Skin-directed therapy and biologic response modifiers in mycosis fungoides

Vieri Grandi, Virginia Alba Colantuono, Nicola Pimpinelli

Dermatology Unit, Department of Health Sciences, University of Florence Medical School, Florence; Melanoma and Skin Cancer Unit, Central Tuscany Health District, Italy

Abstract

The most common and widespread type of cutaneous T-cell lymphoma is mycosis fungoides (MF), and it has a multiphasic clinical and biological course, with early stages being indolent for many years and later stages being faster and more aggressive. The clinical stage has a significant impact on the management and course of treatment: in the early stages, skin-directed therapies (SDT) plus/or biologic response modifiers (BRM); in the later stages, radiotherapy and/or systemic therapies. Even though national and international societies and groups periodically update their clinical recommendations, there is still no universally accepted approach. This paper reviews and discusses the various SDT and BRM options, either separately or in combination.

Introduction

Mycosis fungoides (MF) stands as the most common and prevalent form of cutaneous T-cell lymphoma (CTCL).[1,2] MF is a chronic and indolent lymphoma, manifesting in the early stages as erythematous patches and/or plaques: in advanced stages, tumors or erythroderma do occur. Extracutaneous spread to blood, lymph nodes, and visceral organs are rare and generally late events, yet associated with dismal prognosis.[2] The management of MF is a unique challenge, requiring a nuanced approach that balances efficacy with tolerability, particularly in the early stages. Numerous therapeutic options exist for managing CTCL, especially MF and Sézary syndrome (SS), a rarer, form of CTCL characterized by *de novo* erythroderma, diffuse lymphadenopathy, and peripheral blood involvement. Therefore, the selection of treatment is frequently influenced by physicians' experience and patient preferences.[3]

Unfortunately, none of the available treatments significantly improve overall survival. Therefore, the main objective is to improve progression-free survival and preserve the quality of life, which is usually obtained by reducing highly disturbing symptoms like itch, and cutaneous tumor load. While doing so, it is pivotal to avoid overtreatment, to minimize side effects related to prolonged treatments or uselessly toxic regimens.

In the early phases of MF, skin-directed therapies (SDT) play a pivotal role in mitigating signs and symptoms. Phototherapy, including psoralen plus ultraviolet A (PUVA) and narrowband ultraviolet B (nbUVB), stands out as a cornerstone in the armamentarium against MF. Alongside phototherapy and other SDT, MF can be managed with a series of compounds grouped under the umbrella term "biologic response modifiers" (BRM). With this term, we include all treatments that exert their antitumoral activity without inducing cytotoxicity. BRM include retinoids/rexinoids, interferons, extracorporeal photopheresis, and low-dose methotrexate.[3]

Treatment modalities skin directed therapies

Topical corticosteroids

Topical corticosteroids have proven effective in managing patch-stage (particularly stage IA) MF. Although the mechanisms of action are not yet completely explained, steroids are able to directly trigger apoptosis in malignant T-cells. Additionally, they can reduce the population of resident epidermal Langerhans cells, disrupting their chronic stimulation of malignant T-cells.[4]

In the pioneer study by Zackheim *et al.*, seventy-nine patients with patch or plaque stage MF were analyzed. Of these, fifty-one had less than 10% skin involvement (T1), and twenty-eight had 10% or more involvement (T2). After a median follow-up of 9 months, 63% of T1 patients achieved complete remission, and 31% achieved partial remission, resulting in a total response rate of 94%. For T2 patients, the corresponding figures were 25%, 57%, and 82%, respectively. Clinical examination indicated that 39 patients achieved clinical clearing, with post-treatment biopsies in seven cases confirming histological clearing. However, 10

Correspondence: Vieri Grandi, Dermatology Unit; Department of Health Sciences, University of Florence Medical School, Hospital P. Palagi, viale Michelangelo, 41, 50125 Florence, Italy.
E-mail: vieri.grandi@unifi.it

Key words: mycosis fungoides; retinoid; methotrexate; topical therapy; phototherapy.

Conflict of interest: the authors declare no potential conflict of interest.

Ethical approval and consent to participate: not applicable.

Informed consent: the manuscript does not contain any individual person's data in any form.

Received: 3 January 2024.
Accepted: 15 January 2024.

Licensee PAGEPress, Italy
Dermatology Reports 2024; 16;(s2):9926
doi:10.4081/dr.2024.9926

patients (13%) experienced reversible depression of serum cortisol levels, 2 had minor skin irritation, and 1 exhibited localized, reversible skin atrophy.[5,6]

Kartan *et al* analyzed 163 MF patients treated with topical corticosteroids. Of these, 23% received topical steroid monotherapy, with 73% showing improvement [65% BSA decrease, 67% Modified Severity-Weighted Assessment Tool (mSWAT) reduction], 27% not responding or progressing (51.6% BSA increase, 57% mSWAT increase), and 33% achieving CR, with prolonged topical steroid use. Responders were more common in early-stage MF and among females. In conclusion, topical steroid monotherapy in early-stage MF demonstrated measurable improvements and achieved complete remission in a specific subset of patients.[7]

Chlormethine gel

Chlormethine (2-chloro-*N*-(2-chloroethyl)-*N*-methylethan-1-amine, mechlorethamine) is a drug of the group of nitrogen mustards(alkylating agents), which has been used in the treatment of MF in 1947 intravenously.[8]

Subsequently, nitrogen mustards have been tested topically in order to minimize systemic side effects.[9] In the late 70s, a form of mechlorethamine ointment is commonly used in the treatment of MF.[10-12] In order to improve the tolerability, Lessin *et al*. conducted a phase II randomized clinical trial comparing a novel formulation mechlorethamine hydrochloride, 0.02% gel, *vs*. mechlorethamine, 0.02%, compounded ointment in the treatment of MF.[13] The gel showed higher response rates (58.5% *vs*. 47.7% by Composite Assessment of Index Lesion Severity, and 46.9% *vs*. 46.2% by mSWAT). The gel met the noninferiority criteria [ratio 1.23; 95% confidence interval (CI), 0.97-1.55] and demonstrated better time-to-response (P<.01). No serious drug-related adverse events were reported. Withdrawals due to drug-related skin irritation occurred in 20.3% (gel) and 17.3% (ointment) patients. Moreover, there was no detectable systemic absorption. In summary, mechlorethamine, 0.02%, gel is effective and safe in mycosis fungoides treatment, with detailed response percentages provided.

The novel gel preparation was hence approved by the United States (US) Food and Drug Administration in 2013 for 'the topical treatment of stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma in patients who have received prior skin-directed therapy' and – with a broader indication – in 2017 by the European Medicines Agency (EMA) 'for the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma in adult patients'. Chlormethine gel is currently recommended as 1st line treatment of early-stage disease (stages IA to IIA) alternatively to phototherapy.[3] It can also be successfully used in refractory and/or "shadow" areas in patients undergoing phototherapy. In real-world practice, there is increasing evidence that combination/rotation with topical steroids is able to highly improve acceptability and in the end efficacy of the treatment with topical chlormethine.

Psoralen plus ultraviolet A/narrowband ultraviolet B

PUVA (320-400 nm) phototherapy involves the uptake of psoralen (5 or 8 – methoxsalen) by cutaneous cells, forming bifunctional and monofunctional DNA adducts upon photoactivation. The first documented use of PUVA for MF dates to 1976.

Initial UVA doses may start at 0.5 J/cm2 in cases of phototype I, or at 1 J/cm2 in cases of phototype II, progressively increasing by 0.5 J/cm2 each time.

In the case of phototypes III and IV, the starting dose may be 1.5 and 2 J/cm2 respectively, progressively increasing by 1 J/cm2. In the case of phototypes V and VI instead, the starting dose may be 2.5 and 3 J/cm2 respectively, progressively increasing by 1.5 J/cm2.[14] Treatment frequencies vary, typically ranging from two to four times per week until skin lesions are cleared.[3]

In a recent review and meta-analysis conducted by Phan *et al*.,[15] the effectiveness and adverse effects incidence rates of PUVA and nbUVB were compared. Incorporating data from seven studies with 778 patients (mean age 52; 55.9% men) with histologically confirmed early-stage MF (stages IA, IB, IIA), PUVA treatment (n=527) showed an overall response of 90.9% like 87.6% of nbUVB [odds ratio (OR), 1.40; 95% CI, 0.84-2.34; P=.20]. Notably, complete response rates were significantly better with PUVA (73.8%) than nbUVB (62.2%) (OR, 1.68; 95% CI, 1.02-2.76; P=.04). Partial response rates were similar (18.0% *vs*. 27.5%; OR, 0.58; 95% CI, 0.33-1.04; P=.07). No significant differences were observed in adverse effects incidence rates between PUVA and NBUVB.[15]

Because of the known increased risk of NMSC associated with PUVA, nbUVB should be the first choice in patients with MF and consider PUVA only in more severe (mainly plaques) or refractory cases. The protocol of nbUVB recommended by the US Cutaneous Lymphoma (CL) Consortium involves a starting dose of 0.13 J/cm2 in case of phototype I, progressively increasing 0.15 J/cm2 each time; 0.22 J/cm2 starting dose for phototype II, increasing 0.25 J/cm2; 0.26 J/cm2 starting dose for phototype III, increasing 0.4 J/cm2; 0.33 and 0.35 starting dose for phototype IV and v respectively, progressively increasing by 0.45 in the first case and 0.6 in the second; 0.4 J/cm2 starting dose for phototype VI lastly, increasing 0.65 J/cm2 each time.[14] The usefulness of maintenance therapy, highlighted by the US CL Consortium study, has not been validated or at least considered crucial in a recent multicenter Italian study.[16]

Localized radiotherapy

Radiotherapy (RT) is a common treatment option in CTCL and is fruitfully used in both early and advanced diseases with different goals. The advantages of using RT in CTCL are multiple: first, CTCL are extremely radiosensitive, therefore low doses are associated with high overall response rates, often lasting for (even many) months. The incidence of acute and chronic adverse events to RT are dose-dependent. Hence, schedules with low dosages are extremely safe and well tolerated. Secondly, RT has a short time to respond, meaning rapid improvement of pain, wound bleeding, or itching. Third, RT can be used before, alongside, or sequentially to systemic agents. This allows, for example, to improve responses in cases with good partial remissions but with persistent symptomatic lesions, or to control early relapses rapidly. Unfortunately, due to the rarity of CTCL, there is no RCT comparing RT to any other treatment. Also, several treatment schedules have been used in the literature, with no clear standardization of protocols. Despite cumulative doses ranging from 10 to 40 Gy seem associated with similar response rates (89-96%),[17] increasing cumulative dose leads to reduction of the incidence of local relapses. Generally speaking, localized RT has mostly a palliative role. However, unilesional MF cases have been successfully cured with localized RT. In the pivotal work by Micaily *et al.*,[18] data from 18 patients with unilesional MF treated with RT (doses ranging between 22 and 40 Gy) were retrospectively reviewed. The complete clearance rate was 100%, with a 10-year relapse-free survival and overall survival of 86 and 100%, respectively. In a more recent work by Chan *et al.*,[19] the authors were able to pool data from all available literature on this topic, demonstrating a 1-year and 5-years disease-free survival rates of 92,7% and 83,4%, respectively.

Total skin electron beam therapy

Total skin electron beam therapy (TSEBT) is a skin-directed approach employing linear accelerator-generated electron beams to treat the entire skin surface to a limited depth. It is recommended as a second-line therapy for early-stage MF and as a first-line option for MF tumor stage and erythrodermic MF.[3] The standard treatment course involves a total dose of 30-36 Gy over 8-10 weeks, demonstrating high overall response rates (ORR) and complete response rates (CRR) in both early and advanced MF stages.[11,20] Over time, expert centers moved towards lower doses, with the aim of reducing acute and long-term side effects and increasing tolerability. A study by Georgakopoulos *et al*. compared conventional (36 Gy, n=6) to low-dose (12 Gy, n=8) TSEBT. Both regimens demonstrated excellent treatment outcomes, were well-tolerated, and resulted in comparable response rates, with an overall response rate exceeding 87.5%. The treatments showed mild toxicity and were well-tolerated. The low-dose TSEBT schedule of 12 Gy proves to be an effective treatment option, offering acceptable therapeutic results, excellent compliance, and minimal toxicity. Additionally, its safety for repeated administration enhances its attractiveness compared to the standard 36 Gy scheme, aligning with treatment guidelines for radiation therapy referral.[21]

Grandi *et al*.'s systematic review and meta-analysis offer a thorough analysis of the efficacy of low-dose (ld) and standard-dose (sd) TSEBT in managing MF across early and advanced stages. Ld TSEBT is linked to lower CRRs but high ORRs, while sd TSEBT shows high CRR (especially in early stages) and remarkably high ORR. Every patient experiences at least one G1-G2 adverse event during or after treatment, with sd-TSEBT patients encountering multiple concurrent G1-G2 adverse events. In advanced-stage MF, the likelihood of achieving CR may be reduced compared to early stages when treated with TSEBT. In the early-stage cohort, ld TSEBT yields a CRR of 28% (7 studies, 122 patients) and an ORR of 93%, while in the advanced-stage cohort, ld TSEBT results in a CRR of 18% (7 studies, 101 patients) and an ORR of 75%. For standard-dose TSEBT, the early stage exhibits a CRR of 72% (4 studies, 127 patients) and an ORR of 100%, while in advanced stages, sd TSEBT shows a CRR of 55% (4 studies, 274 patients) and an ORR of 95%. Adverse event rates for ld TSEBT include a mild rate of 93% and a severe event rate of 5%, while sd TSEBT demonstrates a mild adverse event rate of 100%, with a severe adverse event rate of 7%. All evidence is derived from non-randomized, single-center studies, often with a retrospective design.[20] As a general statement, it should be emphasized that ld TSEBT can be repeated multiple times, even short-term if needed, differently form hd TSEBT.

Photodynamic therapy

Photodynamic therapy (PDT) is considered a safe alternative to conventional SDT for MF. PDT involves the use of light-activated substances such as aminolaevulinic acid (ALA) or methyl ALA (MAL) to target and selectively destroy cancer cells. In their systematic review,[22] Hooper *et al.* evaluated 44 pertinent cases across eight distinct publications, focusing on the use of PDT in stage IA MF. Among these patients, 36 (81.8%) had received prior treatments, ultraviolet A1 light, topical steroids, or PUVA.

MAL was used in almost all analyzed reports. Notably, CR was achieved in 67.3%, partial response (PR) in 13.5%, and no response (NR) in 3.8% of cases. Stable disease (SD) was reported in 3.8%, with clinical response data not available in 11.5%. The preference for MAL is based on its advantages in PDT, including increased lipophilicity and deeper skin penetration.

MAL, with shorter occlusion times (3 hours), is assumed to require less prolonged application due to its enhanced penetrative properties. Studies used red light (630 nm) more often than blue light (400 nm) (65.9% *vs.* 34.1%). The hypothesis is that longer wavelengths may be more effective in treating MF thicker lesions. The mean treatment number was 9.5 (range 1-46), suggesting that multiple PDT sessions are key for successful MF treatment. However, the exact parameters remain unknown, as there have been no randomized, controlled trials addressing this question to date.[22]

PDT efficacy depends mostly on the internalization of an adequate amount of the drug inside the tumor cells but also on the amount of light that reaches the targeted cells. Certain disease characteristics, such as lesion thickness and involvement of adnexal structures in follicolotropic MF may theoretically impair PDT efficacy. Future research aimed at understanding PDT's efficacy in MF treatment should involve randomized controlled trials to refine protocols based on lesion type, thickness, and location. A key focus of this research lies in optimizing the PDT protocol, including the selection of prodrugs and specific light wavelengths. Additionally, the potential of PDT as a first-line treatment for MF remains unexplored.

Biologic response modifiers

Extracorporeal photopheresis

Extracorporeal photopheresis (ECP), also referred to as extracorporeal photochemotherapy, extracorporeal photoimmunotherapy, or simply photopheresis, is a therapeutic approach based on leukapheresis. During an ECP treatment, a small amount of the patient's blood undergoes external processing. White blood cells are exposed to ultraviolet A (UVA) light within a distinct plastic chamber and subsequently reintroduced into the patient.[23] To circumvent challenges associated with oral 8-MOP administration, such as gastrointestinal adverse events and individual variability in blood concentrations, a liquid formulation of 8-MOP has been devised. This formulation is directly added to the buffy coat/blood fraction, addressing these issues.[24]

ECP has therefore enhanced the safety profile of PUVA, mitigating potential complications associated with prolonged UVA skin exposure. This improvement allows the extension of ECP therapy benefits to patients in more advanced disease stages, including those with peripheral blood involvement.[25] Despite these advancements, the limited prevalence of CTCL and the exclusive availability of ECP therapy in specialized centers have resulted in a lack of prospective, placebo-controlled, randomized clinical trials assessing the impact of ECP treatment on survival in the existing literature.[24]

Raphael *et al*. presented the most comprehensive case series of CTCL patients undergoing ECP treatment. Drawing from a 25-year experience involving 98 erythrodermic CTCL patients treated with ECP for a minimum of 3 months, the group observed a significant clinical improvement in 75% of patients through multimodality therapy, with 30% achieving complete remission.[26] Notably, most studies involving ECP in CTCL predominantly feature patients in advanced disease stages. While recent guidelines advocate for ECP as a first- or second-line therapy for erythrodermic MF and SS, its use in relapsing/refractory early stages MF remains controversial but merits further investigation.[24]

Methotrexate

Methotrexate (MTX), identified chemically as 4-amino-4-deoxy-N10-methylpteroylglutamic acid, is a derivative of

aminopterin and acts as an analog of folic acid. Classified within the category of anti-metabolic drugs, the specific mechanism through which MTX operates in the treatment of CTCL remains incompletely elucidated. The ongoing inquiry into whether its primary mechanism is anti-inflammatory, immunomodulating, immunosuppressive, or cytostatic continues to be unresolved.[27]

In the context of CTCL, the impact of MTX is associated with modulation in the expression of various genes, notably an increase in Fas/Fas ligand expression. This, in turn, enhances the sensitivity of neoplastic cells to apoptosis.[28]

Typically prescribed as a second-line treatment following the recommendations of the European Organization for Research and Treatment of Cancer (EORTC) and World Health Organization for stages IA-IIA MF, MTX is administered subcutaneously or orally. The recommended dosage ranges from 5 to 25 mg per week as a single administration. MTX may also be used in combination with glucocorticoids, PUVA, or INF-a as part of the therapeutic approach.[29]

Low-dose methotrexate is commonly utilized for the treatment of MF and SS. Yet, there is a limited body of research assessing its efficacy.

A retrospective study analyzed data from 79 MF patients in Poland treated with single-agent MTX. Results revealed an ORR of 71%. The median duration of response ranging between 4 to 6 months. A 12-month remission was confirmed in 25%, with 2-year and 3-year remissions in 10% and 5%, respectively. Time to remission correlated with disease stage and MTX dosage. Higher MTX doses were associated with prolonged remissions, at a cost of increasing rate of systemic side effects.[27]

Alenezi *et al.* performed a retrospective analysis on patients treated with low-dose MTX, aiming to assess the risk-to-benefit ratio specifically on skin lesions. The study included forty-eight patients followed for at least one year in a tertiary referral center. Results indicated that 21% achieved a CR, while 52% experienced a PR, with no significant variation between MF and SS. Among responders, 57% relapsed after a median time of 11 months. Discontinuation of MTX occurred in forty-four out of forty-eight patients, mostly due to primary or secondary failure and/or limiting toxicity (9 patients). Despite these challenges, the overall benefit-to-risk ratio of low-dose MTX in MF and SS is deemed favorable, underscoring its continued relevance as a viable treatment option for these conditions.[28]

Retinoids and rexinoids

Retinoids, derived from vitamin A, demonstrate the ability to modulate cell proliferation and differentiation across various neoplasms.[30] In MF, these effects extend to keratinocytes and potentially influence the immunoregulation of mononuclear skin infiltrates. *In vitro* studies have shown that 13-cis-retinoic acid induces cellular differentiation, apoptosis, and DNA fragmentation in sensitive T-cell lines.[31] Commonly utilized retinoids include acitretin and isotretinoin, with typical starting doses of 25-50 mg/day and 1 mg/kg/day, respectively.[32] These substances are generally well tolerated, exhibiting common adverse effects typical of their class, such as teratogenicity, dryness of the skin and mucous membranes, and hyperlipidemia. Additionally, each retinoid has its unique toxicity profile, for instance, central hypothyroidism for bexarotene.[3,31-33]

However, based on the available published evidence, it is currently impossible to draw a definitive conclusion regarding the superiority of one retinoid over another.[3]

Over the past decade, research has revealed that many effects of retinoids are mediated by their interaction with a family of nuclear receptors known as retinoic acid receptors (RARs). A second family of nuclear receptors, the retinoid X receptors (RXRs), also binds retinoic acid derivatives, exhibiting distinct structural and functional characteristics from the RARs.[34]

Bexarotene, the first 'rexinoid' to undergo clinical development, demonstrates high selectivity for RXRs. It has received approval from the EMA for treating skin manifestations in advanced CTCL.[35] While the precise mechanisms remain unknown, *in vitro* studies suggest that bexarotene can inhibit growth in tumor cell lines and induce *in vivo* tumor regression in animal models, accompanied by the stimulation of apoptosis. Typically administered at 300 mg/m2/day, treatment with bexarotene is continued indefinitely for responsive patients, often at a reduced dose to mitigate the side effects.[3] However, it's important to be aware that bexarotene can lead to severe central hypothyroidism, frequently associated with marked reductions in serum concentrations of thyroid-stimulating hormone and thyroxine. Therefore, continuous monitoring of thyroid function and hypertriglyceridemia is advised during treatment.[3,33]

Additionally, concomitant use of a lipid-lowering agent is often necessary, with caution against gemfibrozil due to its potential to increase plasma concentrations of bexarotene, likely through the inhibition of cytochrome P450 3A4, resulting in a paradoxical elevation of triglycerides.[3]

Studies on bexarotene's mechanisms of action demonstrated its capacity to induce apoptosis in CTCL lines by activating caspase-3, independently of the Fas-FasL apoptotic pathway. The drug also decreases levels of the antiapoptotic protein survivin, suggesting a role in caspase-3 activation.[36]

Importantly, bexarotene induces apoptosis in association with the downregulation of both RXRa and RARa proteins in CTCL.

Further investigations indicate that bexarotene influences cytokine regulation, specifically reducing IL-4 levels in CTCL, potentially impacting Th2 cytokines predominant in SS. Additionally, studies propose that bexarotene may decrease skin trafficking of malignant cells by downregulating CCR4 expression, impacting chemotaxis, and suggesting a precursor event to apoptosis. The drug's antineoplastic effects involve cell cycle arrest, with upregulation of proapoptotic proteins such as Bax and downregulation of p34, cyclinB1, and survivin. Bexarotene may also increase functional regulatory T-cells (Tregs), contributing to its therapeutic effects. Notably, studies in keratinocytes and Langerhans cells showed no significant effects, reinforcing the idea that the primary target of bexarotene is apoptosis of malignant T-cells. Molecular marker analyses associated bexarotene response with chromosome 12 polysomy, proposing potential immune response modulation. While these findings are promising, larger studies are essential for a comprehensive understanding and validation of bexarotene's intricate mechanisms of action in the context of CTCL.[36]

Bexarotene has demonstrated its effectiveness not only in monotherapy but also in combination with other modalities, offering promising results for patients with treatment-resistant CTCL, particularly MF. Combining it with PUVA yields positive outcomes, with initial responses and complete remissions observed. Comparative studies indicate the combination's efficacy, with response rates comparable to or better than PUVA alone.[36]

Combining phototherapy with bexarotene elicited diverse response rates among adult patients with early stages MF. The ORR varied between 65% and 70%, with prospective studies indicating potentially higher rates. Despite some individual studies reporting elevated overall response rates for this combination ther-

apy, a systematic review by Ginsburg *et al*. demonstrated response rates up to 70%. An explanation is that several patients in the systematic review had previously experienced treatment failure with skin-directed therapies, and seventeen of them had received prior systemic therapies. This suggests that patients undergoing combination therapy may present with more severe disease, making them less likely to respond effectively.[37]

Singh *et al.,* in 2004, analyzed eight patients with CTCL ranging from stage IA to IIB who failed multiple single-agent treatment regimens and found a response in five patients treated with low-dose oral bexarotene and PUVA combination therapy.[38]

Papadavid *et al.*, in 2008, found out that in a specific group of patients who did not show positive responses to at least one monotherapy for early-stage MF, the combination of low-dose oral bexarotene and PUVA demonstrated effectiveness. The treatment achieved a ORR of 67% of patients and it was generally well-tolerated.[39] Whittaker *et al.*, in 2012, reported the first randomized prospective controlled study that compared PUVA alone *vs*. a combination of PUVA and bexarotene in treating stage IB/IIA MF, finding both treatments safe and well-tolerated. However, no significant differences were observed in ORR or DOR between the two groups after a 16-week maximum treatment period. Nevertheless, it is important to highlight that the recruitment for this study fell short of the necessary numbers to attain adequate statistical power for a conclusive evaluation of the primary endpoint.[33] Rupoli *et al.*, published in 2015 a prospective study demonstrating the efficacy of a combined treatment using bexarotene and PUVA for both early and advanced MF/SS, achieving positive responses with minimal toxicity. At the end of the maintenance phase, there was a promising 76.2% overall response, including a 33.3% CRR, with an event-free survival lasting up to 31 months.[40] In comparison to other studies, the proposed protocol showed superior outcomes in early-stage MF. However, comparisons for advanced stages were challenging due to differing therapeutic approaches in other studies. The protocol, including both induction and maintenance therapy, emphasizes the potential properties of bexarotene, particularly during the maintenance phase, which highlights its slow onset of action, and which should assume greater importance in future studies.[40]

In a recent study of the Japanese group, Morita *et al.*, found out that both bexarotene monotherapy and the combination of bexarotene with photo(chemo)therapy were effective treatments for Japanese patients with CTCL, and they were well-tolerated.[41] The efficacy analysis, based on the mSWAT reduction, showed a response rate of 81.0% in the combination therapy group and 83.3% in the monotherapy group, with no statistically significant difference between them. Notably, the combination therapy group demonstrated a higher rate of complete or partial clinical responses and superior resolution of skin lesions compared to the monotherapy group. Importantly, in the safety analysis, which included 46 treated subjects, no adverse events or drug-related reactions were reported in either group.[41] These findings suggest that combining bexarotene with PUVA may be a valuable approach for CTCL patients, especially those resistant to monotherapy. Ongoing research aims to further clarify the benefits and safety profiles of these combinations.

Interferon α

Interferon (IFN)-α has played a crucial role in the treatment of MF and SS. Currently, the only remaining available pharmacological form is pegylated IFN-α 2a (PEG-IFN α-2a),[3] which is given once a week because of its extended half-life, compared to the previous forms. While IFN-α shares cytostatic and antiviral properties with other interferons, its distinctive immunomodulatory effects appear well-suited for addressing immune dysfunctions seen in CTCL. These dysfunctions include heightened TH2 activity, reduced TH1 activity, and diminished numbers and activities of natural killer cells and CD8+ T-cells.[31,42]

The European Society of Medical Oncology clinical practice guidelines recommend IFN-α for patients with extensive infiltrated plaques or refractory to skin-directed therapies in CTCL, often in combination with PUVA or other skin-directed therapies.[43]

Schiller *et al.*, in an open-label, multicenter, dose-escalation study, evaluated the safety, tolerability, and efficacy of subcutaneous pegylated (40 kD) IFN α-2a (PEG-IFN α-2a) assessed in CTCL patients. Administered at 180 µg (n=4), 270 µg (n=6), or 360 µg (n=3) once weekly for 12 weeks, PEG-IFNα-2a demonstrated well-tolerated doses up to 360 µg. Efficacy evaluation revealed a major response rate (CR or PR) of 50% in the 180 µg group, 83% in the 270 µg group, and 66% in the 360 µg group. Notably, the 270 µg group exhibited a CR of 67% and PR of 17%. Overall, PEG-IFNα-2a showed promising response rates across dose groups in CTCL patients, supporting its potential as a treatment option. The most common adverse events included fatigue, acute flu-like symptoms, and hepatotoxicity.[44]

A retrospective study on 28 CTCL patients treated with PEG-IFNα in Germany and the Netherlands revealed promising outcomes. Results showed that 36% achieved complete remission, 36% partial remission, and 29% SD. Adverse events led to treatment discontinuation in two patients (18%). Combination therapies were prevalent (26/28), with PUVA (54%) and local radiotherapy (29%) being the most common. Complete remission rates varied among treatments: PUVA+PEG-IFNα (40%), local radiotherapy + PEG-IFNα (38%). Notably, stage IIB and III patients seemed to benefit the most from PEG-IFNα treatment. In summary, PEG-IFNα, especially in combination with PUVA or local radiotherapy, demonstrated efficacy in CTCL, with notable CR rates, though adverse events were observed in a subset of patients. Stage IIB and III patients appeared to derive significant benefits from this treatment approach.[45]

Patsatsi *et al.*, studied 31 MF patients, primarily with classic MF (83.9%). Most had IB-stage disease (38.7%) at peg-IFN initiation which was often combined with other treatments. Administered as third-line therapy in twenty-one cases, PEG-IFN resulted in a 54.8% ORR (CR: 9.7%, PR: 45.2%). Response rates were similar across gender, disease stage, and presence of folliculotropism. Two patients experienced progression, and 25.8% had dose reduction due to intolerance. Adverse effects, including neutropenia and fatigue, were observed in 67.7%. The treatment was discontinued in 9/31 patients after a mean of 3.4 months. Despite toxicity, PEG-IFN appears promising as an MF treatment, with optimal dosing needing further exploration in future studies.[46]

Conclusions

In conclusion, the management of MF involves a carefully balanced choice between SDT and BRM, leaving systemic chemotherapies as later options in patients experiencing rapidly progressive, symptomatic, advanced refractory disease. This approach allows in most cases to obtain appreciable control of signs and symptoms for prolonged periods without experiencing long lasting side effects due to systemic agents. Moreover, in case of relapsing disease, the various treatments can be repeated or

switched. Among all agents, topical corticosteroids and chlormethine gel should be considered in all patients, as single agents for early-stage disease or combined in advanced stages as maintenance. nbUVB phototherapy, with its excellent safety profile, is recommended as a first-line treatment in diffuse early-stage stages MF, while PUVA therapy becomes valuable in more severe and refractory cases with folliculotropism and thick plaques. TSEBT emerges as a useful approach for extensive relapsing / refractory disease, or as rapid relief in highly symptomatic patients with more advanced cutaneous disease Among BRM, low-dose methotrexate is a viable option alongside retinoids and bexarotene. No head-to-head study has been performed so far, and therefore it is still not possible to draw conclusions on which drug should be used first. Extracorporeal photochemotherapy is a feasible option in specialized centers and for cases of more severe disease, especially in frail patients with significant comorbidities.

Combined approaches, such as PUVA + bexarotene or combining IFN-α with retinoids and utilizing combinations of both substances alongside phototherapy may have a significant role in managing refractory/relapsing disease. As our understanding evolves, these treatment modalities underscore the importance of tailored and nuanced therapeutic strategies for optimizing outcomes in MF. Continued research and clinical validation will further refine the landscape of treatment options.

Despite this, there is a lack of conclusive evidence demonstrating the superiority of these combinations over monotherapy in general. As a result, the EORTC/International Society for Cutaneous Lymphomas recommendations do not endorse the use of combinations as first-line options in MF/SS.[3]

References

1. Dobos G, de Masson A, Ram-Wolff C, et al. Epidemiological changes in cutaneous lymphomas: an analysis of 8593 patients from the French Cutaneous Lymphoma Registry. Br J Dermatol 2021;184:1059-67.
2. Willemze R, Cerroni L, Kempf W, et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. Blood 2019;133:1703-14.
3. Latzka J, Assaf C, Bagot M, et al. EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome - Update 2023. Eur J Cancer 2023;195:113343.
4. Kim EJ, Hess S, Richardson SK, et al. Immunopathogenesis and therapy of cutaneous T cell lymphoma. J Clin Invest 2005;115:798-812.
5. Zackheim HS, Kashani-Sabet M, Amin S. Topical corticosteroids for mycosis fungoides. Experience in 79 patients. Arch Dermatol 1998;134:949-54.
6. Zackheim HS. Treatment of patch-stage mycosis fungoides with topical corticosteroids. Dermatol Ther 2003;16:283-7.
7. Kartan S, Shalabi D, O'Donnel M, et al. Response to topical corticosteroid monotherapy in mycosis fungoides. J Am Acad Dermatol 2021;84:615-23.
8. Henstell HH, Tober JN. Treatment of mycosis fungoides with nitrogen mustard. J Invest Dermatol 1947;8:183-8.
9. Zackheim HS. Treatment of mycosis fungoides with topical nitrosourea compounds. Arch Dermatol 1972;106:177-82.
10. Price NM, Constantine VS, Hoppe RT, et al. Topical mechlorethamine therapy for mycosis fungoides. Br J Dermatol 1977;97:547-50.
11. Price NM, Deneau DG, Hoppe RT. The treatment of mycosis fungoides with ointment-based mechlorethamine. Arch Dermatol 1982;118:234-7.
12. Price NM, Hoppe RT, Deneau DG. Ointment-based mechlorethamine treatment for mycosis fungoides. Cancer 1983;52:2214-9.
13. Lessin SR, Duvic M, Guitart J, et al. Topical chemotherapy in cutaneous T-cell lymphoma: positive results of a randomized, controlled, multicenter trial testing the efficacy and safety of a novel mechlorethamine, 0.02%, gel in mycosis fungoides. JAMA Dermatol 2013;149:25-32.
14. Olsen EA, Hodak E, Anderson T, et al. Guidelines for phototherapy of mycosis fungoides and Sézary syndrome: a consensus statement of the United States Cutaneous Lymphoma Consortium. J Am Acad Dermatol 2016;74:27-58.
15. Phan K, Ramachandran V, Fassihi H, Sebaratnam DF. Comparison of narrowband UV-B with psoralen-UV-A phototherapy for patients with early-stage mycosis fungoides: a systematic review and meta-analysis. JAMA Dermatol 2019;155:335-41.
16. Grandi V, Baldo A, Berti E, et al. Italian expert-based recommendations on the use of photo(chemo)therapy in the managemnent of mycosis fungoides: results of an e-Delphi consensus. Photodermatol Photoimmunol Photomed 2021;37:334-42.
17. Cotter GW, Baglan RJ, Wasserman TH, Mill W. Palliative radiation treatment of cutaneous mycosis fungoides—a dose response. Int J Radiat Oncol Biol Phys 1983;9:1477-80.
18. Micaily B, Miyamoyo C, Kantor G, et al. Radiotherapy for unilesional mycosis fungoides. Int J Radiat Oncol Biol Phys 1998;42:361-4.
19. Chan DV, Aneja S, Honda K, et al. Radiation therapy in the management of unilesional primary cutaneous T-cell lymphomas. Br J Dermatol 2012;166:1134-7.
20. Grandi V, Simontacchi G, Grassi T, et al. Short-term efficacy and safety of total skin electron beam therapy in mycosis fungoides: systematic review and meta-analysis. Dermatol Ther 2022;35:e15840.
21. Georgakopoulos I, Papadavid E, Platoni K, et al. Clinical application of total skin electron beam (TSEB) therapy for the management of T cell cutaneous lymphomas. The evolving role of low dose (12 Gy) treatment schedule. Clin Transl Radiat Oncol 2019;15:26-30.
22. Hooper M, Hatch L, Seminario-Vidal L. Photodynamic therapy of mycosis fungoides: A systematic review of case studies. Photodermatol Photoimmunol Photomed 2021;37:549-52.
23. Schooneman F. Extracorporeal photopheresis technical aspects. Transfus Apher Sci 2003;28:51-61.
24. Knobler R, Arenberger P, Arun A, et al. European dermatology forum - updated guidelines on the use of extracorporeal photopheresis 2020 - part 1. J Eur Acad Dermatol Venereol 2020;34:2693-716.
25. Geskin L. ECP versus PUVA for the treatment of cutaneous T-cell lymphoma. Skin Therapy Lett 2007;12:1-4.
26. Raphael BA, Shin DB, Suchin KR, et al. High clinical response rate of Sezary syndrome to immunomodulatory therapies: prognostic markers of response. Arch Dermatol 2011;147:1410-5.
27. Olek-Hrab K, Maj J, Chmielowska E, et al. Methotrexate in the treatment of Mycosis fungoides. a multicenter observational study in 79 patients. Eur Rev Med Pharmacol Sci 2018;22:3586-94.
28. Alenezi F, Girard C, Bessis D, et al. Benefit/risk ratio of low-dose methotrexate in cutaneous lesions of mycosis fungoides and Sézary syndrome. Acta Derm Venereol 2021;101:1031.
29. Willemze R, Hodak E, Zinzani PL, et al. Primary cutaneous

lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol 2013;24:vi149-vi154.
30. Siegel RS, Pandolfino T, Guitart J, et al. Primary cutaneous T-cell lymphoma: review and current concepts. J Clin Oncol 2000;18:2908-25.
31. Cheng AL, Su IJ, Chen CC, et al. Use of retinoic acids in the treatment of peripheral T-cell lymphoma: a pilot study. J Clin Oncol 1994;12:1185-92.
32. Smith BD, Wilson LD. Management of mycosis fungoides: Part 2. Treatment. Oncology (Williston Park) 2003;17:1419-28.
33. Whittaker S, Ortiz P, Dummer R, et al. Efficacy and safety of bexarotene combined with psoralen-ultraviolet A (PUVA) compared with PUVA treatment alone in stage IB-IIA mycosis fungoides: final results from the EORTC Cutaneous Lymphoma Task Force phase III randomized clinical trial (NCT00056056). Br J Dermatol 2012;167:678-87.
34. Ahuja HS, Szanto A, Nagy L, Davies PJA. The retinoid X receptor and its ligands: versatile regulators of metabolic function, cell differentiation and cell death. J Biol Regul Homeost Agents 2003;17;29-45.
35. European Medicines Agency. Targretin. European Medicines Agency, Sci Med Health. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/targretin
36. Pileri A, Delfino C, Grandi V, Pimpinelli N. Role of bexarotene in the treatment of cutaneous T-cell lymphoma: the clinical and immunological sides. Immunotherapy 2013;5:427-33.
37. Ginsburg E, Hennessy K, Mhaskar R, Seminario-Vidal L. Treatment of early-stage mycosis fungoides with oral bexarotene and phototherapy: a systematic review and meta-analysis. Dermatol Ther 2022;35:e15418.
38. Singh F, Lebwohl MG. Cutaneous T-cell lymphoma treatment using bexarotene and PUVA: a case series. J Am Acad Dermatol 2004;51:570-3.
39. Papadavid E, Antoniou C, Nikolaou V, et al. Safety and efficacy of low-dose bexarotene and PUVA in the treatment of patients with mycosis fungoides. Am J Clin Dermatol 2008;9:169-73.
40. Rupoli S, Canafoglia L, Goteri G, et al. Results of a prospective phase II trial with oral low-dose bexarotene plus photochemotherapy (PUVA) in refractory and/or relapsed patients with mycosis fungoides. Eur J Dermatol 2016;26;13-20.
41. Morita A, Tetishi C, Ikumi K, et al. Comparison of the efficacy and safety of bexarotene and photo(chemo)therapy combination therapy and bexarotene monotherapy for cutaneous T-Cell lymphoma. Dermatol Ther (Heidelb) 2022;12:615-29.
42. Spaccarelli N, Rook AH. The use of interferons in the treatment of cutaneous T-Cell lymphoma. Dermatol Clin 2015;33:731-45.
43. Willemze R, et al. Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29:iv30-iv40.
44. Schiller M, Tsianakas A, Sterry W, et al. Dose-escalation study evaluating pegylated interferon alpha-2a in patients with cutaneous T-cell lymphoma. J Eur Acad Dermatol Venereol 2017;31:1841-7.
45. Gosmann J, Stadler R, Quint KD, et al. Use of pegylated interferon alpha-2a in cutaneous T-cell Lymphoma: a retrospective case collection. Acta Derm Venereol 2023;103:adv10306.
46. Patsatsi A, Papadavid E, Kyriakou A, et al. The use of pegylated interferon a-2a in a cohort of Greek patients with mycosis fungoides. J Eur Acad Dermatol Venereol 2022;36:e291-e293.