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Isotretinoin and Cutaneous Helper T-Cell Lymphoma (Mycosis Fungoides)

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• **Retinoids, including isotretinoin, have demonstrated antiproliferative and antineoplastic activity in laboratory and clinical trials. In a phase II trial, 25 patients with extensive mycosis fungoides were evaluated for response to isotretinoin. There was a 44% (11 patients) objective clinical response rate with three clinical complete responses without concomitant evidence of pathologic clearing of the disease. An additional 24% (six patients) showed a minor degree of clinical improvement. The median time to response was two months (range, 0.5 to eight months) and the median response duration was eight months or longer (range, one to 25 months). Chronic toxic reactions consisted primarily of drying of the skin and mucous membranes and resulted in dose reduction in the majority of patients. It is concluded that isotretinoin produces significant clinical benefit to some patients with mycosis fungoides.**

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Vitamin A and its analogues, the retinoids, have demonstrated antiproliferative activity in a number of malignant and premalignant conditions.[1-5] In the laboratory, these agents can block phenotypic cell transformation induced by radiation, chemical agents, and growth factors.[6,7] Additionally, they have induced cellular maturation in promyelocytic leukemia and neuroblastoma cells in culture[8,9] and have demonstrated the capability to modulate a number of immunologic functions, particularly cell-mediated cytotoxicity.[10,11] These promising features have prompted clinical evaluation of these compounds in a variety of cancerous and precancerous lesions as well as in benign proliferative disorders.

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For editorial comment see p 189.

Mycosis fungoides is an indolent cutaneous T-cell lymphoma for which a number of partially successful treatments have been used, including electron beam irradiation to the skin surface, topical mechlorethamine, and oral methoxsalen plus ultraviolet A light (PUVA). We have previously reported our experience with isotretinoin in a broad phase II anticancer trial that included four patients with mycosis fungoides, all of whom achieved an objective response.[12] Because of this encouraging initial experience, we have treated 21 additional patients with mycosis fungoides. In our total group there were three complete responses and eight additional partial responses.

PATIENTS AND METHODS

Patients with clinically and histologically documented mycosis fungoides or Sézary syndrome were eligible. Pathologic evaluation included light microscopy, electron microscopy, and immunopathologic study (indirect immunofluorescence with OKT3, OKT4, and OKT8) of skin biopsy specimens (performed by N.L. or P.J.L.). All biopsies were performed and specimens reviewed by University of Arizona (Tucson) pathologists. All patients were required to have at least advanced plaque stage disease (Committee on Staging and Classification of Cutaneous T-Cell Lymphomas, skin stage T2 or greater).[13] No exclusions were made for lymph node or visceral involvement, previous treatment, or reduced performance status. Informed consent was obtained in all cases in a protocol approved by the University of Arizona Institutional Review Board.

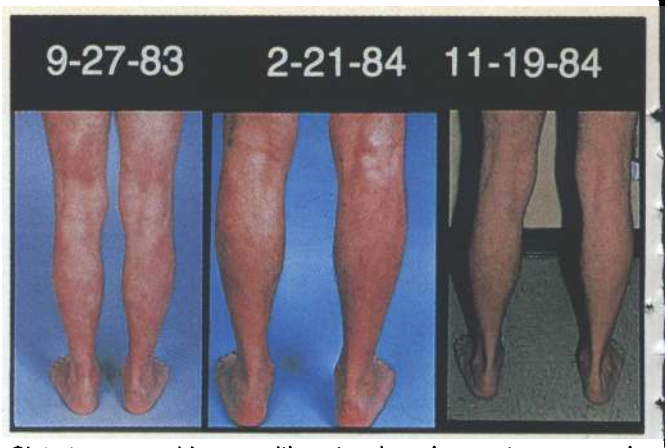
Patient evaluation included a history and physical

Table 1.—Characteristics of Patients* With Mycosis Fungoides Treated With Isotretinoin

Characteristics	No. (%)
Stage	
Skin	
Plaques (T2)	15 (64%)
Nodules (T3)	3 (12%)
Erythroderma (T4)	7 (27%)
Adenopathy	
Present	10 (40%)
Absent	15 (64%)
Visceral involvement	0 (0%)
Blood involvement	5 (20%)
Prior treatment	
None	3 (12%)
Topical steroids	20 (80%)
Prednisone	8 (32%)
Topical mechlorethamine carmustine	7 (28%)
PUVA†	7 (28%)
Electron beam radiation therapy	8 (32%)
Systemic chemotherapy	9 (36%)
≥3 modalities	10 (40%)

*The mean age of the patients was 65 years (range, 42 to 93 years). There were 18 male and seven female patients.

†PUVA indicates oral methoxsalen plus ultraviolet A light.



Sixty-two-year-old man with extensive plaque-stage mycosis fungoides over his entire body (his face was spared). Representative baseline photographs of his legs are shown at left. He was started on a regimen of isotretinoin, 1 mg/kg/d, and partial clinical response was noted after five months of therapy (center). Although his skin lesions subsequently completely cleared and clinical complete response was obtained (as represented in photograph at right), biopsy specimen of previously involved skin revealed residual atypical lymphocytes. His clinical response continues with low-dose (10 mg daily) maintenance isotretinoin therapy for more than 21 months.

examination, complete blood cell count and differential cell count, examination of the buffy coat by light microscopy for Sézary cells, routine fasting blood chemistry studies and lipid profile, retinoid blood levels, color photographs of skin involvement, and a baseline toxic reaction evaluation. Appropriate roentgenograms and scans were obtained only for suspected visceral involvement. Follow-up of patients was generally at monthly intervals.

In the first 16 patients, treatment consisted of isotretinoin initiated at a dose of 2 mg/kg/d orally in single or divided doses. Reduction in dose was allowed in accordance with previously published toxicity scales.[14] Subsequent patients were started at lower doses (1.0 mg/kg/d). Treatment was continued until disease progression or intolerable toxic reactions ensued. Response durations were calculated from the time of initial response. The clinical response criteria were as follows: A *complete clinical response* (CCR) was defined as complete disappearance of all lesions lasting at least four weeks. In those patients achieving a CCR, a biopsy specimen of the previously most-involved areas was obtained one month following a clinical complete remission. A *partial response* (CPR) was at least a 50% decrease in assessable lesions that lasted at least four weeks, while a *minor response* involved definite improvement but less than a CPR. Disease progression was characterized by the unequivocal appearance of new lesions or a greater than 25% increase in size of the old lesions.

RESULTS

Twenty-eight patients were entered in the study. Three were rendered ineligible because of a lack of follow-up information (one patient) or because of being reclassified on review as having the more aggressive entity, peripheral T-cell lymphoma (two patients). These two patients developed early visceral involvement and died shortly thereafter. The characteristics of the 25 assessable patients are shown in Table 1. The mean age was 65 years, with a range of 39 to 93 years. Eighteen patients were male and seven were female. Skin involvement included advanced plaques composed of more than 10% of the skin surface in 15 patients, tumor nodules in three patients, and erythroderma in seven patients. Palpable adenopathy was present in ten patients: four of these had lymph nodes that were soft and small. Two patients underwent lymph node biopsy and specimens from both revealed involvement with atypical lymphocytes consistent with mycosis fungoides. No patient had detectable visceral involvement. Blood involvement with Sézary cells was found in five patients, with greater than 5% of circulating lymphocytes in three patients. Seven patients had received one prior treatment modality, six individuals had received two, and ten had been treated with three or more modalities. Two patients had not received prior treatment.

There were 11 (44%) objective clinical responses to isotretinoin. An example of an objective clinical response is shown in the Figure and described in the legend. Three CCRs were noted with total disappearance of all visible skin lesions; however, random skin biopsy specimens of previously involved skin revealed residual atypical lymphocytes in the epidermis. Eight patients achieved CPRs. Objective responses occurred with advanced plaques (seven [43%] of 15) and with erythroderma (four of seven), but not with tumor nodules (T3) (zero of three). There were three responses noted among the nine patients who had received three or more prior treatments. Palpable adenopathy improved in the three

responders with palpable nodes; however, two of these patients had small soft nodes, and the third had no residual adenopathy following biopsy.

In addition to the 11 patients with significant responses, there were six patients with minor responses. The improvement in these latter patients was characterized by reduction in pruritus and a decrease in the degree of plaque infiltration but with minor change in plaque area. Seven patients had no response to the retinoid.

The time from initiation of treatment to clinical response (CCR and CPR) ranged from two weeks to eight months, with a median of two months. The median duration of response (CCR and CPR) was more than eight months, with a range of one to 25 months. Patients continued to receive isotretinoin as long as stabilization or response was clinically evident.

TOXIC REACTIONS

The toxic reactions that were encountered are shown in Table 2. Most problems involved drying of the skin and mucous membranes and were usually controlled with emollients or reductions of the retinoid dose. Additional effects included mild to moderate fatigue, arthralgias, myalgias, minor mental status changes (usually irritability), and mild to moderate headache.

The only laboratory change detected was in the fasting serum triglyceride levels that occurred early in the treatment course. The mean baseline triglyceride level was 205 mg/dL (2.31 mmol/L) (range, 89 to 395 mg/dL [1.00 to 4.46 mmol/L]) and the mean peak triglyceride level with treatment was 463 mg/dL (5.23 mmol/L) (range, 151 to 1485 mg/dL [1.70 to 16.77 mmol/L]). Posttreatment levels returned promptly to baseline at 172 mg/dL (1.94 mmol/L) (range, 90 to 285 mg/dL [1.02 to 3.22 mmol/L]). Individuals with initially elevated triglyceride levels experienced the largest changes. No symptomatic hypertriglyceridemia was encountered. There were no treatment-related changes in cholesterol level, liver enzymes, or renal function. One patient's serum creatinine concentration increased with treatment but was best ascribed to her underlying renal disease. No hematologic toxic reactions were encountered.

Dosage adjustments were needed in most patients, usually due to skin and mucous membrane dryness or fasting hypertriglyceridemia. Of the 16 patients starting treatment with 2 mg/kg/d, 14 patients required dose reductions (usually to about 1 mg/kg/d), 12 for mucous cutaneous side effects and two for markedly elevated hypertriglyceridemia. One patient tolerated an increase in dose to 3 mg/kg/d. Of six patients starting treatment with less than 2 mg/kg/d, two patients required dose reductions and two tolerated increases. Responses were seen at all dose levels whether initiated at 2 mg/kg/d or less. Sustained responses as long as 15 months or more have been noted with doses as low as 10 to 20 mg daily in several patients whose plaques cleared at higher doses but who were unable to tolerate these higher levels because of continued cutaneous toxic reactions.

Table 2.—Side Effects in 25 Patients Treated With Isotretinoin

Toxic Reaction	Percent of Patients		
	Mild	Moderate	Severe
Dry skin	36	36	20
Cheilosis	32	28	0
Conjunctivitis	20	36	0
Fatigue	16	12	8
Arthralgia/myalgia	20	8	8
Mental status change	16	8	0
Headache	20	8	0

COMMENT

We have demonstrated that isotretinoin produces an objective clinical response rate of 44% (11 patients) with significant improvement in an additional 24% (six patients) of patients with mycosis fungoides. Similar results have been noted by others using this retinoid and other derivatives as well. Warrell et al[15] reported responses in three of seven patients treated with isotretinoin, and a report by the Scandinavian Mycosis Fungoides Study Group described objective responses in 19 of 24 patients treated with isotretinoin.[16] Mahrle et al,[17] using an arotinoid noted CCRs in three of five patients and one CPR. Arotinoid responses occurred in the plaque- and tumor-stage of the disease but not in one patient with Sézary syndrome. Claudy and Rouchouse[18] reported improvement in 11 patients with parapsoriasis en plaques treated with the ethyl ester retinoid derivative (Etretinate).[18] Pathologically, they noted clearing of intraepidermal infiltrates, including Pautrier microabscesses. These studies and our report substantiate that retinoids can suppress or reverse the clinical manifestations of mycosis fungoides.

As has been found with other dermatologic conditions, different retinoids may exhibit different degrees of activity in the treatment of specific diseases. A large number of retinoids have been developed using laboratory systems, many of which exhibit more favorable therapeutic indexes than isotretinoin. It remains to be determined whether isotretinoin is the most active retinoid in mycosis fungoides.

Retinoid treatment should probably not supplant such standard treatment methods as electron beam radiation therapy, a topical nitrogen mustard, or PUVA, as these have resulted in long-term disease control.[19,20] The majority of patients relapse and require further therapy, however, and retinoids may be a relatively nontoxic, relatively effective alternative. Cytotoxic therapy, while demonstrating activity in this disease, is accompanied by considerable potentially debilitating or even life-threatening toxic reactions and is not considered curative.[21]

Other therapeutic strategies should also be explored. Combinations of retinoids with interferon, an active agent for the treatment of mycosis fungoides,[22] would be plausible, perhaps allowing dose reductions of both agents. Additionally, the use of retinoids in patients at high risk of relapse following electron beam radiation therapy (ie, advanced disease) should be evaluated as a maintenance regimen, as has been successfully done with topical mechlorethamine.[19]

Isotretinoin produces significant clinical response of mycosis fungoides in heavily pretreated patients. We recommend a starting dose of 1 mg/kg/d in two divided doses. In some cases cutaneous toxic reactions from the drug were initially difficult to distinguish from progress or flare of the disease. In such situations the dose was decreased by 50% to determine the appropriate interpretation. The role of isotretinoin in previously untreated patients remains to be determined, but we recommend that isotretinoin be used after more conventional simple measures, such as topical steroids and perhaps PUVA, have been exhausted. Alternatively, use of isotretinoin with topical steroids may be well worth considering.

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