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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Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma. Its incidence is increasing in the United States and Europe.1,2 It is characterized histologically by an infiltrate of epidermotropic atypical T lymphocytes.3 It has been demonstrated that patients with early-stage MF (T1) have a long-term survival outcome that does not differ significantly from an age-, sex-, and race-matched population.3-7 Most patients with cutaneous T-cell lymphoma will not die of their disease.3,6 Median survival of patients with early-stage MF ranges from 10 to 25 years.3 The effectiveness of daily applications of mechlorethamine hydrochloride (N-methyl-2,2’-dichlorodiethylamine) has been clearly demonstrated in the treatment of early-stage MF.8-10 The rate of complete response reported in patients with T1 and T2 MF (ie, patients with patch lesions involving less or more than 10% of the body surface area) treated with daily applications of mechlorethamine ranges from 30% to 80%.7,11-13 Cutaneous intolerance to mechlorethamine (ie, irritant and/or allergic dermatitis) represents a frequent and major adverse reaction, since it occurs in 30% to 80% of patients and often leads to treatment discontinuation.7,14-17 Moreover, the need for daily applications is another disadvantage of this treatment.18 We tested the hypothesis that reducing the frequency of mechlorethamine applications and following these by an application of topical corticosteroids could decrease the frequency of cutaneous reactions of intolerance to mechlorethamine. Thus, the aim of the present study was 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.
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 erythoderma 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 intolerance 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, 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 χ² test.

**RESULTS**

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, 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.
Table 1. Rates and Delay of Complete Remission Reported in Patients With Early-Stage Mycosis Fungoides Using Daily Applications (Literature Series) or Twice-Weekly Applications (Present Study) of Topical Mechlorethamine*

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Disease Stages</th>
<th>Complete Remission, %</th>
<th>Delay of Complete Remission, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zachariae et al,1995</td>
<td>33</td>
<td>I and II</td>
<td>42</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Hoppe et al,1987</td>
<td>101</td>
<td>I (n = 68); IIA (n = 33)</td>
<td>43</td>
<td>7.9</td>
</tr>
<tr>
<td>Ramsay et al,1988</td>
<td>107</td>
<td>I (n = 63); II (n = 44)</td>
<td>61</td>
<td>10.9</td>
</tr>
<tr>
<td>Kim et al,2003</td>
<td>195</td>
<td>I (n = 177); IIA (n = 18)</td>
<td>50</td>
<td>12</td>
</tr>
<tr>
<td>Present study</td>
<td>64</td>
<td>I (n = 59); IIA (n = 5)</td>
<td>59</td>
<td>3.6</td>
</tr>
</tbody>
</table>

*Administered as mechlorethamine hydrochloride.

Table 2. Reported Frequencies of Cutaneous Intolerance Reactions to Mechlorethamine* Used for the Treatment of Patients With Mycosis Fungoides, Including Mild and Severe Reactions

<table>
<thead>
<tr>
<th>Source</th>
<th>Rates of Intolerance Reactions, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamminga et al,1982</td>
<td>62</td>
</tr>
<tr>
<td>Hoppe et al,1987</td>
<td>66</td>
</tr>
<tr>
<td>Ramsay et al,1988</td>
<td>68</td>
</tr>
<tr>
<td>Estève et al,1999</td>
<td>53</td>
</tr>
<tr>
<td>Present study</td>
<td>33</td>
</tr>
</tbody>
</table>

*Administered as mechlorethamine hydrochloride.

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 therapy 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 to occur in up to 80% of patients, and frequently mechlorethamine was discontinued. Moreover, the need for daily applications is another drawback of this treatment, since it may impair patients' quality of life and necessitate expensive nursing care. The present study was thus designed to test the hypothesis that a therapeutic regimen of twice-weekly applications of mechlorethamine and topical corticosteroids could be an effective treatment for patients with early-stage MF while decreasing the incidence of severe cutaneous intolerance reactions.

Our results demonstrated the efficacy of this regimen in the treatment of early-stage MF: the 58% rate of CR observed in the present study appeared close to those reported in other studies using daily applications of mechlorethamine (Table 1). The 61% and 58% rates of CR that we observed in patients with stage IA and stage IB MF, respectively, were close to the rates reported in different studies of the literature, which ranged from 50% to 80% and 26% to 68% in patients with stage IA and stage IB MF, respectively. These rates of CR are also similar to those reported in patients treated with psoralen–UV-A and more recently with narrow-band UV-B phototherapy. Mean time to obtain CR in our study (3.6 months) was shorter than that reported in other series of the literature (Table 2). The systematic use of topical corticosteroids may have been responsible for this short delay.

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. Of these reactions occurring 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. Foule et al recently tested short-term (1-hour) daily applications of mechlorethamine. These authors observed a 49% rate of cutaneous
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 mechlorethamine 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 mechlorethamine were associated with a lower rate of CR (33% vs 67%; P = .01). This was probably due to the need to definitely stop mechlorethamine therapy in most of these patients or to use lower concentrations of the drug. It is likely that the lower frequency of mechlorethamine 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 mechlorethamine 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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REFERENCES