

Recent clinical evidence for topical mechlorethamine in mycosis fungoides

Mycosis fungoides (MF) is a rare, potentially life-threatening cutaneous T-cell lymphoma characterized by cutaneous homing of neoplastic T lymphocytes. MF can mimic other diseases; clinicopathologic evaluation and imaging studies are essential. Biopsy of suspicious skin sites is essential for diagnosis. Topical mechlorethamine has been clinically tested over decades for the treatment of MF. Safety concerns include contact dermatitis, pruritus and hyperpigmentation. Nonmelanoma skin cancers have been reported with topical mechlorethamine use, including in patients who received therapies known to cause nonmelanoma skin cancer. Noninferiority to mechlorethamine ointment in a Phase II controlled trial led to the US FDA 2013 approval of VALCHLOR™ (mechlorethamine gel) for treatment of stage IA/IB MF after prior skin-directed therapy.

Keywords: cutaneous T-cell lymphoma • mechlorethamine hydrochloride • mycosis fungoides • nitrogen mustard

Mycosis fungoides

Cutaneous T-cell lymphoma (CTCL) comprises approximately 4% of non-Hodgkin's lymphomas in the USA [1]. Of the cutaneous lymphomas reported in the USA from 2001–2005, CTCLs accounted for 71% of the cases [2], and have an overall annual age-adjusted incidence of 9.6 per million persons [1]. CTCLs, characterized by localization of neoplastic T lymphocytes to the skin, encompass a broad group of cutaneous lymphomas that include the slower progressing mycosis fungoides (MF) and the more aggressive Sézary syndrome (SS).

MF is the most common type of CTCL (54% of CTCLs were MF in a USA study from 2001 to 2005) [2]. First described in the early 1800s [3], MF is characterized by epidermal and dermal infiltration of clonal T cells. There are many variants of MF including folliculotropic, hypopigmented and granulomatous MF [4–6].

MF is a rare disease. Although prevalence is difficult to determine, the annual incidence of MF in the USA has been reported at between

3.6 [7] and 4.1 per million people a year [2], with no strong evidence of increasing incidence rates. MF incidence rates do increase with patient age, peaking at around 80 years [2,7], although MF cases in children have also been reported [1,7,8]. Incidence rates were similar among males and females at ages younger than 30 years, but rose among males at older ages, with the male:female ratio doubled by age 60 years [2].

Mean age at diagnosis is 55 to 60 years of age [2,9,10], with reports in older and younger patients [11]. 71% of patients presented with early-stage disease [9,10]. Women presented with early onset of MF before the age of 40 years more often than men [12].

One of the challenges with treating MF is possible long-term misdiagnosis as other disease states such as chronic contact dermatitis, folliculitis, eczema, vitiligo, pigmented purpuric dermatoses, pityriasis lichenoides chronica, pityriasis lichenoides et varioliformis acuta or psoriasis [13–16]. Because of incorrect diagnosis, the proper treatment of MF may be delayed, resulting in poorly directed therapies.

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Adding to the difficulty of diagnosis, the pathophysiology of MF is not well understood. T cells found in MF seem to function as T cells under normal physiologic conditions that home to the skin, become activated and develop into a clonal state [13]. Chemokine receptors can play an important role in this process. The activation of T-cell integrins can lessen T-cell adhesion to skin endothelial cells and a gradient of chemokines (e.g., CC chemokine ligand 17 [CCL17] and 27 [CCL27]) attract chemokine receptors (e.g., CC chemokine receptor 4 [CCR4]) on the malignant T cells that help the T cell migrate to the epidermis. The CD4⁺ T cells often cluster around antigen-presenting dendritic cells, such as Langerhans cells, forming Pautrier's microabscesses that result in T-cell activation and the release of inflammatory cytokines. Kinases (e.g., PI3K and Akt) are upregulated, and downstream effectors are activated that can allow T cells to survive and proliferate [17,18].

Studying the band-like infiltrate of lymphocytes permeating the papillary dermis from a skin biopsy may help with diagnosis of MF. Small, medium-sized and sometimes large mononuclear cells with atypia (pleomorphic, hyperchromatic or cerebriform nuclei) may be seen [19,20]. Pautrier's microabscesses are not frequently seen upon histologic examination; however, immunohistochemical staining generally shows atypical CD4⁺ T cells [11]. Pautrier's microabscesses have been seen in 4–37% of patch biopsies in patients diagnosed with early MF [21,22].

Advanced stages may lead to the formation of generalized erythroderma associated with lymphadenopathy and neoplastic T lymphocytes with cerebriform nuclei (Sézary cells) in skin, lymph nodes and peripheral blood, known as the leukemic variant of MF, SS. MF accounts for approximately 50–80% of CTCL, whereas SS accounts for approximately 1–3% of cases [1,2,23]. SS may be similar to MF except that cellular infiltrates are more likely a single type of cell and epidermotropism, or cellular movement towards the epidermis, may be absent [1,2,23].

Etiologic factors of MF are indeterminate but have included infectious agents, environmental exposures and genetic mutations [19]. It is believed that the uncontrolled clonal accumulation of T lymphocytes is a result of chronic antigenic stimulation [13]. Ulceration of tumors, with secondary infection with *Staphylococcus aureus*, *Enterobacteriaceae* and *Pseudomonas aeruginosa*, is a common cause of morbidity [19]. Minimal evidence may also support viral etiology for MF secondary to Epstein–Barr virus and cytomegalovirus [24]. Patients with later-stage MF and SS are at a significantly increased risk of developing a second lymphoma, in particular Hodgkin lymphoma, as well as nonhematologic malignancies [1,25].

To help diagnose MF, staining skin-biopsy specimens with a panel of lymphocyte markers and polymerase chain reaction analysis of T-cell receptor genes to determine clonality may be performed [13]. If a patient appears to have advanced disease or if their lymph nodes are enlarged on physical examination or imaging studies, lymph node biopsies may be carried out. If SS is suspected, peripheral blood is examined for the presence of circulating malignant cells [19].

Diagnosis of MF must be clinicopathologic; histopathologic, immunopathologic and molecular biology findings must be correlated with clinical presentation. Clinical presentation of MF can include a combination of erythematous patches, plaques and, less frequently, ulcerative tumors (Figure 1) [17]. Lesions can be localized or widespread, often starting around the beltline. Scaling may be seen around patches or plaques but usually not to the degree seen in patients with psoriasis [17].

Patients with MF typically have many lesions that last months or years and are located on areas of the body that have been infrequently exposed to sunlight. Sometimes lesions are atrophic and dyspigmented (poikilodermatous MF). Lesions may become variably thickened or could coalesce together to form larger plaques [13]. Lesions are less commonly located on the face except when the disease reaches tumor-stage, or in folliculotropic MF [26]. Plaques and tumors in MF may ulcerate unexpectedly or following radiation therapy, which requires care to prevent bacterial infection and sepsis [27,28].

Overall median survival for patients with CTCL was 18.3 years, 24.1 years for women and 13.4 years for men [9]. In an earlier study, median survival for patients with MF in the USA who received topical mechlorethamine as initial therapy was less at 16.3 years (Figure 2). As the disease stage progresses, median survival and overall survival/disease-specific survival decreases with the relative risk for death due to disease being 21.6-times greater in patients with stage T4 compared with stage T1a [9]. Median survival decreased in patients with MF from 35.5 years for stage IA to 1.4 years for stage IVB [9]. The 5-year survival rate of patients with MF is 88–91% [2,23], and the 10-year rate is 67% [29]. SS is a more aggressive disease with overall 5-year survival rate at 10–25% [23]. Advanced stage, increased age, being male, increased lactate dehydrogenase and large-cell transformation were associated with reduced survival and increased risk of disease progression [1,9,10].

General management approach

Given the long duration of disease for most patients who have MF, decisions regarding therapy should include clinical stage, overall prognosis and quality-of-life



Figure 1. Cutaneous lesions of mycosis fungoides and Sézary syndrome. (A) Patch stage T1–2, **(B)** plaque stage T1–2, **(C)** tumor stage T3 and **(D)** erythroderma stage T4. **(A, C & D)** reproduced with permission from Youn H Kim. **(B)** Reproduced with permission from Joya Sahu.

considerations. Patients with MF believe the disease has had a severe impact on their functioning, emotional and social well-being [31].

The clinical stage of MF, especially with regard to the degree of skin involvement, is crucial to determine prognosis. Stages of MF have been outlined by a number of organizations [32] and the most recent classification is summarized in [Table 1](#). Early clinical stage MF (stages IA–IIA) where disease is primarily limited to the skin as patches alone and patches/plaques has a favorable prognosis [33]. Advanced stage MF (stages IIB–IVB), which can also include SS and may include lymph node and peripheral-blood involvement, has a more unfavorable prognosis [20,29,33].

The goals for treating patients with early stage MF are to relieve symptoms and achieve remission,

while avoiding long-term treatment-related toxicity. For patients with early stage MF, therapeutic options include topical corticosteroids, topical mechlorethamine such as the newly approved VALCHLOR™ [35], local radiation, topical retinoids (bexarotene gel/Targretin® Gel), ultraviolet B therapy, topical imiquimod, topical carmustine (BCNU), psoralen plus ultraviolet A (PUVA) and total skin electron beam therapy [13,28,34].

For patients with advanced-stage disease, treatments aimed at reducing tumor burden or delaying disease progression are utilized [33]. Systemic therapies may be needed such as oral bexarotene, antifolates (methotrexate, pralatrexate), extracorporeal photopheresis, IFN- α , histone deacetylase inhibitors (vorinostat, romidepsin), alemtuzumab,

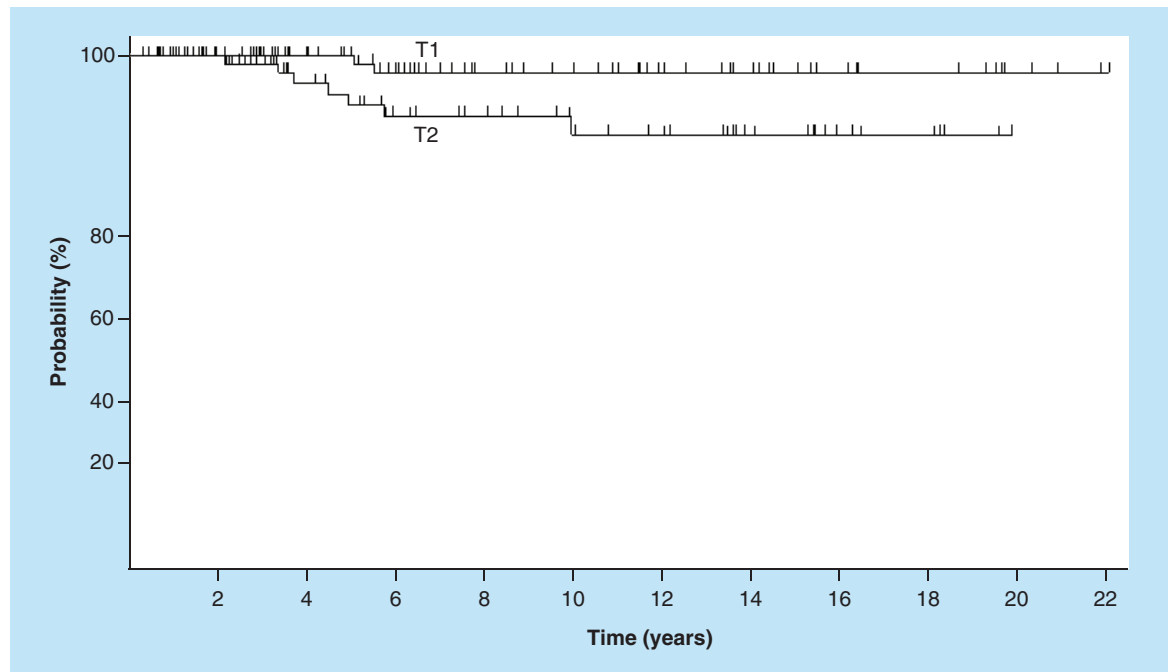


Figure 2. Actuarial disease-specific survival rates of patients with T1 (n = 107) and T2 (n = 88) disease, treated with topical mechlorethamine as initial primary therapy (p < 0.05).

Adapted with permission from [30].

liposomal doxorubicin, gemcitabine or allogeneic stem cell transplantation [33,34]. Given no reliable treatment for long-term clinical benefit, new agents are under clinical development and participation in clinical trials is highly encouraged. These newer agents include brentuximab vedotin (anti-CD30 antibody–drug conjugate), mogamulizumab (anti-CCR4 defucosylated antibody), proteasome inhibitors and checkpoint inhibitors (anti-PD-L1 or PD-1 antibodies).

Treatment: mechlorethamine

Topical mechlorethamine (mechlorethamine hydrochloride, chlormethine, nitrogen mustard, methylbis[2-chloroethyl]amine hydrochloride) is an alkylating agent that has been used for the management of MF since the 1940s [36]. A number of organizations, such as the National Comprehensive Cancer Network and the European Organization for Research and Treatment of Cancer, have recommended topical mechlorethamine as a primary treatment option for CTCL [34,37]. Commonly used to treat early stage MF, mechlorethamine is thought to induce apoptosis of malignant T cells [38] and possibly affect keratinocyte–Langerhans cell–T-cell interactions via immune mechanisms [39].

Initially, lyophilized mechlorethamine (Mustargen[®]) was dissolved in water. This aqueous solution had limited stability [40] and was associated with high rates (up to 67%) of delayed type cutaneous hypersensitivity, which limited long-term use [41]. Mustargen

is currently an intravenous formulation administered to treat later stage MF [42], since the toxicity profile, particularly bone marrow toxicity, is not acceptable for treatment of early stage (IA, IB and IIA) disease.

Since the 1980s, USA clinical use of mechlorethamine hydrochloride compounded by pharmacists has been suspended in a petrolatum-based ointment such as Aquaphor[®] [30,43]. Hypersensitivity rates in clinical studies were lower in ointment preparations compared with aqueous preparations ($\leq 10\%$ vs almost two-thirds, respectively) and stability was increased in ointment preparations, however, drug decomposition was noted within a week [40].

Diethylene glycol monoethyl ether, or Transcutol[®], has been shown to increase permeability into and solubility within the outer most layer of the skin, the stratum corneum [44]. In a test of six topical formulations, mechlorethamine was found to be most stable in formulations containing Transcutol and the free radical inhibitor butylated hydroxytoluene, [45], which are excipients found in the approved VALCHLOR (mechlorethamine).

VALCHLOR received US FDA approval in 2013 for the treatment of stage IA and IB MF in patients who have received prior skin-directed therapy [35]. VALCHLOR contains 0.016% w/w mechlorethamine (equivalent to 0.02% mechlorethamine HCl). In contrast to mechlorethamine compounded in ointment, VALCHLOR is a quick-drying, greaseless gel that is designed to be easier to apply [41]. VALCHLOR is developed under

good manufacturing practice with consumer-grade materials, has longer stability, consistent potency and noninferiority versus mechlorethamine compounded in ointment.

Patients can apply a thin film of VALCHLOR once daily to affected areas of the skin. Patients should apply VALCHLOR to completely dry skin at least 4 h before or 30 min after showering or washing. Patients should allow treated areas to dry for 5–10 min after the application before covering with clothing. Patients must wash hands thoroughly with soap and water after handling or applying VALCHLOR [35].

Published studies

Clinical studies of mechlorethamine can be traced back to 1942 when Gilman and Philips conducted the first trial in patients with malignant lymphomas using intravenous water-soluble hydrochloride salts of mechlorethamine [36]. Since then, numerous clinical studies have been conducted to evaluate the efficacy and safety

of topical mechlorethamine for the treatment of MF. Below is a summary of studies published in English in which approximately 100 patients or more with MF received topical mechlorethamine (Table 2).

Efficacy

Ramsay 1988

Ramsay and colleagues from New York University Medical Center studied 117 patients with histologically determined MF (1970–1986) [50]. Disease stage was classified according to Vonderheid *et al.* [51], with additional designations A and B to signify <10% or >10% cutaneous surface involvement, respectively. Complete remission was defined as the clearance of all lesions. Probabilities of complete remission, relapse, and survival were calculated via the Kaplan–Meier method.

Patients were treated with an aqueous solution containing 10 mg of mechlorethamine in 60 ml of water once daily for 6 months, tapering over the following

Table 1. Mycosis fungoides-cutaneous T-cell lymphoma clinical stage adapted from the International Society for Cutaneous Lymphomas and the European Organization of Research and Treatment of Cancer.

Clinical stage	Classifications			
	Skin	Lymph nodes	Viscera	Blood
IA	T1	N0	M0	B0–1
IB	T2	N0	M0	B0–1
IIA	T1–2	N1–2	M0	B0–1
IIB	T3	N0–2	M0	B0–1
IIIA	T4	N0–2	M0	B0
IIIB	T4	N0–2	M0	B1
IVA ₁	T1–4	N0–2	M0	B2
IVA ₂	T1–4	N3	M0	B0–2
IVB	T1–4	N0–3	M1	B0–2

T: Skin involvement:
T1: Limited patches, papules and/or plaques (<10% body surface area [BSA]).
T2: Patches, papules or plaques covering ≥10% BSA.
T3: ≥1 tumor(s) ≥1 cm in diameter.
T4: Generalized erythroderma (≥80% BSA).
N: Lymph node involvement:
N0: No clinically abnormal (palpable; ≥1.5 cm diameter) peripheral lymph nodes.
N1: Clinically abnormal lymph nodes; histopathology Dutch grade 1 or National Cancer Institute (NCI) lymph nodes₀₋₂ (LN₀₋₂).
N2: Clinically abnormal lymph nodes; histopathology Dutch grade 2 or NCI LN₃.
N3: Clinically abnormal lymph nodes; histopathology Dutch grade 3–4 or NCI LN₄; clone positive or negative.
M: Visceral involvement:
M0: No visceral organ involvement.
M1: Visceral involvement (pathology confirmation of specific organ involved).
B: Presence of cancerous cells in blood:
B0: Absence of significant blood involvement (≤5% of peripheral blood lymphocytes are atypical/Sézary cells).
B1: Low blood tumor burden (>5% of peripheral blood lymphocytes are atypical/Sézary cells, but does not meet criteria of B2).
B2: High blood tumor burden defined as one of the following: ≥1000 Sézary cells/μl with positive clonal rearrangement of T-cell receptors; CD4:CD8 ratio ≥10 with positive clone; or CD4⁺CD7⁻ cells ≥40% or CD4⁺CD26⁻ cells ≥30% with positive clone.
Adapted from [20,34].

Table 2. Clinical trials of topical mechlorethamine that included 100 or more patients.

Study (year)	Description (number of mycosis fungoides patients)	Treatment(s)	Results	Ref.
Ramsay <i>et al.</i> (1988)	Retrospective analysis of medical records (117) 63 stage I 44 stage II 10 stage III Male: 56% Median age: 57 years	10 mg of MCH dissolved in 60 ml of water applied once daily until 6 months after complete remission, tapering over the following 18 months; concomitant therapy not allowed except for stage III (local RT)	Median time for complete remission: I: 6.5 months; II: 41.1 months; III: 39.1 months (T stage not noted) Complete remission* at 2 years: I: 75.8%; II: 44.6%; III: 48.6% *Clearance of all lesions Adverse events not noted Death as a result of MF occurred in nine cases (unrelated causes: three; unknown: one)	[50]
Vonderheid <i>et al.</i> (1989)	Retrospective analysis of medical records (331) 89 stage IA 66 stage IB 46 stage IIA 39 stage IIB 37 stage III 38 stage IVA 9 stage IVB 7 Lymphomatoid papulosis Male: 65% Mean age: 58 ± 0.7 years	10–20 mg of MCH dissolved in 40–60 ml of water applied once daily until CR then daily or every other day depending on response; adjunct therapy allowed for slowly responsive, extensive or otherwise problematic disease	CR*: IA: 80%; IB: 68%; IIA: 61%; IIB: 49%; III: 60%; IVA: 13%; IVB: 11% (T stage not noted) *Complete disappearance of clinically detectable disease and was confirmed in most cases by skin biopsy lesions Sustained remission for 4 and 8 years: 65 and 35 patients, respectively Of the patients for whom the duration of CR was >8 years, 12 (35%) experienced allergic contact dermatitis Significantly elevated risks were found for the development of SCC, BCC, Hodgkin's disease, and colon cancer (relative risk: 7.8, 1.8, 58.9 and 2.6, respectively)	[47]

Please note that the trials above were conducted under varying conditions, including trial design, additional treatments and response rates. AEs cannot be directly compared with one another and may not reflect the rates observed in clinical practice.
 AE: Adverse event; BCC: Basal cell carcinoma; CAILS: Composite Assessment of Index Lesion Severity; CR: Complete response; EORTC: European Organization for Research and Treatment of Cancer; ISCL: International Society of Cutaneous Lymphoma; MCH: Mechlorethamine; MF: Mycosis fungoides; PR: Partial response; PY: Patient years; RT: Radiation therapy; SD: Standard deviation; SSC: Secondary skin cancer; TSEBT: Total skin electron beam therapy.

Table 2. Clinical trials of topical mechlorethamine that included 100 or more patients (cont.).

Study (year)	Description (number of mycosis fungoides patients)	Treatment(s)	Results	Ref.
Kim <i>et al.</i> (2003)	Retrospective analysis of medical records (203) 107 T1 (103 stage IA, 4 IIA) 88 T2 (74 stage IB, 15 IIA) 4 T3 (4 stage IIIB) 4 T4 (1 stage IIIA, 3 IIIB) Male: 61%	10–20 mg of MCH dissolved in 100 ml of water until 1980; Aquaphor®-based since 1980, applied once daily until complete clinical clearance achieved then continued for 6 months to 2 years as maintenance; slow responders received >20 mg/100 ml at intervals of 2–3 months; 68% received MCH monotherapy; patients who received significant concurrent or preceding therapy (radiation, phototherapy, systemic) were excluded	CR and PR*: T1: 65% CR, 28% PR; T2: 34% CR, 38% PR; T3+T4: 50% CR, 33% PR; overall response rate for all patients (PR + CR): 83% *Complete clinical regression of all MF lesions; PR: any response less than complete but greater than 50% clinical improvement Median overall time for CR: 12 months (T1: 10 months; T2: 19 months) Median time to relapse: 12 months Median survival time: 16.3 years Most common acute AEs were irritant or allergic contact dermatitis; nearly all were managed via reduced dose or frequency; most patients were able to intensify frequency and strength of MCH 8/203 developed SCC or BCC after beginning MCH treatment; 6/8 received ≥1 treatment, including TSEBT or phototherapy after initial MCH and before developing these SCC or BCC; the other two received MCH monotherapy; both developed carcinomas at sites unrelated to MCH application; one developed cutaneous melanoma and had history of BCC prior to MCH therapy	[39]

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AE: Adverse event; BCC: Basal cell carcinoma; CAIS: Composite Assessment of Index Lesion Severity; CR: Complete response; EORTC: European Organization for Research and Treatment of Cancer; ISCL: International Society of Cutaneous Lymphoma; MCH: Mechlorethamine; MF: Mycosis fungoides; PR: Partial response; PY: Patient years; RT: Radiation therapy; SD: Standard deviation; SCC: Secondary skin cancer; TSEBT: Total skin electron beam therapy.

Table 2. Clinical trials of topical mechlorethamine that included 100 or more patients (cont.).

Study (year)	Description (number of mycosis fungoides patients)	Treatment(s)	Results	Ref.
Lindahl et al. (2013)	Retrospective analysis of medical records (116) 14 T1* (11 stage IA, 2 IIA, 1 IVA) 78 T2 (68 stage IB, 8 IIA, 2 IVA) 15 T3 (13 stage IIB, 1 IVA, 1 IVB) 9 T4 (9 stage III)	20 mg MCH dissolved in 40 ml water once daily for 14 days, applied once daily for 14 days then given as two treatments every fourth to eighth week until treatment was no longer indicated or treatment was stopped due to side effects or progressive disease; 98.3% received adjunct therapy (all received topical; a total of 51.7% received systemic); patients with slowly responsive disease, extensive skin or extracutaneous involvement were usually treated with adjunctive systemic therapies	CR and PR*: T1: 78.6% CR, 21.4% PR; T2: 51.3% CR, 39.7% PR; T3: 40.0% CR, 46.7% PR; T4: 55.6% CR, 33.3% PR *Complete clinical regression of all skin lesions; PR: any response less than complete but greater than 50% clinical improvement Median duration of MCH treatment: 16.4 months (range: 2 days–25.6 years) Contact dermatitis most frequent AE (64.7%) Treatment-limiting AEs in 22 patients (19.0%) SSC observed in six patients (5.2%); total of 372.9 PY treatment and observed in 585.1 PY: one SSC and five BCC All SSC developed during or after MCH	[48]
Lessin et al. (2013)	* <2007: Mycosis Fungoides Cooperative Group staging; ≥2007: ISCL/EORTC staging Median age: 68 years (range: 14–98) Male: 66%	Phase II, multicenter, randomized, observer-blinded, noninferiority trial in stage I–IIA (260) 141 stage IA 115 stage IB 4 stage IIA	Systemic side effects not observed CALLS*: 13.8% CR, 44.6% PR (gel); 11.5% CR, 36.2% PR (ointment); gel noninferior to ointment by prespecified criteria (T stage not noted) *Severity score for up to five lesions; CR: 100% improvement from baseline score; PR: 50 to <100% improvement No serious AEs reported Skin-related AEs in the gel and ointment treatment arms, respectively, included skin irritation (n = 32, 18), pruritus (25, 20), erythema (22, 18), contact dermatitis (19, 19), skin hyperpigmentation (7, 9) and folliculitis (7, 5) 11 patients were diagnosed with 20 nonmelanoma skin cancers	[41]

Please note that the trials above were conducted under varying conditions, including trial design, additional treatments and response rates. AEs cannot be directly compared with one another and may not reflect the rates observed in clinical practice.
AE: Adverse event; BCC: Basal cell carcinoma; CALLS: Composite Assessment of Index Lesion Severity; CR: Complete response; EORTC: European Organization for Research and Treatment of Cancer; ISCL: International Society of Cutaneous Lymphoma; MCH: Mechlorethamine; MF: Mycosis fungoides; PR: Partial response; PY: Patient years; RT: radiation therapy; SD: Standard deviation; SSC: Secondary skin cancer; TSEBT: Total skin electron beam therapy.

Table 2. Clinical trials of topical mechlorethamine that included 100 or more patients (cont.).

Study (year)	Description (number of mycosis fungoides patients)	Treatment(s)	Results	Ref.
Kim <i>et al.</i> (2014)	6 month, Phase II, open-label extension study for patients completing Lessin 2013 study, but who did not achieve a CR after 12 months (98) Male: 55.1% Mean age: 53.4 years (SD: 13.97) Caucasian: 68.4%	MCH 0.04% gel applied once daily for 7 months; adjunct therapy not allowed	<p>CAILS*: 6% CR, 20.4% PR (T stage not noted)</p> <p>*As defined in Lessin 2013</p> <p>No drug-related severe AEs reported during the trial</p> <p>Drug-related skin and subcutaneous AEs reported by 31 patients (31.6%); most common: skin irritation (11.2%), erythema (10.2%), pruritus (6.1%), contact dermatitis (4.1%) and skin hyperpigmentation (4.1%)</p> <p>No deaths during or within 30 days of treatment</p> <p>No nonmelanoma skin cancers occurred during open-label study</p>	[49]

Please note that the trials above were conducted under varying conditions, including trial design, additional treatments and response rates. AEs cannot be directly compared with one another and may not reflect the rates observed in clinical practice.
 AE: Adverse event; BCC: Basal cell carcinoma; CAILS: Composite Assessment of Index Lesion Severity; CR: Complete response; EORTC: European Organization for Research and Treatment of Cancer; ISCL: International Society of Cutaneous Lymphoma; MCH: Mechlorethamine; MF: Mycosis fungoides; PR: Partial response; PY: Patient years; RT: Radiation therapy; SD: Standard deviation; SSC: Secondary skin cancer; TSEBT: Total skin electron beam therapy.

18 months. Patients with stage I or II disease received no alternative therapies. Median time for complete remission was higher in patients with later disease stages (6.5, 41.1 and 39.1 months in stages I, II and III, respectively). The probability of achieving complete remission after 2 years was lower in the later disease stages (75.8, 44.6 and 48.6% in stages I, II and III, respectively).

Vonderheid 1989

Between 1968 and 1982, Vonderheid and colleagues studied the medical charts of 331 patients with MF [47]. Diagnosis was made based on manifestation of clinical characteristics and conclusive or compatible histopathologic findings for the disease. The T rating and probable stage was recorded for each patient according to the Mycosis Fungoides Cooperative Group recommendations [52]. Stage was determined as 'probable' since lymph node biopsy specimens were not obtained routinely. End points were complete response and remission sustained for 4 or 8 years as determined by physician assessment. A complete response was defined as the complete disappearance of clinically detectable disease for at least 2 weeks and confirmed by skin biopsy specimens in most cases.

Patients were treated with an aqueous solution containing 10–20 mg of mechlorethamine in 40–60 ml of water once daily. After 2 weeks of treatment, response was noted and patients continued to receive topical mechlorethamine daily or every other day. Patients with advanced disease may have received additional treatments (i.e., local radiation, electron beam radiation, PUVA, ultraviolet B and chemotherapy such as intravenous methotrexate and mechlorethamine). Complete response was reported in a higher number of patients who had less severe disease: 71 (80%), 45 (68%), 28 (61%), 19 (49%), 22 (60%), 5 (13%) and 1 (11%) of stages IA, IB, IIA, IIB, III, IVA and IVB, respectively. Of these seven groups, 64 patients had sustained remission for 4 years and 34 patients had sustained remission for 8 years.

Update of the Stanford experience (2003)

Of the patients with MF treated at the Stanford University Cutaneous Lymphoma Clinic from 1958 to 1999, 203 patients with stage I–III MF who were treated with topical mechlorethamine as initial primary therapy within 60 days of their initial evaluation were included in this study [30]. Diagnosis of MF was determined by clinical and histological evaluation and disease staging was classified according to Bunn and Lamberg [52]. Clinical response was defined as complete response (complete clinical regression of all MF lesions), partial response (any response less than

complete but greater than 50% clinical improvement), or no response (less than 50% clinical response to therapy). Progression of disease was defined as worsening of disease to a higher T classification or worse clinical stage. Actuarial survival was calculated via the Kaplan–Meier technique. Patients were treated with topical mechlorethamine daily until complete clinical remission was achieved. Prior to 1980, patients were treated with 10–20 mg of mechlorethamine in 100 ml of aqueous solution. After 1980, most patients were treated with an Aquaphor-based ointment. Treatment was continued for 6 months as maintenance therapy after clinical clearance. Patients who received other significant concurrent or preceding therapy, such as irradiation (local and total skin), phototherapy or any systemic therapies were excluded.

The majority of patients in this study (139 patients, 68%) were treated with mechlorethamine alone as initial therapy and throughout their follow-up course. Overall patient response rate was 83% with half of the patients achieving a complete response. Percentages of complete responses were higher in patients with earlier disease: 70 (65%), 30 (34%), 0 (no percentage given) and two (no percentage given) of stages T1, T2, T3 and T4, respectively. Median time to achieve complete response was 12 months (10 months for stage T1, 19 months for T2). Median time to relapse was also 12 months. Median survival was 16.3 years, and survival rates at 5, 10 and 20 years were 85, 71 and 40%, respectively.

Lindahl 2013

Retrospective data from 116 patients with MF who received mechlorethamine from 1991 to 2009 were analyzed by Lindahl *et al.* [48]. Diagnosis of MF was verified by histology. Until 2007, disease stage was classified as per the Mycosis Fungoides Cooperative Group staging system [52] and thereafter as per the European Organization for Research and Treatment of Cancer staging system [37]. Clinical response, determined by physical examination, included complete (clinical regression of all skin lesions), partial (any response less than complete but greater than 50% clinical improvement), or no response as stable or progressive disease (worsening to a higher T classification or clinical stage). Complete response, relapse and progression event curves were calculated via the Kaplan–Meier method. Patients were treated with an aqueous solution containing 20 mg of mechlorethamine in 40 ml of water daily for 14 days. Maintenance therapy was given as two treatments every fourth to eighth week until treatment was no longer indicated, or treatment was stopped due to side effects or progressive disease. Adjunctive therapies were used by 98.3% of patients

with MF. All these patients received various topical therapies, including corticosteroids and phototherapy. A total of 51.7% received various systemic therapies.

Median duration of mechlorethamine treatment was 16.4 months (range: 2 days–25.6 years).

Although not statistically different, more patients achieved complete responses who had less skin involvement (11 [78.6%], 40 [51.3%], 6 [40.0%] and 5 [55.6%] patients in stages T1, T2, T3 and T4, respectively). The overall frequency of disease progression observed was 25.0% (T1: 28.6%, T2: 25.6%, T3: 26.7% and T4: 11.1%, respectively).

Lessin 2013

The pivotal study conducted by Actelion (Protocol 2005NMMF-201-US, NCT00168064 [53]) was a Phase II, multicenter, randomized, observer-blinded, noninferiority trial that compared mechlorethamine gel 0.02% (equivalent to 0.016% w/w mechlorethamine, VALCHLOR) versus mechlorethamine Aquaphor (ointment) 0.02% administered daily to 260 patients with stage I or IIA MF in 13 centers in the USA [41]. Histologic criteria [54] and a diagnostic algorithm for defining early MF/CTCL staging [55] were employed.

Primary efficacy end point was $\geq 50\%$ improvement in the baseline Composite Assessment of Index Lesion Severity (CAILS) [32,56]. Secondary efficacy end points included $\geq 50\%$ improvement in the modified Severity Weighted Assessment Tool (SWAT) [32,57]. Baseline and each study visit CAILS and SWAT scores were calculated for complete response (100% improvement with a score = 0), partial response ($\geq 50\%$ to $< 100\%$ reduction from baseline) and stable disease ($< 50\%$ reduction from baseline). Confirmed responses were those observed at equal or greater than 4 weeks. Duration of response was defined as the time from first appearance of confirmed response to first assessment of loss of response (CAILS score $< 50\%$ improvement from baseline) or progressive disease (CAILS score was $\geq 25\%$ above baseline). Noninferiority of the gel to the ointment was established if the 95% CI lower bound around the ratio of the response rates (complete response and partial response for gel/ointment) was ≥ 0.75 (Kaplan–Meier methodology for the time to first confirmed response and duration of response curves).

Patients could have received prior therapies (topical corticosteroids, phototherapy, Targretin gel and topical mechlorethamine) but patients were not required to be refractory to or intolerant of prior therapies. Concomitant use of topical corticosteroids was not permitted during the study. Treatments were applied once daily to affected skin areas (lesions) or total skin surface (depending on stage) for up to 12 months.

Both primary (CAILS score) and secondary (SWAT) end points met the prespecified criteria for noninferiority. Response rates for mechlorethamine gel and ointment were 58.5 and 47.7% by CAILS, and 46.9 and 46.2% by SWAT, respectively. The estimated time to a 50% response rate was significantly earlier for patients who received mechlorethamine gel (26 weeks) than for patients who received mechlorethamine ointment (42 weeks, $p < 0.01$, Figure 3). There was no statistically significant difference between the two treatments with respect to duration of response. Analysis of the Kaplan–Meier curves estimated that at least 90% of responses for both gel and ointment will be maintained for > 10 months.

Kim 2014

A 6-month, Phase II, open-label extension study (Study 2007NMMF-202-US, NCT00535470 [53]) for patients completing study 2005NMMF-201-US [41] but who did not achieve a complete response (i.e., CAILS score remained > 0 as of baseline of study 2007NMMF-202-US) after 12 months, was conducted to evaluate the safety and efficacy of mechlorethamine gel 0.04% in patients with stage I or IIA MF [49]. This represents the first clinical trial to evaluate mechlorethamine 0.04% gel for patients with MF.

Primary end point was the response rate (complete response rate and partial response rate) defined as $\geq 50\%$ improvement of baseline CAILS score (total severity score of up to five index lesions) of the double-blind study that was confirmed at the next visit at least 4 weeks later in the open-label study. The index lesions in this open-label study were either the same index lesions that were evaluated during double-blind study that did not have a complete response or, if there were fewer than five original lesions at the start of the double-blind study, additional index lesions could be included if they were present and treated consistently throughout the double-blind study. Complete and partial responses for CAILS were the same as defined in the double-blind study [41]. The secondary efficacy end point, $\geq 50\%$ reduction in the baseline SWAT score by two or more consecutive observations over at least 4 weeks, was determined by measuring each involved area as a percentage of body surface area and multiplying by a severity-weighting factor (1 = patch, 2 = plaque, 3 = tumor).

In total, 98 patients with MF (stages IA, IB and IIA) applied mechlorethamine, 0.04% gel once daily to affected areas for an additional 7 months after the initial 12-month course in the double-blind study. Use of topical corticosteroids to treat skin adverse events was not allowed during the study. During the study, other therapies to treat MF were prohibited; emollients

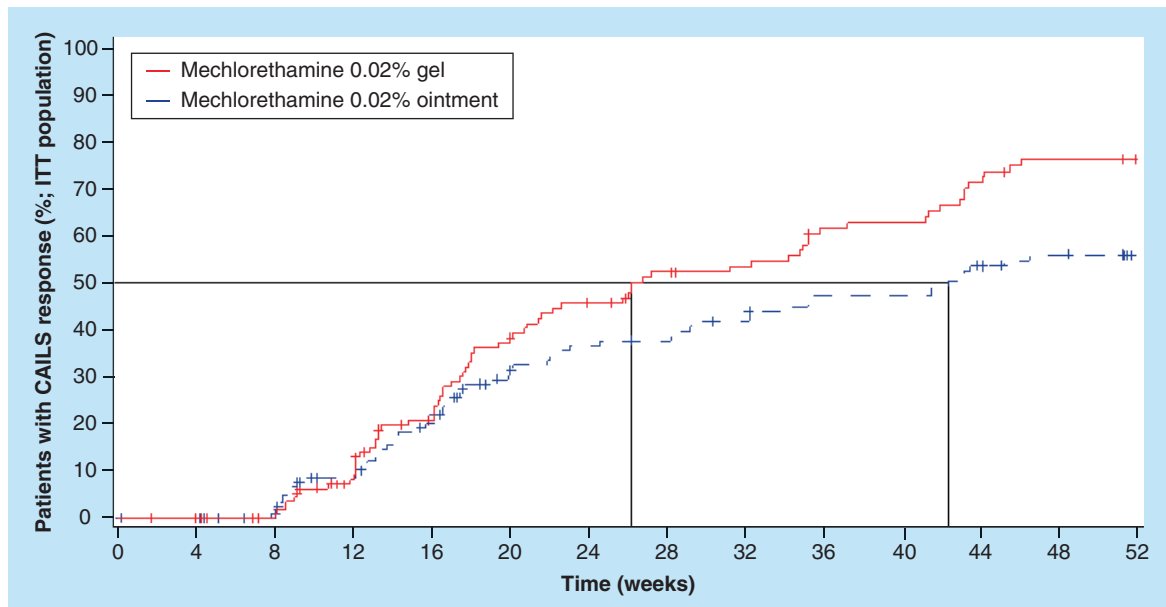


Figure 3. Kaplan–Meier curve of time to confirmed response from Composite Assessment of Index Lesion Severity Assessment in intent to treat patients by treatment group showing estimated time to a 50% response rate for patients treated with gel (26 weeks) and ointment (42 weeks, $p < 0.01$).

CAILS: Composite Assessment of Index Lesion Severity; ITT: Intent-to-treat. Adapted with permission from [41].

and/or oral antihistamines could be used to treat dermatitis (data on file).

In total, 26 patients (26.5%) achieved a confirmed response as measured by $\geq 50\%$ reduction in the baseline CAILS (6 [6.1%] complete responders, 20 [20.4%] partial responders). 14 additional patients (14.3%) achieved their first CAILS response at their final visit for an overall (unconfirmed) response rate of 40.8%.

Evaluating only index lesions followed in both the double-blind and open-label studies, 23 additional patients (23.5%) achieved a confirmed response above those responses achieved in the double-blind study. A total of 13 additional patients (13.3%) achieved their first response at their final visit for an overall (unconfirmed) response rate of 36.7%.

By week 88, the end of the open-label study, 33 patients (84.4%) who had previously received mechlorethamine 0.02% gel and 39 patients (67.9%) who had previously received mechlorethamine 0.02% ointment in the double-blind study achieved responses over the course of both studies (Figure 4). At the end of the open-label study, 20 patients (20.4%) achieved a confirmed response based on a $\geq 50\%$ reduction in SWAT from the double-blind study baseline; 67 patients (68.4%) achieved a confirmed response based on a change in SWAT score from the double-blind study baseline. The results demonstrated that mechlorethamine 0.04% gel is well tolerated in patients previously treated with mechlorethamine 0.02% gel or ointment.

Mechlorethamine 0.04% gel may provide an additional option for treating patients who do not achieve a complete response or have progressive disease following treatment with mechlorethamine 0.02%.

Tolerability & safety

Cutaneous side effects have been observed following topical administration of mechlorethamine, such as burning sensations, pruritus and eczematous reactions [41,58]. The irritant reactions were usually mild, severe reactions were uncommon.

Hyperpigmentation resulting from the direct melanogenic effects of mechlorethamine has been reported in a large percentage of treated patients [41,49]. Hyperpigmentation is reversible and gradually decreases in most patients even if topical therapy is continued [59].

Delayed contact hypersensitivity, that is, allergic contact dermatitis from minor to blistering, is a common complication of topical mechlorethamine [30,43,46,47,50,60–63], and more often noted following application of aqueous formulations versus ointment-based. The recently approved topical mechlorethamine, VALCHLOR, is contraindicated in patients with known severe hypersensitivity to mechlorethamine [35].

There may be a small increased risk (1–5%) of developing nonmelanoma skin cancers (i.e., squamous cell carcinomas, basal cell carcinomas), especially with concomitant radiation and PUVA, or in areas that are exposed to the sun [30,47,48,60,62]. However, in a 30-year population-based cohort study from Danish registries

comparing 110 patients with MF who received mechlorethamine versus 193 patients who did not, secondary cancers were not significantly increased between groups [48]. Further subanalyses showed no significantly increased risk of nonmelanoma skin cancers, malignant melanomas and cancers in the respiratory organs, or any increased risk of comorbidity in the patients who received mechlorethamine.

Systemic absorption of topical mechlorethamine has not been detected [30,41,51,64]. In contrast to intravenous administration of mechlorethamine, topical administration is not known to cause cytopenias or secondary leukemias.

A rare adverse event following topical mechlorethamine is urticaria [65]. Since mechlorethamine is known to break down quickly in aqueous environments, it poses minimal environmental risk [66].

In the double-blind study [41] and the open-label extension [49] of VALCHLOR, most drug-related adverse events observed following topical administration of the mechlorethamine studied were skin related (i.e., skin irritation, pruritus, erythema and hyperpigmentation); these adverse events were self-limiting and managed by reductions in frequency of mechlorethamine applications. The incidence of skin irritation was higher in the gel arm ($p = 0.04$). Patients in other studies were able to continue therapy by decreasing the frequency of application or the concentration of mechlorethamine preparation [30].

Clinicians should monitor patients for redness, swelling, inflammation, itchiness, blisters, ulceration

and secondary skin infections [35]. Exposure of the eyes to mechlorethamine causes pain, burns, inflammation, photophobia and blurred vision; blindness and severe irreversible anterior eye injury may occur [35]. Sensitive skin, such as the face, genitalia, anus and intertriginous skin are at increased risk of dermatitis and should be avoided when applying topical mechlorethamine [35].

Although no algorithm has been proposed to date, an array of approaches can be used to decrease the irritation and erythema sustained from topical application of mechlorethamine. When considering initiation of full body application, one method is to slowly incorporate application of mechlorethamine while using a class 1 topical steroid ointment or cream on 'off' days to minimize irritation, that is, using mechlorethamine on day 3 and 6, while using steroid ointment on the remaining days of the week. This method then can be slowly uptitrated at the discretion of the patient until the application pattern has been reversed, with mechlorethamine being used 5 days of the week.

Another approach is to apply mechlorethamine three to four times a week, with intervening 'off' days without application of any skin directed therapy. The goal of this therapy would be a comfortable, low-grade level of irritation tolerable to the patient. Often emollients can be applied post-mechlorethamine application to mitigate topical side effects, similar to usage when combating retinoid dermatitis. If irritation and erythema are severely distressing to the patient or result in vesiculation, a 7–10-day prednisone taper may be

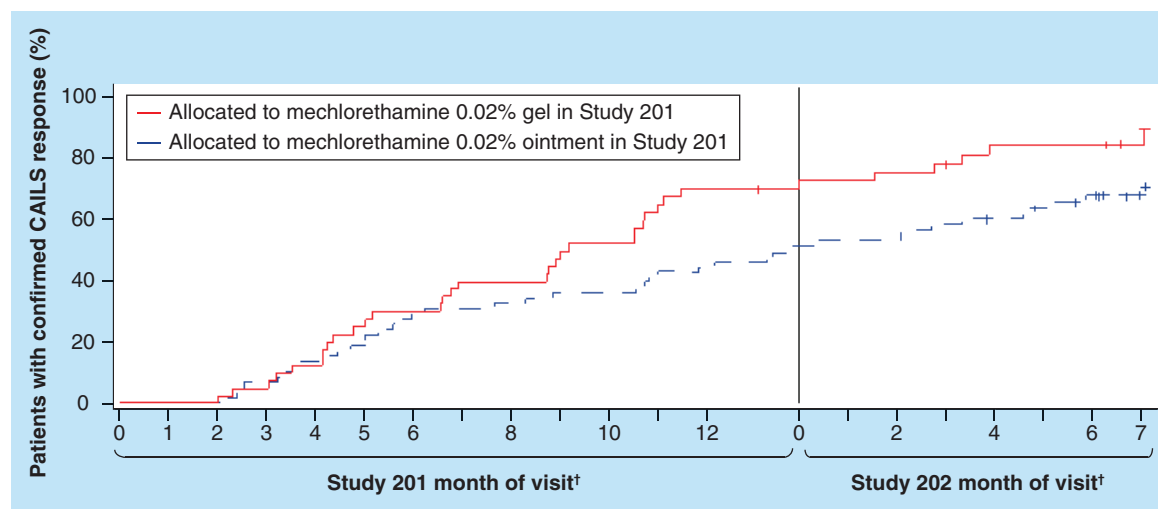


Figure 4. Kaplan–Meier estimates of proportions of patients with a confirmed Composite Assessment of Index Lesion Severity response from start of the double-blind study (study 201) to the end of the open-label study (study 202) by original treatment group.

[†]All patients in study 201 received mechlorethamine 0.02% (gel or ointment); all patients in study 202 received mechlorethamine 0.04% gel.

CAILS: Composite Assessment of Index Lesion Severity.

Adapted with permission from [49].

initiated to obtain relief. Mechlorethamine may also be used in combination with other therapies for more treatment resistant areas such as the fingertips, palms and soles of patients who are receiving ultraviolet light therapy, or on oral Targretin. Lastly, patient education regarding performing a personal patch test prior to initiation of mechlorethamine therapy to reduce contact dermatitis as well as written guidelines and demonstration of proper application amount per unit body surface area are recommended for successful therapy.

Conclusion

Treatment outcomes from published medical literature on MF patients following topical mechlorethamine treatment can be challenging to equate since there may be differences in the institutions' patient selection, disease staging methods, MF diagnostic criteria, preparation of topical mechlorethamine, specific treatment algorithms utilized, duration of maintenance treatment after complete response and various median follow-up time periods. Well-controlled, multicenter, prospective studies are needed to elucidate the clinical characteristics of topical mechlorethamine. Retrospective studies that evaluate real-world utilization of topical mechlorethamine are also warranted.

Physicians may employ more of a multimodal approach in treating MF, such as the combination of topical mechlorethamine and corticosteroids. Studies about the interaction of topical mechlorethamine with other agents could help determine the efficacy and safety of combination treatments for MF.

The mechanism of action of topical mechlorethamine remains uncertain. Many believe that the effectiveness of mechlorethamine may stem not only from its alkylating properties but also via immune

stimulation or interaction with the epidermal cell–Langerhans cell–T-cell axis [30].

Patients who used topical mechlorethamine as a maintenance regimen had a longer lasting response during maintenance therapy compared to patients who did not [30], suggesting that patients may benefit from a maintenance regimen of mechlorethamine as part of a longer maintenance regimen. Additionally, patients have responded well to topical mechlorethamine following relapse with more aggressive therapies; topical mechlorethamine may be used as part of sequential therapy in the future.

A consensus statement about the management of dermatitis should be developed; techniques such as adjusting the frequency of topical mechlorethamine applications and uptitrating the mechlorethamine dose once dermatitis subsides should be addressed. Following this consensus statement, patient education about the proper amount to apply to the skin and how to perform a personal patch test prior to applying topical mechlorethamine is needed for treatment to be successful.

Mechlorethamine ointment formulations are compounded at pharmacies and are not subject to rigorous quality assurance standards. Most health insurance formularies would rarely include compounded medicine, or medicines without FDA approval. Additionally, petrolatum-based ointments may be difficult to apply and could compromise patient compliance [41]. Given the recent FDA approval, VALCHLOR provides patients with access to a quick-drying, greaseless mechlorethamine gel that has been developed under good manufacturing practices and has a longer stability, consistent potency and noninferiority to compounded ointment.

Executive summary

Mycosis fungoides

- Mycosis fungoides is a rare, potentially life-threatening cutaneous T-cell lymphoma characterized by cutaneous homing of neoplastic T lymphocytes.

Treatment: mechlorethamine

- Topical mechlorethamine has been used to treat mycosis fungoides since the 1940s in retrospective studies, as well as a double-blind and open-label studies, leading to the approval of VALCHLOR™.
- Mechlorethamine acts as an alkylating agent and mostly likely immune stimulation properties.
- With the approval of VALCHLOR [35], patients have access to a quick-drying, greaseless mechlorethamine gel with longer stability, consistent potency and noninferiority to compounded ointment that has been developed under good manufacturing practice.

Tolerability & safety

- Following topical administration of mechlorethamine, dermatitis and hyperpigmentation have been seen as mild adverse events and a small increased risk (1–5%) of developing nonmelanoma skin cancers, especially with concomitant radiation and psoralen plus ultraviolet A or areas exposed to the sun.

Conclusion

- Topical mechlorethamine may be used in the future as part of maintenance regimens, multimodal treatments and sequential therapy following more aggressive treatments.

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matter or materials discussed in the manuscript apart from those disclosed.

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