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Chlormethine gel effectiveness as second-line treatment in mycosis fungoides: a single-centre retrospective study

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Abstract

Background Chlormethine gel is a promising treatment for early-stage mycosis fungoides (MF) with strong efficacy and manageable side effects. This study evaluates its effectiveness as a second-line treatment in patients unresponsive to prior skin-directed therapies (SDTs) or combined systemic treatments, hypothesising significant therapeutic benefits with manageable adverse reactions.

Methods A retrospective observational study was conducted from April 2021 to December 2022, including adult patients with histologically confirmed MF who had not responded to at least one prior SDT. Patients received daily chlormethine gel applications, and responses were evaluated at 3, 6, and 12 months using the Modified Severity-Weighted Assessment Tool (mSWAT). Statistical analyses were performed using SPSS ver 26 (IBM), including one-way ANOVA and univariate regression.

Results The study included 21 patients (12 males, 9 females; mean age 61 years). 81% had early-stage MF, and 19% had advanced-stage disease. Chlormethine gel showed a 90% response rate, with 33.3% achieving complete response (CR) and 57.1% partial response (PR). Adverse reactions were primarily contact or irritative dermatitis, which were manageable and did not significantly affect outcomes. Median mSWAT scores significantly reduced from baseline at 3, 6, and 12 months ($P = 0.002$).

Conclusions Chlormethine gel appeared to be efficacious and safe as a second-line treatment for MF, including in advanced stages. Despite limitations like small sample size and retrospective design, these findings highlight its potential in combination therapies and the importance of continued treatment for optimal outcomes. Future research should confirm these results in larger, prospective studies.

Keywords Mustine · HN2 · Gel · Nitrogen · Mustard · Topical · Lymphoma · Lymphoid · Malignancies · Cancer

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1 Introduction

The therapeutic landscape for mycosis fungoides (MF) has evolved over the years, from traditional approaches like local treatments and phototherapy [1–3] to classical [4, 5] and emerging novel targeted drugs and immunotherapeutic agents [6, 7]. The ultimate goal of MF treatment is to achieve disease control, alleviate symptoms, prevent disease progression, and optimise the patient's quality of life [8, 9].

In recent years, chlormethine gel, a novel topical therapy, has emerged as a promising first-line treatment option for early-stage MF [10]. Chlormethine, the active ingredient, is a bifunctional alkylating agent [11] that inhibits rapidly proliferating cells by binding and crosslinking DNA strands [10, 12].

Many guidelines recommend it as a first-line skin-directed therapy for early-stage MF due to its proven efficacy and safety profile. However, in real-world clinical practice, initial treatment often prioritises topical steroids and phototherapy [13, 14]. Accessibility, safety profiles, physician familiarity, and cost considerations for the healthcare system drive this preference. Consequently, chlormethine gel is frequently used as a subsequent option when these therapies fail or are contraindicated.

This study emphasises the role of chlormethine gel as a second-line treatment, focusing specifically on patients who were unresponsive to other first-line therapies. While chlormethine has been extensively studied as a first-line option for skin-directed treatments, reflecting real-life clinical scenarios.

Studies have reported significant reductions in the severity of skin lesions, improvement in pruritus, and an overall favourable response rate [15]. Moreover, chlormethine gel has a manageable safety profile, with local skin reactions being the most commonly reported adverse events [16].

The success of chlormethine gel in early-stage MF warrants further investigation into its potential [12]. Collectively, integrating in vitro, ex vivo, and in vivo studies, we have insights endorsing the application of topical chlormethine gel as a very effective treatment for early MF lesions with disease-modifying properties [16]. The indication of selective apoptosis in malignant T-cell clones through various approaches is evidence for alterations in the cutaneous micro-environment.

Since most studies have been performed on the use of chlormethine gel as a first-line treatment in early-stage MF [15–17], we aimed to study and provide the results of chlormethine gel in a real-life context, alone or in combination with systemic therapies, used as a second-line therapy after the failure of the classical therapeutic strategies currently utilised in the management of MF since our objective was to assess its efficacy in a cohort with a potentially lower probability of response.

2 Materials and methods

This is a retrospective observational study of patients treated by our Dermatological Unit, conducted with the approval of the local ethical committee and according to the good clinical practice guidelines of the Helsinki Declaration.

The study included all the patients affected by MF and treated with chlormethine gel from April 2021 to December 2022 with a minimum of 6 months follow-up. Exclusion of patients with less than 6 months of follow-up was chosen to allow sufficient time to develop a complete response to the systemic treatment and its stability. Patients had to have discontinued phototherapy at least 1 month before initiating chlormethine treatment.

The specific inclusion criteria established to identify the population suitable for the objective of the study and, therefore, to be subjected to analysis were the following:

- Timeline of dermatological evaluation and beginning of the treatment between 1/04/2021 and 31/12/2022
- Adult patient with histological diagnosis of MF (All variants included)
- Patients receiving chlormethine gel that previously did not respond to one prior skin-directed therapy (SDT), including Psoralen and Ultraviolet A therapy (PUVA) and Narrow Band-UVB (NB-UVB), highly potent topical steroids

The exclusion criterion was:

- Systemic therapy was introduced in the last 6 months.

Systemic therapies were excluded from this study if they were initiated within 6 months before the start of chlormethine gel treatment to minimise potential confounding effects on the evaluation of efficacy and safety. However, patients receiving systemic therapies for more than 6 months before the study period were included, as these treatments were considered stable and unlikely to influence the response to chlormethine gel significantly.

During the first prescription visit, instructions on how to use chlormethine gel were given. The gel was to be applied daily only to the skin-affected area.

All the patients enrolled have been registered for mSWAT (Modified Severity-Weighted Assessment Tool) at therapy and after 3, 6, and 12 months with age, sex, ethnic group, comorbidity, concomitant therapies for MF, frequency of the gel application, adverse reactions (AEDs), clinical aspect of the MF, number of lesions treated, and response on treated lesions (considered as Complete Remission, Partial Remission, stable disease, disease progression) [13].

Response to chlormethine gel was assessed by calculating the reduction of the lesions according to the EORTC/ISCL criteria [13, 18] and evaluated as follows: complete response CR, 100% clearance of skin lesions; partial response PR, 50%–99% clearance of skin lesions from baseline; stable disease (SD), 25%–50% clearance of skin lesions; and progressive disease (PD), ≥ 25% increase in skin lesions from baseline.

One-way analysis of variance (ANOVA) was used to evaluate the difference in averages between groups for continuous variables; otherwise, the nonparametric Mann–Whitney test calculated by the exact method for small samples was used. The normal distribution was assessed using the Smirnoff test, while the Lavene test was used to evaluate the influence of variables. Univariate regression analysis determined the relationship between the AEDs and the response to therapy. All data have been analysed using SPSS version 26 (IBM).

3 Results

We retrieved 21 patients, 12 males and 9 females, with a mean age of 61 years (standard deviation 17.744): 17 patients (81%) had early stages of MF (of which 13 stage IA, 4 stage IB) and 4 (19%) advanced stage (IIB).

Of the enrolled patients, 47.6% (n = 10) had patchy lesions, 33.3% (n = 7) had patches and plaques, and 19% (n = 4) had patches, plaques and nodules.

Histopathologically, 52.4% (n = 11) of patients have classic MF, 23.8% (n = 5) have folliculotropic MF, and 23.8% (n = 5) have transformed MF. Prior therapies received included topical steroids in 38.1% (n = 8), Nb-UVB in 38.1% (n = 8), and PUVA in 23.8% (n = 5). The data are summarised in (Table 1).

Regarding concomitant therapy for MF, four patients underwent retinoid therapy (three on bexarotene and the last on acitretin), and two received Brentuximab-vedotin.

Following adverse skin reactions, 9 reduced the frequency of chlormethine gel application during therapy.

The only AEDs reported were contact or irritative dermatitis (CD or ID) as defined by national and international societies [19–21]. Of all the patients experiencing dermatitis, only 6 needed a temporary interruption of treatment; however, the disease did not progress during the suspension of chlormethine gel, and the lesions further regressed after the reapplication of the drug. All other cases of dermatitis were resolved using topical steroids.

Response to chlormethine gel therapy occurred in 90% of patients (n = 19): 33.3% (n = 7) achieved a CR (4 patients within the third month of treatment), and 57.1% achieved a PR.

Only 2 patients experienced disease progression (Fig. 1).

13 patients (61.9%) showed post-inflammatory hyperpigmentation on the lesions treated with chlormethine, indicating an excellent response to the therapy (Fig. 2).

Median mSWAT scores decreased significantly from the start of therapy, with significative reductions at months 3, 6 and 12 of chlormethine gel application (P = 0.002) (Fig. 3).

4 Discussion

Several studies have demonstrated the favourable risk/benefit profile of chlormethine gel in different cohorts of patients with MF. Specific trials highlighted how the efficacy of chlormethine gel increases steadily over time: in a post hoc analysis, response rates increased from 8.5% at month 1 to 78.9% at month 10 [17], while Wehkamp et al. [10] showed a peak response rate observed at 18 months. A study by Alberti-Violetti et al. [15] also evaluated the real-world effectiveness and tolerability of chlormethine gel and found similar response rates and manageable safety profiles. Those works

Table 1 Patient demographics and baseline characteristics

Demography	N = 21
Gender (%)	
M	12 (57.1)
F	9 (42.9)
Median age	61 yrs ds (17.7)
Stage	
IA	13 (61.9)
IB	4 (19)
IIA	0
IIB	4 (19)
Lesion type	
Patches	10 (47.6)
Plaques	7 (33.3)
Nodule	4 (19)
Previous therapies	
Topical Steroids	8 (38)
Nb-UVB	8 (38)
PUVA	5 (23.8)
Histological type	
Classical	11 (52.4)
Folliculotropic*	5 (23.8)
Transformed*	5 (23.8)
Therapy	
Monotherapy	15 (71.5)
Combined (gel + systemic)	6 (28.5)

* Sub-analysis of these subgroups in Table 2

Table 2 Table summarising the responses in patients with large cell transformation (LCT) and folliculotropic mycosis fungoides (MF), highlighting their lesion types, initial stages, treatment responses

Type of MF	Type of lesions	Response to treatment	Time to response
LCT	Plaques, nodules	Partial response (PR)	6 Months
LCT	Plaques, nodules	Complete response (CR)	3 Months
LCT	Single nodule	Complete response (CR)	6 Months
LCT	Multiple nodules	Partial response (PR)	6 Months
LCT	Plaques, nodules	No response	/
Folliculotropic Mf	Folliculo-prominent	Partial response (PR)	6 Months
Folliculotropic Mf	Thick plaques	Complete response (CR)	3 Months
Folliculotropic Mf	Papulo-pustules	Partial response (PR)	6 Months
Folliculotropic Mf	Thick plaques	No response	/
Folliculotropic Mf	Thick plaques	Complete response (CR)	3 Months

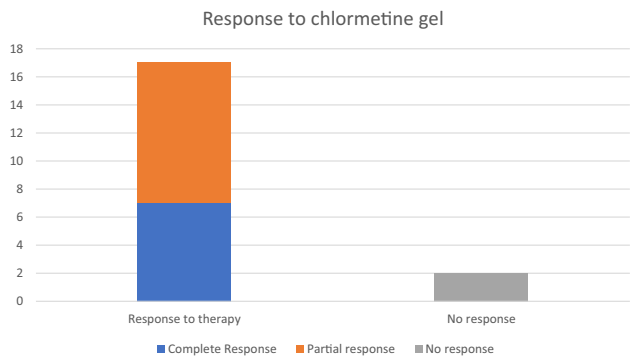

Fig. 1 Response to therapy at 6 months (21 patients)

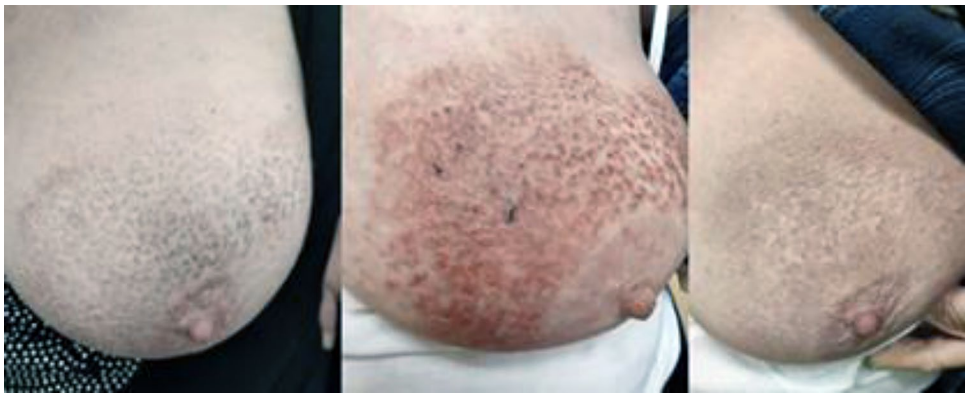

Fig. 2 Image of a patient before and after Topical therapy with a CR

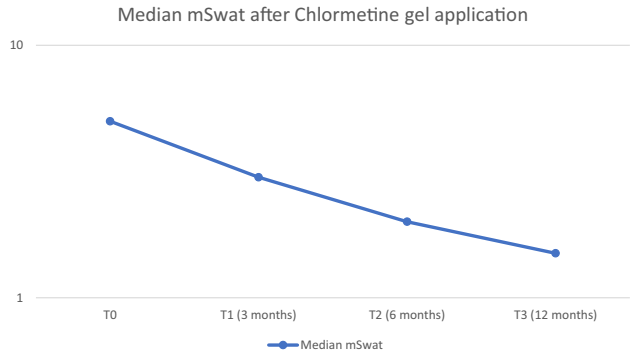

Fig. 3 Significative reduction of the median mSWAT evaluated at baseline and after 3 months, 6 months and a year of topical treatment with chlormethine gel

underscore the consistency of our results with broader clinical experience and that patients may have different response patterns: some responded early to gel treatment and maintained the response over time, while others started responding at least 6 months after the beginning.

Also, in one of the most extensive real-world data collection on chlormethine gel, the PROVe study, the rates of responses increased over time, with a peak response of 66.7% observed 18 months after patient enrolment [16]. Retrieved data underscore the importance of continuing treatment with chlormethine gel to allow patients to achieve maximum response. Finally, the PROVe study shows a significant decrease in mSWAT during treatment with chlormethine gel and the correlation with improved quality of life assessed by Skindex-29 [22].

Notably, some patients affected by stage IIB benefited significantly from chlormethine gel treatment combined with systemic therapy. This is noteworthy as advanced-stage MF typically presents with thicker plaques and nodules, which are more challenging to treat and which could have benefited from a better absorption of the gel formulation [11, 17, 23]. Compared to the studies of Querfled et al. [17] and Koumourtzis et al. [24], we found that chlormethine gel, even in advanced-stage MF, could achieve meaningful clinical responses when used as part of a combination therapy regimen. Specifically, the response rates were substantial, and the gel effect seemed to be enhanced when integrated with other systemic treatments, but more data are needed to confirm this statement.

Regarding adverse reactions, those were primarily contact or irritative dermatitis, which were manageable and did not significantly affect treatment outcomes. This is consistent with existing literature that reports common skin-related adverse effects such as irritation, pruritus, erythema, and hyperpigmentation [16, 25, 26].

The potential risk of secondary malignancies associated with alkylating agents like chlormethine in our study was not assessed due to the study design and the limited follow-up timing. It is known that the increased cancer risk related to the systemic assumption of nitrogenous agent [27, 28], but the topical formulation risk of chlormethine gel has been already widely debated and recent studies seems to be not significantly increased [23, 29, 30].

In this retrospective observational study, patients presented patch plaque and nodule lesions; Most patients (71.5%, n = 15) were treated with chlormethine gel in monotherapy, while 28.5% (n = 6) received the gel in combination with other systemic therapies. A response rate to treatment of 90% (n = 19) was obtained; in particular, 33.3% (n = 7) achieved a CR (4 patients within the third month of therapy), while 57.1% achieved a PR.

Our study data chlormethine gel is very effective in achieving response, has minimal side effects and does not interfere with other possible therapies of MF, both topical (such as corticosteroids) and systemic. It could be employed as a

compound for combination therapy with both safety and efficacy. We must also underline that the result was achieved by including patients with stage IIB disease, which underlines the effectiveness of chlormethine even in thicker lesions.

This study has some limitations, including the small sample size that reduces the statistical analyses' power and specificity and the study's retrospective design, including possible selection, recall, detection and reporting biases.

However, this research adds valuable insight into a novel and now widespread available therapy to target MF.

We can highlight how chlormethine gel treatment is a very effective and safe solution, even as a second-line therapy, after the failure of a previous SDT. The development of contact dermatitis from chlormethine gel should not discourage its use and does not influence the response to treatment.

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Data availability Data available on request from the authors.

Declarations

Ethics approval and consent to participate All subjects gave informed consent to participate in the study. Study approved by the Ethical committee under n° Clin.Isto. Tp.19, Bologna local ethical committee.

Consent for publication The patients in this manuscript have given written informed consent to the publication of their case details.

Competing interests The authors declare no competing interests.

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