Outline of the Treatment of Mycosis Fungoides

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Abstract

The early identification, diagnosis and management of Mycosis fungoides is imperative in a dermatology out patient setting. This activity reviews the etiolopathogenesis, epidemiology, clinical and histological features, diagnosis and treatment of Mycosis fungoides. For patients with early-stage mycosis fungoides (IIA or below), the various treatment options are topical corticosteroids, topical nitrogen mustards (mechlorethamine, HN2), topical bexarotene, imiquimod, psoralen-ultraviolet A (PUVA) therapy or ultraviolet B (UVB) therapy. Local radiation therapy may be used for localized lesions (such as in pagetoid reticulosis). Systemic therapies, such as retinoids or interferons, histone deacetylase (HDAC) inhibitors, or low-dose methotrexate are used if skin-directed therapies fail, if skin symptoms are extensive/severe, or if patients have a worse prognostic profile such as folliculotropic mycosis fungoides, large cell transformation, or early blood involvement. Advanced stage (IIB to IV) mycosis fungoides is a heterogeneous group that encompasses those patients that present with extracutaneous disease or advanced skin lesions (e.g., tumors). It is often a chronic or persistent disease with a relapsing course. The main goals of therapy are long-term disease control, prompt symptom relief, and management of life-threatening (aggressive) disease. For patients with generalized tumors, total skin electron beam therapy (TSEBT) or systemic therapies are acceptable treatment options. TSEBT can be followed by other skin-directed therapies or systemic therapies to prolong response duration. For more extensive disease, combinations of skin-directed therapies and systemic therapies are used. The various systemic options available include methotrexate, bexarotene, targeted immunotherapy (such as alemtuzumab), polychemotherapy.

Keywords: Mycosis Fungoides, treatment

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Introduction:

Primary cutaneous lymphomas are the second most common extranodal non-Hodgkin Lymphomas. They may be of either T cell, B cell, or NK cell origin. Cutaneous T Cell lymphomas (CTCL) comprise a group of heterogeneous lymphomas which clinically differ from systemic lymphomas, even though they might show similar histology.

Various guidelines have been published by the National Comprehensive Cancer Network (NCCN), EORTC, and European Society for Medical Oncology (ESMO), among others. All concur that the quality of the evidence generated is hampered by the small number of randomized, well controlled clinical trials performed in MF/SS. A stepwise, stage-adapted approach is, therefore, recommended for the treatment of these patients, considering age, patient general status, extent of lesions, rate of disease progression, and previous therapies. In general, skin-directed therapies are used to treat early stages of MF and FMF as a first-line treatment, while systemic therapies, usually combined with skin-directed treatment, are more commonly used to treat more advanced stages. The treatment for FMF can be similar to that for classic MF, but the time to response and treatment duration in early FMF is more prolonged. **(1)**

Based on stage directed treatment, the early stage MF is treated with using skin directed therapies (SDTs), which include topical corticosteroids (TCS), phototherapy, topical chemotherapy or retinoids, and radiotherapy. There is no specific algorithm for management of early-stage disease and treatments should be tailored according to individual patient's needs and their side-effect profile **(1)**

As the majority of CTCL patients present with patch/plaque stage MF and have an excellent prognosis, the initial goal of therapy is to improve symptoms and quality of life while avoiding treatment related toxicity. For many patients, this may involve either expectant management (i.e., “watch and wait”) or skin-directed therapies. Topical steroids are the first-line treatment for limited-stage MF. In an uncontrolled prospective study, topical clobetasol propionate was used in 85% of patients with stage 1A/B disease, had an overall response rate of 94%, and is associated with minimal to no toxicity. For refractory and persistent cutaneous lesions, bexarotene 1% topical gel may be considered. Prospective trials have demonstrated an ORR between 44% and 63%. Topical TLR agonists such as Imiquimod a TLR7 agonist and Resiquimod, a potent TLR7/8 agonist which lead to local production of interferons, and other cytokines, induce cell death and promote host anti-tumor immunity and have demonstrated efficacy in limited-stage MF **(2)**

Corticosteroids impair not only lymphocyte binding to the endothelium, but also

intercellular adhesion. They are widely used as a palliative treatment for individual lesions in the early patch/plaque stage. In a single study of 79 patients with stage IA/IB, the twice-daily use of high-potency topical corticosteroids showed an overall response rate (ORR) of 94% for stage IA and 82% for stage IB, with complete response (CR) rates of 63% and 25%, respectively. High-

potency topical corticosteroids are usually used in daily practice. Responses are frequent but short-lived. Mechlorethamine, also known as nitrogen mustard (NM), is a cytotoxic chemotherapy agent approved by the United States Food and Drug Administration (FDA) for the treatment of MF stage IA/IB in patients who have previously received skin-directed therapy. The 0.02% gel preparation gave response rates of 58.5% with 13.8% CR. It was recently authorized in Europe as a first-line treatment for early MF stages **(3)**

Table (1) SDT therapy tailored to individual patient's needs (4)

Therapy	Pros†	Cons†
Topical corticosteroids: potent/very potent (smaller surface areas treated)	Ease of use	Timely applications if large areas
	Cheap	Repeat prescriptions, large volumes
	Available	Skin thinning, striae
	Effective against inflammation/ itch +/– anti-CTCL	Systemic absorption, cortisol suppression
Phototherapy; (UV-B & PUVA)	Highly effective	Travel specialised centres
	Durable response	Longer term increase skin cancers
Radiotherapy: localised superficial radiotherapy; 8 Gy in 2 fractions, total skin electron beam (TSE); 2 weeks low dose course (12 Gy in 8 fractions)	Treatment over 2–3 days	Travel to hospital
	Few systemic side effects	Increased cancer risk especially repeated treatments in younger patients
Alkylating agents: topical chlormethine (nitrogen mustard)—new gel formulation EMA approved 2017 (LEDAGA®), topical carmustine (BCNU)	Ease of use	Availability
	Convenient application	Dermatitis

†, pros and cons for each treatment are the expert opinions of Dr. J Scarisbrick. BCNU, bis-chloroethylnitrosourea; CTCL, cutaneous T-cell lymphoma; EMA, European Medicines Agency; FDA, Food and Drug Administration; MF, mycosis fungoides; NB-UVB, narrow-band ultraviolet B; PUVA, psoralen and ultraviolet A; SDT, skin-directed therapy; TSE, total skin electron beam therapy. Phototherapy is a frequent key therapy in managing patients with MF and tends to produce high complete remission rates with variable response duration. Broadband, narrowband UVB light and PUVA are traditional treatments, but more recently UVA1 and excimer laser are other emerging modalities. UVB therapy is recommended for patch or thin plaque MF and PUVA for thicker plaques **(5)**

Phototherapy is an important treatment modality that may be used alone, or in combination with topical therapies, in patients with limited-stage disease, and includes narrowband UVB (NBUVB, 311 nm) and PUVA. NBUVB is used in both patch and plaque stage MF. PUVA is the modality of choice in skin of color. Phototherapy is widely available and has demonstrated efficacy in many retrospective and prospective studies, and a comprehensive consensus statement on the use of phototherapy was recently published **(2)**

NB-UVB is the most readily available type of phototherapy in Egypt. It can cause complete remission of patches ranged from 54% to 90%. It is administered as 3 sessions per weeks in most of the studies. Studies did not show increased carcinogenesis with NB-UVB. Interestingly, patients who have not previously responded to PUVA may show improvement with NB-UVB. PUVA is an effective treatment for early MF especially in patients with thick plaques, dark phenotypes, and those refractory to NB-UVB. It is more effective than NB-UVB in inducing complete clearance. The NCCN and BAD recommend PUVA as a first line for predominately plaque disease. PUVA is often prescribed with 8-methoxypsoralen (MOP), that is available in Egypt and given 2-3 times weekly. High cumulative dose of PUVA can lead to photodamage and photocarcinogenesis. Lifetime PUVA exposure should be limited to 1200 J·cm2 and/or 250 sessions **(6)**

PUVA can be combined with systemic treatment as interferon and retinoids to increase the efficacy in refractory/advanced cases and to decrease the cumulative dose of UVA, thus, reducing the long-term side effects. According ESMO guidelines, it is considered as a 1st line in the advanced stage and a 2nd line therapy in refractory cases of the early stage. However, sufficient data regarding the efficacy of combined treatment over PUVA monotherapy are lacking **(7)**

Drugs available in Egypt that can be combined with PUVA are retinoic acid receptor (RAR) agonists and methotrexate. RAR agonists include acitretin and isotretinoin. In a recent multicenter retrospective study in Greece, acitretin was shown to be more effective when patients concomitantly received PUVA or topical steroids than when patients receiving acitretin alone. Most of the patients were at early stage (92%), and 18% had FMF **(6)**

UVA1 phototherapy (340–400 nm) penetrates more deeply into the dermis, compared with UVB and UVA, recent case series with 19 early stage MF patients (IA–IIA) received UVA 5 times weekly for 5 weeks, and CR was 63% and partial response 37%. However, there was a high relapse rate within 3 months of stopping UVA1, affecting over half of patients who had achieved a CR. UVA1 has been shown to be effective in advanced stage MF with widespread plaques, nodules and erythrodermic MF in a case series with 13 patients. CR was achieved in 85% and the remaining 15% achieved partial response, whilst the patients' own unirradiated control lesions did not improve. These studies suggest UVA1 may be a useful addition to the MF treatment options but availability is limited.Recent evidence suggests the excimer 308 nm laser is safe and potentially effective in early stage MF. Small case series have demonstrated its efficacy on isolated patches or difficult to reach anatomical sites. Its role within MF management has not been formalized yet and availability is limited **(4)**

Treatment of MF patients with phototherapy includes 3 phases: induction, consolidation, and maintenance with dose of UV is escalated during the induction phase with fixation of the frequency of sessions, while both the dose and the frequency are fixed during the consolidation phase. During the maintenance phase, there is a gradual decrease of the frequency of the sessions with fixation of the dose. Complete response is determined clinically, and has to be ≥ 4 weeks; biopsy is only

required when assessing postinflammatory hyperpigmentation or erythema versus the presence of residual lesion. Though previous reports did not show solid evidence for the use of maintenance therapy with phototherapy, multicenter prospective randomized clinical trial with low dose, low-frequency PUVA maintenance regimens showed prolonged median disease-free remission. Patients with CR were randomized to receive PUVA maintenance for 9 months. This prolongs the median disease-free remission from 4 months to 15 months (Level 2). Maintenance NB-UVB can also prolong the remission in the early stage. Moreover, in a recent review, maintenance therapy was found to be necessary in most of the cases **(8)**

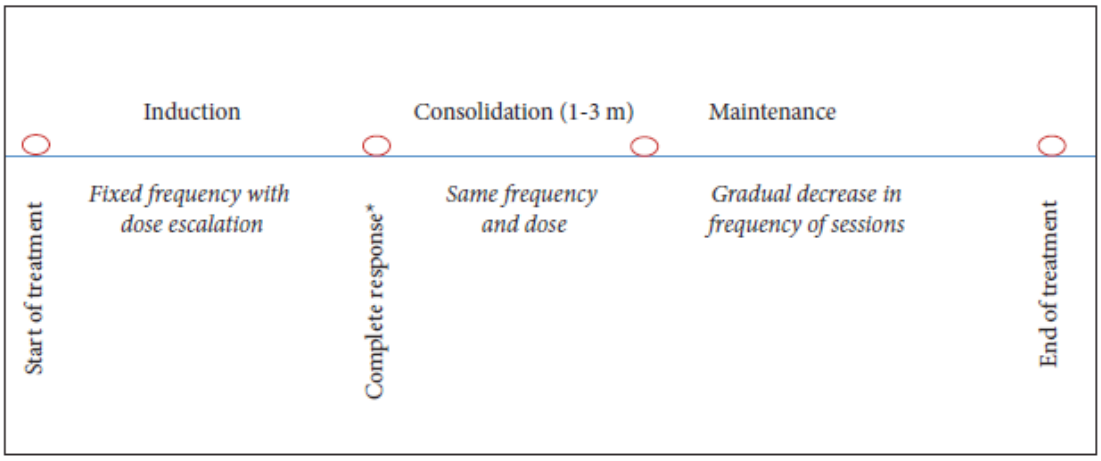

Figure 1: Maintenance regimen with phototherapy (6)

The main aim of treatment is to improve the patients' quality of life (QOL). It is important to mention that the early use of systemic treatment does not lead to a better outcome than using skin directed therapy. Treatment options are presented in a stepwise pattern as the main objective of the treatment is to control the patients' disease with minimal toxicity. Therefore, SDT is given as a frontline in patients with early classic MF, while systemic and combined therapy is reserved for the late cases and transformed MF**(6)**

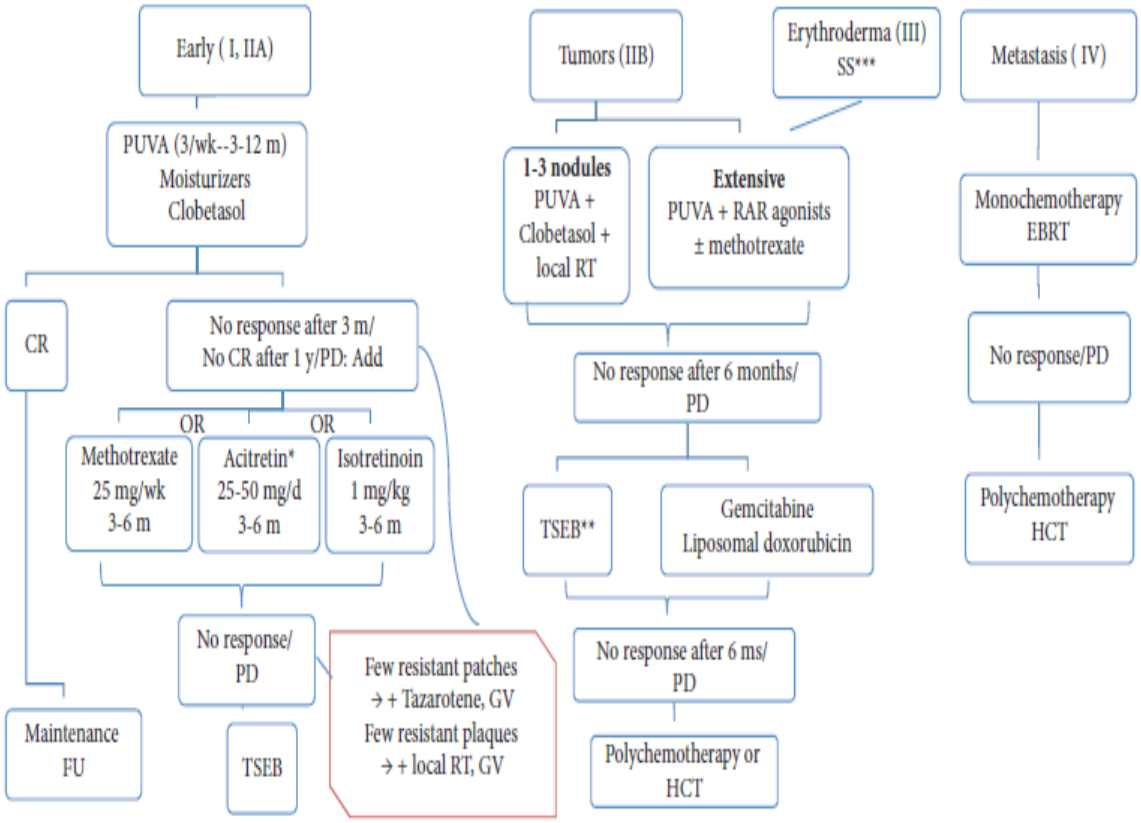

Figure 2: Algorithm for treatment of classic MF/SS. the treatment is presented in a stepwise pattern where patients shift to the next line of therapy in case of the absence of complete response (CR) after 1 year of the current line of therapy, no response after 3–6 months, or the occurrence of progressive disease (PD). For early MF, phototherapy is given where PUVA is more recommended than NB-UVB for our patients with dark skin phenotype (level 2). Potent steroids (level 3) and moisturizers (level 5) are additional basic treatment. Addition of either RAR agonist (level 2) or methotrexate (level 5) is recommended as a second line. Moreover, methotrexate can be combined with acitretin (level 4). TSEB is considered a third line option (level 2). Topical tazarotene (level 3) or gentian violet (level 5) can be added to resistant patches; and localized radiotherapy (level 4) or gentian violet can be added to resistant plaques. Patients with stages (IB-IIA) who show CR should enter a maintenance and follow-up regimen (level 2). For stage IIB with limited disease (up to 3 nodules), localized radiotherapy can be added to SDT (level 4). For stage IIB with multiple nodules, stage III and SS, PUVA plus RAR agonists (level 2) or methotrexate (level 5) or combined methotrexate and acitretin is recommended as a 6rst line (level 4), TSEB is considered a second line option (level 2). Monochemotherapy with gemcitabine or liposomal doxorubicin can be given instead (level 4). Polychemotherapy and allogenic HCT are regarded as a 6nal option (level 3). For stage IV, monochemotherapy is the 6rst line (level 4), followed by polychemotherapy and allogenic stem cell transplantation (level 3). _Acitretin can be combined with methotrexate. __TSEB is preferable than monochemotherapy if feasible to the patient. Phototesting and slow dose escalation are mandatory in case of erythroderma in stage III and IV.

CR: complete response, PD: progressive disease, FU: follow-up, TSEB: total skin electron beam, GV: gentian violet, RT: radiotherapy,

RAR: retinoic acid receptor, EBRT: external beam radiotherapy, HCT: hematopoietic cell transplantation.

Many of the current mainstay treatment options for MF, such as_bexarotene, extracorporeal photophoresis, interferon, histone deacetylase inhibitors, nitrogen mustard, and biologics are either unavailable or not covered by medical insurance in Egypt and other countries with limited resources **(9)**

Immunotherapy has emerged as effective therapeutic option for patients with CTCL which characterized by progressive impairment of multiple arms of the immune system._Immunotherapy targets these deficits to stimulate a more robust antitumor response, thereby both clearing the malignant cells and repairing the immune dysfunction. The established CTCL immunotherapies, such as interferons, photopheresis and retinoids and the emerging therapies such as interleukin-12 and Toll-like receptor agonists and the new approaches to targeting tumor antigens and checkpoint molecules such as mogamolizumab, anti-programmed cell death protein1, anti CD47,and chimeric antigen receptor T cell therapy **(10)**

Retinoids are immunomodulating agent derivatives of vitamin A whose function is to interact with nuclear receptors (both retinoic acid (RAR) and retinoic X (RXR) receptors). Responses of acitretin and etretinate, both targeting RARs, have been shown in 44–67% of patients. Bexarotene is an inductor of apoptosis, which inhibits metastasis and angiogenesis, and it is the only retinoid specifically developed and approved for the treatment of refractory, advanced-stage CTCL. It has shown an ORR of 45–54%, although it is commonly used in combination or as maintenance therapy. The most popular combination is with PUVA. This has a UVA-sparing effect, reducing the risk of the long-term problems of ultraviolet irradiation. Other combinations with extracorporeal photopheresis or interferon are frequently used. **(11)**

Reported treatment for the hypopigmented MF includes NB-UVB, PUVA, topical steroids, topical bexarotene, topical tazarotene, and topical carmustine. Phototherapy is the most commonly used treatment and is usually combined with topical steroids Recurrence is common and maintenance PUVA showed lower rate of relapse compared to patients not receiving maintenance treatment **(12)**

The explanation for relatively better improvement for the hypopigmented MF with combined therapy of the NB-UVB and topical steroid is attributed to the synergic effects on IL-2R (CD25). Hyperpigmented MF is associated with an increased amount of melanin. It is postulated that NB-UVB photons will be absorbed by the melanin which in turn leads to the hyperpigmented skin lesions not getting an optimal therapeutic dose of NB-UVB, thereby leading to a slower response **(13)**

Phototherapy is recommended as a first line treatment for HMF, where NB-UVB is given to children less than 10 years and PUVA is the preferred treatment modality for patients older than 10 years. Moisturizers and mid potent steroid are basic treatment for all patients. Low-dose methotrexate is only reserved for recalcitrant cases **(6)**

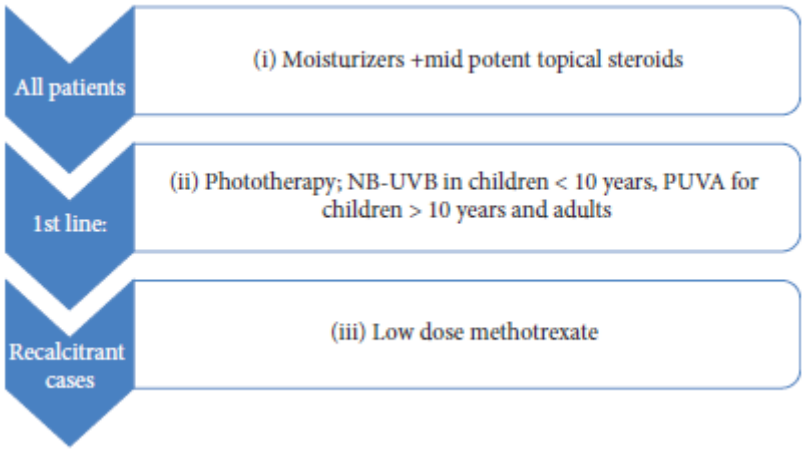

Figure 3: Algorithm for the treatment for hypopigmented MF in Egypt **(6)**

MF/SS are radiosensitive, thus radiation therapy, with curative intent, may be considered in patients with localized, unilesional M. For those with more widespread disease, palliative local radiation or low dose total skin electron beam therapy (TSEBT) are effective. In TSEB, electrons are generated in a linear accelerator and attenuated to penetrate the skin to a limited depth, thereby limiting its potential toxicity to internal organs. TSEB is recommended for first-line treatment of MF from stage IIB to stage IVB and as a second-line treatment for stages IA, IB, and IIA. Reduced radiation doses (12 Gy) were successful compared with higher doses, with an ORR of 87.5% and lower toxicity. Progression-free survival is higher for patients in stage IB than stage IIB **(14)**

According to EORTC guidelines, TSEB can be used for patients with all stages of MF, and remains a very important treatment for these patients, even for those with SS. Moreover, the recent NCCN guidelines 2020 stated that TSEB can be considered as early as stage IB. The response rates and duration of response are higher in earlier stage disease. The aim of treatment (curative or palliative) varies depending on the stage .The goal of TSEB is to deliver a relatively uniform dose of radiation to the entire skin while limiting acute and long-term toxicities **(15)**

The TSEBT beams are limited to a particular skin depth, thus reducing systemic toxicity. Acute adverse effects are dose-dependent and include local skin reactions, pain, loss of nails, and anhidrosis. Long-term effects include telangiectasias, alopecia, and secondary cutaneous cancers have been reported in patients having received multiple TSEBTs. Patients with advanced-stage MF/SS require a multidisciplinary approach, as various combinations of skin-directed therapies, biologic response modifiers, and ultimately the sequential use of systemic chemotherapeutic agents are frequently employed in the management of these patients. As for limited-stage disease, multi agent chemotherapy is not appropriate. Instead, a “risk-adapted” and stage-based approach,

consistent with NCCN guidelines, incorporating biologic response modifiers (e.g., bexarotene and interferon-alpha), histone deacetylase inhibitors (e.g. romidepsin), or monoclonal antibodies or antibody-drug conjugates (e.g. mogamulizumab, brentuximab vedotin) is generally preferred **(16)**

According to NCCN 2020 guidelines, methotrexate ≤ 50 mg per week is considered as category A systemic treatment for treatment of patients with tumor stage. Category B systemic treatment, which are more toxic include Gemcitabine and pegylated liposomal doxorubicin can be used for patients with advanced stage MF/SS. Multiagent chemotherapy, though effective, are more toxic and associated with higher risk of mortality, so are reserved only for refractory cases or for nodal or visceral metastasis. They can also be used as a bridge to allogeneic hematopoietic cell transplantation (HCT). Methotrexate can be used from stage IIB, gemcitabine or liposomal doxorubicin can be used from stage IV and polychemotherapy is regarded as a final treatment option **(6)**

Table 2 Monoclonal antibodies in MF/SS that are currently in use or in clinical development (17)

Antibody	Target	Mechanism of action
Mogamulizumab[1]	CCR4 (C-C chemokine receptor type 4): CCR4 regulates T-cell skin homing by interacting with its ligands CCL17 and CCL22. CCR4 is highly expressed in tumor stage MF and SS (30)	ADCC and immunomodulation via reduction of Tregs (31,32)
IPH4102	KIR3DL2 (killer cell immunoglobulin like receptor, three Ig domains and long cytoplasmic tail 2): KIR3DL2 is a co-inhibitory signal present on NK cells and on a subset of malignant T cells in MF/SS patients (33,34)	ADCC (33,34)
Alemtuzumab	CD52: CD52 is a glycosylated peptide antigen expressed on most malignant B and T cells but not on hematopoietic stem cells (35)	ADCC and CDC (35)
Brentuximab Vedotin[2]	CD30: CD30 is a transmembrane molecule of the tumor necrosis factor receptor family and is expressed in a subset of patients with MF (36)	Upon receptor binding, the antibody-drug conjugate (anti-CD30/MMAE) is internalized into lysosomes and MMAE release leads to cell cycle arrest and apoptosis (37,38)

1, mogamulizumab was recently approved by the FDA for patients with stage IB–IV MF/SS who have received at least one prior systemic therapy; 2, brentuximab vedotin has been approved by the FDA in 2017 for patients with CD30-expressing MF who have received prior systemic therapy. MF, mycosis fungoides; SS, Sézary syndrome; ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity; CCL17, C-C motif chemokine ligand 17; CCL22, C-C motif chemokine ligand 22; MMAE, monomethyl auristatin E. Alemtuzumab is a humanized IgG1 monoclonal antibody directed against CD52, an antigen widely expressed by B-cells, T-cells, and monocytes. In a phase II study in 22 patients with advanced stage MF/SS, overall and complete

response rates of 55% and 32%, respectively, were observed, with a median time to treatment failure of 1 year. Most patients in this study received 3 mg of subcutaneous alemtuzumab on day 1 followed by a 10 mg dose on alternating days until the Sézary count was <1000/mm3. With the exception of a single patient whose best response was stable disease, 9 out of 10 patients treated in this manner achieved a response, 3 of which were complete. For most patients, the time to treatment failure exceeded 12 months. The infectious complications were not observed in patients treated with the lowest dose (i.e., 10 mg) of alemtuzumab. Similar results, with no infectious complications, were recently reported in a small cohort of patients treated with modified, low-dose, subcutaneous alemtuzumab for 6 weeks **(18)**

Mogamulizumab (KW-0761) is a humanized monoclonal antibody specific for the chemokine receptor CCR4 that has been defucosylated and is consequently associated with enhanced antibody-dependent cell-mediated cytotoxicity (ADCC). In addition to ADCC-mediated clearance of malignant T cells, mogamulizumab may inhibit Treg-mediate immune suppression, and may warrant further investigation with immunomodulatory therapies, including immune checkpoint blockade. Overall, treatment with mogamulizumab was well tolerated, with few ≥grade 3 adverse events(AE's). Infusion-related reactions were the most common grade 1 or 2 adverse events (AE's) **(18)**

Mogamulizumab-associated rashes are observed, and may clinically and histopathologically mimic CTCL, but may be without discontinuation of therapy. Treatment-associated rashes are characterized by macrophage- and CD8+ T-cell-rich infiltrates and have been associated with superior disease control in Sezary patients. These positive findings led to mogamulizumab's approval by the FDA in 2018 for MF/SS patients who have failed at least one prior systemic therapy. With regard to the other MF variants, PR and GSS, treatment with radiotherapy or surgical excision has been recommended **(19)**

The approval of Brentuximab vedotin and mogamulizumab for advanced and refractory MF and SS has broadened the therapeutic spectrum for this incurable disease group with poor prognosis. Lacutamab and PD-1/L-1 inhibitors have demonstrated encouraging results in phase 1 and phase 2 trials. More promising novel therapeutic agents are currently undergoing clinical trial and will continue to expand the therapeutic options available in the management of advanced-stage MF und SS. Microbiome targeting may be a therapeutic strategy. A small clinical study by Lindahl et al. demonstrated that a short term aggressive treatment with a SA-targeting antibiotic regimen resulted in a marked long-lasting clinical improvement in advanced-stage CTCL patients, leading to a decrease in the proliferation of malignant cells, STAT3 signaling, and the expression of CD25. These observations encourage the conduction of studies combining the targeting of SA together with STAT signaling **(20)**

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