In childhood, other non-scarring alopecias should be considered. Alopecia areata does not present at birth with subsequent sparse growth of normally pigmented hairs. Tick bite alopecia is transient (2). The presence of normal length hairs within the hypotrichotic area excludes trichotillomania.

Alterations in hair growth are often recognized as naevoid in origin. Hair follicle naevi (3), straight hair (4) and woolly hair naevi (5) have been described. We conclude that the hypotrichotic areas in this child's scalp are naevoid in origin.

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Retinoids and Systemic Chemotherapy in Cases of Advanced Mycosis Fungoides. A Report from the Scandinavian Mycosis Fungoides Group

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Molin L, Thomsen K, Volden G, Jensen P, Knudsen E, Nyfors A, Schmidt H. Retinoids and systemic chemotherapy in cases of advanced mycosis fungoides. A report from the Scandinavian mycosis fungoides group. Acta Derm Venereol (Stockh) 1987; 67: 179–182.

In cases of advance mycosis fungoides, the systemic chemotherapy combination of bleomycin, cyclophosphamide and prednisolone was given to 8 cases, and the same 3-drug combination with the addition of oral retinoids given to 12 cases. All cases were in a progressive phase of the disease. Remission was obtained in 5/8 cases treated with the combination and in 7/12 cases treated with the combination plus retinoids. The remissions were complete in half of the cases, but relapse occurred within 3 to 6 months in all but 2 cases. The two treatment patient groups were not fully comparable but the conclusion is that the addition of retinoids to systemic chemotherapy combination regimens is of some advantage. There still exists, however, need of more adequate treatment modalities in advanced mycosis fungoides. *Key word: Tumour stage.* (Received June 5, 1986.)

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Need still exists for more efficient treatment of cases of advanced mycosis fungoides. Hitherto no treatment regimen has been able reliably to induce remission in cases where mycosis fungoides has entered the tumour stage or has disseminated to lymph nodes or viscera. Previously, bleomycin has been used in a short series of such patients (1). Although remission was obtained in a high proportion of cases, an unacceptably high incidence of side effects often led to abandonment of this treatment. Cyclophosphamide

also has an effect upon mycosis fungoides and a regimen including cyclophosphamide, bleomycin in reduced dosage and prednisolone was introduced in 1979.

It soon became apparent, however, that this treatment modality was unable to control cases of advanced mycosis fungoides for longer periods of time, and in 1980 oral retinoid was added to the 3-drug combination. The addition of retinoid appeared to enhance the therapeutic effect, and a preliminary report was published in 1982 (2). In that study, however, transfer factor was also used in patients treated with the retinoid combination. The present study demonstrates that the addition of retinoids to systemic chemotherapy seems to be of some advantage in cases of mycosis fungoides in the tumour stage.

MATERIAL AND METHODS

Eight patients with mycosis fungoides in tumour stage were treated with the 3-drug combination of bleomycin, cyclophosphamide and prednisolone (Table I) and in 12 patients oral retinoid was added to this combination regimen.

All patients had multiple cutaneous tumours. Five patients were in stage III of mycosis fungoides, by definition without signs of lymph node or visceral involvement. Three patients were in stage IVa with dermatophatic lymphadenopathy, and 7 in stage IVb with lymphomatous involvement of lymph nodes, verified by histology or abnormal lymphangiography. Extracutaneous involvement in other organs that lymph nodes, defined as stage V, occurred in 4 patients.

All patients had progressive disease when treatment was instituted. Prior to the present treatment most of the patients had been treated with PUVA, many of them also with other kinds of single drug or combinations of systemic chemotherapy. Systemic chemotherapy was given in 3-week-cycles: Bleomycin 5 mg intramuscular injection day 1 and day 5; cyclophosphamide 100 mg per m^2 body surface orally daily; prednisolon 40 mg orally daily (initially only day 1 through 7 in 2 patients of each treatment group for 2–3 cycles). Retinoid was given as etretinate (Tigason®) 1.5 mg per kg body weight orally daily in 10 cases and as isotretinoin (Roaccutan®) 0.5 mg per kg body weight in 1 case. These dosages were adjusted according to side effects. Additional treatment: X-ray or Grenz rays (Bucky) on isolated residual tumours in all cases. All but 3 patients in a progressive state of the disease were already on PUVA treatment prior to the chemotherapy treatment in whom PUVA was continued.

RESULTS

The therapeutic response is presented in Table I. In the 3-drug combination treated group, initially (within 2 months) complete remission was obtained in 2 cases and partial remission of more than 50% of the mycosis fungoides lesions in another 3 cases. Progression of the disease despite treatment occurred in 3 cases.

In the group treated with retinoids plus the 3-drug combination, complete remission was obtained initially in 3 cases and partial remission in 4 cases. No change or remission to less than 50% occurred in 5 cases. Remission lasted 3–9 months (median 3 months) in the 3-drug treated group and 3–10 months (median 6 months) in the retinoid treated group.

Two cases (nos. 1 and 11) are still in remission after 9 and 13 months, respectively, both from the retinoid treated group. Relapse occurred in 4 cases in the 3-drug treated group and in 4 cases in the retinoid group.

Two patients, one in each group (cases 2 and 9) died of unrelated causes while in remission. Six cases in the 3-drug group and 4 in the retinoid group eventually died of the disease.

Gastro-intestinal complaints occurred in 5 cases and bone marrow depression in 1 case leading to reduction of the cyclophosphamide dosage to ½–⅓ of the initial dosages. Mucosal and skin dryness occurred in the majority of cases and caused reduction to ½ of the initial retinoid dosage. Cyclophosphamide induced haemorrhagic cystitis in 2 cases. In 1 of the cases cyclophosphamide treatment was stopped for 3 weeks and then, when the

Table I. *Clinical data of 8 patients with mycosis fungoides tumour stage treated with systemic chemotherapy (bleomycin, cyclophosphamide, prednisolone) and 12 patients with the same systemic chemotherapy combined with retinoids (etretinate or isotretinoin)*

Duration of the disease and duration of actual stage of the disease, respectively, is given in months. Stage of mycosis fungoides, see text. Response to treatment: (in brackets treatment time until response in months) CR = complete remission, verified by histology, PR = partial remission with >50% regression of lesions, NC = no change or remission <50%, PD = progressive disease. Initial response within 2 months of treatment, late response during treatment for more than 2 months. Total duration of treatment in months

Pat no.	Age	Sex	MF stage	Duration MF/stage	Retinoid type	Response		Total duration of treatment
						Initial (<2 m)	Late (>2 m)	
1	54	M	IVa	1 y 2 m	–	CR 2 m	PR 9 m	9 m
2	75	M	IVa	9 y 3 m	–	PR 1 m	PR 3 m	3 m
3	67	F	IVb	6 y 3 m	–	CR 2 m	PD 3 m	3 m
4	55	F	IVb	5 y 2 m	–	PR 1 m	PD 5 m	5 m
5	63	M	IVb	1 y 2 m	–	PR 2 m	PD 5 m	5 m
6	49	M	IVb	7 y 1 y	–	PD 1 m	–	2 m
7	62	F	IVb	8 y 4 m	–	PD 2 m	–	2 m
8	72	M	V	12 y 2 m	–	PD 1 m	–	1 m
9	81	M	III	2 y 5 m	etr	CR 1 m	–	3 m
10	58	F	III	7 y 4 m	etr	CR 1 m	PD 5 m	5 m
11	74	M	III	4 y 6 m	etr	PR 2 m	PR 13 m	13 m
12	70	M	III	2 y 6 m	etr	NC 2 m	NC 4 m	4 m
13	69	M	III	1 y 4 m	etr	NC 2 m	NC 4 m	4 m
14	54	M	IVa	4 y 8 m	etr	CR 2 m	PR 6 m	7 m
15	55	M	IVa	5 y 4 m	etr	PR 2 m	PR 8 m	8 m
16	66	M	IVb	3 y 1 y	etr	PR 2 m	PD 6 m	6 m
17	48	M	IVb	4 y 8 m	etr	NC 2 m	NC 4 m	4 m
18	44	F	V	2 y 6 m	etr	PR 2 m	PD 7 m	7 m
19	60	M	V	1 y 2 m	etr	NC 2 m	PD 3 m	3 m
20	64	M	V	3 y 2 y	iso	NC 2 m	PD 4 m	5 m

patient had recovered from the cystitis, cyclophosphamide was reinstituted in the dosage of 1 000 mg i.v. days 1 and 5 in combination with uromethexan. Slight pulmonary fibrosis was registered in 1 case causing withdrawal of bleomycin. The prednisolone dosage was reduced to less than ½ of the initial dosages in 3 cases due to development of Cushingoid features.

DISCUSSION

In mycosis fungoides, T cells multiply to form a clone of malignant lymphomatous cells with strong affinity for the epidermis, particularly observed in the early stage of the disease. As the cells proliferate they eventually lose their affinity for the epidermis and then disseminate to lymph nodes and viscera (3). Claudy et al. (4) speculated whether transformation of an epidermotropic infiltrate into a more aggressive non-epidermitropic infiltrate by retinoids might facilitate the progression of the disease, causing the malignant cells to lose their affinity for epidermis and permitting invasion of internal organs. When retinoids were used as single drug treatment we have, however, seen no evidence of such a tendency to progression in mycosis fungoides patients (5).

In the present series we have not seen any progression of the disease in the retinoid group, as compared to the 3-drug group, which could support the hypothesis of increased dissemination caused or facilitated by the retinoids.

On the contrary, in our experience the addition of retinoids to the chemotherapy regimen seems to be an advantage although it is hard to draw definite conclusions from a limited number of cases as in the present study.

In this series, the majority of cases were treated with etretinate and only one with isotretinoin and it is therefore not possible to evaluate any difference between the two types of retinoids in this respect. However, in another study where retinoids were used as single drug treatment of various stages of mycosis fungoides including tumour stages, we could not, however, find any difference between the efficacy of etretinate and isotretinoin (5).

Probably, the retinoids modify cell proliferation and differentiation (6) and there is evidence that the antineoplastic activity of retinoids is mediated by stimulation of the host-immune response to tumour antigens (7). It remains an open question whether one of these mechanisms is mainly responsible for the effect of retinoids in mycosis fungoides or whether it is a combined effect.

We conclude that the addition of oral retinoids to systemic chemotherapy regimen seems to be an advantage in advanced cases of mycosis fungoides, in particular in the induction phase of the treatment. We also think that retinoids should be used as longterm treatment even after remissions have been obtained and the systemic chemotherapy is withdrawn in order to attempt to prolong the relapse-free period. This proposal needs to be verified in larger patient samples.

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