Mechlorethamine gel for early stage mycosis fungoides-type CTCL

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The orphan drug mechlorethamine gel was approved by the US Food and Drug Administration for the topical treatment of stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma (CTCL) in patients who have received previous skin-directed therapy. It is the first and only approved topical formulation of mechlorethamine. Mechlorethamine, also known as nitrogen mustard, is an alkylating agent that inhibits rapidly proliferating cells. It is applied topically once a day and dries on the skin.

The approval last fall was based on an observer-blinded noninferiority trial in which 260 patients with stage IA, IB, or IIA mycosis fungoides-type CTCL who had received one or more previous skin-directed therapy were randomized to receive mechlorethamine, 0.016%, gel (equivalent to mechlorethamine HCl 0.02%; 130 patients) or mechlorethamine HCl, 0.02%, ointment (130 patients) stratified by disease stage.[1,2] Mechlorethamine was applied once daily to specific lesions or to the total skin surface, depending on T classification, for up to 12 months. Patients who had been treated with topical corticosteroids, phototherapy, bexarotene, and topical nitrogen mustard within 2 years of study initiation were excluded as were those who had received topical carmustine or radiation therapy within 1 year of study initiation. The patients were not required to be refractory to or intolerant of prior therapies. Concomitant use of topical corticosteroids was not permitted. Dosing could be suspended or reduced in frequency for dermatitis.

Patients were evaluated for response monthly for the first 6 months and then every 2 months using the Composite Assessment of Index Lesion Severity (CAILS) score. The CAILS score is obtained by adding the severity scores for erythema, scaling, plaque elevation, and surface area for up to 5 index lesions.1 Severity is graded from 0 (none) to 8 (severe) for erythema and scaling, 0-3 for plaque elevation, and 0-9 for surface area. Response was defined as 50% or greater reduction in baseline CAILS score that had to be confirmed at the next visit at least 4 weeks later. Complete response was defined as a confirmed CAILS score of 0. Noninferiority was achieved if the lower bound of the 95% confidence interval (CI) for the ratio of response rates (gel vs ointment) was 0.75 or more. Patients were also evaluated using the Severity Weighted Assessment Tool (SWAT) score, derived by measuring each involved area as a percentage of total body surface area (BSA) and multiplying it by a severity weighting factor, consisting of 1 for patch, 2 for plaque, and 3 for tumor or ulcer. Response was defined as a reduction of 50% or more in baseline SWAT score, also to be confirmed at the next visit at least 4 weeks later.

The gel and ointment groups were balanced for age (median, 57 and 58 years, respectively), sex (59% male in both), race (75% and 74% white), stage (IA in 58.5% vs 50%, IB in 40% and 48.5%, IIA in 1.5% in both). The median number of previous therapies was 2 in both arms, with the most frequently used being topical corticosteroids (86% and 87%), phototherapy (38.5% and 41%), and bexarotene (18% in both). Median BSA involvement was 8.5% (range, 1%-61%), compared with 9% (1%-76%).

The mean daily usage of gel was 2.8 g (1-2 tubes a month), and the maximum daily usage was 10.5 g (5-6 tubes a month). Overall, 63% of patients in the gel group and 67% in the ointment group completed 12 months of treatment.

CAILS response was achieved in 60% of patients in the gel group, including 14% with complete response, and in 48% of patients in the ointment group, including 11% with complete response. The gel was noninferior to the ointment based on a CAILS overall response rate ratio of 1.24 (95% CI, 0.98-1.58). SWAT response occurred in 50%, including complete response in 7%, vs 46%, including complete response in 3%. Time-to-response analyses showed superiority of gel compared with ointment ($P < .01$).1

The most common cutaneous adverse events of any grade for the gel compared with the ointment were dermatitis (56% and 58%, respectively), pruritus (20% and 16%), bacterial skin infection (11% and 9%), skin ulceration/blistering (6% and 5%), and skin hyperpigmentation (5% and 7%). The most common moderately severe or severe reactions were dermatitis in 23% and 17%, pruritus in 4% and 2%, and skin ulceration/blistering in 3% and 2%. No drug-related serious adverse events were observed. Adverse events resulted in discontinuation of treatment in 22% and 18% (67% of cases within the first 90 days of treatment), temporary treatment suspension in 34% and 20%, and reduced dosing frequency in 23% and 12%. Reductions in hemoglobin, neutrophil count, or platelet count occurred in 13% and 17% of patients. No systemic absorption of the study medication was detected.

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How I treat CTLC

Cutaneous lymphomas are rare skin cancers. Mycosis fungoides is the most common type of the cutaneous T-cell lymphomas seen and is a primarily indolent non-Hodgkin lymphoma (NHL) localized to the skin. The diagnosis of mycosis fungoides-type CTCL is difficult, because dermatologists see only 1 or 2 cases in their careers. Clinicopathologic correlation is key. A dermatologist following a series of diagnostic tests and procedures, including a physical examination and history of a rash that does not respond to common eczema treatments and a skin biopsy, usually makes the diagnosis. Routine histology is the single most important laboratory tool.

Subsequently, it's routine for our clinic to request the original skin biopsy slides and blocks for a consultative review by a dermato-pathologist or hemato-pathologist with immunotyping of the lymphocytes (high CD4–CD8 ratio) or T-cell receptor rearrangement study, which document whether a clonal population of T-cells is absent or present.

Other useful tests include an imaging test such as positron emission tomography to determine whether the cancer has spread to lymph nodes or other organs or immunophenotyping – specific for CD3, CD4, CD27, and CD7 markers – on the surface of the cells in the blood. Bone marrow biopsies are included as an option in National Comprehensive Cancer Network (NCCN) guidelines but are often not useful in staging. Current clinical management of CTCL is derived from NCCN practice guidelines and is dictated by staging.

In summary, mycosis fungoides is a primarily indolent NHL localized to the skin. Diagnosis is difficult, and in all patients with a new diagnosis, the staging and treatment plan of CTCL should be collaborative. Early-stage disease can be managed with skin-directed therapy, whereas late-stage disease has no defined stage of care. Patient management should be shared between dermatologists and cancer centers, or a specialist, for all patients with stage IB disease or higher.

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Mechlorethamine gel is marketed as Valchlor by Ceptaris Therapeutics Inc. It carries warnings and precautions for mucosal or eye injury (which may be severe, including blindness from eye injury), dermatitis, nonmelanoma skin cancer, secondary exposure (persons other than the patient should avoid skin contact), embryo-fetal toxicity, and flammability of gel (the gel is alcohol based and flammable until it has dried).

References

1. Valchlor (mechlorethamine) gel prescribing information, Ceptaris Therapeutics Inc, August 2013. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202317lbl.pdf.
2. 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.