Treatment of Early-Stage Mycosis Fungoides With Twice-Weekly Applications of Mechlorethamine and Topical Corticosteroids

A Prospective Study

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Objective: To determine if a therapeutic regimen of twice-weekly applications of mechlorethamine hydrochloride and betamethasone dipropionate cream is effective in the treatment of early-stage mycosis fungoides while increasing cutaneous tolerance.

Design: Prospective nonrandomized study conducted from November 1999 to November 2002.

Setting: Eleven university or hospital dermatology departments in France.

Patients: Sixty-four consecutive patients with newly diagnosed early-stage mycosis fungoides (stage IA, n=33; stage IB, n=26; stage IIA, n=5).

Interventions: Patients were treated with twice-weekly applications of a 0.02% aqueous solution of mechlorethamine followed by an application of betamethasone cream during a 6-month period.

Main Outcome Measures: The primary end point was the rate of complete response during the treatment. Secondary end points were mean delay to achieve complete response, rate of severe cutaneous reactions of intolerance, and rate of relapse after achieving complete response.

Results: Thirty-seven patients (58%) had a complete response after a mean±SD treatment duration of 3.6±2.5 months: 20 (61%) of 33 patients with stage IA disease, 15 (58%) of 26 patients with stage IB disease, and 2 (40%) of 5 patients with stage IIA disease. Eighteen patients (28%) developed severe cutaneous reactions of intolerance that necessitated treatment discontinuation. Relapse was observed in 17 patients (46%) after a mean±SD time of 7.7±6.5 months.

Conclusions: A regimen of twice-weekly applications of mechlorethamine and betamethasone cream is an effective treatment for early-stage mycosis fungoides. The decreased frequency of applications provides an advantage to the patient by being easy to use with limited adverse effects.

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ent study was to assess whether a regimen of twice-weekly applications of a 0.02% mechlorethamine solution and betamethasone cream could be effective in the treatment of early-stage MF while improving cutaneous tolerance of treatment.

**METHODS AND SETTING**

A multicenter prospective study was conducted between November 1999 and November 2002 in 11 university or hospital dermatology departments in France. Consecutive patients with newly diagnosed MF were eligible for entry if the following criteria were met: (1) clinical features suggestive of early-stage MF: stage IA (T1 N0), limited patch or plaque that involved less than 10% of the body surface area; stage IB (T2 N0), generalized patch or plaque that involved more than 10% of the body surface area; or stage IIA (T1/T2 N1), patch or plaque with clinically enlarged lymph nodes without histologic involvement; and (2) immunohistologic examination of a skin biopsy specimen showing an infiltrate of atypical CD3+ and CD4+ mononuclear cells in the superficial dermis and the epidermis with Pautrier microabscesses. Exclusion criteria were: (1) patients with erythroderma or tumors (T3 or T4) and (2) treatment with mechlorethamine, psoralen–UV-A, topical or systemic corticosteroids, interferon, retinoids, or carmustine in the previous 3 months.

**PROCEDURE**

A 0.02% mechlorethamine solution (10 mg per 50 mL of water) was applied with a gauze over the total skin surface except on the head, twice weekly, on 2 nonconsecutive days. During the same day, up to 15 g of betamethasone cream was applied 10 minutes after mechlorethamine administration. Patients were instructed to leave the mechlorethamine on the skin surface for 24 hours. Treatment was planned to last 6 months. Patients were followed up monthly during this period. Investigators were allowed to discontinue mechlorethamine applications in patients with a severe cutaneous reaction or in those with worsening of MF lesions during treatment. Patients who achieved complete response (CR) had their treatment stopped after the 6-month treatment period and were then followed up every 2 months during an additional period of at least 6 months.

**PRIMARY OUTCOME**

The main end point was the rate of CR during the 6-month treatment period. Complete response was defined as the disappearance of all clinical lesions of MF. Partial response was defined as the disappearance of more than 50% of initial lesions. Minor response was defined as a clinical improvement less than 50%.

**SECONDARY OUTCOMES**

Secondary end points were mean delay to achieve CR, rate of severe cutaneous reactions of intolerance, and rate of relapse after treatment withdrawal. A severe cutaneous reaction was defined as the occurrence of severe erythema, pruritus, burning sensation, or eczema that necessitated the discontinuation of mechlorethamine applications.

Because clinical and histologic interpretation of skin patch test results is difficult in patients with a cutaneous reaction of intolerance to mechlorethamine,33 skin patch tests were not routinely performed in these patients. Even in patients with clear spongiotic dermatitis, it is not clear whether mechlorethamine applications should be discontinued. In patients with a severe cutaneous reaction of intolerance, we pragmatically decided to test a lower concentration of 0.01% mechlorethamine after resolution of the initial cutaneous intolerance reaction. Results were compared with data reported in the literature concerning mechlorethamine applied daily in patients with early-stage MF. Comparison between the rates of CR among patients who had a severe reaction of intolerance and those with no reaction was performed using the chi-square test.

Sixty-four patients were included in this prospective study. Their mean age was 63 years (range, 7-82 years). The male-female ratio was 2:1 (43 males and 21 females). According to the TNM classification,19 33 patients (51%) had stage IA MF, 26 patients (41%) had stage IB MF, and 5 patients (8%) had stage IIA MF. Mean±SD body surface area involved was 44%±26% in patients with stage IB MF and 62%±25% in patients with stage IIA MF.

During the 6-month treatment period, CR was achieved in 37 patients (58%) after a mean±SD duration of 3.6±2.5 months. Complete response was achieved in 20 (61%) of 33 patients with stage IA MF, 15 (58%) of 26 with stage IB MF, and 2 (40%) of 5 with stage IIA MF after mean durations of 3.3, 3.8, and 3.0 months, respectively. Partial and minor responses were achieved in 5 patients (8%) (3 [9%] with stage IA disease, 1 [4%] with stage IB disease, and 1 [20%] with stage IIA disease) and 22 patients (34%) (10 [30%] with stage IA disease, 10 [38%] with stage IB disease, and 2 [40%] with stage IIA disease), respectively. Treatment was stopped in 10 patients (16%) because of worsening of skin lesions.

Forty-three patients (58%) did not experience any adverse cutaneous reaction during mechlorethamine treatment. Severe cutaneous reactions of intolerance were observed in 18 patients (28%) and consisted of erythema, severe pruritus, or burning sensation in 11 cases and eczematous reaction in 7 cases. Cutaneous reactions occurred after a mean±SD time of 3.4±2.7 months after starting mechlorethamine applications. Treatment was stopped in all these cases. Four of these 18 patients were able to successfully resume applications of a lower concentration of 0.01% mechlorethamine after resolution of the initial intolerance reaction. Other treatments, including psoralen–UV-A, carmustine, and topical corticosteroids, were used in the 14 remaining patients after regression of the cutaneous intolerance reaction to mechlorethamine. In addition, 3 patients had a mild reaction of intolerance that consisted of slight and transient pruritus or erythema, which did not necessitate treatment discontinuation. No local or systemic adverse effects of topical corticosteroids were observed during the study period. The rate of CR in patients who developed a severe reaction of intolerance to mechlorethamine (6 [33%] of 18) was lower than that of patients with a mild reaction (2 [67%] of 3) or no reaction of intolerance (29 [67%] of 43; P=.01). Of the 6 patients who had a CR and a severe reaction of intolerance, 5 experienced CR before the occurrence of the cutaneous reaction, and the last patient had a CR after using lower concentrations of mechlorethamine.

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Of the 37 patients who achieved CR, 20 (54%) were still in CR at the end of the study after a mean±SD follow-up time of 13.5±8.4 months from when mechlorethamine was started. Seventeen patients (46%) experienced relapse after a mean±SD time of 7.7±6.5 months after CR. In 4 patients who were still receiving treatment, relapse occurred early within the first 6 months, whereas the 13 others experienced relapse after a mean±SD delay of 6.8±5.2 months after mechlorethamine withdrawal. The mean±SD delay of remission was 3.7±2.3 months in the 43 patients without a reaction of intolerance, 6.0±3.0 months in the 3 patients with a mild reaction of intolerance, and 2.3±1.6 months in the 18 patients with a severe reaction of intolerance.

Daily applications of mechlorethamine have been considered the mainstay of MF treatment for the past 50 years. Its efficacy in the treatment of patients with early-stage MF has been clearly demonstrated. Nevertheless, this treatment is responsible for numerous cutaneous reactions of intolerance (ie, allergic and irritant dermatitis). This condition has been reported in up to 80% of patients, and frequently mechlorethamine applications of intolerance include burning sensations, pruritus, and eczematous reactions. We recently reported a 53% rate of intolerance reactions to mechlorethamine in a series of 43 patients with MF treated with daily applications of mechlorethamine. One of these reactions occurred within the first 3 months of treatment. In the present study, we observed a lower rate of cutaneous intolerance reactions, since only 18 patients (28%) experienced a severe reaction to mechlorethamine that necessitated treatment withdrawal. Several studies have reported rates of cutaneous reactions of intolerance to mechlorethamine between 41% and 62% (Table 2). Our results compare favorably with those previously reported, suggesting that a lower frequency of mechlorethamine applications might be responsible for the fewer irritant dermatitis reactions. Moreover, the routine use of topical corticosteroids may have been responsible for the decreased frequency of both irritant and allergic cutaneous reactions. It has been suggested that the use of ointment instead of an aqueous preparation of mechlorethamine could improve treatment tolerance. In a study by Kim et al, two thirds of patients treated with the aqueous solution experienced an irritant reaction compared with less than 10% of patients using the ointment preparation. Unfortunately, only the aqueous solution is currently available in France. Foulc et al recently tested short-term (1-hour) daily applications of mechlorethamine. These authors observed a 49% rate of cutaneous tolerance to mechlorethamine that necessitated treatment withdrawal.

The second important finding of the present study is the favorable tolerance of this treatment regimen. Cutaneous tolerance of daily applications of mechlorethamine is usually poor. The most frequently observed cutaneous reactions of intolerance include burning sensations, pruritus, and eczematous reactions. We recently reported a 53% rate of intolerance reactions to mechlorethamine in a series of 43 patients with MF treated with daily applications of mechlorethamine. One of these reactions occurred within the first 3 months of treatment. In the present study, we observed a lower rate of cutaneous intolerance reactions, since only 18 patients (28%) experienced a severe reaction to mechlorethamine that necessitated treatment withdrawal. Several studies have reported rates of cutaneous reactions of intolerance to mechlorethamine between 41% and 62% (Table 2). Our results compare favorably with those previously reported, suggesting that a lower frequency of mechlorethamine applications might be responsible for the fewer irritant dermatitis reactions. Moreover, the routine use of topical corticosteroids may have been responsible for the decreased frequency of both irritant and allergic cutaneous reactions. It has been suggested that the use of ointment instead of an aqueous preparation of mechlorethamine could improve treatment tolerance. In a study by Kim et al, two thirds of patients treated with the aqueous solution experienced an irritant reaction compared with less than 10% of patients using the ointment preparation. Unfortunately, only the aqueous solution is currently available in France. Foulc et al recently tested short-term (1-hour) daily applications of mechlorethamine. These authors observed a 49% rate of cutaneous tolerance to mechlorethamine that necessitated treatment withdrawal.

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intolerance reactions with no evidence of a reduction of the frequency of these reactions compared with standard regimens. Interestingly, the study by Foulc et al did not find any difference in the rate of CR between patients who received fewer than 3 applications of mechloretamine per week compared with those who received more than 5 applications weekly. These results are in accordance with the findings of the present study.

Cutaneous intolerance reactions to mechloretamine were associated with a lower rate of CR (33% vs 67%; P = .01). This was probably due to the need to definitely stop mechloretamine therapy in most of these patients or to use lower concentrations of the drug. It is likely that the lower frequency of mechloretamine applications in this treatment regimen is counterbalanced by a lower rate of treatment withdrawal.

To conclude, this study demonstrated that a therapeutic regimen of twice-weekly applications of mechloretamine and topical corticosteroids could be considered an effective treatment for patients with early-stage MF. The decreased frequency of applications provides an advantage to the patient by being easy to use with limited cutaneous adverse effects.

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