

PHOTOCHEMOTHERAPY (PUVA) IN THE PRETUMOUR STAGE
OF MYCOSIS FUNGOIDES: A REPORT FROM THE SCANDINAVIAN
MYCOSIS FUNGOIDES STUDY GROUP

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Abstract. Fifty-one patients with mycosis fungoides of pretumour stage were treated with oral 8-MOP and UVA photochemotherapy (PUVA). Complete remission was induced within 2-3 months in 58% of the cases. Twenty-seven patients are still in remission on maintenance therapy 9-53 months after starting treatment. In 9 cases PUVA treatment was stopped due to therapeutic failure and in another 15 cases due to various side effects. Maintenance therapy was given weekly, monthly, or at even longer intervals. Maintenance at long intervals seems preferable.

Key words: Mycosis fungoides; Pretumour stage; Photochemotherapy; PUVA; Remission rate; Maintenance treatment; Skin cancer

Sunlight or artificial ultraviolet light often improves the skin lesions of mycosis fungoides. Gilchrist et al. (2) reported regression of cutaneous mycosis fungoides lesions following treatment with psoralens and long-wave ultraviolet light, PUVA, a finding later confirmed by others (1, 3, 4, 5, 6, 7, 8, 12, 13, 14). The mechanism of action of PUVA is not fully understood, although its efficacy in neoplastic

disorders such as mycosis fungoides is commonly believed to be linked to its action on DNA synthesis (11).

This report concerns the experience of the Scandinavian Mycosis Fungoides Study Group with PUVA treatment in the pretumour stage of mycosis fungoides. The results of PUVA treatment in the tumour stages are being presented separately (9).

PATIENTS

Fifty-one patients (29 males, 22 females) from ten dermatological clinics in Denmark, Norway and Sweden, aged between 15 and 82 years (median 67 years), were treated with PUVA from 1975 to 1979 inclusive. Previously 37 patients had received topical corticosteroids, 14 topical mechlorethamine, 22 superficial X-rays or Grenz rays, 2 systemic chemotherapy, and 6 no prior therapy.

The Group operates with five stages of mycosis fungoides (Table 1). The pretumour stage (stage II) is defined as infiltrated skin lesions of less than 3 mm palpatory thickness histologically consistent with mycosis fungoides. The diagnosis was established by the dermatologist and pathologist responsible for the patient.

Table 1. Staging of mycosis fungoides

MF = mycosis fungoides, DL = dermatopathic lymphadenopathy

Stage	Skin lesions	Histology of the skin	Lymph nodes ^a	Internal organs ^b
I	Plaques	0	0	0
II	Plaques	MF	0	0
III	Tumours, ulceration	MF	0	0
IVa	Tumours, ulceration	MF	DL	0
IVb	Tumours, ulceration	MF	MF	0
V	Tumours, ulceration	MF	MF	MF

^a Confirmed histologically.

^b Confirmed histologically or by X-ray.

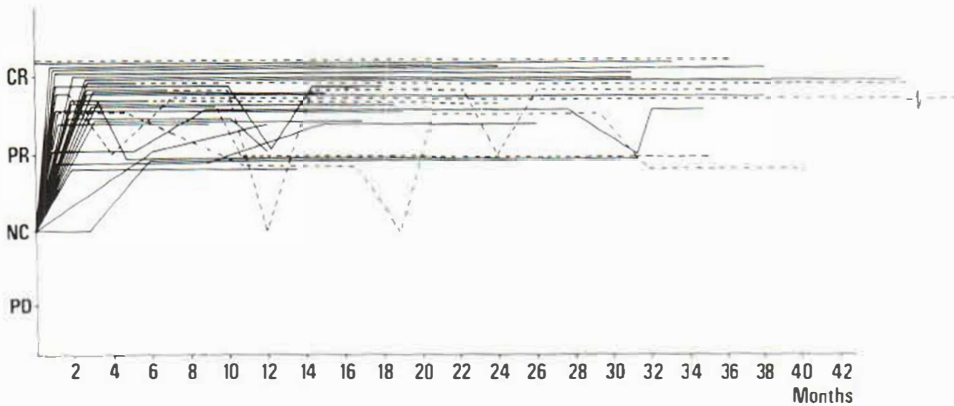


Fig. 1. PUVA treatment in 27 patients with the pretumour stage of mycosis fungoides. —, Treatment continued regularly; ---, treatment continued irregularly. CR, com-

plete remission; PR, partial remission (improvement by more than 50%); NC, no change; PD, progressive disease as compared with first day of treatment.

The patients in this series presented five clinical forms:

1. *Solitary plaques* in 9 patients. The plaques had been present for 3–4 months in 4 patients and for 1–5 years in 5 patients. Three patients had been aware of itching and erythema for a period of 2–5 years and 2 for more than 10 years before infiltration became evident.

2. *Disseminated plaques* in 32 patients with the actual infiltrative stage present for less than 6 months in 9 patients, between 6 months and 2 years in 20 cases, and 5–6 years in the remaining 3 patients. The disease had preceded the infiltrated lesions for less than 6 months in 9 cases, between 1 and 3 years in 16 cases and more than 6 years in the remaining 7 cases, over 15 years in 3 cases being the longest.

3. In 2 patients *Poikiloderma atrophicum vasculare* preceded the infiltrated plaques of mycosis fungoides for 6–7 years and in one patient for more than 40 years. The actual plaque stage had been present for some months in one and for 4–5 years in the other two patients.

4. A *follicular type* of mycosis fungoides occurred in 2 patients with a disease history of 3 and 15 years, and with infiltrated plaques for 2 years and 6 months respectively.

5. *The erythrodermic form* appeared in 5 cases with the onset of the disease 2–10 years earlier. The erythroderma had been present for 1–3 months in 3 cases and for one year and 2 years in 2 cases respectively.

Staging procedure

The patients were examined clinically and by means of multiple skin biopsies. Lymph node biopsy was performed on palpable lymph nodes. Chest X-ray was taken in all cases. Bone marrow biopsy was carried out in 25 cases and liver biopsy or liver scintillography in 16 cases.

Laboratory investigations included hemoglobin, erythrocytes, leukocyte, differential and thrombocyte counts, serum ALAT (serum GPT), serum ASAT (serum GOT), alkaline phosphatase, prothrombin, bilirubin, creatinine, uric acid, and immunoglobulin. All tests were performed in each patient before treatment and repeated at intervals.

TREATMENT

10-mg tablets of 8-methoxypsoralen (8-MOP) manufactured under licence from Memphis Chemical, Cairo, Egypt, were supplied by Pharma-Medica (Denmark), Nyco (Norway) and Draco AB (Sweden) and given in a dose of 0.6–0.8 mg/kg body weight, i.e. the same dosage as commonly used in the treatment of psoriasis. Two hours after intake, irradiation with long-wave ultraviolet light was performed. The irradiation equipment varied from one treatment centre to another. During the induction phase, treatment was given four times a week. The irradiation dose was increased as fast as tolerable.

After remission, maintenance treatment with the maximum UVA dose was given according to one of two schedules, either 2 days every week or 4 days every fourth week. In 9 cases it was later possible to prolong the intervals between the PUVA sessions.

In a few cases with a high degree of light sensitivity the induction treatment could only be given twice a week.

In 3 cases a complete remission had already been achieved by topical whole body mechlorethamine but owing to severe contact dermatitis, PUVA was chosen as maintenance treatment.

RESULTS

Effect of treatment

Complete clinical remission of the skin lesions was obtained within 4–12 weeks in 28 cases. In addition to the 3 cases treated with mechlorethamine, PUVA treatment produced a complete remission in 28 out of 48 cases (58%). The total UVA dose necessary to induce complete remission consistently was low, in 5 cases less than 25 J/cm², and only in 2 cases more than 200 J/cm².

Fig. 1 presents the long-term effects of PUVA treatment. At present 27 patients have been under

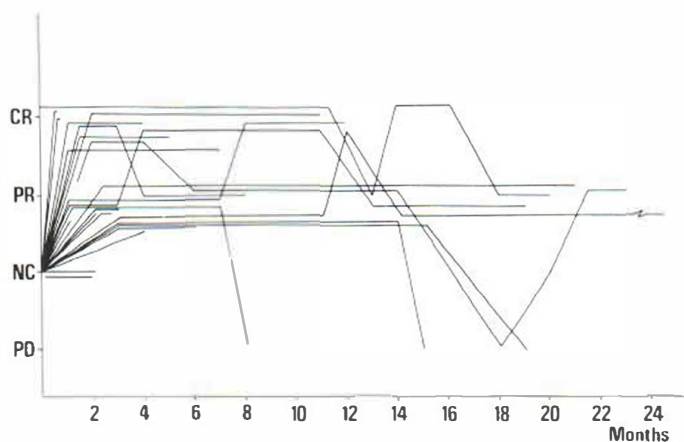


Fig. 2. PUVA treatment in 24 patients with the pretumour stage of mycosis fungoides, in whom treatment was interrupted.

treatment for a period of 9–53 months; 22 are still in complete remission on maintenance treatment. In some patients, maintenance could be reduced to once a week or once every second week. In 9 cases maintenance treatment has been given 2–4 times weekly for 3–5 weeks and such a treatment series was repeated with intervals of 2 up to 16 months, i.e. "irregular maintenance".

Cessation of treatment

PUVA treatment was withdrawn in 24 cases for various reasons (Fig. 2). In 5 patients PUVA treatment was stopped within one to 19 months owing to progression of the disease. In a further 6 cases only partial remission could be obtained. In 3 of these, complete remission was subsequently achieved by adding superficial X-ray irradiation or soaking with mechlorethamine (16).

Six patients in complete and one in partial remission had to cease treatment owing to old age or mental illness, but remission lasted at least another 4–19 months without further treatment. One patient was "burned" after a few treatment sessions ($3 \times 1.5 \text{ J/cm}^2$) but went into complete remission, still present 12 months later, without further therapy. Treatment was stopped due to impetigo (herpes simplex?) in one patient, gastrointestinal complaints in one and the appearance of a skin cancer (see below) in one.

Two patients, 71 and 77 years old, respectively, died of myocardial infarction.

Side effects

In this series of 51 cases the following side effects were encountered: severe nausea in 4 cases, severe

itching in 4, fever initially in one, bullous or generalized erythematous phototoxic reactions in 6, stellate lentigo (lentigo eruptiva) in one case, and impetigo (activated herpes simplex?) in one case.

Squamous cell carcinoma was diagnosed in 2 cases. One of them, a 68-year-old man had been treated with PUVA for 3 years on the diagnosis of parapsoriasis en plaque, premycotic stage, and a cancer on the left outer ear was found shortly after the mycosis fungoides diagnosis had been established. The other patient, a bricklayer aged 55, developed cancer on the cheek 7 months after PUVA had been started.

DISCUSSION

This work demonstrates the efficacy of PUVA in controlling the cutaneous lesions of mycosis fungoides, stage II. To obtain optimum therapeutic response we think it important to start this form of treatment aggressively by increasing the irradiation dosage rapidly until it gives a moderate erythematous reaction. Mycosis fungoides patients are usually more sensitive to UVB and the phototoxic effect of PUVA than are healthy individuals (17) and psoriatic patients and remissions can often be brought about and maintained by PUVA treatment using very low doses of irradiation.

In the present series of patients with mycosis fungoides the response to PUVA treatment was excellent. Most patients went into remission during the induction phase. In some cases isolated lesions remained in the scalp or skin folds such as the neck, axillae and groins, which led to the registration of partial remission. It should therefore be stressed that

in this series the difference between complete and partial remission was often marginal. On the other hand it is evident that PUVA is not always potent enough to eradicate all plaques. In most of these cases superficial X-rays or soaking with mechlorethamine, when added to the PUVA treatment, resulted in complete clinical clearing of lesions. However, a few cases seem resistant to PUVA treatment.

The remission rate induced by PUVA in the plaque stage of mycosis fungoides is of the same magnitude as that obtained with topical whole body mechlorethamine (10). In both forms of treatment modalities the maintenance therapy can often be individualized.

In some cases the PUVA-induced remissions persisted for a long time after the treatment was withdrawn. In cases of relapse the intensity of the disease often was reported as milder than before PUVA treatment and could now be more easily controlled by reinstatement of irregular PUVA therapy.

In this series the maintenance treatment given monthly or at longer intervals, i.e. irregularly, was at least as good as the once weekly regimen and of course much more convenient.

However, it is essential to confirm the remission histologically before temporarily withdrawing PUVA treatment.

Therapeutic resistance seems to develop in some cases during continuous PUVA treatment, perhaps contributing by the induction of pigmentation, although other mechanisms would be possible.

Attention is drawn to the observation that therapeutic resistance to topical mechlorethamine in cases of mycosis fungoides diminishes after a temporary interruption (15). A similar mechanism may also be involved in PUVA treatment. If this is so, maintenance treatment with PUVA in the pre-tumour stage of mycosis fungoides should preferably be given intermittently.

In this series we have also seen some patients in relapse responding very well to sporadically given PUVA. In contrast, the disease in other patients relapsing during weekly maintenance could not be brought under control despite intensified PUVA. This observation could be interpreted in different ways. It could mean that resistance was induced by the continuous maintenance treatment itself or also be an expression of individual variation in sensitivity to the therapy.

In a malignant disease such as mycosis fungoides, certain side effects of treatment may have to be accepted. Even though squamous cell carcinomas were found in 2 patients during PUVA therapy, the connection with the therapy remains in doubt especially as the cancer in both cases appeared in sun-exposed areas, and also taking into account that one was an elderly patient and the other a man with an outdoor occupation.

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