13-cis-Retinoic Acid Effective in Mycosis fungoides

A Report from the Scandinavian Mycosis Fungoides Group

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Twenty patients with mycosis fungoides and four with Sézary's syndrome were treated with 13-cis-retinoic acid as single therapy in an intitial dose of 1 to 2 mg per kg body weight in most cases. Complete remission in mycosis fungoides was obtained in six cases (33%) and partial remission in another ten cases (50%). No convincing response was observed in three cases, and progression of limited nodular lesions occurred in one case. In cases responding to treatment the first sign of remission was observed within two to four weeks. Our short-term experience is that the drug is effective in early as well as advanced stages of mycosis fungoides. Patients with Sézary's syndrome, however, did not respond to the same extent. (Received March 15, 1984.)

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As well as naturally occurring forms of vitamin A, synthetic retinoids can prevent experimental cancer. It has been shown that synthetic vitamin A promotes cellular differentiation and maturation and inhibit cellular proliferation both in experimental cancer and in human malignant diseses including those of epithelial origin (1, 2, 5). The retinoid 13-cis-retinoic acid has also been demonstrated to have an effect not only on benign skin disorders but also on malignant skin tumours. Recently Kessler et al. (3) used 13-cis-retinoic acid in the treatment of 4 patients with mycosis fungoides with complete clearing in one and pronounced improvement in three. Further Warrell et al. (7) reported improvement in three of seven patients with cutaneous T-cell lymphoma. Prompted by these promising results we have treated 24 patients with mycosis fungoides and Sézary's syndrome with surprisingly good results.

MATERIALS

Twenty-four patients from the Scandinavian Mycosis Fungoides Group were treated with 13-cis-retinoic acid (Roaccutan®). The clinical data of the patients are given in Table I. There were twenty cases of mycosis fungoides. Three of them were in plaque stage with histology suggestive but not conclusive of mycosis fungoides (MF I). The other seventeen cases were all histologically verified: eleven in plaque stage (MF II), five in tumour stage without signs of extracutaneous spreading (MF III) and one in tumour stage with lymphomatous involvement of lymph nodes (MF IV). Four cases with histologically verified Sézary's syndrome were also treated. The initial dosage varied from 2 mg in most cases to 0.1 mg per kg body weight per day. Due to side effects such as mucocutaneous dryness the dosage was usually subsequently reduced to 0.2 to 0.5 mg per kg body weight. The duration of treatment varied from 2 weeks to 6 months.

RESULT

Complete remission was obtained in six cases (5 plaque stage, 1 tumour stage) and partial remission with more than 50% regression of lesions was seen in eleven cases (7 plaque stage, 3 tumor stage, 1 Sézary's syndrome). In 6 cases no convincing response was observed (1 plaque stage, 2 tumour stage, 3 Sézary's syndrome). Progression of limited nodules on a foot was seen in one case in plaque stage, in whom the remaining plaque lesions went into partial remission.

In cases responding, the first sign of remission was observed as early as within two to four weeks after treatment was started and was heralded by decreasing itching. Complete remission was established within two months.

Alopecia mucinosa occurring in two cases of the mycosis fungoides plaque stage disappeared completely during an early phase of the treatment. Partial remission with virtual clearing of the skin lesions was seen after three to four weeks in two patients having extensive tumours and ulcerations. Enlarged lymph nodes involved by lymphoma present in one of these patients underwent regression which was also verified by lymphangiography.

In three out of four patients with Sézary's syndrome no beneficial response was noted but rather a pronounced exfoliation and increased redness of the skin for which reason treatment was discontinued.

In four cases of mycosis fungoides plaque stage an increased scaly redness of the plaques was observed.

DISCUSSION

The mechanism of action of retinoids in cancer prevention and therapy still remains unknown. Although there is some evidence that retinoids have effects on cellular immunity (5) this is not necessarily the only possible anti-tumour mechanism. Squamous metapla-

Table I. *Clinical data of 24 patients treated with 13-cis-retinoic acid*

MF I: clinical, but histological non-diagnostic, mycosis fungoides. MF II: mycosis fungoides plaque stage. MF III: mycosis fungoides tumor stage. MF IV: mycosis fungoides with lymphomatous involvement of lymph nodes. SS: Sézary's syndrome. The dosage of 13-cis-retinoic acid is given as mg per kg body weight per day initially—after reduction. Response to treatment (in brackets treatment time until response in weeks): CR: complete remission, verified by histology, PR: partial remission with >50% regression of lesions. NC: no change or remission <50%. PD: progressive disease. Total duration of treatment in months

Pat. no.	Age	Sex	Diag-nosis	Retinoid dosage	Response	Total dura-tion of treatment	Comments
1	46	F	MF I	1–0.5	CR (4 w.)	5 mo.	Circumscript dermatitis Transversal nail banding
2	64	M	MF I	2–0.5	CR (6 w.)	3 mo.	Circumscript dermatitis
3	55	F	MF I	0.5	PR (3 w.)	4 mo.	
4	85	M	MF II	2–0.5	CR (4 w.)	5 mo.	Alop. mucin.
5	75	M	MF II	2–0.5	CR (8 w.)	3 mo.	
6	36	F	MF II	1–0.5	CR (6 w.)	3 mo.	
7	60	M	MF II	1–0.3	PR (2 w.)	6 mo.	Alop. mucin.
8	67	F	MF II	0.5–0.5/week	PR (2 w.)	4 mo.	
9	80	F	MF II	0.3	PR (2 w.)	4 mo.	Circumscript dermatitis
10	30	F	MF II	0.2–0.4	PR (4 w.)	1 mo.	
11	69	M	MF II	0.5	PR (4 w.)	1 mo.	Circumscript dermatitis
12	61	M	MF II	0.5	PR (3 w.)	1 mo.	
13	64	M	MF II	2–1	NC	2 mo.	
14	81	F	MF II	2–1	PD	4 mo.	
15	75	M	MF III	1–0.5	CR (6 w.)	5 mo.	
16	77	M	MF III	2	PR (3 w.)	2 mo.	
17	63	F	MF III	0.5	PR (2 w.)	2 mo.	
18	76	F	MF III	0.2	NC	1 mo.	
19	33	F	MF III	2–1	NC	2 mo.	
20	75	M	MF IV	2–1.5	PR (3 w.)	5 mo.	
21	65	M	SS	0.2	PR (2 w.)	2 mo.	
22	61	M	SS	1–0.1	NC	2 mo.	Exfoliation
23	64	F	SS	2–0.2	NC	1 mo.	Exfoliation
24	68	M	SS	0.5–0.2	NC	1 mo.	Exfoliation

sia produced by carcinogens can be inhibited or reversed by retinoids (4, 6). This action seems to be opposite to that of tumour promoters, the drug thus acting as an anti-promoter.

The response to 13-cis-retinoic acid therapy has been rapid in the present series. In cases responding the first sign of remission was observed after two months. If no effect at all is obtained within two to three months it is our impression that further treatment is probably without value.

In this report we have shown that treatment with 13-cis-retinoic acid resulted in a pronounced improvement in 17 out of 24 cases with cutaneous T-cell lymphoma in various stages.

Sézary's syndrome apparently does not respond to this kind of treatment to the same extent as mycosis fungoides. In addition the Sézary patients were much more sensitive as regards mucocutaneous side effects.

Our present experience, which is still of a short-term nature, is that 13-cis-retinoic acid is undoubtedly effective in early as well as advanced stages of mycosis fungoides. Whether it should be used as a single drug or as part of a combination regimen including chemotherapeutic agents is a matter still left unsettled.

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