Chlormethine Gel for the Treatment of Skin Lesions in All Stages of Mycosis Fungoides Cutaneous T-Cell Lymphoma: A Narrative Review and International Experience

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ABSTRACT

Mycosis fungoides (MF), the most common form of primary cutaneous T-cell lymphoma, is a disease typically with an indolent course that is initially characterized by localized patches and plaques. In the early stages of the disease, treatment involves skin-directed therapies (SDTs) such as topical corticosteroids and retinoids. Chlormethine gel (also known as mechlorethamine) was the first SDT purposely developed to treat MF and is currently endorsed by international guidelines for the treatment of adult patients with MF as a first-line therapy. While chlormethine is an efficacious therapy, its usage may be complicated by the development of cutaneous reactions at the sites of application. Herein, we discuss the supportive guidelines for MF and the suitability of chlormethine as a therapeutic option in patients with MF. In addition, we present real-world experience on the use of chlormethine gel from clinics in the USA, Israel, and France with the aim of demonstrating the efficacy of chlormethine gel in routine clinical practice and outlining strategies that are being used to manage emergent cutaneous reactions.
**Key Summary Points**

Mycosis fungoides (MF) is a cutaneous T-cell lymphoma typically with an indolent course that is initially characterized by localized patches and plaques.

Chlormethine gel is a therapeutic option recommended by international guidelines for patients with MF skin lesions; a range of retrospective, prospective, and observational clinical data supports its use in all disease stages.

While chlormethine is an efficacious therapy, its usage may be complicated by the development of cutaneous reactions at the sites of application.

Real-world experience from clinical practice in the US, Israel, and France has shown that chlormethine gel is used as a skin-directed therapy in the first- and second-line setting in patients with early-stage MF and as an adjunctive therapy in patients with advanced-stage disease.

The emergent cutaneous adverse reactions can generally be managed through chlormethine gel dose adjustments or the use of topical steroids.

**INTRODUCTION**

Cutaneous T-cell lymphomas (CTCLs) are a heterogeneous family of T-cell lymphoproliferative disorders, of which mycosis fungoides (MF) is the most common. Early-stage MF follows a slow, indolent course [1], with symptoms present for extended periods of time. Due to the clinical similarity between benign skin diseases (such as eczema and psoriasis) and early-stage MF, as well as the lack of a singular diagnostic test or specific tumor markers, median time between MF symptom onset and biopsy-confirmed diagnosis is 4–6 years [2]. Most patients with early-stage MF have an average life expectancy following treatment but reduced quality of life [3]. Median survival for those with stage III or IV disease is low (< 5 years), and ≥ 50% die of their disease [4–7]. MF treatment goals are symptom control and quality of life improvement [8], as there are no curative therapeutic options aside from allogeneic stem cell transplantation [9].

In this review, we will briefly present the treatment guidelines for the management of patients with MF, discuss the role of topical chlormethine gel as part of the treatment paradigm, provide an overview of the clinical data demonstrating the effectiveness of the gel, and present real-world experience of chlormethine gel usage from four different dermatology practices.

This review is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. Informed consent was provided by the patient whose case was included.
| First author (year) | Study description | Patients, n | Treatment(s) administered | Efficacy findings | Safety findings |
|---------------------|------------------|-------------|----------------------------|-------------------|----------------|
| Price et al. (1977) [29] | Retrospective case analysis | 51 | Topical chlormethine as adjuvant therapy after TSEB therapy vs. TSEB therapy alone | Disease-free interval: 25 months for chlormethine plus TSEB therapy vs. 17 months for TSEB therapy alone | Patients receiving adjuvant topical chlormethine had a low incidence of contact allergy |
| Vonderheid et al. (1979) [30] | Retrospective case analysis | 243 | Topical chlormethine given as a dilute aqueous solution with or without systemic chemotherapy | Disease-free interval > 3 years in 32 (13%) patients | NA |
| Price et al. (1983) [31] | Retrospective case analysis | 43: stage IA, 17; stage IB, 22; stage II, 2; stage III, 2 | Topical chlormethine ointment | CR occurred in 26 patients over a 42-month evaluation period | Contact dermatitis occurred in 1 of 31 (3%) chlormethine-naive patients and 3 of 12 (25%) previously treated patients |
| Ramsay et al. (1984) [32] | Retrospective case analysis | 76 | Topical chlormethine | Of 64 patients who continued therapy, 43 (67%) achieved CR and 12 (19%) achieved PR | Allergic contact hypersensitivity reactions occurred in 51 (67%) patients |
| Zachariae et al. (1985) [33] | Retrospective case analysis | 33 (with early MF in plaque stage) | Topical chlormethine | 14 patients in CR and 7 in PR, with a relapse-free survival of 50% after 6 and 12 years, respectively | 3 deaths due to disease, 3 patients discontinued due to treatment-related contact dermatitis |

Notes: TSEB = topical skin excision and burn; CR = complete response; PR = partial response; AEs = adverse events.
| First author (year) | Study description | Patients, n | Treatment(s) administered | Efficacy findings | Safety findings |
|---------------------|-------------------|-------------|---------------------------|-------------------|----------------|
| Hoppe et al. (1987) [34] | Retrospective case analysis | 123 (median age, 59 years [range 20–90]; 88% White, 6% Black, 5% Hispanic, 1% Asian): stage IA, 38; stage IB, 30; stage IIA, 33; stage IIB, 13; stage IIIA, 2; stage IIIB, 7 | Topical chlormethine 10–20 mg/dl given either as aqueous solution or ointment | Efficacy was similar for aqueous vs. ointment formulations ORR and CR rate: all, 72% and 32%; stage I, 88% and 51%; stage II, 69% and 26% Among those with CR, 40% of patients with stage I disease and 60% with stage II disease later relapsed Subsequent therapies including repeat treatments with chlormethine were successful in achieving later skin clearance Long-term remissions noted in 42% of patients with stage I and 31% with stage II disease No patients with stage III disease (n = 13) had CR, and all had progression 2 of 9 patients with stage IV disease had CR, but both later relapsed | When deaths occurred, they were typically unrelated to disease in stage I patients Half of deaths among stage II patients were attributable to disease Among 22 patients with stage III or IV disease, 80% were attributable to MF Cutaneous hypersensitivity was more common with aqueous than with ointment formulation 14 (11%) patients developed cutaneous malignancies |
| First author (year) | Study description | Patients, n | Treatment(s) administered | Efficacy findings | Safety findings |
|---------------------|------------------|-------------|---------------------------|------------------|----------------|
| Ramsay et al. (1988) [35] | Retrospective analysis of medical records | 117 (median age, 57 years; 56% male): stage IA, 28; stage IB, 35; stage IIA, 12; stage IIB, 32; stage IIIA, 1; stage IIIB, 9 | Chlormethine 10 mg dissolved in 60 ml of water applied QD until 6 months after CR, tapering over the following 18 months; concomitant therapy not allowed except for local RT for stage III disease | Median time to CR: stage I, 6.5 months; stage II, 41 months; stage III, 39 months | Delayed hypersensitivity reactions: 58% | 1 patient discontinued due to hypersensitivity |
| Vonderheid et al. (1989) [26] | Retrospective analysis of medical records | 331 (mean age, 58 ± 0.7 years; 65% male): stage IA, 89; stage IB, 66; stage IIA, 46; stage IIB, 39; stage III, 37; stage IVA, 38; stage IVB, 9; lymphomatoid papulosis, 7 | Chlormethine 10–20 mg dissolved in 40–60 ml of water applied QD until CR, then continued QD or EOD depending on response; adjunctive therapy allowed for slowly responsive, extensive disease, or extracutaneous involvement (e.g., local RT, TSEB therapy, UV phototherapy, methotrexate, or other alkylating agents) | Initial CR defined as complete disappearance of clinically detectable disease ≥ 2 weeks and confirmed by skin biopsy: stage 1A, 80%; stage 1B, 68%; stage IIA, 61%; stage IIB, 49%; stage III, 60%; stage IVA, 13%; stage IVB, 11% | Sustained remission for 4 and 8 years: 65 and 35 patients, respectively | Of patients with CR > 8 years, 12 (35%) experienced ACD |
| First author                  | Study description    | Patients, n | Treatment(s) administered                                      | Efficacy findings | Safety findings |
|------------------------------|----------------------|-------------|-----------------------------------------------------------------|-------------------|-----------------|
| Licata et al. (1995) [39]    | Retrospective case analysis | 164 (who had received TSEB therapy between 1974 and 1990; median age, 59 years [range 20–88]; 62% males; 88% White, 10% Black) | Evaluated effects of therapy beyond TSEB, including topical chlormethine | NA                | 6 patients developed malignant melanoma 12–95 months after TSEB therapy, including 2 treated with chlormethine. During median follow-up of 6 years, no patient died of secondary cutaneous malignancy. Additional use of chlormethine following TSEB therapy was associated with nonmelanoma skin cancer. |
| Estève et al. (1999) [40]    | Multicenter, prospective study | 52 (mixed population of patients with CTCL including 35 with MF; age 18–87 years; 67% males) | Topical chlormethine 0.02% given as aqueous solution | NA                | Follow-up data from 43 patients. Intolerance to chlormethine developed in 23 patients (14 males, 9 females) 4 days to 9 months after initiation, including 15 of 35 (43%) patients with MF. 12 patients overall were able to resume chlormethine after resolution of symptoms. |
| First author (year) | Study description | Patients, n | Treatment(s) administered | Efficacy findings | Safety findings |
|---------------------|-------------------|-------------|---------------------------|-------------------|----------------|
| Foulc et al. (2002) [36] | Open-label, prospective study | 39 with CTCL (including 34 with MF: mean age, 63 years [range 31–82]; 59% males: stage IA, 8; stage IB, 14; stage IIA, 3; stage IIB, 8; stage IVA, 1) | Topical chlormethine 0.2% diluted in 10 ml solvent and 50 ml water and given either QD or intermittently | Response rate was 69%, with no difference between QD and intermittent application | Cutaneous intolerance occurred in 19 of 39 (49%) patients, including 6 with ACD after a mean of 9 weeks; the other 13 patients developed contact dermatitis after a longer period (3 weeks to 17 months) |
| Kim et al. (2003) [37] | Single-center, retrospective cohort analysis | 203 (with stage I–III disease; median age, 56 years [range 12–87]; 61% males; 86% White): stage IA, 103; stage IB, 74; stage IIA, 18; stage IIB, 4; stage III, 4 | Topical chlormethine 10–20 mg/100 ml aqueous solution or ointment | ORR and CR rate: all, 83% and 50%; stage I, 93% and 65%; stage II, 72% and 34% | Contact hypersensitivity reactions occurred in < 10% when used as ointment |
|                      |                   |             |                           | Median time to CR: all, 12 months; stage I, 10 months; stage II, 19 months | 8 (4%) patients developed secondary cutaneous malignancies, with none attributed to chlormethine |
|                      |                   |             |                           | Median time to relapse: 12 months | No significant toxic effects were observed |
|                      |                   |             |                           | When administered as salvage therapy, response rates were similar to initial therapy | Efficacy similar for aqueous vs. ointment formulations |
| First author          | Year       | Study description                           | Patients, n                                                                 | Treatment(s) administered                                          | Efficacy findings                                                                 | Safety findings                                                                 |
|----------------------|------------|---------------------------------------------|----------------------------------------------------------------------------|---------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| de Quatrebarbes et al. (2005) [38] |            | Multicenter, prospective, nonrandomized study | 64 (newly diagnosed, early-stage disease; mean age, 63 years [range 7–82]; 67% males): stage IA, 33; stage IB, 26; stage IIA, 5 | Topical chlormethine 0.02% aqueous given twice weekly followed by betamethasone cream over 6 months | CR in 58% after a mean of 4 months, including 61% with stage IA disease, 58% with stage IB, 40% with stage IIA disease | Relapse in 17 (46%) patients after a mean of 7.7 months 58% of patients did not experience any adverse cutaneous reactions Severe cutaneous reactions requiring discontinuation developed in 18 (28%) patients, including erythema, severe pruritus, or burning sensation in 11 cases, and eczematous reaction in 7 cases |
| Lindahl et al. (2013) [27] |            | Retrospective analysis of medical records (116) | 116: stage IA, 11; stage IB, 68; stage IIA, 10; stage IIB, 13; stage III, 9; stage IVA, 4; stage IVB, 1 | Chlormethine ointment (concentration not mentioned) | ORR, 92%; CR rate, 53% | |
| First author (year) | Study description | Patients, n | Treatment(s) administered | Efficacy findings | Safety findings |
|---------------------|-------------------|-------------|---------------------------|-------------------|----------------|
| Lessin et al. (2013) [15] | Phase II multicenter, randomized, observer-blinded, noninferiority trial in patients with persistent/recurrent stage I–II disease | 260 (median age, 58 years [range 11–88]; 59% male; 74% Caucasian): stage IA, 141; stage IB, 115; stage IIA, 4 | Chlormethine 0.02% gel or ointment applied QD for 12 months; no concomitant corticosteroids were permitted | CAILS (severity score for ≤ 5 lesions; CR, 100% improvement from BL; PR, ≥ 50 to < 100% improvement from BL; gel, 14% CR and 45% PR; ointment, 12% CR and 36% PR) | No drug-related severe AEs were reported |
|                      |                   |             |                           | Chlormethine gel was noninferior to ointment by prespecified criteria | Drug-related skin AEs in the gel and ointment arms were reported by 62% and 50% of patients, respectively |
|                      |                   |             |                           |                   | These included: skin irritation (n = 32 vs. 18); pruritus (n = 25 vs. 20); erythema (n = 22 vs. 18); contact dermatitis (n = 19 vs. 19); skin hyperpigmentation (n = 7 vs. 9); folliculitis (n = 7 vs. 5) |
|                      |                   |             |                           |                   | 11 patients overall including 3 in gel arm and 8 in ointment arm were diagnosed with 20 secondary nonmelanoma skin cancers |
| Kim et al. (2014) [17] | Phase II extension study with patients who completed the Lessin 2013 [15] study (12 months of treatment) but did not achieve CR (N = 98) | 98 (mean age, 53 ± 14 years; 55% male; 68% Caucasian) | Chlormethine 0.04% gel applied QD for 7 months (application frequency could be reduced for toxicity) | CAILS (severity score for ≤ 5 lesions, confirmed ≥ 4 weeks later): CR in 6 patients and PR in 20 patients | Mild-to-moderate drug-related skin AEs were reported by 31 (32%) patients |
|                      |                   |             |                           |                   | Most common drug-related skin AEs were skin irritation (11%), erythema (10%), and pruritus (6%) |
| First author (year) | Study description | Patients, n | Treatment(s) administered | Efficacy findings | Safety findings |
|---------------------|-------------------|-------------|---------------------------|-------------------|----------------|
| Lindahl et al. (2014) [41] | Population-based cohort study | 303; including 110 using chlormethine (mean age, 69 years [range 30–98]; 69% males: stage IA, 14; stage IB, 39; stage IIA, 8; stage IIB, 25; stage IIIA, 15; stage IV, 9) | Topical chlormethine | NA | Secondary cancers were not significantly increased (HR 0.8; 95% CI 0.5–1.6) in patients receiving chlormethine. Subanalyses showed no significantly increased risk of nonmelanoma skin cancers, malignant melanomas, or cancers of the respiratory organs. Mortality and cause-specific mortality were not influenced by treatment. |
| Kim et al. (2020) [42] | Prospective, observational, noninterventional study | 301 (298 monitored) stage IA–IIA: 62%; stage IIB–IV: 8% | Topical chlormethine gel in combination with other therapies | ORR of 44% in patients who received chlormethine gel plus corticosteroids and/or NBUVB phototherapy, oral bexarotene, PUVA, local electron-beam therapy, topical bexarotene, and imiquimod. ORR of 45% in patients who received chlormethine gel plus any other treatment. | 42% experienced ≥ 1 AE. Most common skin-related AEs were: dermatitis (13%); pruritus (10%); skin irritation (7%); and erythema (5%). |
| First author (year) | Study description | Patients, n | Treatment(s) administered | Efficacy findings | Safety findings |
|---------------------|-------------------|------------|---------------------------|------------------|----------------|
| Gilmore et al. (2020) [43]; Alexander-Savino et al. (2020) [44] | Phase II, nonrandomized, open-label, split-face, two-arm study in patients with stage IA and IB disease | 28 | 0.016% w/w topical chlormethine gel (once nightly) applied over a minimum of 8 cm², over a 4-month period 0.016% w/w topical chlormethine gel (once nightly) plus triamcinolone 0.1% ointment QD applied over a minimum of 8 cm², over a 4-month period | CAILS scores were comparable between the two arms Addition of triamcinolone ointment significantly decreased the SCORAD score ($p < 0.05$) | 32% developed severe contact dermatitis 31% developed ACD vs. 66% of patients from historical data using aqueous formulation 4% developed ICD |

The trials 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.

ACD allergic contact dermatitis; AE adverse event; BL baseline; CAILS Composite Assessment of Index Lesion Severity; CI confidence interval; CR complete response; CTCL cutaneous T-cell lymphoma; EOD every other day; HR hazard ratio; ICD irritant contact dermatitis; MF mycosis fungoides; NA data not available; NBUVB narrowband ultraviolet B; ORR overall response rate; PR partial response; PUVA psoralen and ultraviolet A; QD once daily; RT radiotherapy; SCORAD SCORing Atopic Dermatitis; TSEB total skin electron beam; UV ultraviolet
For asymptomatic patients with early-stage MF (stage IA), “watch and wait” is considered an appropriate option. For symptomatic patients, those with adverse prognostic factors (such as plaque stage disease or large cell transformation), or those with extensive disease involvement (stage IB), skin-directed therapies (SDTs) should be initiated. The most commonly used SDTs for treating early-stage MF are topical corticosteroids [8, 14], topical chlormethine or retinoids [15, 16], and phototherapy; superficial radiotherapy may also be employed. Patients with advanced-stage disease generally receive systemic single-agent or combination therapy with SDTs. Addition of an effective SDT can alleviate symptoms and shorten time to response compared with systemic therapy alone [11].

CHLORMETHINE AS TOPICAL CHEMOTHERAPY FOR MANAGING MF

All major guidelines recommend the use of chlormethine for first-line treatment in adult patients with MF [10–13]. Chlormethine is a bifunctional alkylating agent that inhibits rapidly proliferating cells by binding and crosslinking DNA strands. The original aqueous and ointment formulations were not approved as a therapy for MF, and it was subsequently developed as a topical gel [15, 17]. This formulation was approved by the US Food and Drug Administration (FDA) in 2013 for treating stage IA and IB MF in patients who received prior SDT, has been registered in Israel since 2016 (for the same indication as in the USA), was approved by the European Medicines Agency in 2017 for treatment of adult patients with MF [18], and is now available commercially in a number of European countries. Chlormethine gel has been available in France since 2014 under a “temporary authorization for use” program that ended in July 2019, with 876 patients having participated [19].

The chlormethine gel (chlormethine 0.016% w/w, equivalent to 0.02% chlormethine hydrochloride) formulation was designed to maximize efficacy and tolerability. Its nonaqueous nature imparts high stability, and the active solvent, diethylene glycol monoethyl ether (Transcutol®), promotes delivery of the drug to the epidermis [20–22], although there is no evidence of systemic absorption of chlormethine following application [15]. Efficacy is enhanced by inclusion of the excipient, Klucel™ hydroxypropylcellulose (Ashland) [23], which results in a fast-drying, nongreasy formulation with a viscosity that is more likely to remain at the administration site, which makes it easier to apply at home. The intrinsic antimicrobial nature of the active ingredients [24] removes the need for antimicrobial preservatives (which frequently cause skin reactions), thus potentially reducing the risk of allergy, although further investigations are required to confirm this.

Chlormethine may be used as monotherapy in early-stage MF, in combination with systemic therapy in advanced-stage disease [25–27], and as maintenance treatment [11, 28]. The chlormethine gel label indicates daily application; however, the frequency of application may be reduced according to the patient’s needs. For severe skin reactions, treatment should be suspended (in some cases permanently) and upon improvement can be restarted gradually up to daily frequency, if tolerated.

CHLORMETHINE IN MF MANAGEMENT: A REVIEW OF THE LITERATURE

There is a substantial body of prospective and retrospective evidence underlying the recommendation of chlormethine as a treatment option for patients with MF in all stages of the disease (summarized in Table 1 [15, 17, 26, 27, 29–44]). These studies have demonstrated that chlormethine is efficacious, with a durable response that may be sustained for up to 8 years in some cases.

The pivotal registration 201 study evaluated chlormethine gel versus chlormethine ointment for the treatment of patients with persistent or recurrent stage I or II disease who received no concomitant corticosteroids. Response rates for chlormethine gel were
Table 2  Summary of the real-world experience from four centers

| Characteristic                  | Penn Dermatology Cutaneous T-Cell Lymphoma Clinic, USA | Cutaneous Oncology Clinic, Columbia University, USA | Rabin Medical Center, Israel | Hôpital Saint-Louis, France |
|--------------------------------|--------------------------------------------------------|----------------------------------------------------|-------------------------------|-------------------------------|
| Number of patients with MF seen/year | ~ 200                                                  | > 350                                              | 300                          | ~ 320                         |
| Disease stage of patients with MF | Mostly early stage                                     | Ranging from stage IA or IB to Sézary syndrome    | Early stage                  | Early and advanced stages     |
| Chlormethine gel usage         | Early stage: treatment after corticosteroids failure   | For patients with early stage, skin-limited disease | Second-line treatment in patients for whom at least 1 previous SDT failed (topical steroids or phototherapy) | Early stage: second-line treatment after failure of high-potency corticosteroids, mainly when phototherapy is not possible or contraindicated |
|                               | Advanced stage: adjunctive treatment to systemic therapies or other SDTs | Advanced disease: in combination with systemic therapies |                             |                              |
| Chlormethine gel initial application frequency | Alternative evenings or 2 nights/week                   | 1–2 times/week, alternating with topical steroids | Gradually, up to a maximum of QD, sometimes with 1–2 times/week topical steroids | 3 times/week alternating with topical steroids. If well tolerated and PR, increase to QD |
| Response time                  | 4–6 weeks; 4–24 months to achieve CR                   | 1–2 months; 80% of patients respond                | NA                           | Beginning of response: 1–2 months. CR: 9–12 months; in some patients, 12–15 months required to achieve CR |
| Incidence of dermatitis        | ICD/ACD: 20–25% of patients in first 6 months          | ICD: ~ 30%; 10% develop severe ICD                 | ICD is the most commonly diagnosed AE, and is usually mild | Mostly ICD (25% of cases) Real ACD rare |

ICD/ACD: ICD = irritant contact dermatitis, ACD = allergic contact dermatitis
consistently higher than those for the ointment for the primary endpoint of Composite Assessment of Index Lesion Severity (CAILS), and once-daily (QD) treatment with chlormethine gel met all prespecified criteria for noninferiority. In the efficacy-evaluable population, overall response rates (ORRs) were 77% and 59% for the gel and ointment, respectively [15]. Additionally, the 95% confidence interval of the CAILS score in the efficacy-evaluable population not only exceeded the noninferiority threshold ($C_{0.75}$), but also lies entirely above 1. On the basis of a post hoc approach of switching from noninferiority to superiority testing, these results are consistent with superiority ($p < 0.05$) findings for chlormethine gel.

The gel formulation had a faster time to response (50% response in 26 weeks) than the ointment (42 weeks). Response rates at 52 weeks were 76% for the gel and 56% for the ointment. Maximum response to chlormethine gel treatment occurred between 8 and 10 months, emphasizing the importance of continued treatment and close follow-up of patients to maximize the response potential [15]. A follow-up 7-month extension study evaluated a higher dose of chlormethine gel (0.04%) in patients who did not have a complete response (CR) after previously receiving chlormethine gel or ointment for 12 months. In total, 27% of patients had a confirmed response, which could occur as late as 16 months after initiation of the lower-dose chlormethine treatment [17], thereby reinforcing the value of continued chlormethine treatment.

In the 201 study, > 50% of patients in each group experienced a skin-related adverse event (AE). Irritant contact dermatitis (ICD) was most common, although this was managed with treatment adjustments, such as suspension or reduction of chlormethine treatment and the use of emollients/oral antihistamines. No treatment-related serious AEs were reported, and there was no evidence of systemic absorption of chlormethine [15, 17].

The prospective, observational, noninterventional US-based PROVe trial was designed to provide information on the use of chlormethine gel in a real-world practice setting (NCT02296164). Patients who were diagnosed

### Table 2 continued

| Characteristic                  | Penn Dermatology Cutaneous T-Cell Lymphoma Clinic, USA | Cutaneous Oncology Clinic, Columbia University, USA | Rabin Medical Center, Israel | Hôpital Saint-Louis, France |
|--------------------------------|--------------------------------------------------------|-----------------------------------------------------|-----------------------------|-----------------------------|
| Management strategy for dermatitis | Temporary suspension of treatment                      | ICD: application of mid-to-high-potency ophthalmic steroid (chlormethine gel discontinuation if severe ICD) | Mild ICD: avoid treatment discontinuation if possible; temporary addition of topical corticosteroids | Moderate-to-severe dermatitis: chlormethine gel discontinuation plus topical steroids; chlormethine gel reintroduced after reactions have disappeared; and frequency of application has progressively increased |
| Potent topical steroids BID for 2–3 weeks | Potent topical steroids BID for 2–3 weeks | ACD: discontinue chlormethine gel | | |

*ACD* allergic contact dermatitis; *AE* adverse event; *BID* twice daily; *CR* complete response; *ICD* irritant contact dermatitis; *MF* mycosis fungoides; *NA* data not available; *PR* partial response; *QD* once daily; *SDT* skin-directed therapy

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with any stage of MF and were being treated with chlormethine gel in combination with other MF therapies were enrolled. At 12 months, the proportion of stage IA and IB responders (defined as \( \geq 50\% \) reduction from baseline in body surface area [BSA] involvement) was 44\% in patients who received chlormethine plus topical corticosteroids plus other treatment and 45\% in patients who received chlormethine plus other treatment. A peak response occurred at 18 months for patients with stage IA and IB disease in the chlormethine plus other treatment group (67\%). Overall, 28\% of patients experienced a treatment-related AE; the most common skin-related AEs deemed to be therapy related were dermatitis (12\%), pruritus (7\%), skin irritation (7\%), and erythema (4\%) [45].

Other studies using compounded formulations of chlormethine (ointment or solution) have reported response rates of 58–69\% in patients with early-stage disease [26, 30, 36–38] and 13–53\% in patients with advanced disease [26, 30, 37]. Moreover, one trial has reported a 10-year overall survival rate of 71\% in patients with mainly T1 or T2 disease (96\%). For those patients who attained a CR with topical chlormethine, a 5-year relapse-free survival rate of 42\% was observed [37]. Another study found that the probability of achieving clinically apparent remission rates at 2 years was 76\% for stage I MF, 45\% for stage II, and 49\% for stage III disease [35].

### REAL-WORLD EXPERIENCE OF CHLORMETHINE GEL IN THE MANAGEMENT OF PATIENTS WITH MF (TABLE 2)

**Penn Dermatology Cutaneous T-Cell Lymphoma Clinic**

At the Penn Dermatology Cutaneous T-Cell Lymphoma Clinic (USA), \( \sim \) 200 patients with newly diagnosed MF are seen annually; of these, 70\% have early-stage disease. This center uses chlormethine gel as a first-line SDT in patients with early-stage disease for whom topical corticosteroids have failed. It is applied as a localized spot treatment or, for patients with more-extensive BSA involvement, as full-body treatment (from the neck down). In advanced-stage disease, chlormethine gel is used as an adjunctive SDT to systemic therapy and other SDTs. For at-home administration, patients must take appropriate precautions to avoid inadvertent mucosal exposure to chlormethine gel in other household members/pets.

Patients are instructed to apply chlormethine gel thinly, initially only every other night or 2 nights/week, then slowly increase the application frequency as tolerance permits, to minimize irritant dermatitis. Patients may apply topical steroids every other day to the same area, but this treatment is eventually tapered if no AEs result from chlormethine gel treatment. Patients using full-body treatment are advised that they may notice new lesions during the first month; however, these are subclinical MF lesions unmasked by chlormethine gel, not necessarily a sign of true disease progression.

In our experience, a response to chlormethine gel treatment can be expected within 4–6 weeks. It takes 4–24 months to achieve a CR; the ORR is 70\%, with 10\% of these achieving a CR and 90\% achieving a partial response (PR). ICD or allergic contact dermatitis (ACD) is observed in 20–25\% of patients and occurs mostly within the first 6 months of therapy. When dermatitis or other skin AEs occur, we temporarily discontinue chlormethine gel treatment and apply potent topical steroids to the affected area twice daily (BID) for 2–3 weeks. A “patch test,” where chlormethine gel is applied daily to a small unaffected skin area, is then performed. If dermatitis reappears, this is suggestive of ACD, and chlormethine gel is discontinued permanently. If no dermatitis appears, the prior reactions are most likely ICD, and chlormethine gel may be reintroduced slowly with applications every other night or 2 nights/week. This practice of “starting low and going slow” with application frequency is analogous to how we use other SDTs with known irritant effects (e.g., topical retinoids). Patients who experience a moderate-to-severe dermatitis reaction to chlormethine gel may have complete clearance of the original MF
lesion once the dermatitis is cleared with potent topical steroids, as has been observed in the literature [46].

The Cutaneous Oncology Clinic at Columbia University

At the Comprehensive Cutaneous Oncology Clinic at Columbia University (USA), a range of disease stages are seen, from early-stage IA and IB MF-CTCL to stage IV disease, including Sézary syndrome. The patients are managed according to published algorithms in a stage-based approach. For patients with early-stage skin-limited disease, topical steroids, narrow-band ultraviolet B (NBUVB), and chlormethine gel are the first-line treatments. Based on their schedule, personal preferences, or medical history, and in consultation with their physician, patients choose a therapy that best fits their lifestyle and disease state. Light therapy is an effective way to treat cutaneous manifestations of MF, but it may necessitate frequent visits to the physician’s office and may not be convenient for people with busy work and family schedules. Some of the benefits of chlormethine gel include the ability to apply the gel at home, reducing the need for office visits for light therapy in those patients unable to incorporate visits into their daily schedule. Chlormethine gel treatment can continue away from home, provided refrigeration is available, so travel need not interfere with the treatment schedule. Additionally, chlormethine gel is recommended over NBUVB for patients with high risk of melanoma or nonmelanoma skin cancers, including patients with significant personal history of these diseases as well as light skin, numerous atypical nevi, or immunosuppression [47]. Given that a link between chlormethine gel use and development of nonmelanoma skin cancers has been suggested, concurrent NBUVB and chlormethine gel treatment is not typically advised in our patient population [48].

While chlormethine gel is FDA approved for treating stage IA and IB MF in patients who received one prior treatment, we also use chlormethine gel therapy in combination with systemic therapies in more advanced disease, including Sézary syndrome.

At Columbia University, over 350 patients per year are treated with chlormethine gel, all with relatively low toxicity. The main AE is irritant dermatitis, seen in ~30% of treated patients. ACD may be observed, and chlormethine gel should be discontinued in these cases. However, ICD is generally well controlled with mid- to high-potency topical steroid use, and chlormethine gel treatment can be continued in most patients. Approximately 10% of patients develop severe ICD, with lymphomatoid papulosis observed in a few patients; this resolves upon discontinuation of chlormethine gel [49].

Patients generally start chlormethine gel with less frequent applications (one or two times/week, alternating with topical steroids). If the patient can tolerate the gel without ICD or other concerns, the frequency is increased to daily use. In some patients, the gel may be used BID depending on symptoms. In our experience, response rates of up to 80% have been seen in patients with early-stage disease. Initial response is typically observed 1–2 months after starting treatment, and therapy is continued for 12 months in responders. Frequency can subsequently be reduced during the “maintenance phase,” which may last from several months to several years, or chlormethine gel can be discontinued when cutaneous lesions disappear completely. A significant proportion of patients use skin-directed (mostly topical steroids) or systemic agents in combination with chlormethine gel.

The Cutaneous Lymphoma Clinic at Rabin Medical Center

In Israel, in daily practice the first-line treatment for early-stage MF (after topical steroids) is usually phototherapy, while chlormethine gel is used as a second-line treatment in patients for whom phototherapy has failed or who have developed intolerability. Chlormethine gel as a first-line therapy (after topical steroids) is reserved for patients with early-stage MF who have contraindications to phototherapy (e.g., history of melanoma or multiple nonmelanoma
skin cancers) or those who foresee adherence problems to phototherapy. Regional or whole-body application depends on the distribution of lesions and extent of cutaneous involvement. Since chloromethine gel has the potential to cause irritation, treatment initiation involves gradually increasing the application frequency up to the maximal tolerable frequency, but no more than QD, to minimize the occurrence and degree of irritation. The process is similar to that adopted with other topical treatments with irritant potential (e.g., retinoids) [50]. The skin folds and face are generally more susceptible to irritant reactions; hence, the maximal recommended application frequency is usually alternate days.

ICD is the most common AE and is usually mild. In the case of mild irritation, patients may benefit from temporary addition of topical steroids without a change in chloromethine gel application frequency, although in some patients, emollients are sufficient to alleviate symptoms. If irritation is moderate to severe, topical steroid application is advocated along-side temporary reduction (moderate irritation) or temporary discontinuation (severe irritation) of chloromethine gel application. Once irritation is under control or resolved, the application frequency is gradually increased or

Fig. 1 Patient case images. a Epidermotropism and atypical lymphocytes, diagnostic of mycosis fungoides. b Skin lesions on the patient’s legs before and after 3 and 6 months of once-daily chloromethine gel application.
chlormethine gel is reintroduced at the highest tolerable frequency. In many patients, topical steroids may be withdrawn or minimized to once-weekly application. In the case of severe irritation, reintroduction of chlormethine gel may be attempted but is initially limited to a small area to assess tolerability.

The main differential diagnosis of ICD is ACD. Patch tests are not done routinely, and the diagnosis is based solely on clinical judgment. Key diagnostic features are: (1) timing of appearance, with delayed-type hypersensitivity occurring at least 2–4 weeks following treatment initiation versus primary irritation, which may develop as early as a few days after application; (2) distribution, where extension of dermatitis beyond treated areas indicates delayed-type hypersensitivity versus primary irritation, which is localized to treated areas only. ACD is suspected in few patients. If the allergic reaction is mild to moderate, the protocol is the same as for severe irritation. For patients with severe ACD, permanent discontinuation is required. It is important that any type of dermatitis is distinguished clearly from the unmasking effect of chlormethine gel, where new lesions are observed in the treated areas; this is seen in a small fraction of patients and usually occurs during the first month of treatment. Patients should be encouraged to continue with treatment, and whole-body application should be considered.

Hôpital Saint-Louis

Hôpital Saint-Louis (France) sees ~ 320 patients per year with cutaneous lymphomas of any MF stage; ~ 80% have early-stage and 20% have advanced-stage disease. In patients with early-stage IA MF, chlormethine gel is prescribed after failure of high-potency corticosteroids, whereas for patients with stage IB, chlormethine gel may be prescribed as a first-line therapy, particularly in patients for whom phototherapy is not possible or contraindicated. In patients with late-stage disease, chlormethine gel is used in combination with systemic treatments when insufficient effect is observed on patch or plaque lesions. Response to chlormethine gel may occur 9 months after treatment initiation, but in some patients a period of 12 or 15 months may be required to achieve remission. In our experience, 19% of patients achieve a CR, and 66% have a PR.

The most common AE is skin reactions, mostly contact irritation versus real allergic dermatitis. When severe skin reactions are observed (e.g., moderately severe to severe dermatitis), chlormethine gel is discontinued and topical steroids are prescribed. Once the reactions have disappeared, chlormethine gel may be applied to a limited zone with persisting lesions on the trunk or the limb, with a reduced schedule (one or two times/week). If the patient presents with real sensitization, contact allergy will develop on the limited area, thereby indicating the patient has a true allergy, and chlormethine gel is contraindicated. In most patients, however, this limited application is well tolerated, and it is possible to apply chlormethine gel to the whole skin, up to three times/week, and often every day. Real patch testing to determine whether the response is ICD or ACD may be very informative in such situations.

A 58-year-old male with a history of melanoma on his back presented with stage IB MF. The patient had disseminated pruriginous erythematous plaques and plaques, although there were no adenopathies or blood involvement. A cutaneous biopsy demonstrated a band-like infiltrate with epidermotropism and atypical lymphocytes, and the patient was diagnosed with stage IB MF. Treatment with topical clobetasol yielded no response, while treatment with phototherapy was not possible due to the history of melanoma. Consequently, this patient was treated with chlormethine gel QD. Due to the dissemination of lesions, chlormethine gel was applied to the whole body, except for the face and scalp, where no lesions were present. After 9 months of chlormethine gel treatment, the patient was in full remission and treatment was stopped (Fig. 1).
CONCLUSIONS

Chlormethine gel is a therapeutic option for patients with MF skin lesions, and a range of retrospective, prospective, and observational clinical data supports its use in all disease stages. Its validity as a treatment is supported by international guidelines, which all recommend chlormethine gel as a first-line treatment for patients with early-stage MF. In later stages of MF, systemic treatments are usually indicated and prescribed, although patch and plaque lesions in these patients may be only partially responsive to systemic treatments; the addition of topical treatments, such as chlormethine gel, may be very useful in such cases. Moreover, chlormethine gel may be important as an adjunctive therapy in patients with late-stage disease (especially for persisting patches and plaques) to palliate symptoms and to improve the overall response and as a maintenance treatment since systemic therapies do not typically result in durable CRs.

Indeed, experience from clinical practice in the USA, Israel, and France has shown that chlormethine gel is used both as an SDT (often in the first line) in early-stage MF and as an adjunctive therapy in advanced-stage disease. The strategies employed by the centers demonstrate that emergent cutaneous reactions can be managed if the appropriate protocols are followed. Time to response varies slightly between centers, perhaps reflecting the diversity of patients who were seen (Table 2). ICD is the most frequently observed form of dermatitis, and all centers use topical steroids to manage this AE, although discontinuing chlormethine treatment may be required for severe reactions.

Efforts are ongoing to gain a more in-depth understanding of the utility of chlormethine gel in patients with MF and the nature of the emergent skin reactions. The PROVe trial found that chlormethine gel is an effective treatment across all disease stages [45]. No chlormethine gel-related serious AEs occurred in the study, and the reported emergent skin-related AEs were manageable and less prevalent than in the pivotal clinical trial [15], possibly because of frequent dose adjustments and the co-administration of corticosteroids, which reflect the real-world experience reported herein.

The Mechlorethamine Induced Contact Dermatitis Avoidance Study (MIDAS; NCT03380026), which evaluated the incidence and severity of contact dermatitis following treatment with chlormethine gel alone or in combination with triamcinolone ointment in patients with MF, aimed to gain a greater understanding of chlormethine-related contact dermatitis. The study found that contact dermatitis with and without hypersensitivity responses was seen, and histopathology revealed a superficial and deep lymphocytic infiltrate with spongiosis and eosinophils similar to arthropod assault [43, 44]. Evaluation of the patient samples is ongoing to provide more information about the nature of the skin reactions, which should further help to guide management of patients who develop contact dermatitis. Additional information that may be used to guide treatment and manage contact dermatitis in patients who receive chlormethine gel may come from the REACH trial (Study to Determine the Aetiology of Chlormethine Gel-Induced-skin Drug Reaction in Early-stage Mycosis Fungoides Cutaneous T Cell Lymphoma; NCT04218825), which is currently recruiting.

In conclusion, chlormethine gel is an effective treatment for patients with all stages of MF. While contact dermatitis is an emergent skin-related AE, it can be managed effectively in most cases if the appropriate strategies are in place.

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