Topical Nitrogen Mustard in the Management of Mycosis Fungoides

Update of the Stanford Experience

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Objective: To evaluate and update the response and survival outcomes and toxic effects in patients treated with topical nitrogen mustard (mechlorethamine hydrochloride) as primary therapy.

Design: A single-center, retrospective cohort analysis.

Setting: Academic referral center for cutaneous lymphoma.

Patients: A total of 203 patients with mycosis fungoides (clinical stages I-III) treated with topical nitrogen mustard as initial therapy.

Main Outcome Measures: Long-term actuarial survival, freedom-from-relapse, and freedom-from-progression results as calculated by the Kaplan-Meier method.

Results: The overall response rate for the 203 patients was 83%, with a complete response rate of 50%. The median time to achieve complete response was 12 months (T1, 10 months; T2, 19 months), and the median time to relapse was 12 months. The duration of complete response increased with longer maintenance therapy; however, after completion of therapy, the response duration or relapse rate was similar regardless of maintenance regimen. Patients with T1 disease had better response and survival outcomes than those with T2 disease, with overall and complete response rates in T1 of 93% and 65%, respectively, and in T2, 72% and 34%, respectively. A similar clinical response was seen for patients with stage IIA vs IB. Sixty-eight percent of 203 patients received only topical nitrogen mustard therapy throughout their follow-up course, including most of the patients who achieved an initial complete response. The clinical response to topical nitrogen mustard as salvage therapy was similar to initial response rates. The efficacy results were similar in patients treated with aqueous vs ointment preparations. Freedom-from-progression rates in T1 disease (no progression to higher T classification or worse clinical stage) at 5 and 10 years were 92% and 85%, respectively, and in T2, 83% at 5 and 10 years. Fewer than 10% of patients experienced contact hypersensitivity reactions when topical nitrogen mustard was used as an ointment preparation. Only 8 patients (4%) developed secondary cutaneous malignancy, none attributable to topical nitrogen mustard monotherapy. Pediatric patients experienced no significant toxic effects with topical nitrogen mustard therapy.

Conclusions: Topical nitrogen mustard remains an effective primary initial or salvage therapy in mycosis fungoides for patients with T1 and T2 disease. Long-term follow-up results confirm its safety.

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during the course of their disease; 82% of these patients had T1 or T2 disease. In that study, complete and partial response rates were 51% and 37%, respectively, in patients with T1 disease and 26% and 43%, respectively, in T2 disease. Topical nitrogen mustard as primary monotherapy has limited utility in patients with tumor stage (T3) or erythrodermic (T4) disease, and it should not be used alone in patients with extracutaneous disease.

In the present study we update the long-term results in patients treated with topical nitrogen mustard as an initial therapy described in our group's earlier report, and we evaluate subsequent patients who were managed at the Stanford University Cutaneous Lymphoma Clinic; Stanford, Calif, with topical nitrogen mustard. Our goals were to (1) assess the long-term clinical response and survival outcome of patients treated with topical nitrogen mustard as primary therapy and (2) report any toxic effects related to long-term or repeated use of topical nitrogen mustard therapy.

**PATIENT SELECTION AND STAGING**

A total of 688 patients with MF were evaluated and treated at the Stanford University Cutaneous Lymphoma Clinic from 1958 to 1999. For classification and staging, patients underwent a complete physical examination, complete blood cell count with examination for Sézary cells, a general chemistry panel, chest radiography, and skin biopsy. Patients with palpable lymph nodes clinically suggestive of involvement with MF underwent needle aspiration or lymph node biopsy. When indicated because of advanced skin involvement or palpable adenopathy, patients had additional staging evaluation, including bone marrow biopsy and/or imaging studies. Any suspected visceral sites of involvement were confirmed with biopsy specimen analysis whenever possible. All patients were staged according to the TNMB categories and overall staging system described at the National Cancer Institute workshop (Table 1).

From our main database, we identified 203 patients with clinical stage I to stage III disease who were treated with topical nitrogen mustard as initial primary therapy within 60 days of their initial evaluation. Excluded from this number were those patients who received other significant concurrent or preceding therapy, such as irradiation (local and total skin), phototherapy, or any systemic therapies. Also excluded were those patients whose treatments were continued for less than 1 month or not followed up at Stanford. Two patients discontinued therapy within 1 month for reasons related to poor compliance and not adverse reactions to therapy. Analysis of our 203 patients who underwent nitrogen mustard therapy included patients who used either aqueous or ointment-based preparation. For analyses involving our entire cohort of patients or patients treated with agents other than nitrogen mustard therapy, 543 patients were included with stage I to stage III disease (T1, 158; T2, 199), of which 340 were treated with non–nitrogen mustard initial primary therapy within 60 days of their initial evaluation at Stanford.

**TOPICAL NITROGEN MUSTARD TREATMENT**

Between 1968 and 1980, patients were treated with an aqueous solution of nitrogen mustard. A 10 to 20 mg/100 mL solution was prepared, and the patients promptly applied this to their entire skin surface once a day. Since 1980, most patients have been treated with an ointment-based preparation of nitrogen mustard in Aquaphor (Beiersdorf Inc, Wilton, Conn). The ointment-based preparation has less risk of hypersensitivity, lower cost, and improved emollient effect. The ointment-based nitrogen mustard was prepared by a pharmacist at an institutional concentration of 10 to 20 mg/100 mL. It was applied either to the entire skin surface if the patient’s disease was generalized or to localized sites if the disease was limited. If a hypersensitivity reaction developed, patients underwent a topical desensitization program. If the cutaneous disease was slow to respond, the concentration was increased to greater than 20 mg/100 mL at intervals of 2 to 3 months.

In general, the topical nitrogen mustard treatment was continued until complete clinical clearance was achieved. Treatment was continued for 6 months to 2 years as maintenance therapy after clinical clearance before termination. The maintenance duration was shortened to 6 months to reduce cost, minimize toxic effects, and address the manufacturer’s decreased production of nitrogen mustard in recent years.

Clinical response to treatment was determined primarily by physical examination. Skin biopsy specimens were obtained in some patients. For the purpose of these analyses, complete response (CR) was defined as complete clinical regression of all MF lesions; partial response (PR), as any response less than complete but greater than 50% clinical improvement; and no response, as less than 50% clinical response to therapy. Progression of disease was defined as worsening of disease that progressed to stage IIA or worse clinical stage. Thus, patients with T1 or T2 disease whose disease worsened to T2-A or T3-A, respectively, and patients with stage IA or IB disease that progressed to stage IIA or worse clinical stage were considered to have progressive disease.

**STATISTICAL ANALYSIS**

Actuarial survival was calculated from the date of initial visit to the Stanford University Cutaneous Lymphoma Clinic when the diagnosis was confirmed and was plotted according to the Kaplan-Meier technique. Freedom-from-relapse curves of patients with CR were plotted from the date of achieving CR. Freedom-from-progression (FFP) curves were plotted from the date of achieving CR.

<table>
<thead>
<tr>
<th>NM Characteristics</th>
<th>T1: Limited Patch/Plaque (&lt;10% BSA)</th>
<th>T2: Generalized Patch/Plaque (≥10% BSA)</th>
<th>T3: Tumor</th>
<th>T4: Erythroderma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodes clinically uninvolved, N0 M0</td>
<td>IA</td>
<td>IB</td>
<td>IB</td>
<td>IIIA</td>
</tr>
<tr>
<td>Nodes enlarged, histologically uninvolved, N1 M0</td>
<td>IIa</td>
<td>IIa</td>
<td>IIb</td>
<td>IIIB</td>
</tr>
<tr>
<td>Nodes enlarged, histologically involved, N3 M0</td>
<td>IVA</td>
<td>IVA</td>
<td>IVA</td>
<td>IVA</td>
</tr>
<tr>
<td>Visceral involvement, N0-N3 M1</td>
<td>IVB</td>
<td>IVB</td>
<td>IVB</td>
<td>IVB</td>
</tr>
</tbody>
</table>

Abbreviation: BSA, body surface area.
of initiation of therapy, also using the Kaplan-Meier method. Events in FFP curves represent times at which patients’ disease progressed to either a higher T classification or a worse clinical stage. Disease-specific survival was defined as a survival calculation where death events were specifically related to MF, such as progressive disease, fatal infections, and complications related to MF. Analysis of differences in actuarial curves was performed by using the Gehan test. All P values correspond to 2-sided significance tests, and 95% confidence intervals (CIs) were determined using standard methods.

RESULTS

DEMOGRAPHICS AND DISEASE STATUS

The clinical characteristics of 203 patients with topical nitrogen mustard as initial primary therapy are summarized in Table 2. Patient age at presentation ranged from 12 to 87 years, with a median age of 56 years. The female:male ratio was 1.1:6; 86% of our patients were white. Ninety-six percent of our 203 patients had either T1 (n = 107, 53%) or T2 (n = 88, 43%) disease; thus, most of our analyses are limited to these patients. Of the 107 patients with T1 disease, only 4 patients (4%) had stage IIA disease, and among the 88 patients with T2 disease, 14 patients (16%) had stage IIA.

Current patient status, categorized by initial T classification, is summarized in Table 3. Fifty-four (27%) of the 203 patients died; however, only 10 deaths (19% of all deaths) were attributable to MF. Fifteen deaths occurred among the 107 patients with T1 disease, and only 2 (13%) of these deaths were attributable to MF. Among 88 patients with T2 disease, 34 patients died and 7 (21%) of these deaths were related to MF. Other causes of death include second cancer and cardiopulmonary disease.

OVERALL, DISEASE-SPECIFIC, AND RELAPSE-FREE SURVIVAL OF NITROGEN MUSTARD–TREATED PATIENTS

The overall and disease-specific survival of our 203 patients treated with nitrogen mustard as initial primary therapy are shown in Figure 1. The median survival was 16.3 years, and the actuarial survival rates at 5, 10, and 20 years were 85%, 71%, and 40%, respectively. The median follow-up time was 5.5 years (range, 0.4–22.8 years). The disease-specific survival curve shows that most of the deaths were not attributable to MF. Most of the deaths related to MF occurred within 6 years of diagnosis. None of the patients at risk beyond 10 years died due to MF.

The overall response rate for the entire cohort of patients treated with topical nitrogen mustard as initial therapy was 83%, with CR observed in 50% and PR in 33% of our patients (Figure 1 and Table 4). The median time to achieve CR was 12 months (range, 1–106 months). The maintenance treatment duration varied greatly, with a range of 0 to 57 months and a median duration of 6 months. The median time to relapse of the patients with CR was 12 months (range, 1–60 months). Among the 102 patients who attained CR with initial topical nitrogen mustard therapy, 43 patients experienced relapse. All of these relapses occurred within 5 years of the CR date, and 70% occurred within 2 years. In patients with CR, relapse-free rates at 2 and 5 years were 66% and 42%, respectively. Eleven percent of 102 patients with CR were relapse free after 10 years.

IMPACT OF EXTENT OF SKIN INVOLVEMENT IN SURVIVAL OUTCOMES AND CLINICAL RESPONSE

The extent of skin involvement (T classification) had significant impact on survival and clinical response in patients treated with topical nitrogen mustard as initial primary therapy. Only patients with T1 or T2 disease are included in the analysis illustrated in Figure 2 and Figure 3 because there were too few patients to analyze with T3 or T4 disease. Patients with T1 disease (n = 107) had significantly improved overall and disease-specific survival compared with that of patients with T2 disease (n = 88) (P < .001 and P < .05, respectively) (Figure 2). The median survivals of patients with T1 and T2 disease treated with topical nitrogen mustard were 20.9 years and 14.6 years, respectively. The overall survival rates were 97% at 5 years and 69% at 15 years (95% CIs, 93%-101% and 53%-84%, respectively) for patients with T1 disease and 72% at 5 years and 48% at 15 years, (95% CIs, 62%-84% and 33%-62%, respectively) for those with T2 disease.

Table 4 lists the clinical response rate comparisons of patients with T1 disease vs those with T2 disease. The CR rates for T1 and T2 disease are 65% (n = 70) and 34% (n = 30), respectively, with significantly improved overall relapse-free outcome for patients with T1 disease (P < .001). The overall response rates (CR + PR) with topical nitrogen mustard as initial therapy were 93% and 72% in patients with T1 and T2 disease, respectively. Among the 100 patients who attained CR with initial topical nitrogen mustard therapy, relapse-free rates at 2 years were 72% for T1 and 54% for T2 (95% CIs, 60%-83% and 34%-82%).

Table 2. Clinical Characteristics of 203 Patients Who Underwent Initial Topical Nitrogen Mustard (Mechlorethamine Hydrochloride) Therapy

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. (%) of Patients</th>
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<tbody>
<tr>
<td>Median age, 56 y (range, 12-87 y)</td>
<td>203 (100)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>124 (61)</td>
</tr>
<tr>
<td>Female</td>
<td>79 (39)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>175 (86)</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>28 (14)</td>
</tr>
<tr>
<td>T Classification and Clinical Stage</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>107 (53)</td>
</tr>
<tr>
<td>IA</td>
<td>103</td>
</tr>
<tr>
<td>IIA</td>
<td>4</td>
</tr>
<tr>
<td>T2</td>
<td>88 (43)</td>
</tr>
<tr>
<td>IB</td>
<td>74</td>
</tr>
<tr>
<td>IIA</td>
<td>14</td>
</tr>
<tr>
<td>T3</td>
<td>4 (2)</td>
</tr>
<tr>
<td>IIB</td>
<td>4</td>
</tr>
<tr>
<td>T4</td>
<td>4 (2)</td>
</tr>
<tr>
<td>IIIA</td>
<td>1</td>
</tr>
<tr>
<td>IIIIB</td>
<td>3</td>
</tr>
</tbody>
</table>
There were no differences in overall (disease-specific) survival outcomes of 203 patients with mycosis fungoides treated with topical nitrogen mustard (mechlorethamine hydrochloride) as initial primary therapy. 74%, respectively) and 52% at 5 years for T1 and 19% for T2 (95% CIs, 36%-68% and −2% to 39%, respectively). None of the patients at risk beyond 5 years after attaining CR have relapsed. The follow-up times for patients with T1 and T2 disease were 0.4 to 22.1 years (median, 6.0 years) and 0.4 to 19.9 years (median, 4.5 years), respectively.

The impact of the presence of clinically significant lymphadenopathy (histologically negative for lymphoma, N1) was evaluated for patients with T2 disease. Fourteen of the 88 patients with T2 disease had stage IIA disease. There were no significant overall (P = .36), disease-specific (P = .97), or freedom-from-relapse (P = .18) survival differences between patients with stage IB (n = 74) and IIA (n = 14).

### IMPACT OF MAINTENANCE THERAPY

The effect of maintenance therapy with topical nitrogen mustard was evaluated in patients with T1 or T2 disease. Eighty-one patients with CR who completed their initial topical nitrogen mustard treatment were eligible for this analysis. These patients were divided into 3 groups of maintenance duration: 0 to less than 3 months (median, 0 months; n = 22), 3 to 9 months (median, 6 months; n = 37), and longer than 9 months (median, 20 months; n = 22). The comparative results revealed that while CR was better maintained with longer maintenance, the disease relapsed at the same rate from the end date of therapy regardless of maintenance duration (P = .92, P = .94, and P = .81, for the respective durations). There were no differences in overall or disease-specific survival outcome among the 3 groups with different maintenance durations.

### TOPOICAL NITROGEN MUSTARD–ONLY THERAPY FOR DISEASE MANAGEMENT

Among 203 patients who were treated with topical nitrogen mustard as initial therapy, 139 (68%) were treated with nitrogen mustard alone throughout their follow-up course. This group represents the true impact of topical nitrogen mustard treatment alone in disease management without influence or need of other therapies in subsequent treatment courses. The follow-up time for these patients ranged from 5 months to 22 years, with a median of 5 years. Eighty-eight (82%) of 107 patients with T1 disease, 49 (56%) of 88 patients with T2 disease, and 2 (50%) of the 4 patients with T4 disease received topical nitrogen mustard treatment as the only therapeutic modality for their disease management. The response rates for this nitrogen mustard–only group were 96% overall, 68% CR, and 27% PR. The response rates by T classification were 99% overall response and 77% CR in patients with T1 disease and 90% overall response and 53% CR in patients with T2 disease. Most relapses occurred within 2 years of documented CR; no relapses occurred after 5 years of CR. Among the 94 patients who achieved initial CR (T1, n = 68; T2 n = 26), relapse-free rates in T1 at 2 and 5 years were 74% and 54%, respectively (95% CIs, 63%-86% and 38%-70%, respectively) and in T2, 54% and 29%, respectively (95% CIs, 32%-76% and 7%-51%, respectively) (P < .05). The median time to achieve CR was 12 months (range, 1-106 months); median maintenance duration was 6 months (range 0-56 months) and median time for relapse was 12 months (range, 1-55 months).

The FFP analysis reveals that in this topical nitrogen mustard–only therapy group, only 3 of 88 patients with T1 disease and 1 of 49 with T2 experienced progression to a more advanced stage. The FFP rates were 91% and 93% at 20 years for patients with T1 and T2 disease, respectively.

### EFFICACY OF TOPICAL NITROGEN MUSTARD AS SALVAGE THERAPY

Among 203 patients who received topical nitrogen mustard as their initial primary therapy, 46 patients received topical nitrogen mustard for disease relapse after their first CR. In 42 patients where the clinical responses were as-
sessable, the overall response rate was 95% (40/42), and the CR rate was 67% (28/42). For patients with T1 disease, the overall and CR rates were 93% and 73%, respectively, and for T2, 100% and 55%, respectively.

Among 340 patients who received agents other than nitrogen mustard as their initial primary treatment, 81 patients received topical nitrogen mustard as their salvage therapy with disease relapse after initial CR. In 79 patients where the clinical response was assessable, the overall response and CR rates were 77% (61/79) and 41% (32/79), respectively.

EFFICACY OF AQUAPHOR VS AQUEOUS PREPARATION OF NITROGEN MUSTARD

We evaluated the effect of the vehicle, ointment vs aqueous, of the topical nitrogen mustard preparation. Since 1980, most patients have been treated with the ointment-based preparation. Of 195 patients with T1 or T2 disease, 158 used the ointment preparation, while 28 patients used the aqueous preparation as initial therapy. Nine patients used a polyethylene glycol preparation. The median follow-up times for the ointment and aqueous groups were 4.9 years (range, 0.4-20.1 years) and 11.8 years (range, 1.2-22.1 years), respectively. There were no significant differences in the overall survival, disease-specific survival, or freedom-from-relapse rates between the patients who used the ointment-based preparation and those who used the aqueous preparations (P = .63, P = .62, and P = .61, respectively). The overall response (CR + PR) rates for the ointment vs aqueous groups were 86% and 72%, respectively, while the CR rates were 52% and 54%, respectively.

RISK OF DISEASE PROGRESSION

The risk of disease progression to higher T classification or worse clinical stage after initial primary therapy with topical nitrogen mustard was studied using FFP analysis. The analyses were limited to patients with T1 (n = 107) or T2 (n = 88) disease because there were too few patients with T3 (n = 4) or T4 (n = 4) disease to draw any conclusions. The FFP curves of patients treated with topical nitrogen mustard as initial therapy comparing the disease progression rates of patients with T1 and T2 diseases are shown in Figure 4. Although patients with T1 disease treated with topical nitrogen mustard tended to have less risk for disease progression than patients with T2 disease, with 5-, 10-, and 20-year FFP rates of 92%, 85%, and 74% for T1 and 83%, 83%, and 75% for T2, respectively, these differences were not statistically significant (P = .07). In contrast, the FFP results of all T1 patients (n = 158) are statistically better than those of all T2 patients (n = 199), with FFP rates for T1 at 5, 10, and 20 years of 92%, 89%, and 84% (95% CIs, 87%-96%, 83%-95%, and 76%-92%) and for T2 at 82%, 75%, and 69% (95% CIs, 76%-88%, 68%-82%, and 60%-78%), respectively (P < .005). Overall, 13 (12%) of the 107 patients...
These periodic tests were performed only for the patients, as measured by normal blood cell counts and of systemic absorption of nitrogen mustard in these patients using the ointment preparation. Most patients were then desensitized by reduction in the concentration of nitrogen mustard to 0.01 to 1.00 mg/100 mL followed by gradual escalation over a period of months. Usually, the concentration of the ointment preparation did not require lowering below 1 mg/100 mL for the initial strength used for topical nitrogen mustard therapy. The most common acute adverse effect of topical nitrogen mustard treatment was irritant or allergic contact dermatitis. With our ointment preparation, irritant contact reactions were more common than true allergic reactions. A quarter of our patients experienced an irritant reaction, more commonly in the sensitive skin areas such as the face or skin folds. The irritant reactions were usually mild, and severe reactions were uncommon. Nearly all patients were able to continue therapy by decreasing the frequency of application or the concentration of nitrogen mustard preparation. In most cases the irritant reactions improved, thus allowing the patients to intensify the frequency and strength of the nitrogen mustard. Up to two thirds of our patients using the aqueous preparation developed contact hypersensitivity reactions compared with fewer than 10% of patients using the ointment preparation. Most patients were desensitized by reduction in the concentration of nitrogen mustard to 0.01 to 1.00 mg/100 mL followed by gradual escalation over a period of months. Usually, the concentration of the ointment preparation did not require lowering below 1 mg/100 mL for the initial strength used for topical desensitization.

Some patients who have brisk local contact reactions to topical nitrogen mustard may have earlier complete clearance. A small subset of patients (<5%) did not wish to continue with an ointment-based preparation because of its greasiness. Most of these patients were then switched to the aqueous preparation but still continued nitrogen mustard therapy. Others opted for a non-nitrogen mustard topical therapy.

There were 6 patients younger than 18 years in our topical nitrogen mustard cohort. There was no evidence of systemic absorption of nitrogen mustard in these patients, as measured by normal blood cell counts and serum chemistries done every 2 to 3 months during therapy. These periodic tests were performed only for the diagnosis of T1 disease and 15 (17%) of the 88 patients with T2 disease who were treated initially with topical nitrogen mustard experienced disease progression. None of the patients with T1 disease and 2 patients with T2 disease experienced progression to extracutaneous disease.

ADVERSE EFFECTS OF TOPICAL NITROGEN MUSTARD THERAPY

At Stanford, we have participated in the management of more than 700 patients with MF in the past 40 years. For patients with T1 and T2 disease without evidence of extracutaneous involvement, topical therapies such as nitrogen mustard, phototherapy, and electron beam therapy (EBT) have been primary therapeutic choices. Recently, bexarotene gel has become available and has been used in patients who do not respond to or tolerate topical nitrogen mustard therapy. Before 1980, topical nitrogen mustard was prepared in water, which had to be applied immediately to the skin owing to its instability as an aqueous preparation. The aqueous preparation was also associated with frequent hypersensitivity reactions. In the early 1980s, the ointment preparation of topical nitrogen mustard was introduced, which offered several advantages, including a decreased risk of sensitization, decreased cost, ease of application, and an emollient effect. In the present study, we have updated our experience with topical nitrogen mustard therapy, focusing on our patients who received nitrogen mustard as initial primary therapy.

The overall response rate for our 203 patients who received topical nitrogen mustard as initial therapy was 83%, with a CR rate of 50%. As expected, patients with more limited skin involvement had a higher response rate to topical nitrogen mustard treatment, with overall response and CR rates in T1 disease of 93% and 65%, respectively, and in T2, 72% and 34%, respectively. Among the patients with T1 disease who attained CR, relapse-free rates were 52% at 5 years and unchanged at 10 years, indicating that a significant portion of patients with T1 disease who are disease free at 5 years can achieve long-term remission with topical nitrogen mustard treatment. Long-term relapse-free status is lower in patients with T2 disease who achieve CR: 19% at 5 and 10 years. Patients with T2 disease who had reactive or dermatopathic lymphadenopathy (stage IIA) responded as well to topical nitrogen mustard treatment as did those without significant lymphadenopathy; however, the number
of patients with stage IIA was small in our analysis (n = 14 IIA vs n = 74 IB).

The reported benefits and optimal duration of maintenance therapy with topical nitrogen mustard have varied in published studies.2,4-6,12 Our updated results show that patients who used a maintenance regimen had a longer-lasting response during maintenance therapy, but when their maintenance therapy was discontinued, their disease relapsed at the same rate as in patients who did not have significant maintenance therapy, regardless of the duration of their maintenance regimen. Thus, although maintenance therapy can result in longer response duration while maintenance therapy continues, it does not result in greater potential for long-term remission off therapy.

Patients who are treated with topical nitrogen mustard in the second course for disease relapse are just as likely to respond well as in their first course, as evidenced by similar response rates. We can reassure patients that the effectiveness of topical nitrogen mustard treatment is retained at subsequent courses of therapy. Also, patients with disease relapse after initial treatment with agents other than nitrogen mustard respond well to topical nitrogen mustard therapy. Thus, topical nitrogen mustard can be considered for patients who previously received more aggressive initial therapies, such as TSEBT or psoralen UV-A (PUVA) treatment, and who subsequently experienced a relapse with T1 or T2 disease. These updated results confirm previous reports that topical nitrogen mustard is an effective salvage therapy for patients with T1 or T2 disease, regardless of type of initial therapy.2,3,6

Sixty-eight percent of our patients received topical nitrogen mustard as the only therapy for their disease management. These were generally patients with patch-type or thin-plaque diseases, which are known to respond well to topical nitrogen mustard. Thus, in this group the disease progression rate was very low, with FFP rates greater than 90% in T1 or T2 patients at 20 years vs approximately 75% in all patients who received nitrogen mustard as initial therapy. Most (82%) of our patients with T1 disease received nitrogen mustard only as therapy throughout their disease course, whereas nearly half (44%) of our patients with T2 disease required other therapies for management of their disease. Included in this nitrogen mustard–only therapy group were most of the patients who achieved initial CR, which indicates that patients who achieve CR with initial topical nitrogen mustard therapy tend to remain with nitrogen mustard as monotherapy for disease management.

Most of our patients received the ointment preparation of nitrogen mustard since the 1980s. Comparison of efficacy and survival results associated with ointment vs aqueous preparations did not reveal any statistically significant differences. The ointment preparation is more cost-effective and results in much lower incidence of hypersensitivity reactions. A 400-g supply of 10 mg/100 mL nitrogen mustard ointment preparation usually costs $100 to $150 and can last 1 to 2 months when applied to more than 10% of the body surface area per day. It also has an emollient effect, although some patients prefer a non–ointment-based application on their skin.

Comparison of treatment outcome results can be difficult among institutions’ published reports because of differences in patient selection, diagnostic criteria for MF, and treatment regimens and style. There are no well-controlled multicenter prospective studies comparing efficacy of therapies. In addition to previous reports from our group, 2 large single-center experiences with topical nitrogen mustard therapy have been reported in 3 publications: one in Vonderheid et al4 and the other in Ramsay et al.5,12 The CR rate was 51% in our patients with limited or generalized patch and/or plaque disease (T1 and/or T2) compared with 75% observed by Vonderheid et al4 and 63% reported in the articles by Ramsay et al.5,12 Proper comparisons cannot be made because many patients in the study by Vonderheid et al received other treatments concurrently with topical nitrogen mustard, and both groups of researchers analyzed patients with stage IIA separately in their analyses of patients with T1 and T2 diseases. Also, the present study focuses on patients treated with topical nitrogen mustard as initial therapy.

Other differences among the studies include differences in staging methods, nitrogen mustard preparation, maintenance treatment duration after CR, and median follow-up duration. Most patients in the present study used the ointment-based preparation, whereas most patients treated by Vonderheid et al4 and Ramsay et al5,12 groups used the aqueous preparation. Despite differences in study methods among these studies, the 5-year overall survival rates are similar in patients with limited or generalized patch and/or plaque disease. Findings of the present study further confirm the reports that topical nitrogen mustard is an effective therapy for MF in patients with T1 or T2 disease.

Comparisons of efficacy and survival results of topical nitrogen mustard treatment with those of published reports of other topical therapies such as topical steroids,13 carmustine,14 hexarotene,11 UV-B,13 UV-A,16-19 and radiation therapy2,3,32 are again difficult. Among skin-directed treatments, TSEBT offers the highest response rates, with CR rates of 80% to 100% in T1 and T2 diseases.2,3,20 PUVA therapy can result in CR rates of 50% to 90% in patients with T1 and T2 diseases.10-19 A major problem in comparing therapies is variation in selection criteria for different therapies. Patients with generalized infiltrative or thick-plaque disease are more likely to receive PUVA therapy or TSEBT than patients with patch-type or thin-plaque skin involvement. Other difficulties in comparison include differences in treatment technique or regimen. Thus, it can be misleading to directly compare treatment response and survival data among different therapies or published reports, and thus detailed comparisons are avoided in the present report.

Despite differences in management approach and treatment selection, the experience of researchers at Stanford20 has been that the risk of disease progression to life-threatening advanced stage is minimized by keeping the extent of skin involvement to a minimum, regardless of type of therapy. All patients in the present study who developed extracutaneous disease had skin involvement of T2 or greater at the time they were diagnosed with stage
IV disease. Thus, analysis using FFP evaluation is valuable to assess the efficacy of MF-directed therapies, especially in patients with T1 and T2 MF disease, which follows the natural history of other indolent lymphomas with frequent relapses but favorable median survivals. The overall FFP results in patients with T1 and T2 disease treated initially with nitrogen mustard were favorable, with less than 25% risk of disease progression at 20 years. In the patient group treated with nitrogen mustard only for disease management (68%, or 203 patients), which includes most of the patients with initial CR to nitrogen mustard, the FFP results were more favorable, with less than 10% risk of disease progression at 20 years.

The FFP results of our patients with T1 disease treated with nitrogen mustard tended to be more favorable than those of patients with T2 disease, but the differences were not statistically significant (P = .07). Despite these FFP results, the overall and disease-specific survival rates of patients with T1 disease were significantly better than in patients with T2 disease. Most patients with T1 disease who experienced disease progression advanced to T2 disease, whereas patients with T2 disease progressed to T3-T4 or a higher N/M classification; thus, worse survival was found in patients with T2 disease. In contrast to the similar FFP results in patients with T1 and T2 disease treated with topical nitrogen mustard, the FFP results comparing all patients with T1 disease with all patients with T2 disease show significantly worse disease progression in our patients with T2 disease (P < .005). This is largely due to greater disease progression in our patients with T2 disease treated with agents other than nitrogen mustard (mostly TSEBT or PUVA treatment). The patients who received initial therapies with agents other than nitrogen mustard tended to have worse disease with thicker plaques than most patients who received topical nitrogen mustard as initial therapy.

The mechanism of action of topical nitrogen mustard remains uncertain. Administered systemically, nitrogen mustard acts as an alkylating agent with an antimitotic effect. However, its topical activity is not simply related to its alkylating-agent properties and may be mediated by immune mechanisms (eg, immune stimulation) or by an interaction of some type with the epidermal cell–Langerhans cell–T-cell axis. Certainly, we have observed rapid disease clearance in some of our patients who had brisk hypersensitivity reactions to topical nitrogen mustard. However, despite higher frequency of hypersensitivity reactions with the aqueous preparation, the clinical response results are not superior to the ointment-based preparation.

Topical nitrogen mustard can be used safely in patients with MF of all ages. Though the median age of the patients in this study was 56 years, included were 6 patients younger than 18 years. There was no evidence from blood counts serum chemistries of systemic absorption of nitrogen mustard in these younger patients. This is in contrast to possible bone marrow suppression observed with topical Carmustine therapy or possible depression of the serum cortisol level associated with generous use of potent topical steroids. There is also no risk of skin atrophy, which is a risk in patients with long-term or potent topical steroid use. The frequency of hypersensitivity reactions was significantly lower with ointment preparation than with the aqueous vehicle. Irritant reactions were more common (observed in approximately a quarter of our patients), but this reaction improved with continued use of nitrogen mustard.

Incidence of nonmelanoma skin cancers in patients who use topical nitrogen mustard as monotherapy is extremely low and occurred in only 2 (1%) of 139 patients who used nitrogen mustard monotherapy in the present study. Secondary skin cancers were observed more commonly in patients who received subsequent skin-damaging therapies such as PUVA or TSEBT prior to their secondary skin cancer detection and occurred in 6 (9%) of 64 such patients. In the 2 patients who developed skin cancers with nitrogen mustard monotherapy, their skin cancers may not be a direct effect of therapy because the cancers arose at sites of actinic damage (face) unrelated to the sites of nitrogen mustard application, and the patients had risk factors for skin cancers independent of topical nitrogen mustard use. One of the 203 patients had melanoma. This patient was elderly, with Fitzpatrick skin type I and a long history of actinic damage and prior nonmelanoma skin cancer. Vonderheid et al reported a 9.4% incidence of squamous cell carcinoma and 8.6% basal cell carcinoma in patients treated with topical nitrogen mustard. However, it is difficult to make direct comparisons with the present study because Vonderheid et al included patients who received concurrent skin-damaging or immunosuppressive therapies and did not analyze the nitrogen mustard monotherapy group separately for risk of secondary cancer development.

Our long-term follow-up findings confirm that topical nitrogen mustard is an effective and safe therapy in MF for patients with limited or generalized patch and/or plaque disease (T1–T2). Most patients who achieve initial CR with topical nitrogen mustard tend to require nitrogen mustard only for disease management. Topical nitrogen mustard should be considered as primary therapy for patients with T1/T2 disease and can be used effectively as salvage therapy for disease relapse following initial CR to treatment with topical nitrogen mustard or agents other than nitrogen mustard. Patients for whom topical nitrogen mustard monotherapy has failed can be treated with bexarotene gel, phototherapy, or EBT either alone or with nitrogen mustard therapy. In patients with generalized thick plaques or tumor disease, topical nitrogen mustard as monotherapy has a more limited role.

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