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PUVA in Early Mycosis Fungoides May Give Long-term Remission and Delay Extracutaneous Spread

GÖSTA ROUPE[1], MARI HELEN SANDSTRÖM[1] and CHRISTER KJELLSTRÖM[2]

Departments of [1]Dermatology and [2]Pathology, Sahlgrenska University Hospital, Göteborg, Sweden

We report a follow-up for 3–18 years of 24 patients with the non-infiltrated patch and infiltrated plaque stage of mycosis fungoides, treated with psoralen photochemotherapy (PUVA) and on resistant infiltration or development of tumours also with fractionated radiation therapy. All patients with patch and limited plaques showed complete remission after initial PUVA therapy. Half of the patients with patch stage mycosis fungoides and also half of the patients with plaque stage mycosis fungoides were in complete remission when the study ended. Most of them had remission periods for years after early PUVA treatment. Patients with more advanced mycosis fungoides needed repeated periods of PUVA therapy. Two patients with extensive infiltrated plaques did not reach complete remission at all during the study but progressed and finally died of their T-cell lymphoma. Another 4 patients with extensive plaque stage mycosis fungoides died after initial complete remission for a maximum of 3 years.

In this investigation the clinical evaluation was made by one dermatologist and the histopathological evaluation by one pathologist. This is of importance since in the early stages of mycosis fungoides the diagnosis is challenging and may require a combination of clinical, histopathological and molecular evaluations. The identification of early disease is crucial for the rapid implementation of adequate treatment. The study shows that early PUVA therapy may delay extracutaneous spread and possibly also in some cases be curative. *Key word: radiation therapy.*

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G. Roupe, Department of Dermatology, Sahlgrenska University Hospital, S-413 45 Göteborg, Sweden.

Mycosis fungoides (MF) is a slowly advancing T-cell lymphoma, starting with pruritic erythematous areas which become infiltrated and progress into tumours. Lymph nodes and internal organs (i.e. liver, spleen, lungs) successively become involved. Immunohistochemical studies have shown the infiltrating cells to be T-lymphocytes (1), and deleted HTLV-1 provirus (human T-cell leukemia/lymphoma virus type I) has recently been found in cutaneous lesions of patients with MF, indicating a retroviral aetiology (2). Different modes of treatment have been tried for skin involvement of MF.

PUVA therapy was introduced by Gilchrest et al. and found to be effective in MF, inducing and prolonging remissions (3–6). Thin plaques respond better to PUVA therapy than thicker plaques and tumours because of difficulties with UV penetration (6). In patients with more advanced disease, i.e. extensive skin involvement with tumour development and spread to internal organs, different combinations of therapies, i.e. recombinant interferon-alpha (7–9) or systemic therapies (10, 11), have been tried.

We report here a long-term follow-up of 24 patients with early MF treated with PUVA and in cases of resistant infiltration or development of tumours also with fractionated radiation therapy.

PATIENTS AND METHODS

Twenty-four patients, 12 men and 12 women, 25–82 years of age, with non-infiltrated patches or infiltrated plaques of MF were included in the study. The patients entered the study between 1977 and 1994. Some patients had been treated with corticosteroid ointments but no chemotherapy, radiation or PUVA therapy had been used before the start of the study. The patients were treated with PUVA. Thick plaques bordering on tumours were treated with local fractionated radiation therapy. PUVA treatment was started as soon as relapses were noticed. Other treatments during the study are listed in Table I. Etretinate was given in doses from 10 to 50 mg daily, in some patients for many years. All but 2 patients treated with etretinate relapsed after cessation of therapy. In fractionated radiation 3 Gy daily was given 5 days a week for 2 weeks.

Patients with tumours usually received one or two radiation treatments during the observation period (maximum of four treatments during 16 years). Interferon was stopped because of side-effects. Some patients received chemotherapy (i.e. cyclophosphamide, bleomycin, adriamycin and oncovine) in their final, advanced phase of the disease.

Before starting PUVA therapy, the skin of the patients was evaluated and classified as more or less than 10% skin involvement (12). Lymph nodes and viscera were classified according to the TNM categories.

All patients had histopathologically verified MF. Pretreatment skin biopsies were considered diagnostic for MF if groups of atypical lymphocytes formed small epidermal abscesses (Pautrier's microabscesses) or if a dense infiltrate of numerous atypical lymphocytes with irregular nuclei and mitosis was seen in the epidermis and dermis. In Table I patients with Pautrier's microabscesses are marked number 4. In 10 patients T-cell receptor (TCR) γ gene rearrangement (13, 14) was performed. In all cases a monoclonality of the lymphocytic infiltration confirmed the diagnosis (Table I).

Blood tests included a routine blood cell count, a differential count and liver and renal function tests. Palpation of lymph nodes, the liver and the spleen was performed in all patients before and during the study.

The patients were given 8-methoxypsoralen 0.6 mg/kg orally 1.5 h before UVA. The ultraviolet A-dose for individuals with skin type I and II was 1 J/cm^2 and was increased by 1 J/cm^2 or more in each treatment up to 12 to 15 J/cm^2. Treatments were generally given twice a week. In 2 patients tablet-PUVA was changed to bath-PUVA due to side-effects (pruritus, indisposition). Complete remission was defined as clearing of all skin lesions.

RESULTS

Non-infiltrated patch stage (Table I, Fig. 1)

Seven patients (nos. 1–7) with non-infiltrated patch stage MF were treated with PUVA. Six patients had complete clearing within 11 months of therapy. One patient, who failed to attend for treatment, received repeated short periods of PUVA for 8 years before complete remission could be observed. A relapse necessitating further PUVA treatment was seen in 5 patients. The patients who relapsed were in initial complete remission

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Table I. *Clinical information and follow-up data on 24 patients with MF*

CR = complete remission; mtx = methotrexate; rt = fractionated radiation therapy; ct = chemotherapy.

Patient		Years of clinically/	Years from first PUVA	No. of PUVA	Periods without PUVA (years)			Other treatments	Stage of MF		
No.	Age[1] yrs/Sex	histologically verified MF[1]	treatment[2]	treatments	Accumulated since the first treatment[2]	Longest treatment-free period	Time since last PUVA[2]	during study	Beginning of study	Maximum during study	End of study
1	64/F	0/0[4,5]	9.2	537	1.6	0.8	0.8	Etretinate, rt	T1N0M0	T3N0M0	T3N0M0
2	25/M	0/0[4]	16.8	196	15.2	8.8	5.2	—	T1N0M0	T1N0M0	CR
3	63/F	0/0[5]	15.5	131	14.5	5.9	5.9	rt. ct	T2N0M0	T3N0M0	CR
4	64/M	0/0[4,5]	9.4	27	9.0	9.0	9.0	—	T2N0M0	T2N0M0	T1N0M0
5	64/M	0/0[4]	3.5	27	3.2	1.8	1.5	—	T2N0M0	T2N0M0	T1N0M0
6	37/M	9/0[4,5]	5.5	19	5.2	4.1	4.1	rt	T1N0M0	T1N0M0	T1N0M0
7	70/F	0/0[4]	4.8	6+14[3]	4.5	4.5	4.5	—	T1N0M0	T1N0M0	CR
8	49/F	4/4[4,5]	9.9	577	2.2	0.9	0.4	rt, ct, Etretinate Interferon	T2N0M0	T3N3M0	T3N3M1
9	53/M	3/1[5]	15.2	512	4.6	1.9	1.9	rt, ct, Etretinate	T2N0M0	T3N0M0	T3N0M0
10	31/F	0/0[4,5]	17.2	482	10.5	5.4	5.4	rt, Bucky, Etretinate, UVA-Sun	T2N0M0	T3N0M0	CR
11	62/M	0/0[4]	10.9	374	6.3	2.3	2.3	Etretinate	T2N0M0	T2N0M0	CR
12	60/M	7/0[5]	16.8	319	13.6	11.5	11.5	rt	T2N0M0	T3N0M0	CR
13	62/F	0/0	5.3	265	0.9	0.2	0.2	rt, Etretinate	T2N0M0	T3N0M0	T3N0M0
14	65/M	2/0	5.8	263	2.2	0.8	0.2	rt, ct, Etretinate	T2N0M0	T3N0M0	T3N0M0
15	46/F	0/0	15.8	206	13.4	13.4	13.4	—	T2N0M0	T2N0M0	CR
16	28/F	0/0[4,5]	12.0	196	10.3	4.3	0.0	Etretinate	T2N0M0	T2N0M0	T1N0M0
17	63/M	3/3	2.8	160	0.4	0.2	0.1	rt	T2N0M0	T3N3M1	T3N3M1
18	41/F	1/0[4]	9.3	144	6.7	3.0	2.9	rt, ct, Etretinate, Interferon	T2N0M0	T3N0M0	T3N0M0
19	68/M	5/0[4]	10.2	76	9.5	9.5	9.5	Etretinate	T2N0M0	T2N0M0	CR
20	71/F	1/1	7.5	74+34[3]	5.8	3.5	3.5	mtx	T2N0M0	T4N0M0	T4N0M0
21	59/M	1/1[4]	5.8	51	4.8	2.5	2.5	—	T2N0M0	T2N0M0	CR
22	61/M	0/0[4]	6.0	36	5.6	5.6	5.6	—	T1N0M0	T1N0M0	CR
23	82/F	0/0[4,5]	7.5	16	7.3	7.3	7.3	—	T2N0M0	T2N0M0	CR
24	69/F	0/0[4]	6.1	12	5.9	5.9	5.9	Bucky	T1N0M0	T1N0M0	CR

[1] when entering study.
[2] until end of study or until the patient died.
[3] methoxalen (bath) PUVA added.
[4] Pautrier's microabscesses during study.
[5] T-cell receptor gamma gene positive.

for between 4 months and almost 7 years. Two patients reached the tumour stage during treatment. In 3 patients radiation therapy of remaining infiltration or tumour was given after the last PUVA treatment. No lymphadenopathy was noticed in any patient during the study and routine laboratory tests were all normal.

Infiltrated plaque stage (Table I, Fig. 1)

Two patients with limited plaque MF had complete clinical remission within 3 months of therapy. These patients did not show any relapse at all during the study period and had no palpable lymph nodes.

Thirteen out of 15 patients with extensive infiltration showed complete clearing between 2 months and 5 years.

At the end of the study, 7 patients had been in complete remission for years with no palpable lymph nodes and normal routine blood tests. In 2 of them radiation therapy of remaining tumour was given after the last PUVA treatment. Four patients progressed in spite of periods of complete remission.

DISCUSSION

A characteristic histological feature of MF is the affinity of atypical T-cells to the epidermis, an observation designated epidermotropism. Thus, lymphocytes infiltrate not only the dermis but also the epidermis, here often forming groups known as Pautrier's microabscesses. In classical MF circulating pathological T-lymphocytes are usually not seen in the blood. The reason might be that the malignant T-cells are rapidly

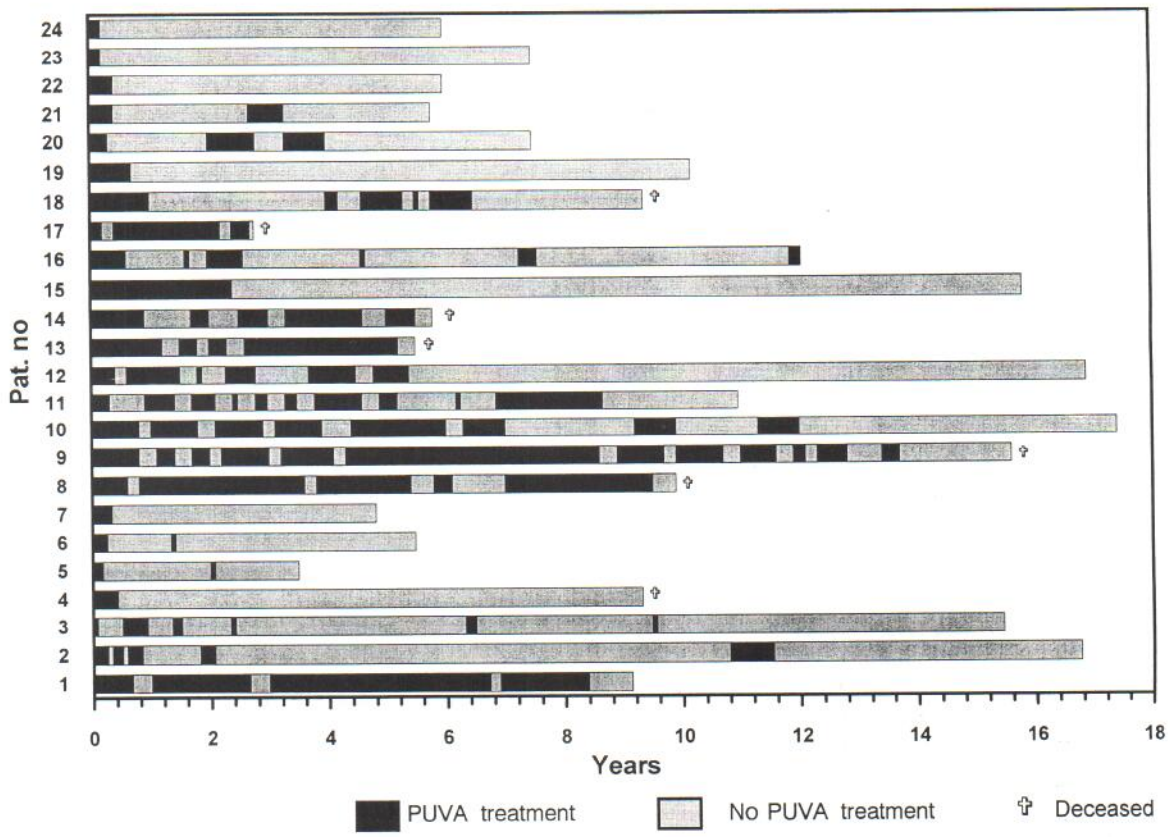

Fig. 1. PUVA treatment of patch and plaque stage MF.

trapped in the skin as a result of the epidermotropism. Epidermal surveillance of the bloodstream in MF may result in depletion of malignant cells from internal organs, leading to a reduction of tumour load. If such an equilibrium exists between skin, blood and extracutaneous organs, treatment with PUVA and radiation could theoretically reduce the entire malignant T-cell mass so that in some patients their own immunological defence forces may finally be curative.

The efficacy of PUVA in the pretumour stage of MF has previously been reported by the Scandinavian mycosis fungoides study group (15). The same group has also demonstrated complete remission after PUVA in 5 of 17 patients with tumours, while in the rest of the patients additional treatment was needed for complete remission (16). PUVA was given four times weekly during an induction period.

In our study PUVA was given twice weekly. With this treatment schedule we were unable to confirm the antitumour effect of PUVA, and this is the reason why radiation therapy was added. The UVA erythema comes on the third day and it is difficult to increase the UVA dose in an adequate way if PUVA is given more often. There is a risk that the patient may be burnt (17).

Antitumour activity has been demonstrated for retinoids alone or in combination with other therapies (PUVA and interferon alpha) in early stages of T-cell lymphomas. Etretinate is effective in plaque stage MF and the combination of etretinate and PUVA resulted in a lower UVA dose and a prolonged duration of remission compared to PUVA alone. However, the response and the relapse rate was the same after etretinate and PUVA as after PUVA (18).

It is important to realize that the degree of epidermotropism of the T-cell decreases during the disease process. Thus, patients may be more or less sensitive to PUVA therapy. Ethical reasons limit studies of a representative control group in a malignant disease and spontaneous remission may occur. However, in patch and plaque stage MF, early PUVA therapy combined with radiation therapy of remaining infiltration or developing tumours seems to give long periods of remission, in our study up to almost 12 years. Long disease-free periods after PUVA seem to be a positive prognostic factor.

Patients with non-infiltrated patch stage MF treated according to our regimen did not develop clinically detectable pathological lymph nodes, or hepato- or splenomegaly. This observation may be due to drainage of lymphocytes from blood to skin where pathological lymphocytes are being eliminated by PUVA. However, in 6 patients with more extensive infiltrated plaques we were unable to control the progression of the disease and these patients are now dead. The extent of skin involvement seems to be an important prognostic variable and probably correlates with patient survival.

The patients usually received PUVA during the first months or years of study. This observation indicates that our treatment regimen may in some patients result in remission of long duration. Furthermore, indications of a considerable decrease of the death rate from MF by PUVA treatment have recently been reported (19).

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