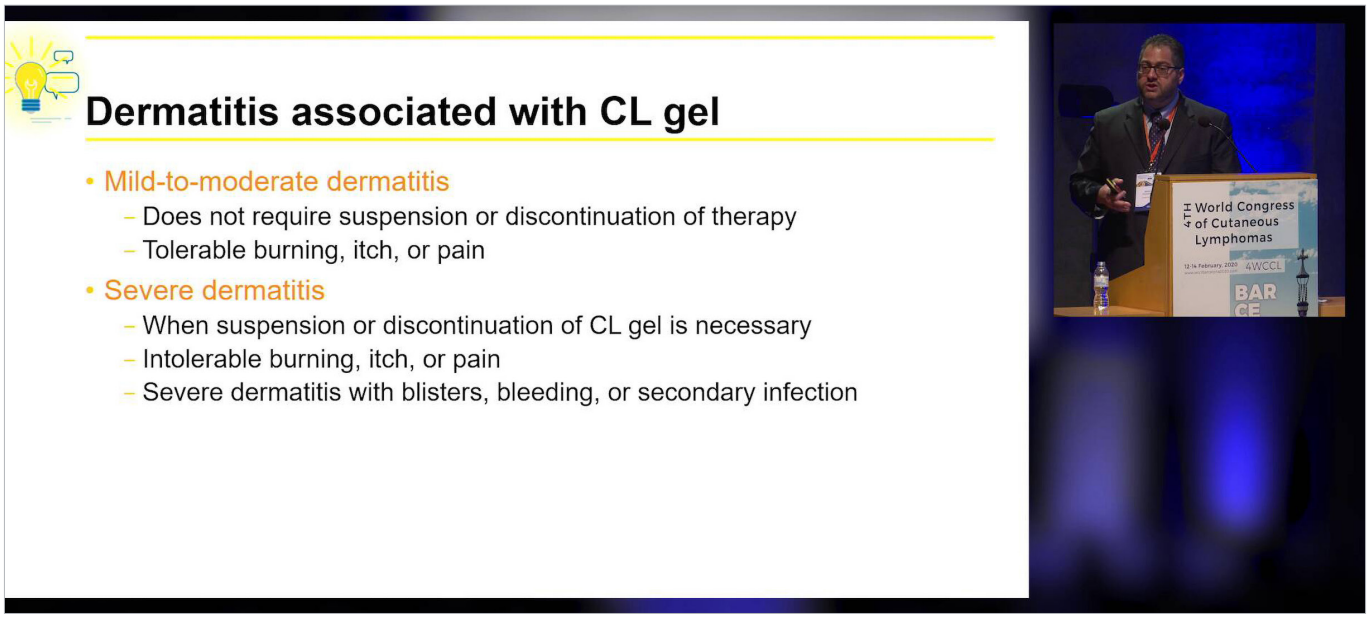
DERMATITIS MANAGEMENT AND CHLORMETHINE GEL: NEW KEY LEARNING POINTS

Report of a symposium presented by Brian Poligone, MD, PhD, of the Rochester Skin Lymphoma Medical Group, Fairport, NY, at the 4th World Congress of Cutaneous Lymphomas on February 12, 2020 in Barcelona, Spain



Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma (CTCL) and presents as early-stage disease in 70% of patients, with itchy skin patches and plaques.[1] The disease has an indolent clinical course, progressing from patches to thicker plaques and eventually to tumours over years or decades. The prognosis is generally good; however, 25% of patients with early-stage disease progress to more advanced disease stages.[2] Quality of life is an important treatment goal, as one of the most common and troublesome symptoms of early-stage MF is pruritus that rarely responds to treatment.[3]

Skin-directed therapies are commonly recommended for MF-CTCL, such as topical steroids, phototherapy and topical nitrogen mustard, also known as mechlorethamine or chlormethine (CL).[4-7] Contrary to prior aqueous and ointment formulations, which presented preparation and application challenges for patients, a novel CL gel formulation was developed.[5-7] In the pivotal registration trial CL gel met all pre-specified criteria for non-inferiority to CL ointment.[8] As a result of these findings, an aqueous formulation of 0.016% w/w topical mechlorethamine gel was approved by the US Food and Drug Administration in 2013 for patients with stage IA or IB MF-CTCL who have received prior skin-directed therapy. In 2017 in Europe, a Marketing Authorisation was granted by the European Commission for all patients with MF-CTCL (CL gel is distributed in Europe by Recordati Rare Disease). CL gel is an optimised, stable, non-greasy, quick-drying topical formulation that allows for convenient, simple, at-home administration.

The most common adverse events with the gel formulation are skin related. In a 2013 study by Lessin et al. the gel formulation was shown to cause skin irritation in 25% of users, including contact dermatitis in 14.8%.[8] This was not a new finding; a 1999 study involving patch testing of a 0.02% aqueous solution of CL found that contact dermatitis occurred in 53% of patients.[9] Since maintaining patients on therapy is essential for antitumor activity, this may represent a limitation for CL gel treatment.

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The Mechlorethamine-Induced Contact Dermatitis Avoidance Study (MIDAS; https://clinicaltrials.gov/ct2/show/NCT03380026) was a phase II clinical trial (n=28) designed to compare the use of 0.016% CL gel and the combined use of CL gel and triamcinolone.[10] Patients with MF-CTCL were treated for 4 months, followed by a 1-month wash out and a 12-month follow up. The primary endpoint was the incidence of dermatitis. The extent and severity of dermatitis was assessed using the SCORD method, a currently unvalidated derivative of the established SCORing Atopic Dermatitis Index.[11] Scoring components included body surface area of Composite Assessment of Index Lesion Severity (CAILS) lesions; intensity, assessed in terms of redness, swelling, oozing/crusting, excoriations/scratch marks, skin thickening/lichenification and dryness; and the Visual Analogue Scale itch score.

Preliminary results showed that SCORD scores peaked at 3 months, but were significantly lower in the combined treatment group compared with those receiving CL alone.[11] A total of nine patients (32%) developed severe dermatitis requiring suspension or discontinuation of CL gel. Of these, eight had allergic contact dermatitis and one had irritant contact dermatitis. The T-cell receptor was also sequenced to examine the aetiology of the dermatitis. One participant had one dominant clone, which decreased after treatment to below the level of detection. Importantly, the addition of triamcinolone to CL gel did not affect the efficacy of the gel.[11]

A number of individual case reports have suggested that some patients clearly benefit from the addition of triamcinolone to CL in order to reduce dermatitis.[10] In these cases, two definitions of dermatitis severity were used: mild-to-moderate dermatitis was defined as not requiring suspension or discontinuation of therapy, with tolerable itching, burning or pain; severe discontinuation was defined as requiring discontinuation of therapy, with intolerable itching, burning or pain, and with blisters, bleeding or secondary infection.

Case 1 was a 57-year-old man with stage IB MF, which was refractory to treatment with clobetasol, an ultra-potent topical steroid. At baseline, he had mainly patch disease that cleared with CL treatment by month 5. At month 12, all lesions were considered to be in complete remission or almost complete remission. The patient did not experience any dermatitis as a result of CL treatment and remained on once-weekly maintenance treatment with CL gel alone. This case illustrates that many patients receiving CL gel have no or limited dermatitis.

Case 2 was an 81-year-old male with stage IB MF, which was refractory to treatment with clobetasol. He had four large lesions, which were treated once daily either with CL gel alone or with CL gel plus triamcinolone. The patient underwent 4 months of treatment plus a total of 12 months follow up. However, he had to decrease the frequency of his treatment with CL gel alone after month 2 to once every 3 days, due to severe dermatitis causing burning, which developed at month 1. A partial response occurred at month 5, and at month 12 the patient had a CAILS reduction of 62% for CL gel alone and 63% for CL gel plus triamcinolone. This case demonstrates that some patients clearly benefit from the addition of triamcinolone to CL. It is also possible that the patient response could have been better if it was possible to treat the lesion once daily.[10]

Case 3 was a 58-year-old male with stage IA MF, which was refractory to treatment with clobetasol. Once-daily treatment was initiated with CL gel alone. However, the patient developed allergic contact dermatitis (ACD) at month 2. Treatment was suspended for a week and started again once daily, but the skin then started to blister. The treatment was again suspended for a week and then restarted every other day. At month 3, the patient began using CL gel alone or CL gel plus triamcinolone every third day, which proved tolerable. At month 12, the patient had experienced a complete response with CL gel plus triamcinolone, and an almost complete response with CL gel alone. This case demonstrated that month 1 (or 2 in some cases) might provide a window into patient response, which could facilitate decisions to continue with treatment, because at this stage there was no dermatitis but there was an obvious response to CL gel.

Case 4 was a 66-year-old female with stage IB MF that was refractory to treatment with clobetasol. The modified skin-weighted assessment tool (mSWAT), used to assess the extent of skin disease, was 63 at baseline. The patient was treated with once-daily CL gel alone for 2 months, at which stage she developed severe ACD and impetigo, as well as contact dermatitis to the vehicle, resulting in treatment suspension for 2 weeks. After the suspension, treatment was restarted every third day.

However, the patient still could not tolerate treatment, and decided to discontinue CL and receive prednisone instead. The combination of impetigo and ACD contributed to and confused the overall picture in this case; however, mupirocin was beneficial for the impetigo.

In summary, these cases have provided some important insights into CL-gel-induced dermatitis:

- There may be a window at month 1 and 2 before dermatitis develops that supports treatment continuation.
- Mild-to-moderate dermatitis does not require treatment suspension but may require emollients, topical steroids or decreased dosing frequency.
- Severe dermatitis due to irritant contact dermatitis/ACD requires treatment suspension or discontinuation. Restarting treatment depends on the patient, not simply the type of reaction. Patients with no immediate reactions can generally restart treatment.
- A high level of expertise in the evaluation of dermatitis is necessary to ensure adherence to CL gel treatment. Dermatologists are suited for this task.
- Impetigo is a secondary adverse event that may cause discontinuation and worsening of SCORD scoring.
- Despite dermatitis and dose adjustment, excellent responses can be achieved with CL gel treatment.

This report provides key highlights from a symposium discussing contact dermatitis management in MF-CTCL, filmed during the 4th World Congress of Cutaneous Lymphomas. To view the full touchSYMPOSIUM HIGHLIGHTS activity, which includes the presentation from Dr Brian Poligone, please visit: **https://www.touchoncologytmc.com/dermatological-cancer/learning-zone/dermatitis-management-and-chlormethine-gel-touchsymposium-highlights/**

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