



Fig. 4. The cornoid lamella with a parakeratotic column. The stratum granulosum is absent.

clones are more sensitive to ultraviolet light than are normal epidermal cells. The degree of penetration and the number of lesions correlate with the amount of sun exposure (3).

The disseminated superficial actinic form of porokeratosis is very rare in Finland, possibly owing to the small amount of sunshine in our country. In 1971 Niemi described a 38-year-old woman with superficial disseminated porokeratosis on the localized non-actinic skin areas, on the buttocks and the right wrist (7). The effect of sunshine on the eruption is not known.

The clinical and histological findings in our patient are suggestive primarily of DSAP, which is more usual in women and begins in middle-age. The unusually late onset of the disease in this case could be explained in terms of the low yearly dosis of sunshine in Finland.

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Epipodophyllotoxin (VP-16-213) in Mycosis Fungoides: A report from the Scandinavian Mycosis Fungoides Study Group

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Abstract. Epipodophyllotoxin (VP-16-213) was administered to 9 patients with mycosis fungoides in various stages, most of them in the advanced tumour stage. In 4 of the patients VP-16 was combined with cyclophosphamide. VP-16 alone or in combination with cyclophosphamide was capable of inducing remission initially in all cases, complete in 2, partial in 3 and improvement to a

Table I. Six patients with mycosis fungoides treated with VP-16

CR=complete remission; PR=partial remission (improvement to more than 50%); IMP=improvement (to a lesser extent); NC=no change; PD=progressive disease, all compared with the situation at the commencement of treatment

	Patients					
	C. M.	N. S.	P. H.	N. S.	I. C.	R. C.
Age, years	90	75	68	67	43	72
Sex	m	m	m	m	f	m
Stage	II	III	III	IV	IV	V
Therapeutic effect						
Initial (2-4 m)	CR	IMP	IMP	IMP	PR	IMP
Late (6-8 m)	CR	PD	PD	PD	PR	—
Bone marrow toxicity	+			+	+	+

lesser degree in the remaining 5 patients, but it was unable to maintain the remission. The induced remission has to be upheld by other agents, possibly added to VP-16.

Key words: Mycosis fungoides; Epipodophyllotoxin; Cyclophosphamide

When epipodophyllotoxin (VP-16-213, Sandoz) was first used in the treatment of mycosis fungoides in the tumour stage, no effect could be registered (6). However, the dose was rather low. Prompted by the encouraging results reported by Jacobs & King (3, 4) a phase-2 investigation was instituted by the Scandinavian Mycosis Fungoides Study Group (2, 5) with the purpose of evaluating the effect of VP-16 in the treatment of mycosis fungoides.

The agent

VP-16 (4'-demethyl-epipodophyllotoxin- β -D-ethylidine glucoside) is a semisynthetic derivate of podophyllotoxin (6). It arrests cells in metaphase and also prevents cells from entering the prophase of mitosis. In cell cultures an inhibition of the incorporation of thymidine into DNA has been

observed (1). The effect on RNA and protein synthesis is minimal.

The compound is practically insoluble in water, but can be made water-soluble by means of organic solvents. It is available in ampoules for intravenous or in ampoules for oral administration. The ampoule solution is diluted in saline or glucose before use. The agent is mainly excreted through the liver and kidneys.

PATIENTS

Nine patients with mycosis fungoides have been treated in this series (Tables I and II). Five of them were treated with VP-16 alone, 3 with VP-16 combined with cyclophosphamide, and one patient first with VP-16 alone and later with the combination. One patient was in the plaque stage of the disease (stage II), 3 patients had cutaneous tumours without dissemination to other organs (stage III), 4 patients cutaneous tumours as well as involvement of lymph nodes histologically verified (stage IV), and 2 patients also had involvement of internal organs (stage V). Various clinical forms of mycosis fungoides were observed: the classical Alibert-Bazin type, the follicular type, the disseminated plaque type, the *d'emblée* type and Sézary syndrome. Prior to VP-16 therapy, most patients

Table II. Four patients with mycosis fungoides treated with VP-16 combined with cyclophosphamide

	Patients			
	E. L.	M. H.	E. P.	N. S.
Age, years	67	72	65	67
Sex	m	m	m	m
Stage	III	IV	IV	IV
Therapeutic effect				
Initial (2-4 m)	CR	PR	PR	IMP
Late (6-8 m)	PD	CR	NC	PD
Bone marrow toxicity	+	+	+	+

had been treated with systemic chemotherapy, whole-body X-ray irradiation and/or topical nitrogen mustard. The VP-16 therapy was instituted during an active phase of the disease.

TREATMENT

In 6 cases of mycosis fungoides, VP-16 was given as an intravenous injection in a dose of 100 mg daily for 5 days, followed by a rest period of 16 days (3-week cycles) or 9 days (2-week cycles). As maintenance, VP-16 was given orally in doses of 100 mg for 5 days followed by similar rest periods.

In 3 other cases as well as in one case in relapse after treatment with VP-16 alone, VP-16 in the dosage mentioned was combined with cyclophosphamide, 500 mg given intravenously every 4th day. During maintenance, 150 mg cyclophosphamide daily was given orally.

RESULTS

The initial effect of the treatment was generally good (Tables I and II), but only 2 cases went into complete remission. One of them was a 90-year-old man in plaque stage of mycosis fungoides who went into complete remission after two cycles of treatment and remained in remission without maintenance for 4 months, when he died of a disease not related to mycosis fungoides.

Of the 5 tumour cases treated with VP-16 alone, one went into partial remission and the other 4 improved somewhat. In only one case could the remission be maintained for more than 4 months with maintenance therapy. In one case the therapy was withdrawn due to bone marrow toxicity.

Four patients were treated with VP-16 and cyclophosphamide (Table II). One of them had the *d'emblée* type of the disease, and went into complete remission within three cycles of treatment. Two patients went into partial remission and one was improved somewhat, initially. In one case the induced remission, initially partial but later complete, was maintained for 9 months with oral therapy. In the remaining cases a progression of the disease was recorded within 4-6 months after the start of treatment.

Side effects

No serious side effects were recorded. In 3 of the 6 cases treated with VP-16 alone and in 3 of the cases treated with VP-16 plus cyclophosphamide, the treatment caused neutropenia and/or thrombocytopenia which, in relation to the failure of

therapeutic effect at that time, was considered unacceptable and warranted withdrawal of the drug. The bone marrow depression was reversible in all cases. Total but temporary alopecia occurred in 2 cases. All patients complained of the unpalatable taste of oral VP-16.

DISCUSSION

Initially VP-16 improved all 9 patients treated alone or in combination with cyclophosphamide, with complete remission in 2 and partial remission in 3 cases. Of the latter, one later went into complete remission. Improvement could in most cases be observed even after one or two cycles of treatment. The duration of remission was usually short, however, and the addition of cyclophosphamide did not prolong the remission.

As with other types of systemic chemotherapy in mycosis fungoides, VP-16 alone or combined with cyclophosphamide clearly affected the lymph nodes more than the cutaneous tumours or ulcerations.

The high degree of bone marrow toxicity, both after VP-16 alone and after the combination therapy, indicates that the dosage given was maximal and could not be further increased.

We conclude that VP-16 alone or in combination with cyclophosphamide is capable of inducing remission in mycosis fungoides but that the agent is unable to maintain the remission. For practical purposes the induced remission has to be maintained by other agents, possibly added to VP-16. The combination of VP-16 and cyclophosphamide does not seem to be capable of maintaining remission.

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Prednimustine in Mycosis Fungoides: A Report from the Scandinavian Mycosis Fungoides Study Group

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Abstract. Prednimustine, a chlorambucil ester of prednisolone, was administered orally to 5 patients with mycosis fungoides in advanced tumour stage. Partial remission was obtained in 2 of the patients. However, we do not consider the agent to be particularly advantageous for the treatment of mycosis fungoides.

Key words: Mycosis fungoides; Prednimustine

Hitherto, systemic chemotherapy of late stage of mycosis fungoides has had only a slight or transient effect (3, 7). Chlorambucil combined with prednisone, however, is highly effective even in small doses in the treatment of the Sézary syndrome, regarded by many as the leukemic variant of mycosis fungoides (9). Few reports exist of its use in mycosis fungoides, but none of them with encouraging results.

Recently, a chemical combination of chlorambucil and prednisolone has appeared in the form of prednimustine, LEO 1031 (4), the chlorambucil ester of prednisolone. After absorption it is split into the active components chlorambucil and prednisolone. For reasons unknown, prednimustine can be administered in far higher doses than can chlorambucil and prednisolone given as separate drugs, and in equipotent doses it is less toxic than either of the two compounds. However, an unexplained, delayed bone marrow toxicity has been reported, possibly a result of accumulation of the drug.

Prednimustine has proved capable of inducing and maintaining remissions in various forms of lymphoma (8), leukemias (1, 2) and in metastasising mammary carcinoma (5). Previously, prednimustine has been administered occasionally to mycosis fungoides patients (6). We therefore considered it of interest to examine the effect of this drug in more advanced stages of mycosis fungoides.

PATIENTS

Five patients with mycosis fungoides, in stages III to V according to the staging criteria of the Scandinavian Mycosis Fungoides Study Group (7), have been treated with prednimustine (Table 1). The age range of the patients was 48 to 90 years and the duration of the disease 1–13 years. All the patients had previously been treated with topical X-ray irradiation, topical nitrogen mustard or PUVA and two of them had also received various forms of systemic chemotherapy. At the onset of therapy the disease was in its active phase in all patients.

TREATMENT

Prednimustine was given orally as tablets of 20 or 100 mg active drug, roughly estimated to contain 50% chlorambucil and 50% prednisolone. Prednimustine was given in a dose of 120 mg/m² daily for 5 days, followed by a rest period, and repeated every third week. The dosage had to be reduced in 2 cases.

Prior to therapy and at weekly intervals during the treatment period the following parameters were measured: hemoglobin, erythrocytes, thrombocytes, leukocytes, differential count, serum creatinine, serum uric acid, aspartate-amino-transferase (ASAT), alanine-amino-transferase (ALAT), alkaline phosphatases, serum bilirubin.

RESULTS

The treatment was given for a total of three to eight cycles. In 2 patients prednimustine induced partial