Topical mechlorethamine in mycosis fungoides: A prospective clinical, histopathological, and molecular analysis of 13 cases

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Introduction

- Mechlorethamine hydrochloride (MCH) is a valid skin-directed therapy (SDT) utilized in mycosis fungoides (MF) since the 1950s.
- The United States Food and Drug Administration (FDA) has recently approved MCH 0.016% gel for stage IA/B MF patients previously exposed to SDT, while MCH 0.02% gel was subsequently licensed for topical therapy of all MF stages by the European Medicines Agency (EMA) . This alkylating agent will thus be available to greater numbers of MF patients.
- Despite decades of clinical use of topical MCH in cutaneous T-cell lymphoma (CTCL), reports on skin tissue changes over the course of treatment are still lacking.

Objective

- To prospectively analyze the histopathologic and molecular skin responses to MCH gel-based monotherapy in MF patients.
- Identify potential correlations predicting long-term clinical outcomes.

Materials & Methods

- A single-center, prospective, paired skin biopsy cohort study conducted between July 2019 and January 2020 at our Cutaneous Lymphoma Outpatient Clinic.
- Adult MF patients topically treated with MCH 0.02% gel once daily were prospectively followed beyond a 1-year period.
- Primary endpoints:
  - Histopathological changes from baseline to week 4-6 of treatment
  - Potential correlations between clinical, histopathologic, and molecular skin responses
- Secondary endpoints:
  - Clinical responses at 1-, 3-, 9- and 12-month follow-up
  - Skin PCR data at week 4-6 vs. baseline
  - Safety profile

Results (I) - Demographic and clinical features

Table 1 Mycosis fungoides patient demographics and clinical features (N=13)

Characteristic	Total N=13
Gender, *n* (%)	
Male	12 (92.3)
Female	1 (7.7)
Age at MCH initiation (yrs), mean ± SD	53.6 ± 20.2
TNM stage at MCH initiation, *n* (%)	
IA	7 (53.8)
IB	4 (30.8)
IIA	1 (7.7)
IIB	1 (7.7)
MF variants, *n* (%)	
Classical	8 (61.5)
▪ Plaque-stage	6 (46.2)
▪ Tumor-stage	1 (7.7)
Folliculotropic	4 (30.8)
Hypopigmented	1 (7.7)
Previous treatments, *n* (%)	
TCS	13 (100)
Bexarotene	1 (7.7)
Acitretin	2 (15.4)
IFN-α2b	1 (7.7)
PUVA	6 (46.2)
UVB	3 (23.1)
RT	1 (7.7)
Follow-up time (months), median (range)	14 (8-17)

Abbr.: IFN, Interferon; MCH, Mechlorethamine hydrochloride; MF, Mycosis fungoides; PUVA, Psoralen plus ultraviolet A photochemotherapy; RT, Radiotherapy; SD, Standard deviation; TCS, Topical corticosteroids; TNM, Tumor-node-metastasis; UVB, Ultraviolet B phototherapy; yrs, years

Demographic and clinical features

- Of 13 patients (12 males; mean ± SD age 53.6 ± 20.2) included, the majority (84.6%) had early-stage disease (≤IIA) at MCH initiation.
- Classical MF was the prevalent type (n=8; 61.5%) followed by folliculotropic MF (FMF; n=4), and hypopigmented MF (n=1).
- Median follow-up was 14 months (range 8-17).

Results (II) – Treatment-related outcomes

Table 2 Mycosis fungoides patient demographics, clinical data, and treatment-related outcomes (N=13)

Case no/age/sex	MF type	TNMB stage	Clinical response				Histologic and molecular skin findings								Local dermatitis	Previous treatment	Associated features
							Before MCH				After MCH						
			1 month	3 months	9 months	12 months	EDT	FT	Infiltrate density	TCRγ -PCR	EDT	FT	Infiltrate density	TCRγ -PCR			
1/60/M	FMF	T1aN0M0B0	SD	SD	SD	SD	–	+	+++	+	+++	+	++	+	severe	TCS, BXT, UVB, PUVA	Stop after 1 month due to skin toxicity
2/28/M	FMF	T1aN0M0B0	PR (60-90%)	PR (60-90%)	PR (60-90%)	PR (60-90%)	–	+	++	+	–	+	++	+	none	TCS	Hair regrowth in some lesions
3/48/M	Classic	T1bN0M0B0	PR (30-60%)	CR	CR	CR	+++	–	+++	+	–	–	+	–	severe	TCS, PUVA	
4/73/M	Classic	T2bN0M0B0	PR (30-60%)	CR	CR	CR	+++	–	+	+	+	–	+	–	none	TCS, Ac, UVB	
5/36/M	FMF	T3N0M0B0	PR (< 30%)	PR (< 30%)	PD	PD	–	+	+++	+	+	+	++	+	severe	TCS, PUVA	Loss of CD30 expression
6/56/M	Classic	T2bN0M0B0	PR (30-60%)	PR (30-60%)	PR (30-60%)	PR (30-60%)	+++	+	+++	–	++	+	+++	–	mild	TCS, RT	
7/30/F	FMF	T1bN0M0B0	PR (30-60%)	CR	CR	PD	+	+	++	–	-/+	–	+	–	generalized	TCS	Stop after 2 months due to skin toxicity
8/44/M	HMF	T2aN0M0B0	PR (60-90%)	CR	CR	CR	+	–	+	+	–	–	–	–	none	TCS, UV	Repigmentation of all skin lesions
9/73/M	Classic	T1aN0M0B0	PR (30-60%)	CR	CR	PD	+++	–	++	–	–	–	–	–	moderate	TCS, Ac, PUVA	
10/32/M	Classic	T1aN0M0B0	CR	CR	CR	CR	+++	–	++	+	–	–	+	–	severe	TCS	
11/85/M	Classic	T1aN0M0B0	PR (60-90%)	CR	CR	CR	+++	–	++	–	–	–	–	–	severe	TCS	
12/40/M	Classic	T1bN0M0B0	PR (30-60%)	PR (30-60%)	PR (60-90%)	PR (60-90%)	++	–	+++	+	+	–	+++	–	moderate	TCS, IFNa2b, PUVA	
13/78/M	Classic	T2bN0M0B0	PR (< 30%)	PR (30-60%)	PD	PR (60-90%)*	+++	–	+++	+	+	–	++	+	severe	TCS, PUVA	Pseudotumor formation; *Partial disease control after addition of MTX and RT

Abbr.: Ac, Acitretin; BXT, Bexarotene; CR, Complete response; EDT, Epidermotropism; F, Female; FMF, Folliculotropic mycosis fungoides; FT, Folliculotropism; HMF, Hypopigmented mycosis fungoides; IFN, Interferon; M, Male; MCH, Mechlorethamine hydrochloride; MF, Mycosis fungoides; MTX, Methotrexate; PD, Progressive disease; PR, Partial response; PUVA, Psoralen plus ultraviolet A photochemotherapy; RT, Radiotherapy; SD, Stable disease; TCRγ-PCR, T-cell receptor gamma polymerase chain reaction; TCS, topical corticosteroids; TNMB, Tumor-node-metastasis-blood; UVB, Ultraviolet B phototherapy.

Histopathologic, immunophenotypic, and molecular skin responses

At baseline, epidermotropism was found in 10/13 (77%) cases but was more common and pronounced in classic MF plaques. Most patients (11/13; 84.6%) displayed moderate (5/13) or dense (6/13) infiltrate patterns, while folliculotropism was present in 5/13 (38.5%) cases, mostly of FMF type (n=4). TCRγ-PCR demonstrated clonality in 9/13 lesional sites.

Following MCH monotherapy, skin biopsies showed that all cases with epidermotropic features (10/13; 77%) displayed loss (5/10; all sustained complete CR) or lower degrees (5/10) of initial epidermotropism. Only 1 of 4 FMF cases showed no signs of follicular infiltration. Dermal infiltrate density decreased in most (69.2%) patients to no/low and moderate in 6 (46.2%) and 3 (23%) cases, respectively, while it remained unchanged in 4 (30.8%) cases. Notably, loss of CD30 expression with significant regeneration of follicular structures after MCH application was detected in 1 FMF patient (Fig. 1). TCRγ-targeted PCR turned negative in 5 of 9 initially positive lesional sites (4 sustained complete CR).

Clinical responses

After 1 month of treatment, 12/13 (92.3%) patients achieved a complete (n=1) or partial (n=11) skin clearance, while nearly 77% (10/13) were responsive to MCH at 9 months. Overall response rate at 12 months was 61.5% (8/13); 1 patient maintained a prolonged stable disease and 4 developed progressive disease. Of the latter, one patient required concurrent use of methotrexate and radiotherapy for partial control of disease activity.

Safety profile

No critical safety concerns were reported. MCH-induced contact dermatitis occurred in 10/13 (77%) subjects. A 78-year-old patient developed an ill-defined, erythematous, subcutaneous tumorous lesion at sites of MCH application demonstrating a pseudolymphomatous histologic pattern of dense dermal infiltrations of small lymphocytes, histiocytes, and eosinophils, coupled with epidermal ulceration (Fig. 2). Treatment was discontinued in 2 cases due to drug-related cutaneous intolerance.

Results (III)

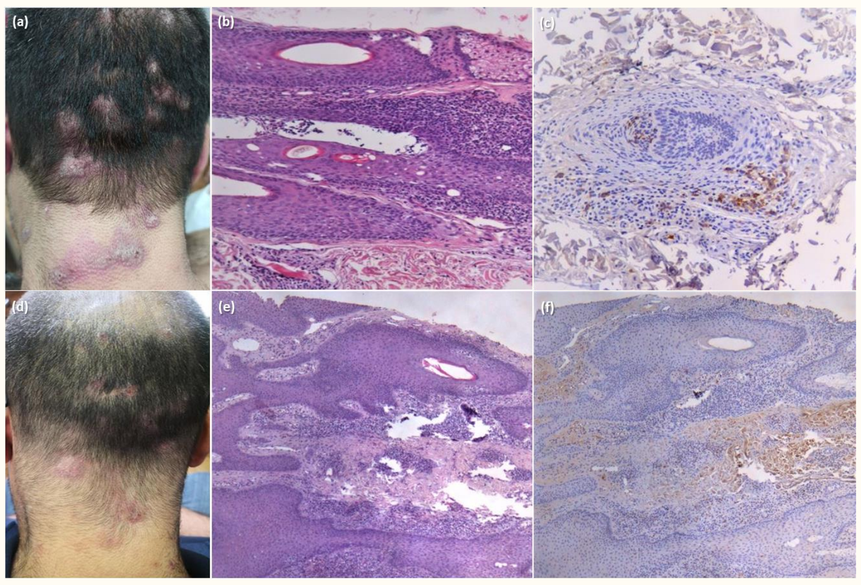

Fig. 1 Patient 5, FMF. Multiple erythematous plaques and nodules on the head and neck region pre-MCH (a) showing partial remission at the 6-month post-initiation visit (d). Pre-treatment, histopathology showed dense folliculotropic infiltrates with partial destruction of follicular appendages (b; H&E, 200x), while immunostaining revealed variable CD30 positivity among large atypical lymphocytes (c; CD30, 200x). After therapy, moderate infiltrate density was found in dermis (e; H&E, 100x) demonstrating complete loss of CD30 expression (f; CD30, 100x). FMF, Folliculotropic mycosis fungoides; H&E, Hemotoxylin and eosin; MCH, Mechlorethamine hydrochloride.

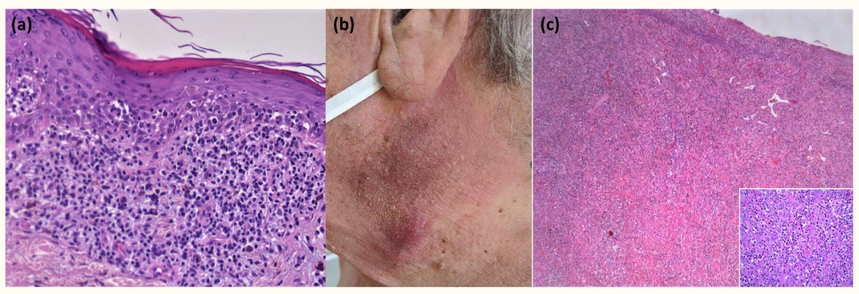

Fig. 2 Patient 13, classic MF. Pre-treatment, several, reddish scaly plaques on the back (a) showing a dense dermal infiltrate of neoplastic T lymphocytes involving the epidermis (b, H&E, 200x). An ill-defined, erythematous tumorous lesion at sites of MCH application (c) characterized by dense dermal inflammatory infiltrates of small lymphocytes, numerous eosinophils, and variable amounts of histiocytes coupled with epidermal ulceration (H&E; d: 100x, Inset: 400x). H&E, Hemotoxylin and eosin; MCH, Mechlorethamine hydrochloride; MF, Mycosis fungoides.

Conclusions

- This is the first to our knowledge study focusing on the histopathological and molecular aspects of MF patients treated with MCH 0.02% gel monotherapy.
- Our results suggest that both histological and molecular skin improvements can occur early in the course of MCH treatment and seem to be associated with sustained clinical responses.
- The potential benefits of topically applied MCH for advanced and/or folliculotropic MF forms warrant further investigation.

References

- *Denis D, Beneton N, Laribi K, Maillard H. Management of mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL): focus on chlormethine gel. Cancer Manag Res. 2019;11:2241-2251.*
- *Liner K, Brown C, McGirt LY. Clinical potential of mechlorethamine gel for the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma: a review on current efficacy and safety data. Drug Des Devel Ther. 2018;12:241-254.*
- *Talpur R, Venkatarajan S, Duvic M. Mechlorethamine gel for the topical treatment of stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma. Expert Rev Clin Pharmacol. 2014;7:591-597.*
- *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;149:25-32.*