Topical Nitrogen Mustard in Early Mycosis fungoides

*A 12-Year Experience**

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A 12-year experience in thirty-three patients suffering from early mycosis fungoides in plaque stage confirms the effectiveness of topical nitrogen mustard therapy. Fourteen patients were in complete remission at the latest time of observation and 7 in partial remission. The probability of freedom from relapse was approximately 50% after 6 and 12 years. Three deaths attributable to mycosis fungoides were recorded. Three patients had to discontinue treatment due to contact dermatitis to nitrogen mustard. Specific precautions were undertaken in order to protect personnel handling the drug. No damaging or toxic effects were observed among staff personnel and no hematological side-effects were observed among the patients. The treatment as a whole was well tolerated. (Received July 3, 1984.)

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Topical nitrogen mustard has been used in mycosis fungoides (MF) since 1959 (1). A number of studies describe initial complete remission rates of approximately 85% (2, 3, 4, 5), and also long-term results (6) indicate the effectiveness of the therapy. We reported our initial results in 1975 (7). We now present our 12-year experience with this therapy in 33 patients with early mycosis fungoides in the plaque stage.

MATERIAL AND METHODS

During the period 1972 to 1984 33 patients, 13 women and 20 men, between 33 and 86 years of age, average 67 years old, with histologically verified MF in plaque stage, stage II according to the Scandinavian Mycosis Fungoides Group (8), were treated. The duration of their illness varied from 6 months to eleven years prior to the introduction of the present treatment. Prior therapy had been topical steroids and grenz-rays.

Initially all patients were treated with 10 to 40 mg nitrogen mustard (Erasol®), within the last 6 years with 20 mg nitrogen mustard (Mustine®) disolved in 40 ml water as whole-body topical treatment daily for 2 weeks. Non-involved skin of face, scalp, and intertriginous sites were not treated.

Maintenance treatment was given once every second week or once to twice a month. Almost all patients entering the study until 1982 also received transfer factor (9) as injections. In 1982, however, a double-blind study revealed no differences between patients receiving active and patients receiving inactive transfer factor (9). Since then no new patients have had transfer factor.

All patients have been treated by our staff. The nurses administering the treatment have been wearing protective clothing, a mask, and heavy rubber gloves and boots. In 1982 new safety standards described elsewhere (10) were introduced, and the treatment was moved to a special section of the department, which is not used for other purposes. The safety precautions were intensified, although we did never observe damaging or toxic effects to our personnel.

All patients were examined regularly. In case of relapse, a new two weeks daily schedule was given, again followed by maintenance therapy. If the disease progressed to tumour stage, the tumours

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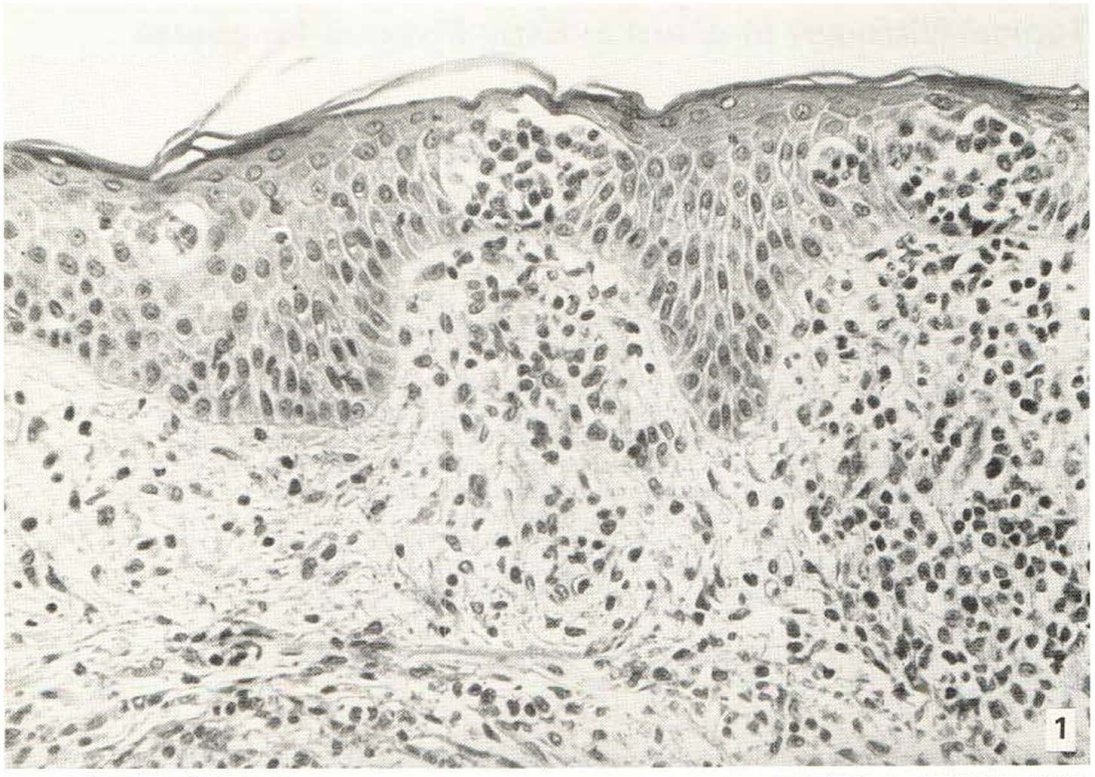
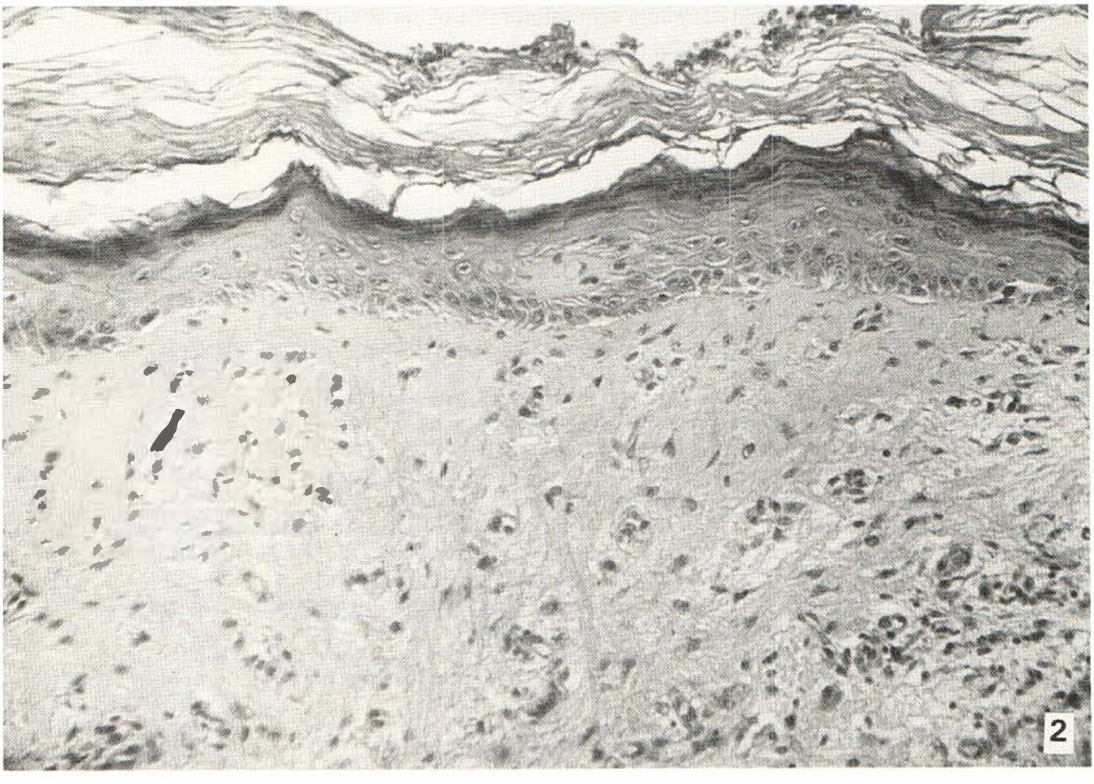




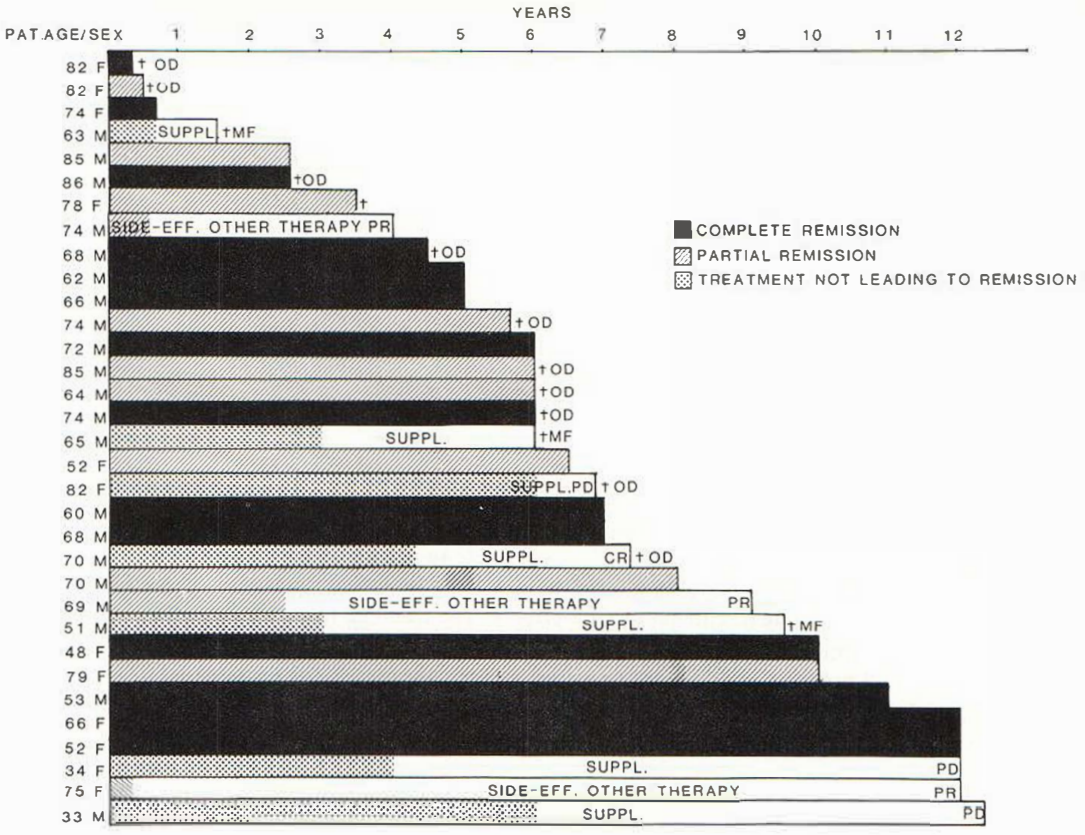


Fig. 3. Status and length of therapy of 33 patients with mycosis fungoides (MF) treated with topical nitrogen mustard. Long-term complete remissions were obtained in 12 patients, while 2 patients were in complete remission after short-term observation. Eleven patients died during the observation period from other diseases not related to MF. Four of these patients were in complete remission and 6 in partial remission at the time of death. Three patients died from MF. Three patients had to change therapy due to cutaneous side-effects. Six received supplementary therapy due to failure to control a relapse with topical HN_2.

were hydrated with the same HN_2 solution in moistened gauze for 10 to 12 min (6). If the disease progressed to involve lymph nodes or internal organs, systemic chemotherapy was added (11).

In cases of contact dermatitis or contact urticaria to HN_2 the concentration was lowered to 5 mg/40 ml water. If intolerable dermatitis also followed treatment with this weaker solution, the patients were changed to PUVA-therapy (8). Patients in complete remission for more than a year, discontinued treatment but continued to be examined regularly at least once a year.

Our department participated in a study within the Scandinavian Mycosis Fungoides Study Group on tolerance induction during the period July 1974 to May 1976. As tolerance induction was not found to be of any value (3), this attempt was given up, and no further patients received tolerance induction.

Laboratory investigations included erythrocyte sedimentation rate, hemoglobin, erythrocyte count, leukocyte and differential counts, thrombocyte count, serum transaminases (SD-GPT and S-GOT), serum alkaline phosphatases, serum bilirubin, serum creatinine and serum uric acid. These tests were repeated at intervals during and after therapy. Histopathology was performed before (Fig. 1) and in a number of cases after therapy (Fig. 2).

Fig. 1. Biopsy from a mycosis fungoides plaque before treatment with nitrogen mustard. Note Pautrier's abscess and the heavy subepidermal pleomorphic infiltrate of irregular lymphocytes and histiocytes (×100).

Fig. 2. Biopsy from mycosis fungoides patient following treatment with topical nitrogen mustard. Note the absence of Pautrier's abscesses and thinning of the dermal infiltrate. Note also the atrophic epidermis and the light edema in upper dermis (×40).

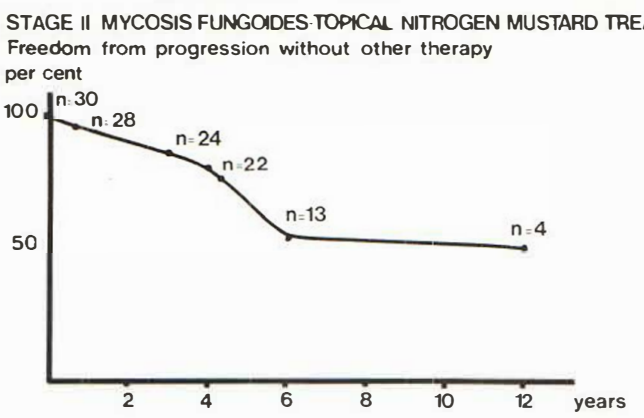


Fig. 4. Probability of freedom from relapse in relation to time after start of therapy.

RESULTS

"Long-term" complete remissions were obtained in 12 patients observed from 2 ½ to 12 years, average 7.3 years. Further 2 patients were in complete remission after "short term" observation (Fig. 3). Seven patients on long-term therapy were in partial remission. Three patients had to stop therapy due to cutaneous side-effects. The freedom from relapse in the 30 remaining patients appears from Fig. 4.

Seven patients in all progressed and had to receive supplementary treatment, in general systemic chemotherapy (11). Three of these patients died from MF, two from other diseases. Two patients receiving supplementary therapy are still alive after 12 years, but have progressed to stage IV with lymph node histology diagnostic of cutaneous T-cell lymphoma. The overall survival can be seen in Fig. 5. Eleven patients in all died from causes considered unrelated to MF.

Almost all patients had some erythema following whole-body applications of HN_2. The erythematous areas often developed tenderness. Intense erythema was occasionally followed by patchy teleangiectasia (Fig. 6). Severe contact dermatitis leading to discontinuation of therapy only occurred in the three above mentioned cases. Two patients observed contact urticaria (Fig. 7). Some hyperpigmentation was found in almost all patients and particularly in darkhzired individuals.

Two patients developed cutaneous carcinomas during the observation period. In one of the patients, the basal cell carcinoma was on the eyelid, which was never treated with

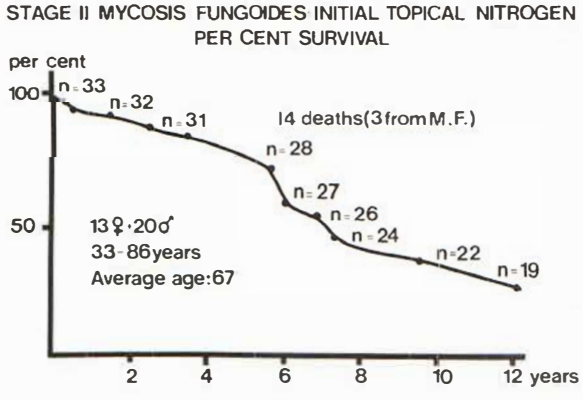
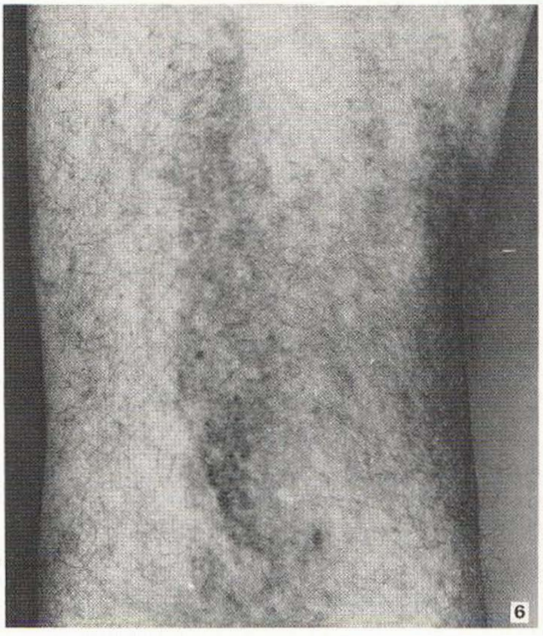


Fig. 5. Survival rate in relation to time after start of therapy. The survival rate is seen in relation to all causes of death. Eleven patients died from disease considered non-related to MF or therapy, 3 died from MF.



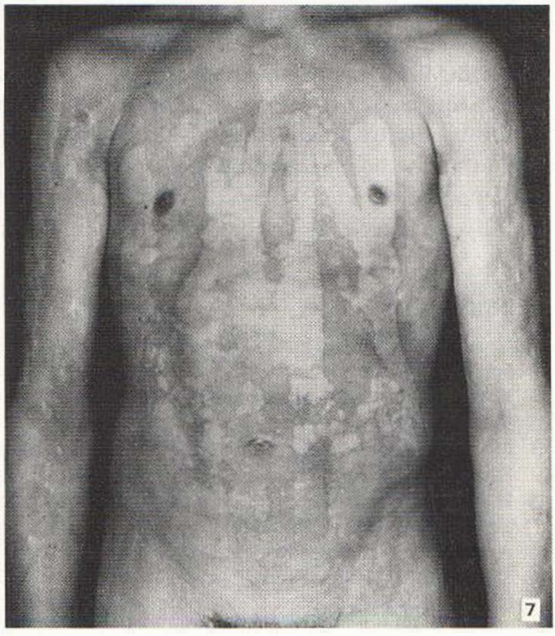


Fig. 6. Patchy teleangiectasias in a patient treated for 12 years with topical nitrogen mustard.
Fig. 7. Contact urticaria induced by topical nitrogen mustard treatment.

nitrogen mustard. Three patients died from internal cancer. No hematological side-effects were observed.

The histo-pathological response to topical HN_2 showed a complete disappearance of Pautrier's microabscesses and a thinning of the dermal infiltrate. Occasional atypical lymphoid cells could still be seen primarily and an edema was often present in the upper dermis (Fig. 2).

DISCUSSION

Topical treatment with nitrogen mustard in our hands (7) as well as in the hands of others (2, 3, 4, 5) results in high initial complete remission rates in MF. The present study based upon our 12-year experience confirms that topical nitrogen mustard should also be considered as an effective long-term treatment for MF of plaque stage. Four of 8 patients observed for 10 years or more are at present in complete remission without any other therapy given. One is in partial remission. Another patient is in partial remission after change of therapy due to side-effects, and only two are in progressive disease (stage IV MF).

The favourable results with only local application suggest that especially in elderly patients, systemic treatment should not be introduced too early in spite of findings indicating the generalized nature of MF (12, 13). Another approach may, however, be followed in younger patients. Our data are in accordance with those obtained with local electron beam (14) or superficial radiotherapy (15).

Surprisingly few cases of contact sensitivity to nitrogen mustard were recorded in our material as compared to the literature (2, 4, 16). This is in accordance with the initial report by the Scandinavian Mycosis Fungoides Study Group (3).

The use of cytostatic drugs carries potential risks also for the persons administering the drug. Some clinics avoid the problem of exposing their staff to nitrogen mustard by instructing the patients in home treatment. We believe that the age group to which most of the patients belong is an argument against this solution. Many of our patients will not be able to handle treatment themselves. We also believe that the administering of nitrogen mustard in the home condition is a greater hazard to family members than to the staff of our department under the circumstances in which the treatment takes place (10). During our 12-year experience no toxic effects were observed to personnel treating the patients.

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