

MYCOSIS FUNGOIDES PLAQUE STAGE TREATED WITH TOPICAL NITROGEN MUSTARD WITH AND WITHOUT ATTEMPTS AT TOLERANCE INDUCTION: REPORT FROM THE SCANDINAVIAN MYCOSIS FUNGOIDES STUDY GROUP

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Abstract. The Scandinavian Mycosis Fungoides Study Group has treated 21 patients with mycosis fungoides in plaque stages with topical, whole-body application of nitrogen mustard, 20 mg in 40 ml water per square metre. Ten patients were treated after previous attempts at intravenous tolerance induction *ad modum* van Scott & Kalmanson and eleven without. Complete remission was initially achieved in 10 patients and partial remission in 9 patients. Contact dermatitis to nitrogen mustard developed in 2/10 after tolerance induction and in 1/11 without tolerance induction. It is concluded that topical, whole-body application of nitrogen mustard gives high remission rates. In this series, however, many relapses occurred, due to inadequacy of the maintenance treatment. Tolerance induction has not been found of any value.

Key words: Mycosis fungoides; Plaque stage; Nitrogen mustard; Tolerance induction; Drug resistance

Since the first reports appeared on the effect of topical whole-body nitrogen mustard application in mycosis fungoides (3, 10), this treatment has been used in many medical centres, with high remission rates—especially in the pretumour stage (5). The main limiting factor of this treatment modality has been the frequent development of contact dermatitis as a reaction to nitrogen mustard, a complication often requiring cessation of treatment. However, van Scott & Kalmanson (9) claimed a decrease in sensitization rate when intravenous toler-

ance induction was given prior to the topical application of nitrogen mustard.

In this report from the Scandinavian Mycosis Fungoides Study Group the results of whole-body application of nitrogen mustard on 21 patients with mycosis fungoides in the plaque stage are presented. Ten cases were treated after tolerance induction according to van Scott & Kalmanson (9) and 11 without tolerance induction. All patients were treated intensively in an induction phase followed by maintenance. The immediate therapeutic effect was assessed as good. The remissions achieved were long lived in most cases during maintenance. In many cases, however, the maintenance treatment was not intensive enough, resulting in relapses. Contact dermatitis to nitrogen mustard was registered in only 3 cases, 2 after and one without previous tolerance induction.

MATERIAL AND TREATMENT

During the period July 1974 to May 1976 a group of 21 patients in Denmark and Sweden, between 42 and 88 years of age, with mycosis fungoides in the infiltrative plaque stage were treated. We used a clinical staging modified from that described by van Scott & Kalmanson (9). Stage II was thus defined as infiltrated plaques of less than 3 mm palpatory thickness. Neither cutaneous tumours nor ulcerations should be present, nor pathological lymph nodes (2).

Patients' data are presented in Table I.

Table 1. Clinical pattern, histopathology as reported by the hospital pathologists and treatment in 21 patients with plaque stage mycosis fungoides

Case no.	Age	Sex	Clinical form	Histopathology of mycosis fung.	Duration of illness	Duration of plaque stage
<i>Nitrogen mustard after tolerance induction</i>						
7	48	F	Classical	Obvious	6 yrs	5 m
9	70	M	Classical	Obvious	4 yrs	10 m
17	52	F	General. plaques	Obvious	2 yrs	19 m
26	85	M	Poikiloderma	Obvious	15 m	15 m
29	74	M	Poikiloderma	Obvious	7 yrs	5 yrs
31	76	M	General. plaques	Compatible	6 yrs	6 yrs
34	74	M	General. plaques	Obvious	8 yrs	8 yrs
36	65	F	Classic	Compatible	2 yrs	2 yrs
38	88	M	Classic	Obvious	3 yrs	2 yrs
40	55	M	Classic	Obvious	Not known	12 m
<i>Nitrogen mustard without tolerance induction</i>						
2	58	M	Classic	Compatible	12 m	12 m
8	82	F	Classic	Obvious	4 yrs	4 m
14	67	M	Classic	Compatible	8 m	7 m
18	60	M	Classic	Compatible	17 m	17 m
25	42	F	Follicular	Obvious	12 m	10 m
28	72	M	Erythroderma	Obvious	12 m	10 m
30	80	F	Classic	Obvious	5 yrs	5 yrs
32	69	M	Erythroderma	Compatible	18 m	18 m
35	51	F	Classic	Obvious	3 m	3 m
37	68	M	Poikiloderma	Compatible	14 yrs	6 yrs
39	73	M	Poikiloderma	Obvious	12 m	9 m

Duration of mycosis fungoides was, in 6 out of 21 cases, 12 months or less before the beginning of the treatment. In 6 cases the disease had lasted 5 years or more; 14 years at the most.

Clinical pictures. Clinically speaking, five types of mycosis fungoides could be distinguished:

1. The "classical" Alibert-Bazin type with well defined infiltrated plaques was represented by 11 patients. Two patients showed a circumscribed form with plaques restricted to a limited skin area. In the other patients larger, solitary plaques were spread out over the body. Plaques had been present for 2–5 years in 4 patients, for 7–12 months in 4 and for 3–5 months in the remaining patients. Itching and erythema had begun some years before the appearance of the skin infiltrates in 4 cases and within one year in the remaining cases.

2. Three patients showed a more disseminated form with multiple minor plaques. The disease had started 2, 6 and 8 years previously and had soon entered the plaque stage.

3. A follicular type of mycosis fungoides occurred in one patient with a disease history of 12 months.

4. Poikiloderma atrophicum vasculare (Jacobi) preceded the infiltrates of mycosis fungoides in 4 cases. The actual infiltrative stage had been present for one to fourteen years.

5. The erythrodermic form appeared in 2 cases, with onset 12 and 18 months earlier.

Histopathology

In biopsies considered as diagnostic for mycosis fungoides, Darier-Pautrier abscesses have to be present in the

epidermis. In these abscesses as well as in the dermal cellular infiltrates, atypical histiocyte-like cells and atypical lymphocytes should be present. Plasma cells and eosinophils may appear in varying numbers in the infiltrates. No Sternberg-Reed cells should be found.

Investigations

All the patients were examined clinically and histopathologically by means of multiple skin biopsies. Lymphnode biopsies were done on palpable lymph nodes. Chest roentgenography was done in all cases.

Laboratory investigations included erythrocyte sedimentation rate (ESR), haemoglobin concentration (Hb), erythrocyte count, leukocyte count, differential leukocyte count, thrombocyte count, serum-aspartat-amino-transferase (s-ASAT, s-GOT), serum-alanin-amino-transferase (s-ALAT, s-GPT), serum alkaline phosphatase, prothrombin, serum bilirubin, serum creatinine and serum uric acid, and which were performed in all patients before treatment.

These tests were repeated at intervals and after treatment.

Treatment

Ten patients were treated with whole-body application of nitrogen mustard after previous tolerance induction and 11 patients were treated without tolerance induction. The patients were selected at random for either of these two groups. No other treatment was given except for topical hydrocortisone cream 1%.

Tolerance induction was given according to van Scott & Kalmanson (9) for a period of 4 weeks. 200 µg of nitrogen

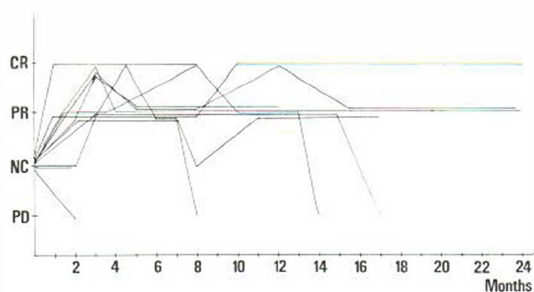


Fig. 1. Results of topical whole-body nitrogen mustard application after previous tolerance induction in 10 patients with mycosis fungoides, plaque stage. CR: complete remission; complete disappearance of all skin lesions, slight erythema accepted. PR: partial remission; significant regression of skin lesions (more than 50%). NC: no change. PD: progressive disease, compared with the status at the onset of treatment.

mustard (Mustine®, Boots) dissolved in 100 ml isotonic saline was given as an intravenous infusion on day -21, -14, -7, 0 and 7.

Induction phase of treatment. 20 mg of nitrogen mustard (Mustine®, Boots) was dissolved in 40 ml of water per square metre of body surface. The solution was freshly prepared in a plastic cup on the day of use, and applied to the whole skin surface using a cotton wool pad. The treatment was performed daily from day 1 to day 15. An exception was made for the face and intertriginous sites, which were treated every 3rd day. The induction treatment was always given on an in-patient basis.

Maintenance. One month after day 15 the maintenance treatment with nitrogen mustard was started and given once a month in the same dosage as mentioned above. The maintenance was either given at the out-patient department or in the patient's home.

Follow-up

All patients were examined regularly over at least 12 months, in some cases for up to 24 months, or until relapse, when intensified nitrogen mustard treatment was given. However, some patients in relapse were referred to a phase 2 study in which transfer factor was combined with the topical nitrogen mustard (12). If the disease progressed to tumour stage, systemic chemotherapy was given according to other treatment modalities in the Scandinavian Mycosis Fungoides Study Group (2).

RESULTS

The results of the treatment are compiled in Figs. 1 and 2 for treatment with nitrogen mustard after (10 patients) and without previous tolerance induction (11 patients).

After previous tolerance induction, complete remission was achieved initially in 5 patients, and

partial remission in another 5. Those patients who achieved complete remission, however, showed a quick relapse in spite of maintenance. In 2 of these cases, a new intensified treatment led once more to complete remission. Altogether, only 2 patients progressed to the tumour stage.

Without previous tolerance induction, 4 patients achieved complete remission initially and an additional patient during the continued treatment, whereas 4 patients went into partial remission. In 5 patients who had obtained complete remission, the disease reappeared during maintenance. For 2 of them a new, intensified treatment once more achieved complete remission. For one patient the treatment had to be stopped after the induction phase, without remission, and the patient died some weeks later of a disease unrelated to mycosis fungoides. In another patient the disease remained totally unaffected by the treatment and progressed rapidly to the tumour stage. Progress to the tumour stage occurred later in another 3 patients. There appears to be no difference in the effect of the therapy between the two groups treated with and without previous tolerance induction. However, the two groups were not completely identical, as they differed somewhat with regard to clinical appearance and duration of the disease (Table I).

We were unable to demonstrate any relationship between effect of treatment and the following factors: sex, age at time of treatment, interval between onset of clinical signs and start of treatment, number and size of infiltrates, clinical form of the disease, histopathological findings.

Decreasing sensitivity to nitrogen mustard was observed in one patient. Initially the disease was controlled by application once a month. However, after one year, application every second week and

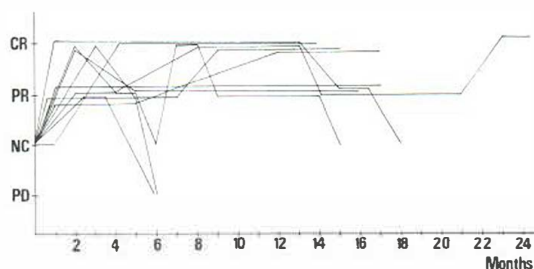


Fig. 2. Results of topical whole-body nitrogen mustard application in 11 patients with mycosis fungoides, plaque stage.

later every week could not maintain complete control over the skin condition.

SIDE EFFECTS

Three cases of severe contact sensitization to nitrogen mustard have been recorded, two among those involving tolerance induction before treatment and one without. A slight irritation dermatitis was common especially early in the induction phase of the treatment, and particularly in the intertriginous skin regions. This declined gradually without reduction of the dose.

A patchy hyperpigmentation often appears. No haematological side effects were to be observed. The treatment as a whole was well tolerated by most patients.

No case of contact sensitization to nitrogen mustard occurred among the staff treating the patients. All personnel coming into contact with nitrogen mustard wore plastic gloves and protective clothing.

DISCUSSION

Topical treatment with nitrogen mustard resulted in remission, complete or partial, in 19 out of 21 patients with mycosis fungoides in the plaque stage.

Our induction phase was short but aggressive, consisting of 15 days' application of 20 mg of nitrogen mustard in 40 ml water per square metre body surface. This technique was successfully used by us in a pilot study but differs from that used by others who apply nitrogen mustard in small daily doses for prolonged periods of time (5, 9). Our maintenance treatment was rather mild, however, being given only once a month. We are certain that this is the reason for the high relapse rate. Consequently we have subsequently increased the frequency of the application during maintenance.

Surprisingly, very few cases of contact sensitization to nitrogen mustard have been recorded in this material, as compared with those mentioned in the literature (5, 9). Nor was any influence of tolerance induction seen, i.e. as many patients developed contact sensitization after tolerance induction as without. In our material, the tolerance induction as described by van Scott & Kalmanson (9) has failed to prevent contact sensitization, which seems to agree with other reports (1, 4, 11). However, we did not carry out patch testing with nitrogen mustard

systematically in order to establish the minimum irritation dose. We refrained from doing so because of the possible risk of sensitization resulting from these tests prior to the treatment, which was considered undesirable when the project was planned.

On the other hand, some reports would now appear to indicate that sensitization may have a beneficial therapeutic effect (8). This observation tallies with the fact that in our series 3 patients sensitized to nitrogen mustard did indeed go into long-lasting remission.

Tolerance induction has not improved the therapeutic effect in this material. Nor was this mentioned by van Scott & Kalmanson (9). The tolerance induction rather postpones commencement of the therapy. Consequently, the Scandinavian Mycosis Fungoides Study Group has abandoned this procedure in the treatment with nitrogen mustard.

The observation of the declining effect of nitrogen mustard during the maintenance as seen in one patient, probably due to the development of resistance to nitrogen mustard, has also been made by Volden (unpublished observation). He noticed a complete cessation of the effect of nitrogen mustard in two patients hitherto successfully treated for a period of about two years. As far as we are aware this phenomenon has not previously been considered as the cause of treatment failure when applying topical nitrogen mustard to mycosis fungoides. The mode of action of topical nitrogen mustard is still not settled. Both an alteration of the DNA molecule (6) and immunological mechanisms have been suggested as the basis of the therapeutic effect. The phenomenon mentioned above, indicating the development of drug resistance, may support the idea of an alkylating effect of nitrogen mustard also via topical application. The aggressive induction phase as scheduled, followed by maintenance more intense than we used initially, is a highly efficacious procedure of topical nitrogen mustard therapy suited to the treatment of the plaque stage of mycosis fungoides. Furthermore, it also seems to have a beneficial effect in the tumour stage of the disease (11).

Current investigations using psoralen and long-wave ultraviolet irradiation (PUVA) have shown therapeutic results initially on the same level as those obtained by us with topical nitrogen mustard (7). We are at the present time in the process of comparing these two treatment modalities.

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