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Retinoids Plus PUVA (RePUVA) and PUVA in Mycosis Fungoides, Plaque Stage

A Report from the Scandinavian Mycosis Fungoides Group

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Sixty-nine patients with mycosis fungoides, plaque stage, were treated in an open study with photochemotherapy (PUVA) or the combination of oral retinoids and PUVA (RePUVA). The response rate of RePUVA was equal to that of PUVA, with complete remission in 73% and 72%, respectively. Remissions were obtained with fewer PUVA sessions, and with a lower UVA dosage, if PUVA was combined with retinoids. A lower UVA dosage was needed if treatment was given four times weekly in stead of twice weekly. The duration of the remissions tended to be prolonged if retinoids were given as maintenance therapy. *Key words: UVA dosage; Therapeutic response.*

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Photochemotherapy (PUVA) is a well established treatment for mycosis fungoides, effective in plaque stage as well as in limited tumour stage (1–8). In the more advanced tumour stage, PUVA can also be of value as a supplement to systemic chemotherapy (2).

The present study shows that in the treatment of mycosis fungoides, the combination of retinoids and PUVA (RePUVA) is in some respects superior to PUVA given alone.

MATERIAL AND METHODS

At four Scandinavian dermatological centres, 69 patients with erythematous plaque stage of mycosis fungoides were treated in an open study. PUVA alone was given to 47 patients and RePUVA to 22 patients. 38 were males and 31 females, with an age range of 21–82 years, median 68 years.

The diagnosis of mycosis fungoides was verified by histologic examination. No patients with tumours, lymph node involvement or other signs of extracutaneous disease were included.

PUVA

PUVA was given as 8-methoxypsoralen (8-MOP) orally in a dosage of 0.6–0.8 mg per kg body weight, 2 h before the exposure to long-wave ultraviolet light (UVA). PUVA was given twice or four times weekly.

The treatment was discontinued about 2 weeks after complete remission.

RePUVA

In patients treated with retinoids plus PUVA (RePUVA), retinoids were instituted 2 weeks before the start of PUVA treatment. PUVA was given 2 or 4 times per week. The retinoids were given in daily oral dosages. The initial dosage of etretinate (Tigason®) was 0.3–1 mg per kg body weight, and that of isotretinoin (Roaccutan®) 0.5–1.5 mg per kg body weight. The dosages were reduced according to mucosal and skin dryness.

PUVA treatment was discontinued about 2 weeks after complete remission. In 8 cases retinoid treatment was continued as maintenance. The complete remission was always verified by histologic examination.

Statistical analysis

Two-way analysis of variance, unequal groups, log transformation of data (9).

RESULTS

In this series all the patients responded with complete or partial remission (Table I). RePUVA induced com-

Table I. *Remission rates in patients with mycosis fungoides, plaque stage treated with RePUVA and PUVA*

Treatment	Number of patients	Complete remission	Partial remission
RePUVA	22	16 (73%)	6 (27%)
PUVA	47	34 (72%)	13 (28%)

plete remission in 16/22 cases (73%) and partial remission in 6/22 cases, while PUVA resulted in complete remission in 34/47 cases (72%) and partial remission in 13/47 cases. The total number of PUVA sessions necessary to obtain complete remission with RePUVA was lower than with PUVA alone ($p<0.05$) (Table II). RePuva four times weekly induced complete remission after a mean of 15 sessions, and RePUVA twice weekly after a mean of 19 sessions. PUVA four times weekly needed a mean of 20 sessions and PUVA twice weekly a mean of 42 sessions, respectively.

The dosage of UVA at remission was significantly lower in RePUVA- than in PUVA-treated patients ($p<0.01$) (Table III), and, moreover, if treatment was given four times weekly instead of twice weekly ($p<0.05$). Two patients, one in the PUVA-treated group and the other in the RePUVA group, were extremely light sensitive, and were burned after only a few treatments, after which they went into complete remission, however.

The relapse rate after complete remission was the same after RePUVA as after PUVA. The duration of the remission seemed to be prolonged if retinoids were given as maintenance treatment after RePUVA.

Table II. *Numbers of PUVA sessions (mean and range) for complete remission in mycosis fungoides, plaque stage, treated with RePUVA and PUVA, 4 and 2 times per week, respectively*

Treatment	Number of patients	Number of PUVA session	
		Mean	Range
RePUVA (4×/w)	10	15	3–28
RePUVA (2×/w)	6	19	10–45
PUVA (4×/w)	29	20	4–75
PUVA (2×/w)	5	42	14–75

DISCUSSION

These data indicate that, at remission, the UVA dose was lower after RePUVA than after PUVA given alone, and, therefore, the cumulative dose of UVA could be reduced. Furthermore, the addition of retinoids to PUVA reduced the number of PUVA sessions needed to achieve remission. However, the addition of retinoids did not improve the response rate in the plaque stage of mycosis fungoides.

When given four times a week, complete remission was achieved with RePUVA after a mean of 15 PUVA sessions, i.e. after 4 weeks' treatment while it took a mean of 19 treatments or 10 weeks if the treatment was given only twice weekly. The same pattern was found in the PUVA treatment group, with complete remission after a mean of 20 treatments after four times weekly, compared with a mean of 42 treatments after twice weekly, which means after 5 and 21 weeks, respectively. In the present study it can be concluded that shorter treatment periods are possible if PUVA is given frequently and combined with retinoids.

Patients with mycosis fungoides are usually more liable to phototoxic erythematous and even bullous reactions induced by PUVA than are psoriatic patients. Remissions can often be achieved with very low doses of UVA irradiation. Patients with mycosis fungoides, irrespective of stage, often relapse when the treatment is withdrawn, indicating that cure has not been obtained. The relapse rate seems, however, to be reduced if oral retinoids are continued even in a low dosage.

PUVA, as well as RePUVA, is indicated mainly in the early plaque stage of mycosis fungoides, but it has also some effect in more advanced cases in combination with other forms of treatment such as systemic

Table III. *UVA dosage at the time of complete remission in J/cm² in mycosis fungoides, plaque stage, treated with RePUVA and PUVA, 4 and 2 times per week, respectively*

Treatment	Number of patients	UVA dosage, J/cm²	
		Mean	Range
RePUVA (4×/w)	10	2.0	1–3
RePUVA (2×/w)	6	2.5	1–3
PUVA (4×/w)	29	3.6	1–7.5
PUVA (2×/w)	5	5.8	3–10

chemotherapy. Whatever the case, both treatments increase the well-being of the patients by reducing the discomfort of the cutaneous lesions.

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Advanced Mycosis Fungoides: Chemotherapy with Etoposide, Methotrexate, Bleomycin, and Prednimustine

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We assessed the efficacy and toxicity of a chemotherapeutic regimen in patients with stage II–IV mycosis fungoides. Eleven previously treated outpatients received etoposide and methotrexate p.o. and bleomycin i.v. every 3 weeks. There was 1 complete remission for 2 months and 7 partial remissions with a median duration of 6 months (range 2–16 months). Three patients showed stable disease lasting 1–5 months (median 2 months). In 4 patients, remissions were maintained with prednimustine after 10 courses of induction chemotherapy. Mild nausea occurred in all patients and severe leukocytopenia and thrombocytopenia in 1 patient. Toxicity of the treatment regimen was acceptable and response rates comparable to those seen by others with more toxic single-agent or combination chemotherapies.

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Mycosis fungoides is an uncommon cutaneous T-cell lymphoma with monoclonal proliferation of helper T-cells. Besides impressive skin tumours, patients frequently develop diffuse lymphadenopathy and visceral organ involvement. Extracutaneous disease may require systemic therapy. Approaches with single-agent or combination chemotherapies are associated with high response rates of approximately 60–80%. However, median duration of remission is 6 months only (1). Moreover, there are no reports of cures using chemotherapy alone in advanced stages of disease. The purpose of this study was to induce remissions with a combination chemotherapy regimen of moderate toxicity even in pretreated patients with poor performance status and to prolong response with maintenance chemotherapy.

MATERIAL AND METHODS

Eleven patients with clinical and histological evidence of mycosis fungoides were studied (Table I). All patients had