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TREATMENT OF CUTANEOUS T-CELL LYMPHOMA (MYCOSIS FUNGOIDES) WITH 13-CIS-RETINOIC ACID

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Summary Four patients with refractory cutaneous T-cell lymphoma (mycosis fungoides) were treated with 13-cis-retinoic acid. Near complete clearing of extensive tumours and plaques was seen in one patient, who remains in partial remission with continued improvement after fifteen months. Two patients showed improvement in pruritus and 50% reduction in plaques by four and six weeks, respectively. The fourth patient had improvement in pruritus and clearing of plaques, but dryness and scaling necessitated reduction and eventually withdrawal of the treatment.

Introduction

VITAMIN A is necessary for normal epithelial cell maturation.¹ Synthetic derivatives of vitamin A (retinoids) can inhibit proliferation and cause differentiation and maturation in malignant disease of epithelial and non-epithelial origin.²⁻¹³ Lately, retinoids have been shown to alter T lymphocyte maturation.¹⁴ We and others have demonstrated potent effects of the retinoid 13-cis-retinoic acid on non-malignant and malignant skin conditions,^{5,15,16} and have now tried this agent in four patients with generalised plaques and erythroderma due to mycosis fungoides.

Case Reports

Case 1

A 39-year-old man presented with a 10-year story of pruritus with nodules and plaques involving 80-90% of the skin surface (figs 1 and 2). Therapy had included topical and systemic corticosteroids, topical nitrogen mustard, electron beam therapy, photochemotherapy with psoralens and ultraviolet light (PUVA), and systemic

cytotoxic chemotherapy with single agent methotrexate and combinations of cyclophosphamide, vincristine, prednisone, and levamisole and later of vincristine, 1,3-bis(2-chlorethyl)-1-nitrosourea (BCNU), doxorubicin, and prednisone. Topical BCNU had given temporary 50% clearing of plaques but the lesions were progressing after 1 year. A short course of oral vitamin A 5 years previously had produced no response.

On physical examination he had total alopecia and 90% of the skin surface was affected by scaly erythematous plaques and nodules. A 2 cm axillary lymph node was palpable. There was no hepatosplenomegaly. A skin biopsy specimen showed hyperkeratosis and atypical mononuclear cells infiltrating the dermal and perivascular tissues. Pautrier's microabscesses were present, consistent with mycosis fungoides. Laboratory indices of hepatic and renal function, serum lipids, and blood picture were normal; in the buffy coat no abnormal cells were seen on light microscopy or electron microscopy. Chest roentgenogram was normal.

He was treated with 13-cis-retinoic acid ('Accutane') 3 mg/kg per day by mouth. After four weeks he noticed increased scaling but his pruritus had diminished and he was more mobile. His skin lesions gradually improved and after ten months the pruritus had almost

Fig 1—Pretreatment photograph of patient 1 showing generalised tumours and plaques of mycosis fungoides.

Fig 2—Close-up photograph of upper arm of patient 1 before treatment.

Fig 3—Patient 1 twelve months after start of 13-cis-retinoic acid. Tumours and plaques have regressed and extensive depigmentation has occurred

Fig 4—Patient 4 before and one month after start of treatment with 13-cis-retinoic acid.

ceased and the tumours and plaques occupied only 20% of the skin surface (fig 3). After fifteen months the plaques involved 10–15% of the skin surface, pruritus remained under control, and there was no evidence of extracutaneous involvement. At no time were there serious toxicity effects from the retinoid; skin dryness was easily controlled with emollients.

Case 2

A man of 68 presented with a 4-year history of red, scaly, pruritic rash refractory to topical steroids. He had erythematous plaques on buttocks, back, and arms, and skin biopsy was consistent with mycosis fungoides, showing Pautrier's microabscesses and mononuclear cell infiltration.

He was started on oral 13-cis-retinoic acid 2 mg/kg per day. After one month the plaques had decreased by 50% and pruritus was reduced. Because of skin dryness, the retinoid dose was reduced to 1 mg/kg per day.

Case 3

A man of 63 was evaluated for a pruritic rash of 7 years' duration. He had erythematous plaques involving 90% of the skin surface. Skin biopsy, examined by light and electron microscopy, was consistent with mycosis fungoides. He was treated with 13-cis-retinoic acid 2 mg/kg per day, reduced to 1 mg/kg per day after one month because of scaling and dryness. After six weeks his scaling had improved and the skin plaques had decreased by 50%.

During his staging evaluation he was found to have a hilar mass on chest roentgenogram and mildly raised liver enzymes. On further investigation he proved to have extensive undifferentiated small-cell lung cancer; the retinoid was therefore stopped and combination chemotherapy was initiated.

Case 4

A woman of 66 had a 4-year story of generalised erythroderma, scaling, and pruritus resistant to all treatment. She had total alopecia and 90% involvement of the skin with an exfoliative dermatitis and extensive plaques. Skin biopsy was histologically and immunologically consistent with mycosis fungoides. She was treated with 13-cis-retinoic acid 2 mg/kg per day. After four weeks the plaques had cleared and her pruritus had improved (fig 4). She could not, however, tolerate the skin dryness and scaling and the dose was reduced to 0.25 mg/kg and then 0.1 mg/kg per day. Because of continued dryness the retinoid was eventually withdrawn. Shortly thereafter her disease activity increased, requiring other investigational therapy.

Discussion

Previous reports have suggested possible benefit from retinoids in mycosis fungoides. Claudy et al¹⁷ described improvement of nodular lesions in a 77-year-old patient with cutaneous T-cell lymphoma; they used an ethyl ester derivative of retinoic acid (RO-10-9359) at 1.0 mg/kg per day. On withdrawal of the drug after four months, the patient relapsed. Zachariae¹⁸ reported complete remission in eight of ten patients treated with a complex regimen including retinoids. Conversely, no response was seen in six patients concurrently treated without additional retinoids. However, other major differences in the treatments obscured the contribution of retinoids to the observed responses. In our investigation, all four patients responded to oral 13-cis-retinoic acid.

The skin lesions of cutaneous T-cell lymphoma are characterised by epidermal infiltration with atypical mononuclear cells, and most patients have an infiltrate of helper T-cells.^{19,20} Lately, natural killer lymphocyte activity has been reported lower in leukaemic and non-leukaemic cutaneous T-cell lymphomas than in normal controls.²¹ Antitumour activity has been attributed to these natural killer

cells.²² Whether retinoids exert an effect on natural killer lymphocyte activity is unknown, but other immunological effects have been observed.

Retinoids influence the immune function of epidermal mononuclear cells and vitamin A has been seen as a possible immunological adjuvant.^{14,23–27} Dennert showed that retinoic acid enhances antigen specific cytotoxic T-cell activity,¹⁴ and Sidell found that retinoids enhance blastogenesis in thymus and tonsil derived lymphocytes but not in those derived from the spleen or peripheral blood.²⁸ Thus, there is ample evidence that retinoids could influence tumour activity by their effects on immunity, although this is not the only possible anti-tumour mechanism.^{13,29,30}

Our experience and that of others justifies further clinical investigation of retinoids in the treatment of cutaneous T-cell lymphoma.

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