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Activity of Isotretinoin Against Squamous Cell Cancers and Preneoplastic Lesions^{1,2}

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SUMMARY

We investigated the effect of the synthetic vitamin A derivative isotretinoin (13-*cis*-retinoic acid) on advanced cancers in 103 patients and on preneoplastic lesions in five patients. Six of 14 patients with squamous cell epithelial cancers had objective regressions of skin or subcutaneous metastases. Three of five patients with preneoplastic lesions had objective responses. The major dose-limiting toxic effects were reversible dermatitis, emotional lability, and headaches. We conclude that the growth of some squamous cell epithelial malignancies can be inhibited by isotretinoin and suggest that other retinoids should be evaluated as antitumor agents.

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Vitamin A is necessary for the normal development of all epithelial tissues (1). This vitamin and its natural and synthetic derivatives (retinoids) have shown significant activity as chemopreventive agents in numerous animal systems, whether the tumor was initiated by chemical or by physical carcinogens (2,3). The retinoids have also shown antiproliferative activity against a large number of animal and human malignant cell lines (4-9). The growth-suppressive effect against cell lines from melanoma (7-9), teratocarcinoma (10), and promyelocytic leukemia (11) has been accompanied by differentiation. In tests on fresh biopsy material from human tumors, we have also observed that retinoids can

sometimes inhibit tumor colony formation in soft agar (12,13). Furthermore, several of the retinoids, including the synthetic vitamin A derivative isotretinoin (13-*cis*-retinoic acid), have shown antiproliferative activity against such dermatologic conditions as psoriasis, rare epithelial dysplasias, and basal cell carcinomas (14,15). No serious cytotoxic effects were recorded in these investigations or in the treatment of a large number of patients with conglobate acne (16).

These results suggest that in addition to chemopreventive effects retinoids may have antineoplastic activity. We have therefore conducted a broad phase II trial of isotretinoin to assess its antineoplastic activity and have detected activity in preneoplastic and neoplastic lesions of squamous cell histology.

MATERIALS AND METHODS

Patient characteristics.—Patients were eligible for treatment with isotretinoin if they had advanced cancer or aggressive preneoplastic conditions with measurable disease that could be evaluated for regression. Patients with advanced cancer received isotretinoin at a dose of 3 mg/kg/day orally, while patients with preneoplastic lesions were started at a dose of 2 mg/kg. These doses were empirically selected based on the extensive experience with iso-

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TABLE 1.—Patient distribution and response rate of eligible and evaluable patients treated with isotretinoin

Histologic class	No. of patients	No. (%) of responses*	
		Including mixed responses	Excluding mixed responses
Epithelial†			
Squamous cell			
Advanced	24	6 (25)	2 (8)
Low-grade (preneoplastic)	5	3 (60)	3 (60)
Non-squamous cell	45	1 (2)	1 (2)
Malignant melanoma	13	1 (7)	1 (7)
Nonepithelial†	21	0	0

*Responses include only mixed, partial, and complete; improvements are not included.

†Tumor types included: epithelial squamous cell, high-grade (8 lung, 10 head and neck, and 6 other); epithelial squamous cell, low-grade (3 multiple basal cell, 1 keratoacanthoma, and 1 epidermal dysplasia verruciformis); epithelial non-squamous cell (8 breast, 12 ovarian, 12 colon, 4 bladder, and 9 miscellaneous); and nonepithelial (3 choriocarcinoma, 5 lymphoma, 4 leukemia, and 9 miscellaneous).

tretinoin against dermatologic lesions (14–16). In a pilot study, doses were escalated by 0.5-mg/kg increments every 1–2 weeks to limiting toxicity in the first 16 patients with advanced cancer. It became clear that most patients (12 of 16) would not tolerate > 4 mg/kg of isotretinoin for much longer than 3–4 weeks. Therefore, subsequent patients were started and maintained at a dose of 3 mg/kg of retinoid, and the toxic effects cited represent side effects at this level of drug. To be eligible for evaluation, patients could not have received chemotherapy within 4 weeks or radiation therapy within 16 weeks of entering the study, and they had to receive daily therapy with isotretinoin for a minimum of 1 month.

Response criteria.—Response criteria were the following: *complete response*—the disappearance of all measurable disease; *partial response*—a > 50% decrease of the sum of the products of the perpendicular diameters of all measurable lesions; *mixed response*—a > 50% decrease in a measurable disease site while other sites of disease showed no regression; *improvement (minor response)*—a > 25% but < 50% decrease in total measurable disease; and *progression*—a > 25% increase of any disease parameter.

Evaluation for toxicity.—Patients were serially monitored. A careful physical examination was done every 2 weeks, and liver function studies (LDH, SGOT, SGPT, bilirubin), cbc, and prothrombin time were done monthly. These studies were also repeated when the patient discontinued therapy. A radionuclide liver/spleen scan was obtained in all patients who had been receiving therapy for at least

4 months and was repeated every 4 months thereafter.

RESULTS

A total of 143 patients were entered in this investigation. Thirty-five patients were considered ineligible or inevaluable for the following reasons: no objectively evaluable disease (18 patients), early death (nine), discontinuation of isotretinoin after 2–3 weeks secondary to “rapid progression” (five), and intolerable cutaneous side effects (three).

Results are reported for 108 eligible and evaluable patients. The patient distribution and responses were grouped by histologic class (table 1). Considerable activity of isotretinoin was seen in patients with squamous cell epithelial disease (table 1). The six objective responses in cancer patients and the responses of the three patients with preneoplastic lesions are detailed in table 2. All responses occurred in subcutaneous or skin disease sites. In 45 patients with non-squamous cell epithelial malignancies, one partial response was seen in a patient with ovarian cancer which included a > 50% decrease in a large pelvic mass and complete disappearance of refractory ascites. This response lasted for 2 months, when the patient discontinued therapy unexpectedly on her own volition. Two minor responses (1-month duration) of skin disease from breast cancer were also seen.

Thirteen patients with metastatic malignant melanoma were treated, and one patient had a > 50% decrease in a large (13 × 10-cm) subcutaneous mass

TABLE 2.—Details of responses of patients with neoplastic or preneoplastic squamous cell disorders to isotretinoin

Patient No.	Diagnosis	Prior treatment	Response description	Response	Response duration (mos)
<i>Neoplastic Disorders</i>					
97	Squamous cell, nasopharynx	5 drugs + radiation therapy	50% decrease in 8 × 5-cm neck mass	Partial	2
123	Squamous cell, epiglottis	Methotrexate	75% decrease in massive (> 12 × 10-cm) neck and jaw mass; resolution of periorbital edema	Partial	2
139	Squamous cell, lung	Radiation therapy	50% decrease in 7 × 9-cm jaw mass; bone lesions stable	Mixed	2
145	Squamous cell, lung	Radiation therapy	Disappearance of axillary lesion (2 × 3-cm); no change in opacified chest roentgenogram	Mixed	7
80	Squamous cell, ear	Radiation therapy	Disappearance of 3 finger lesions and 1 arm lesion; other lesions stable	Mixed	1
3	Squamous cell, face	Multiple surgery, radiation therapy	Remodeling of face; stable orbital lesion	Mixed	10
<i>Preneoplastic Disorders</i>					
109	Keratoacanthomas	Multiple surgery	Disappearance of 24 of 25 lesions, resected (0.5-2-cm)	Partial	12+
43	Multiple basal carcinomas	Concurrent radiation to 2 large face lesions	Complete response of several unirradiated areas; partial response of additional areas	Partial	16+
154	Epidermal dysplasia verruciformis	None	Resolution of 50% of total mass of multiple lesions	Partial	2*

*Discontinued due to skin toxicity; prompt relapse followed.

for 4 months. No responses were seen in 21 patients with nonepithelial malignancies. The pretreatment characteristics of the patients who responded to isotretinoin did not appear to vary significantly from those of patients who did not respond. Careful stratification and more extensive studies of patients with squamous cell malignancies and malignant melanoma are needed and will be required to substantiate this conclusion.

The side effects of isotretinoin at 3 mg/kg are shown in table 3. No bone marrow or hepatic toxicity was recorded. Nausea and vomiting were very mild. Two patients discontinued therapy secondary to skin toxicity after 6 weeks of therapy, and four patients discontinued therapy secondary to emotional lability or headaches after 6, 8, 12, and 16 weeks of therapy. Twenty-three patients also had serial lipid value measurements. Increases in plasma triglyceride levels were recorded in 12 patients. Isotretinoin was not discontinued, and in six patients who lived long enough, additional serum lipid values were obtained 1 month after completing therapy. Plasma triglyceride levels had returned to normal.

DISCUSSION

In the past decade, therapeutic activity of isotretinoin has been reported in numerous dermatologic conditions (15-17). The present study suggests that isotretinoin has antitumor activity in advanced squamous cell epithelial cancers. Our results also confirm that isotretinoin has antiproliferative activity in preneoplastic lesions such as keratoacanthomas (18) and basal cell carcinoma (15). Bollag (19) had noted previously that epithelial tumors of the skin were affected by retinoids. The responses documented here demonstrate that isotretinoin can also inhibit neoplastic squamous cell epithelial lesions in cutaneous and subcutaneous sites. The site selectivity of many of the responses is of interest and warrants further investigation with regard to mechanism.

The biologic actions of retinoids are probably mediated both indirectly by host cells (20,21) and by a number of mechanisms (22). Data suggest that a major effect is modulated through an intracellular binding protein. This receptor molecule has been

TABLE 3.—Toxicity of isotretinoin in phase II trial

Type of effect	Patient reaction
Bone marrow	None
Hepatic	None
Joint pain	Mild (10%–15%)
Nausea and vomiting	6 patients (mild); 2 patients discontinued
Skin and mucosa*	Mild (95%); 2 patients discontinued, 6 patients lowered dose
CNS	Mild emotional changes or headaches (25%); 4 patients discontinued
Lipid	25% increase in triglyceride level in 12 of 23 patients followed serially

*Cheilitis, dermatitis, conjunctivitis.

identified in many human tumors (23–26); however, in some experimental systems the antiproliferative effect of retinoic acid has not always been associated with the presence of retinoic acid-binding protein (6).

The proportion of ineligible and inevaluable patients was high (24%) compared to our usual rate of 5%–7% in phase II investigations. The large number of patients without objectively evaluable lesions (12.6%) or with early death (6.3%) reflected the attitude of “it’s only a vitamin and can’t harm the patient,” even among a staff that was relatively sophisticated about retinoids. Three percent of the patients appeared to have increased progression of their disease, an incidence that is similar to other phase II studies and probably represents the natural history of the underlying disease process. Nevertheless, isotretinoin may in part function as a hormone, and careful observation for this phenomenon should be made in phase III studies.

The toxicity of isotretinoin was different qualitatively and quantitatively from that of most cytotoxic anticancer drugs. The predominant limiting side effects occurred in skin. Additionally, mild CNS changes consisting of emotional lability and headaches were frequent; this finding was anticipated, as similar changes with retinyl palmitate have previously been reported (27). However, these symptoms are different than those seen in patients with dermatologic conditions, and the presence of headaches and emotional lability probably reflects the higher dose used in our studies. Perhaps of relevance is that retinoids are known to concentrate in the brain (28). In contrast to vitamin A, isotretinoin produced no abnormalities in liver function, a finding consistent with the lack of retention of isotre-

tinoin by the liver (28). The increase in triglycerides, which was seen in the 12 of 23 patients in whom this lipid was measured, is similar to results obtained in patients with dermatologic conditions (29). This effect appears to be dose-dependent, is rapidly reversible upon retinoid discontinuation, and does not involve lipid subclasses correlated with atherosclerotic disease. Nevertheless, cancer patients who will receive retinoids long-term should be carefully monitored for lipid abnormalities.

Many retinoids have been synthesized (4). In dermatologic conditions, isotretinoin and an aromatic derivative (etretinate) have a totally different spectrum of activity (19). We used isotretinoin in this trial because its toxicity had already been studied and found to be acceptable in noncancerous conditions, and an oral formulation was available. Our results in squamous cell neoplasms suggest that other retinoids should also be evaluated for antitumor activity (30,31). Additionally, the evidence of isotretinoin activity that we observed in squamous cell epithelial malignancies provides support for the use of retinoids in additional studies of some of these tumor types as well as in chemoprevention studies.

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