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

Caitlin Crimp¹, Ameya Gangal², Erica S Tarabadkar³, Michi M Shinohara¹,⁴

¹Division of Dermatology, University of Washington, Seattle, WA, USA; ²School of Medicine, Emory University, Atlanta, GA, USA; ³Department of Dermatology, Emory University School of Medicine; Winship Cancer Institute, Atlanta, GA, USA; ⁴Fred Hutchinson Cancer Center, Seattle, WA, USA

Correspondence: Michi M Shinohara, University of Washington, 1959 NE Pacific St., Box 356524, Seattle, WA, 98195, USA, Tel +1 206-616-8523, Fax +1 206-598-4768, Email mshinoha@uw.edu

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. Key words: 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
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%.\textsuperscript{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%).\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{9} Additionally, there was a significantly increased incidence of general skin irritation in the gel arm (25%) compared to the ointment arm (14%).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{14} In the Mechlorethamine/Chlormethine Induced Dermatitis Assessment Study (MIDAS),\textsuperscript{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.\textsuperscript{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.\textsuperscript{16} The product insert for NM gel\textsuperscript{17} recommends daily application to affected areas of skin in accordance with the frequency used in the registration trial.\textsuperscript{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.\textsuperscript{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)    | 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 8cm² 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)17     | 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)
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. Several expert groups recommend starting with less frequent application of NM gel (ranging from 1–4 applications per week), alternating with therapy-free days. 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. Urticaria and erythema multiforme-like reactions have also been described, but are rare.

As alkylating agents are genotoxic and known mutagens, 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

### Table 1 (Continued)

| Author (Year) | Study Type | Patients | Treatment(s) Given | Study Endpoints | Special Notes |
|---------------|------------|----------|--------------------|-----------------|---------------|
| Kim et al (2021) | 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) | 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) | 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.
with topical NM, but a more recent larger population-based cohort study did not support an increased risk of secondary cancers in patients treated with topical NM. 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.

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. 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 contraindicated (for example because of history of melanoma). 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. Similar to other NM preparations, widespread NM gel application may “unmask” previously clinically undetectable lesions of MF, which can be confused for progression. 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.

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. 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. 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, 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%). A smaller case series also described the use of NM gel in conjunction with interferon-α. 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. 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.

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. 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.
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. 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.

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. In clinical practice at expert treatment centers, NM gel is used as an adjunctive rather than primary treatment in advanced stage disease.

MF Variants: FMF and LCT

Folliculotropism (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. 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. 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. 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.

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, 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.

Pediatric MF

While pediatric cutaneous lymphomas overall are rare, MF is the most common subtype of cutaneous lymphoma in children. 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. 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. 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.
Pregnancy and Lactation

Mechlorethamine, similar to other alkylating agents, is teratogenic in mice when systemically administered. 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.

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 Aztek 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.

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