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REVIEW

Mechlorethamine Hydrochloride Gel in the Treatment of Mycosis Fungoides–Type Cutaneous T-Cell Lymphoma (MF-CTCL): A Focus on Patient Selection and Special Considerations

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Abstract: Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma (CTCL) and often has an indolent course, particularly for patients presenting with early-stage (patch/plaque) disease. Early-stage MF is primarily managed with skin-directed therapies. Topical mechlorethamine hydrochloride (nitrogen mustard [NM]) gel has increased tolerability compared to prior NM formulations, though contact dermatitis remains a common side effect. The addition of topical steroids can improve tolerability while maintaining the efficacy of NM gel. Real-world experience supports that NM gel also has a role in combination therapy and as adjunctive therapy in advanced-stage disease. Here we review factors that may influence patient selection for use of NM gel, including MF variants, special patient populations, cost effectiveness, and impact on quality of life for patients with MF.

Keywords: cutaneous T-cell lymphoma, nitrogen mustard, skin-directed therapy, chlormethine, NM, CTCL

Introduction

Mycosis fungoides (MF) is a mature cutaneous T-cell lymphoma (CTCL) classified as either early-stage (IA - IIA) or late-stage (IIB or greater). Early-stage MF typically presents with skin-limited disease, including erythematous or hypopigmented patches and plaques, most commonly on the trunk and proximal extremities.[1] MF can be treated with both topical and systemic modalities, with skin-directed therapies playing a key role in patients with early-stage MF.[2] Mechlorethamine hydrochloride/ chlormethine (nitrogen mustard [NM]) is an alkylating agent first deployed as a gas in World War I. NM was first used as topical therapy for MF in 1959 at the Cleveland Clinic; since then, NM has evolved into a key therapeutic and palliative treatment for MF.[3]

NM, as the prototypic alkylating agent, acts by binding to and cross-linking strands of DNA, which prevents DNA replication.[4] This directly cytotoxic mechanism primarily targets rapidly dividing cells. Other theorized methods of cytotoxicity include nucleic acid depurination and aberrant base pairing.[4] In the context of CTCL, NM alters tumor-growth patterns and enhances immunogenic host potential.[5] Topical NM has also been shown to induce double-stranded DNA breaks in the abnormal T-cells of MF skin as well as downregulate or silence DNA repair pathways among T-cells.[6]

Topical NM preparations have evolved from aqueous to ointment to gel-based formulations. Prior to the 1980s, topical compounded aqueous NM preparations were particularly unstable, requiring immediate application to the skin, and use of aqueous NM preparations were complicated by high rates of delayed type hypersensitivity (>50%).[7] In the 1980s, the use of ointment-based formulations resulted in reduced rates of cutaneous hypersensitivity (<10%) and improved ease of application but still required compounding.[8] In 2013, the Food and Drug administration approved use of 0.016% gel formulation of NM as a second-line treatment for early-stage MF based on the results of a pivotal Phase II

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registrational trial.[9] In 2016, 0.016% NM gel formulations were registered in Israel, and in 2017, the same formulation was approved by the European Medicines Agency for MF in adult patients.

Efficacy of Topical NM

Several early case series supported the efficacy of compounded NM preparations in the treatment of MF, with response rates for early-stage MF ranging from 63% to 83%.[10–12] Cohort studies throughout the late 1990s and early 2000s found similar response rates to compounded NM for early-stage MF; in a large cohort from Stanford, stage I–III MF patients treated with compounded NM preparations experienced an overall response rate of 83% and complete response rate (CR) of 50%, with patients with T1 disease achieving a higher response rate (93%) than those with T2 disease (72%).[13]

A gel preparation of NM was FDA approved in 2013 based on the pivotal randomized controlled trial demonstrating non-inferiority of once daily application of a 0.02% gel preparation (equivalent to the later-approved 0.016% gel preparation) when compared to an ointment preparation of NM, demonstrating a response rate of 58.5% (gel) compared to 47.7% (ointment) among those in the intention-to-treat group.[9] Response rates were as high as 76.7% (gel) and 58.9% (ointment) among efficacy-evaluable patients (those treated for longer than 6 months). Time to a 50% response was 26 weeks in the gel treatment arm and 42 weeks in the ointment treatment arm, suggesting faster responses to NM gel (a finding also supported in post hoc analysis).[14] One-third of patients treated with NM gel experienced a 90% reduction from baseline lesion severity compared to 23.8% of patients receiving ointment preparations. Among patients treated with gel, 85.5% maintained their response for 12 months. Data from this trial and other key studies included in this review are summarized in Table 1.

Adverse Effects of Topical NM

Topical NM is largely well-tolerated. The most common adverse effect is contact dermatitis, which is most frequently observed when using aqueous preparations.[13] While no serious adverse effects were reported in the 2013 trial comparing the gel-based and ointment NM preparations, roughly 15% of all patients experienced contact dermatitis.[9] Among the 128 patients who received NM gel, 21 patients withdrew due to treatment limiting adverse effects defined as grade 3 or 4 local dermal irritation; 13 of these patients had a positive patch test (8 were not tested).[9] Additionally, there was a significantly increased incidence of general skin irritation in the gel arm (25%) compared to the ointment arm (14%).[9] In a 2022 study of 58 patients based out of Greece, gel-based NM was also found to be safe and effective in a real-world setting; however, 72.4% experienced some form of skin irritation.[15]

Development of contact dermatitis may lead to better response from NM preparations, including NM gel. The Stanford group observed that patients who have a brisk local contact dermatitis to NM preparations could have earlier and more complete clearance of MF lesions.[13] Similarly, post hoc analysis of the registrational study of NM gel similarly noted an association between the occurrence of contact dermatitis and response, suggesting that contact dermatitis related to NM gel may also be a predictor of response.[14] In the Mechlorethamine/Chlormethine Induced Dermatitis Assessment Study (MIDAS),[16] the severity of contact dermatitis did not appear to correlate with efficacy of NM therapy, though the number of patients evaluated in the MIDAS study (n = 25) was low compared to the Stanford series (n = 203) and the registrational study (n = 260).

Several strategies for mitigating symptoms related to NM-gel related dermatitis have been proposed. In MIDAS, investigators assessed the impact of coadministration of topical triamcinolone ointment 0.1% (TAC) and NM gel on 28 patients with MF.[16] Using TAC in conjunction with NM led to a significant decrease in pruritus and mild-moderate (but not severe) contact dermatitis, particularly at months 2 and 3 of treatment. Importantly, the addition of TAC did not appear to adversely impact the efficacy of NM; in fact there was an improvement noted in the combination treatment group, though this did not reach statistical significance.[16] The product insert for NM gel[17] recommends daily application to affected areas of skin in accordance with the frequency used in the registration trial.[9] In the 2-year observational PROVe study, patterns of use and response of NM gel in a real-world cohort of patients with MF was described. In this group of 298 patients, daily application of NM gel was compared to less frequent application of 1–3 times per week, and application frequency was not found to have an effect on skin-related adverse events or clinical response to NM gel.[18] Other studies, however, have described decreased rates of dermatitis with less-frequent application. In a series of 18

Table 1 Summary of Key Studies of NM Gel

Author (Year)	Study Type	Patients	Treatment(s) Given	Study Endpoints	Special Notes
Lessin et al (2013)[9]	Multicenter, randomized, controlled, observer-blinded non-inferiority phase II clinical trial (study 201)	N = 260 Stage IA–IIA	NM 0.02% gel or NM 0.02% compounded ointment applied once daily to lesions or entire skin surface for 12 months	Primary endpoint was RR or ≥ 50% improvement from baseline CAILS for ≤ 5 lesions. Secondary endpoint ≥ 50% improvement in mSWAT.	NM gel noninferior to NM ointment (ITT population, 59% RR NM gel compared with 48% RR NM ointment). 8 patients with FMF/ LCT included, 4 with PR to NM 0.02% gel or ointment.
Querfeld et al (2022)[14]	Post hoc analysis of study 201	N = 260 Stage IA–IIA	NM 0.02% gel or NM 0.02% compounded ointment applied once daily to lesions or entire skin surface for 12 months	Subgroup analyses by stage of disease and time-to-event analyses performed.	RR higher in stage IA MF patients treated with NM gel (79.8%) compared with NM ointment (49.2%) (p = 0.0014). For patients with IB–IIA MF, difference in RR between NM gel and NM ointment did not reach statistical significance. Development of contact dermatitis associated with CAILs response (p = 0.0001).
Papadavid et al (2022)[15]	Retrospective analysis	N = 58 Stage IA–IIB	NM 0.02% gel monotherapy or combination therapy	ORR assessed as ≥ 50% improvement in mSWAT scores. Quality-of-life assessments via Skindex-29.	ORR increased over time from 37.9% at 1 month to 80.8% at 9 months. ORR at month 3 higher for patients with patches (69.7%) compared with patients with plaques/ tumors (15.2%). Presence or severity of dermatitis not associated with treatment response. Decrease in mSWAT with treatment correlated with decrease in Skindex-29 (p = 0.026).
Alexander-Savino et al (2022)[16]	Prospective, randomized, open-label, two-arm, phase II trial	N = 28 Stage IA or IB	Topical 0.106% NM gel once daily or topical 0.106% NM gel and TAC 0.1% ointment once daily to at least 8cm^2 lesion for 4 months	Primary endpoint impact of TAC 0.1% ointment on prevention of NM-associated dermatitis by adapted SCORD. Secondary endpoint comparing efficacy between arms utilizing CAILS.	Addition of TAC significantly decreased dermatitis severity after 3 months of treatment (p<0.05). No significant difference in CAILS with addition of TAC. No significant difference in CAILS among patients with moderate to severe dermatitis.
Kim et al (2020)[29]	Multicenter, prospective, observational Phase IV trial, preliminary findings	N = 298 Stage I–IV	NM 0.016% gel with variable application frequency and with or without concomitant therapies	Baseline study population characteristics and safety data.	48% of patients used concomitant therapies; 23.5% topical corticosteroids, 11.7% phototherapy, 10.1% systemic retinoids. 44.6% of patients reported at least 1 AE; 12.8% dermatitis, 7.4% skin irritation.

(*Continued*)

Table 1 (Continued).

Author (Year)	Study Type	Patients	Treatment(s) Given	Study Endpoints	Special Notes
Kim et al (2021)[18]	Multicenter, prospective, observational phase IV trial	N = 298 Stage I–IV	NM 0.016% gel with variable application frequency and with or without concomitant therapies monitored for up to 2 years	Primary endpoint response defined by ≥ 50% decrease in %BSA from baseline to 12 months in stage IA-IB patients receiving NM gel + topical corticosteroid + other. Secondary endpoints assessed response as above with other treatment combinations Safety and HRQOL also assessed.	74.5% of patients used NM gel daily, 37.6% of patients used every 2 days, and the remaining less frequently. 77.9% of patients used concomitant skin-directed therapies during study period (60.1% topical corticosteroid) and 30.2% used concomitant systemic therapies (16.1% oral bexarotene). Peak response (66.7%) occurred at 18 months for patients with stage IA-IB disease in the NM gel + other group. HRQOL outcomes were better for responders compared with nonresponders (p<0.001).
Wehkamp et al (2021)[19]	Single center retrospective analysis	N = 18 Stage IA–IIB	NM 0.02% gel daily or 3–4 times per week	Data on treatment regimen, adverse events, and response as defined by ≥ 50% improvement from baseline mSWAT obtained.	57.1% of patients with daily treatment developed dermatitis compared with 42.9% of patients with treatment 3–4x/ week (not statistically significant). 71.4% of patients with dermatitis able to resume NM gel after treatment with topical corticosteroids.
Chinn et al (1999)[31]	Retrospective analysis	N = 148 T2 and T3 MF	TSEBT +/- adjuvant topical NM therapy compared with topical NM alone	Assessment of response.	TSEBT +/- NM higher CR than NM alone for patients with T2 disease (76% vs. 39%, p = 0.03) and T3 disease (44% vs. 8%, p<0.05). Adjuvant NM following TSEBT associated with longer time to relapse compared with observation in patients with T2 disease that had obtained CR.

Abbreviations: CR, complete response; PR, partial response; RR, response rate (CR + PR); CAILS, Composite Assessment of Index Lesion Severity; mSWAT, modified Severity-Weighted Assessment Tool; ITT, intention to treat; FMF, folliculotropic mycosis fungoides; LCT, large cell transformation; AE, adverse events; ORR, overall response rate; TAC, triamcinolone; SCORD, Scoring Dermatitis; BSA, body surface area; HRQOL, health-related quality of life; IFN-α, interferon-alpha; TSEBT, total skin electron beam therapy.

patients with MF, 57.1% of patients developed dermatitis with daily NM gel application compared to 42.9% of those applying 3–4 times per week.[19] Several expert groups recommend starting with less frequent application of NM gel (ranging from 1–4 applications per week), alternating with therapy-free days.[20,21] If tolerated, frequency of application can gradually be increased to daily application.

Other commonly reported skin-related adverse effects of topical NM preparations include skin irritation, pruritus, erythema, hyperpigmentation, and folliculitis.[9] Urticaria and erythema multiforme-like reactions have also been described, but are rare.[22]

As alkylating agents are genotoxic and known mutagens,[23] a potential adverse effect of topical NM is secondary cutaneous malignancy. Evidence supporting NM inducing cutaneous malignancies is mixed and difficult to assess, as many patients with MF also receive phototherapy and/or immunosuppressive therapies during the course of their treatment. Early reports noted an increased relative risk in particular of squamous cell carcinoma in patients treated

with topical NM,[24] but a more recent larger population-based cohort study did not support an increased risk of secondary cancers in patients treated with topical NM.[24,25] Despite effective absorption into the skin, NM does not appear to be systemically absorbed to any meaningful degree, particularly when gel-based preparations are used.[26]

Special Considerations for the Use of NM

NM gel is approved for second-line treatment of early-stage MF (stage IA-IB) in the US and treatment of any-stage MF in adult patients in the European Union. Most patients receive at least two treatments prior to NM gel, with topical steroids, topical or systemic retinoids, and phototherapy being the most frequently reported therapies.[18,27] In a narrative review from four international expert treatment centers, NM gel was most frequently prescribed for patients with early-stage MF either after failure of high-potency topical steroids, or in those patients for whom phototherapy is contra-indicated (for example because of history of melanoma).[20]

NM gel can be used for spot treatment for patients with limited or localized MF (e.g., stage IA), or as a full body treatment for those with more widespread involvement (e.g., stage IB). There are no limitations to the quantity of daily application of NM gel, though responses may vary depending on body surface involvement. Response rates by stage were not reported in the registrational trial of NM gel, however, are assumed to be a similar pattern as for NM ointment, which demonstrates higher response for stage IA compared to IB.[13] Similar to other NM preparations, widespread NM gel application may "unmask" previously clinically undetectable lesions of MF, which can be confused for progression.[20] Patients should be counseled about this possibility, and providers should not discontinue NM gel therapy prematurely. The face and skin folds are more susceptible to irritant reactions; expert groups do still report the use of NM gel in these areas, though at a decreased frequency of application.[20,28]

Patients should be counseled that responses to NM gel are delayed, and that they may need or desire to use NM gel for months or even years. Patients in the PROVe study were followed for up to 24 months, with a response to NM gel of 36.7% after 1 month of treatment, and a peak response rate of 66.7% at 18 months. The authors counsel patients that it may take 4–6 weeks before any response to NM gel is noted, which aligns with other expert centers.[20] Patients often continue NM for long periods. The majority (63.8%) of patients in the PROVe study received NM gel for ≥12 months, with 45.0% using NM gel for ≥24 months.[18] In the authors' experience, patients do not often apply NM gel to the same lesion for years, but instead rotate through different lesions or develop new lesions in untreated areas.

Combination Therapy with NM Gel

Concomitant therapies were not allowed in the registrational trial of NM gel,[9] however, follow up longitudinal studies have shown that combination therapy including NM gel is common in clinical practice. In the PROVe study, the majority (77.9%) of patients used other skin-directed therapies in combination with NM gel, while 30.2% of patients received concomitant systemic therapy. The most frequent skin directed treatment used in combination with NM was topical corticosteroids (60.1% of patients), followed by phototherapy (20.5%), while the most common systemic therapy was systemic retinoid (16.1%).[18,29] A smaller case series also described the use of NM gel in conjunction with interferon-α.[30] Long term safety data for the use of NM gel in combination therapy has not been reported for any cohort.

There is also evidence that the use of NM as adjuvant or maintenance therapy following low dose total skin electron beam therapy (TSEBT) may have longer freedom from relapse than those treated with TSEBT alone.[31] The use of NM gel after TSEBT has also been evaluated in a case series from Jefferson University, who suggest that maintenance therapy with NM gel after low dose TSEBT may lengthen the time to progression compared to those treated with TSEBT alone.[32]

Impact of NM Gel on Quality of Life

Patients with CTCL experience significantly impaired health-related quality of life, with those with higher stage CTCL experiencing a greater impact.[33–36] The PROVe study evaluated the impact of NM gel on HRQoL of patients using NM gel in a real-world clinical setting. Using the Skindex-29, investigators found that patients who responded to treatment regimens that included NM gel had statistically significant reduction in all of the Skindex-29 subscales compared to non-responders.[18]

Cost Effectiveness of NM Gel

The cost of NM gel treatment depends on the extent of body surface area (BSA) involvement and duration of use. For example, the average wholesale price of NM gel for a patient with early-stage MF using approximately one 60g tube monthly for a year is approximately $75,000.[37] In an analysis of commonly used skin directed therapies for early (stage 1A) MF, the cost effectiveness of NM gel fell below local radiation, phototherapy (narrow band UVB and PUVA) and topical corticosteroids, and above topical bexarotene. The authors concluded that NM gel is indicated only after a trial of another topical therapy.[38]

NM Use in Specific Patient Populations

Advanced MF

In the US, NM gel is only approved for use in patients with early-stage MF, though there is some limited data supporting the use of NM gel for patients with higher stage or advanced stage MF. A series of 58 patients from Greece found an overall response rate of 36.4% for patients with late-stage MF after 4 months of NM gel (vs. 71.4% for patients with early-stage MF), suggesting that patients with advanced MF likely have lower response rates to NM gel compared to those with early disease.[15] In clinical practice at expert treatment centers, NM gel is used as an adjunctive rather than primary treatment in advanced stage disease.[20]

MF Variants: FMF and LCT

Folliculotropic MF (FMF) is a distinct clinical and histologic variant of MF that often presents with prominent head and neck involvement, folliculocentric papules or acneiform lesions, and associated alopecia.[39] FMF has been reported to have decreased response to standard MF therapies, increased risk of disease progression, and potentially worse survival particularly for patients with advanced cutaneous FMF.[39–41] There is limited data directly evaluating the efficacy of NM gel in patients with FMF. In the randomized controlled trial demonstrating non-inferiority of NM gel to NM ointment, eight patients with FMF, large cell transformation (LCT), or both were included, with four of eight patients demonstrating partial response to either NM gel or ointment.[9] Lampadaki et al reported a series of three patients with stage IB-IIB FMF with two patients with partial and one with complete response to a combination of NM gel and interferon-α after failure or loss of efficacy of multiple prior therapies.[30]

Patients with Skin of Color

Topical corticosteroids can cause hypopigmentation in patients with skin of color, and phototherapy is not as effective for MF in patients with darker skin tones,[42] potentially making NM gel an attractive alternative to these otherwise first line therapies for this patient group. Unfortunately, literature addressing the use of NM gel in patients with MF and skin of color are lacking. Although not specifically addressed in the study, in a series of patients with MF treated at Johns Hopkins, NM preparations appeared to be used in a higher percent of black patients with MF compared to white patients.[43]

Pediatric MF

While pediatric cutaneous lymphomas overall are rare, MF is the most common subtype of cutaneous lymphoma in children.[44] Pediatric patients are more likely to present with early stage MF compared to adults, and are therefore primarily treated with skin directed therapies, most commonly narrow band UVB phototherapy.[45] Safety and efficacy data for NM gel for pediatric patients with MF are lacking. Reports of topical NM treatment in pediatric patients are limited and almost exclusively described in combination with phototherapy.[44,45] In the Stanford series, six patients with ages ranging from 12–17 years were included, none of whom had any evidence of systemic toxicity from topical NM ointment as evidenced by normal blood counts and chemistries while on treatment.[13]

Pregnancy and Lactation

Mechlorethamine, similar to other alkylating agents, is teratogenic in mice when systemically administered.[46] There is insufficient evidence assessing the safety of NM gel in human pregnancy or lactation, and its use is therefore not recommended in patients who are pregnant (pregnancy category D) or breastfeeding.[17]

Conclusions

NM remains an effective and safe treatment for MF. The development of NM gel has led to decreased adverse cutaneous reactions compared to prior formulations of NM, though contact dermatitis remains a relatively frequent adverse effect. Concurrent topical steroids and/or decreased frequency of application may improve tolerability without impacting efficacy. In the US, NM gel is approved as second line therapy for patients with early-stage MF, and may be particularly suited to patients with MF that fail to respond to topical corticosteroids and patients who cannot pursue phototherapy due to contraindication or impracticality due to access. NM gel has been used in combination therapy with other skin directed or systemic therapies, particularly topical steroids and phototherapy, but there is currently no long-term safety or response data. Limited data supports the use of NM gel as an adjunct or maintenance therapy to prolong the benefits of TSEBT, and as an adjunct therapy for patients with FMF or advanced-stage MF, though with lower response rates compared to early-stage MF.

For patients with skin of color, NM gel may be preferable over some other skin directed therapies, particularly topical steroids, which can cause hypopigmentation in patients in patients with darker skin tones, and phototherapy, which can be less effective for patients with darker skin tones compared to those with lighter skin tones. Further investigation is warranted into the safety, tolerability and efficacy of NM gel in pediatric patients. The known teratogenicity of NM limits its use in pregnant or breastfeeding patients.

Disclosure

Dr Michi M Shinohara is a principal investigator for Elorac, Cabaletta Bio, and Aztex for clinical trial, outside the submitted work; she is a Member of NCCN T-cell Lymphoma Panel, United States Cutaneous Lymphoma Consortium Board of Directors. The authors report no other conflicts of interest in this work.

References

1. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood*. 2005;105(10):3768–3785. doi:10.1182/blood-2004-09-3502
2. Tarabadkar ES, Shinohara MM. Skin directed therapy in cutaneous T-cell lymphoma. *Front Oncol*. 2019;9:260. doi:10.3389/fonc.2019.00260
3. Haserick JR, Richardson JH, Grant DJ. Remission of lesions in mycosis fungoides following topical application of nitrogen mustard. *Cleve Clin Q*. 1983;50(2):91–95. doi:10.3949/ccjm.50.2.91
4. Singh RK, Kumar S, Prasad DN, Bhardwaj TR. Therapeutic journery of nitrogen mustard as alkylating anticancer agents: historic to future perspectives. *Eur J Med Chem*. 2018;151:401–433. doi:10.1016/j.ejmech.2018.04.001
5. Ramsay DL, Halperin PS, Zeleniuch-Jacquotte A. Topical mechlorethamine therapy for early stage mycosis fungoides. *J Amer Acad Dermat*. 1988;19(4):684–691. doi:10.1016/S0190-9622(88)70223-6
6. Chang YT, Ignatova D, Hoetzenecker W, Pascolo S, Fassnacht C, Guenova E. Increased chlormethine-induced DNA double-stranded breaks in malignant T cells from mycosis fungoides skin lesions. *JID Innov*. 2022;2(1):100069. doi:10.1016/j.xjidi.2021.100069
7. Ramsay DL, Meller JA, Zackheim HS. Topical treatment of early cutaneous T-cell lymphoma. *Hematol Oncol Clin North Am*. 1995;9(5):1031–1056. doi:10.1016/S0889-8588(18)30057-1
8. Kim YH. Management with topical nitrogen mustard in mycosis fungoides. *Dermatol Ther*. 2003;16(4):288–298. doi:10.1111/j.1396-0296.2003.01640.x
9. 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(1):25–32. doi:10.1001/2013.jamadermatol.541
10. Van Scott EJ. Complete regressions of mycosis fungoides with topical mechlorethamine hydrochloride. *JAMA*. 1972;222(9):1172. doi:10.1001/jama.1972.03210090052026
11. Van Scott EJ, Kalmanson JD. Complete remissions of mycosis fungoides lymphoma induced by topical nitrogen mustard (HN2). Control of delayed hypersensitivity to HN2 by desensitization and by induction of specific immunologic tolerance. *Cancer*. 1973;32(1):18–30. doi:10.1002/1097-0142(197307)32:1<18::AID-CNCR2820320103>3.0.CO;2-Q
12. Vonderheid EC, Van Scott EJ, Wallner PE, Johnson WC. A 10-year experience with topical mechlorethamine for mycosis fungoides: comparison with patients treated by total-skin electron-beam radiation therapy. *Cancer Treat Rep*. 1979;63(4):681–689.

13. Kim YH, Martinez G, Varghese A, Hoppe RT. Topical nitrogen mustard in the management of mycosis fungoides: update of the Stanford experience. *Arch Dermatol*. 2003;139(2):165–173. doi:10.1001/archderm.139.2.165
14. Querfeld C, Scarisbrick JJ, Assaf C, et al. Post hoc analysis of a randomized, controlled, phase 2 study to assess response rates with chlormethine/mechlorethamine gel in patients with stage IA-IIA mycosis fungoides. *Dermatology*. 2022;238(2):347–357. doi:10.1159/000516138
15. Papadavid E, Koumourtzis M, Nikolaou V, et al. Chlormethine gel is effective for the treatment of skin lesions in patients with early- and late-stage mycosis fungoides in clinical practice. *J Eur Acad Dermatol Venereol*. 2022;36(10):1751–1757. doi:10.1111/jdv.18183
16. Alexander-Savino CV, Chung CG, Gilmore ES, Carroll SM, Poligone B. Randomized mechlorethamine/chlormethine induced dermatitis assessment study (MIDAS) establishes benefit of topical triamcinolone 0.1% ointment cotreatment in mycosis fungoides. *Dermatol Ther*. 2022;12(3):643–654. doi:10.1007/s13555-022-00681-6
17. Helsinn Therapeutics. Valchlor (mechloretheamine) gel 0.016% [package insert]. U.S. Food and Drug Administration website; 2013. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202317lbl.pdf. Accessed July 10, 2022.
18. Kim EJ, Guitart J, Querfeld C, et al. The PROVe study: US real-world experience with chlormethine/mechlorethamine gel in combination with other therapies for patients with mycosis fungoides cutaneous T-cell lymphoma. *Am J Clin Dermatol*. 2021;22(3):407–414. doi:10.1007/s40257-021-00591-x
19. Wehkamp U, Jost M, Gosmann J, Grote U, Bernard M, Stadler R. Management of chlormethine gel treatment in mycosis fungoides patients in two German skin lymphoma centers. *J Dtsch Dermatol Ges*. 2021;19(7):1057–1059.
20. Geskin LJ, Bagot M, Hodak E, Kim EJ. Chlormethine gel for the treatment of skin lesions in all stages of mycosis fungoides cutaneous T-cell lymphoma: a narrative review and international experience. *Dermatol Ther*. 2021;11(4):1085–1106. doi:10.1007/s13555-021-00539-3
21. Assaf C, Booken N, Dippel E, et al. The optimal use of chlormethine gel for mycosis fungoides: an expert consensus from Germany, Austria and Switzerland (DACH region). *J Dtsch Dermatol Ges*. 2022;20(5):579–586.
22. Reddy VB, Ramsay D, Garcia JA, Kamino H. Atypical cutaneous changes after topical treatment with nitrogen mustard in patients with mycosis fungoides. *Am J Dermatopathol*. 1996;18(1):19–23. doi:10.1097/00000372-199602000-00003
23. Povirk LF, Shuker DE. DNA damage and mutagenesis induced by nitrogen mustards. *Mutat Res*. 1994;318(3):205–226. doi:10.1016/0165-1110(94)90015-9
24. Vonderheid EC, Tan ET, Kantor AF, Shrager L, Micaily B, Van Scott EJ. Long-term efficacy, curative potential, and carcinogenicity of topical mechlorethamine chemotherapy in cutaneous T cell lymphoma. *J Amer Acad Dermatol*. 1989;20(3):416–428. doi:10.1016/S0190-9622(89)70051-7
25. Lindahl LM, Fenger-Gron M, Iversen L. Secondary cancers, comorbidities and mortality associated with nitrogen mustard therapy in patients with mycosis fungoides: a 30-year population-based cohort study. *Br J Dermatol*. 2014;170(3):699–704. doi:10.1111/bjd.12620
26. Querfeld C, Geskin LJ, Kim EJ, et al. Lack of systemic absorption of topical mechlorethamine gel in patients with mycosis fungoides cutaneous T-cell lymphoma. *J Invest Dermatol*. 2021;141(6):1601–1604 e1602. doi:10.1016/j.jid.2020.12.009
27. Laghi A, Franceschini C, Mandel VD, et al. Topical chlormethine gel in the treatment of mycosis fungoides: a single-center real-life experience and systematic review of the literature. *Dermatol Ther*. 2022;35:e15683. doi:10.1111/dth.15683
28. NCCN clinical practice guidelines in oncology (NCCN guidelines), primary cutaneous lymphomas. National Comprehensive Cancer Network; 2022. Available from: https://www.nccn.org/professionals/physician_gls/pdf/primary_cutaneous.pdf. Accessed October 07, 2022.
29. Kim EJ, Geskin L, Guitart J, et al. Real-world experience with mechlorethamine gel in patients with mycosis fungoides-cutaneous lymphoma: preliminary findings from a prospective observational study. *J Amer Acad Dermatol*. 2020;83(3):928–930. doi:10.1016/j.jaad.2019.12.070
30. Lampadaki K, Koumourtzis M, Karagianni F, Marinos L, Papadavid E. Chlormethine gel in combination with other therapies in the treatment of patients with mycosis fungoides cutaneous T cell lymphoma: three case reports. *Adv Ther*. 2021;38(6):3455–3464. doi:10.1007/s12325-021-01721-x
31. Chinn DM, Chow S, Kim YH, Hoppe RT. Total skin electron beam therapy with or without adjuvant topical nitrogen mustard or nitrogen mustard alone as initial treatment of T2 and T3 mycosis fungoides. *Int J Radiat Oncol Biol Phys*. 1999;43(5):951–958. doi:10.1016/S0360-3016(98)00517-3
32. Jennings T, Duffy R, Gochoco A, et al. Valchlor maintenance therapy for patients with mycosis fungoides who received low dose total skin electron beam treatment. *Chin Clin Oncol*. 2019;8(1):13. doi:10.21037/cco.2018.10.01
33. Demierre MF, Tien A, Miller D. Health-related quality-of-life assessment in patients with cutaneous T-cell lymphoma. *Arch Dermatol*. 2005;141(3):325–330. doi:10.1001/archderm.141.3.325
34. Molloy K, Jonak C, Woei AJF, et al. Characteristics associated with significantly worse quality of life in mycosis fungoides/Sezary syndrome from the Prospective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) study. *Br J Dermatol*. 2020;182(3):770–779. doi:10.1111/bjd.18089
35. Herbosa CM, Semenov YR, Rosenberg AR, Mehta-Shah N, Musiek AC. Clinical severity measures and quality-of-life burden in patients with mycosis fungoides and Sezary syndrome: comparison of generic and dermatology-specific instruments. *J Eur Acad Dermatol Venereol*. 2020;34(5):995–1003. doi:10.1111/jdv.16021
36. Shinohara MM, Mahurin HM, Tarabadkar E, et al. Health-related quality of life in cutaneous T-cell lymphoma: a cross-sectional survey study. *Skin Health Dis*. 2021;1(3):e45. doi:10.1002/ski2.45
37. VALCHLOR. Micromedex, RED BOOK. Available from: www-micromedexsolutions-com. Accessed October 22, 2022.
38. Xia FD, Ferket BS, Huang V, Stern RS, Wu PA. Local radiation and phototherapy are the most cost-effective treatments for stage IA mycosis fungoides: a comparative decision analysis model in the United States. *J Am Acad Dermatol*. 2019;80(2):485–492.e484. doi:10.1016/j.jaad.2018.07.040
39. Lehman JS, Cook-Norris RH, Weed BR, et al. Folliculotropic mycosis fungoides: single-center study and systematic review. *Arch Dermatol*. 2010;146(6):607–613. doi:10.1001/archdermatol.2010.101
40. Agar NS, Wedgeworth E, Crichton S, et al. Survival outcomes and prognostic factors in mycosis fungoides/Sézary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. *J Clin Oncol*. 2010;28(31):4730–4739. doi:10.1200/JCO.2009.27.7665
41. Charli-Joseph Y, Kashani-Sabet M, McCalmont TH, et al. Association of a proposed new staging system for folliculotropic mycosis fungoides with prognostic variables in a US cohort. *JAMA Dermatol*. 2021;157(2):157–165. doi:10.1001/jamadermatol.2020.4372
42. Nikolaou V, Sachlas A, Papadavid E, et al. Phototherapy as a first-line treatment for early-stage mycosis fungoides: the results of a large retrospective analysis. *Photodermatol Photoimmunol Photomed*. 2018;34(5):307–313. doi:10.1111/phpp.12383

43. Huang AH, Kwatra SG, Khanna R, Semenov YR, Okoye GA, Sweren RJ. Racial disparities in the clinical presentation and prognosis of patients with mycosis fungoides. *J Natl Med Assoc*. 2019;111(6):633–639. doi:10.1016/j.jnma.2019.08.006
44. Wu JH, Cohen BA, Sweren RJ. Mycosis fungoides in pediatric patients: clinical features, diagnostic challenges, and advances in therapeutic management. *Pediatr Dermatol*. 2020;37(1):18–28. doi:10.1111/pde.14026
45. Kothari R, Szepietowski JC, Bagot M, et al. Mycosis fungoides in pediatric population: comprehensive review on epidemiology, clinical presentation, and management. *Int J Dermatol*. 2022. doi:10.1111/ijd.16098
46. Danforth CH, Center E. Nitrogen mustard as a teratogenic agent in the mouse. *Proc Soc Exp Biol Med*. 1954;86(4):705–707. doi:10.3181/00379727-86-21207

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