects of radiation on the fetus depend on gestational age and include increased risk of congenital malformations and future childhood cancer. Chemotherapy may increase the risk of teratogenesis, spontaneous abortions, congenital malformations, and fetal death. Teratogenesis has been demonstrated with animal models for the 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.

5.3. Organ transplant recipients

A rare complication of transplantation is the development of post-transplant lymphoproliferative diseases (PTLD). Most cases are reported to originate from B cells, while those arising from T-cell lineage are less common. The incidence of PTLD varies depending on the organ transplanted with multiorgan/intestinal transplants 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, patients with classical MF are 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 have not been established in patients with organ transplants. As with other alpha interferons, liver and renal graft rejections have been reported on pegylated IFN. [102]

Limitations and Future Research Needs

Many of the recommendations for treatment of MF/SS are based on relatively low quality evidence. The majority of studies have 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 benefit to the patient. The paucity of participants in existing studies on this rare disease presents a significant challenge to conducting research on a diverse and individualised range of treatment options. In order for effective research to be conducted in

the future, it is essential that standardised 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 collated from international guidelines. Generally, patients with early-stage disease should undergo SDT as their initial treatment. In the event of a relapse, they should receive additional courses of the same SDT or consider alternative options. Systemic therapy should mainly be considered for patients with advanced stages and refractory cutaneous disease. At present, there is no established treatment for refractory disease that can consistently produce reliable, durable remissions or curative results. It is recommended that all patients with refractory disease 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.

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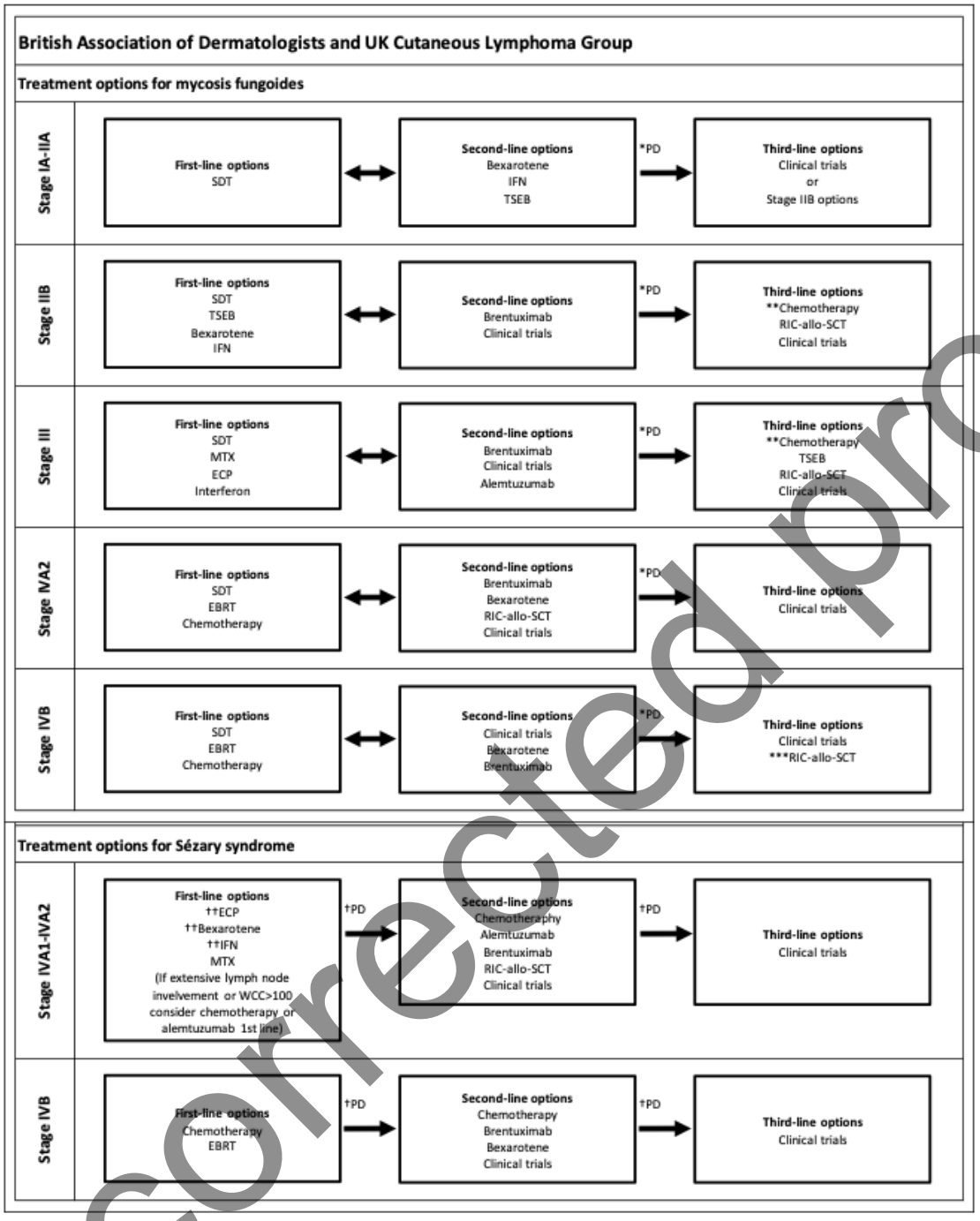

Figure 1: BAD and U.K. CLG guidelines for the treatment of mycosis fungoides and Sezary syndrome [3].

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; WCC, white cell count, x 10^9. ††May be used in combination. * PD, †PD and exhausted first- and second-line options. **Chemotherapy as recommended by the supranetwork multidisciplinary team. ***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.

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

Recommendations for 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 • Localised RT (for localised 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 Localised RT	(Poly-)chemotherapy Brentuximab vedotin Mogamulizumab AlloSCT
Recommendations for treatment of MF stage 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 treatment of MF stages IVA and IVB *	
Chemotherapy (gemcitabine, pegylated liposomal doxorubicine, CHOP and CHOP-like polychemotherapy) Radiotherapy (TSEB and localised) Brentuximab vedotin Mogamulizumab Alemtuzumab (mainly in B2) AlloSCT	
Recommendations for treatment of SS	
First-line	**Second-line**
ECP Systemic therapies in combination with ECP or PUVA • Retinoids • IFN-α	Mogamulizumab Brentuximab vedotin Alemtuzumab Chemotherapy (gemcitabine, pegylated liposomal doxorubicine, CHOP and CHOP-

Chlorambucil + prednisone	like polychemotherapy)
Low dose MTX	AlloSCT

AlloSCT: allogeneic stem cell transplantation, CHOP: Cyclophosphamide Doxorubicin Vincristin Prednisone, ECP: extracorporeal photopheresis, IFN-a: interferon alpha, MF: Mycosis fungoides, MTX: Methotrexate, nbUVB: narrowband ultraviolet-B, PUVA: psoralen plus ultraviolet-A, RT: Radiotherapy, SDT: skin-directed treatment, SS: Sezary syndrome, TSEB: Total skin electron beam therapy

* For stage IV disease, no distinction is made between first- and second-line options due to insufficient evidence to justify such separation.

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	Closely monitor patients with hepatic impairment for adverse reactions Reduce the dosage or

				discontinue as appropriate	discontinue as appropriate

ALL: acute lymphoblastic leukemia; CLcr: creatinine clearance; HPA: hypothalamic-pituitary-adrenal; IFN-a: interferon alpha; ND: no data (safety and effectiveness have not been established); NR: not recommended; NS: Not specified; pJIA: polyarticular juvenile idiopathic arthritis; PUVA: psoralen plus ultraviolet-A; TCI: topical calcineurin inhibitors; TCS: topical cortocosteroids

*The data presented in the table were sourced from the FDA website (accessdata.fda.gov).