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# Treatment of Advanced Squamous Cell Carcinoma of the Skin with Isotretinoin

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**Study Objective:** To determine the efficacy of oral isotretinoin in refractory advanced squamous cell carcinoma of the skin.

**Design:** Case series trial.

**Setting:** Tertiary care center at a university hospital.

**Patients:** A consecutive collection of four patients with advanced squamous cell carcinoma of the skin who failed to respond to standard surgical or radiation therapy.

**Interventions:** Isotretinoin in gelatin capsules was given at a total daily dose of 1 mg/kg body weight in two divided doses for at least 4 weeks.

**Measurements and Main Results:** Bidimensional tumor measurements at monthly intervals showed striking responses to isotretinoin in all four patients. Response durations ranged from 2 to more than 23 months. The drug produced reversible moderate mucocutaneous side effects and asymptomatic laboratory abnormalities.

**Conclusions:** Impressive responses to isotretinoin occurred in our four patients and in six of ten other reported patients. Retinoic acid's mechanism of action in cutaneous squamous cell carcinoma is not precisely known, but may involve the modulation of epidermal growth factor receptors and certain protein kinases. These in-vitro findings and the clinical data suggest that retinoids may be an effective and well-tolerated therapy for refractory advanced squamous cell carcinoma of the skin. The absence of any other effective systemic therapy indicates the need for continuing trials with retinoids in this disease.

**SQUAMOUS CELL CARCINOMA** of the skin is the second commonest cancer afflicting the population of the United States, causing approximately 3000 deaths per year (1-6). Although more than 90% of these patients are cured with surgery or radiation therapy, this outcome depends on the size, site, and cause of the lesion. Chemically induced cancers are the most refractory to treatment. The limited available data on systemic chemotherapy indicate it is highly toxic and yields generally poor results (7, 8).

Vitamin A is essential for normal differentiation of epithelial tissues (9-11). Retinoids primarily accumulate in the skin (12), are active in certain premalignant (13) and malignant (14, 15) cutaneous disorders, and in animals have in-vitro (16) and in-vivo (17) activity against squamous cell carcinoma. These observations provided the strong rationale for our use of isotretinoin to treat four patients with advanced squamous cell carcinoma of the skin who were refractory to standard therapy.

## Case Reports

The protocol was approved by the University of Arizona's Institutional Review Board, and written informed consent was obtained from the patients before starting isotretinoin therapy.

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## PATIENT 1

A 62-year-old white man with a 40-year history of hand exposure to chemicals was referred in 1985 for therapy of advanced recurrent cutaneous squamous cell carcinoma. In May 1981 he had lesions over the dorsal aspect of both hands, which were locally excised and confirmed as well-differentiated squamous cell carcinoma. In May 1984 the lesions recurred. In September 1984 the lesions were widely excised and split-thickness skin grafts were placed. One month later the lesions recurred, and local radiation therapy (6500 rad) resulted in a complete response. The lesions recurred again, and bilateral amputation was considered.

By January 1985 there was again extensive involvement of both hands. The dorsal aspect of his right hand had a 4.5-cm × 4.0-cm erythematous and ulcerated lesion, surrounded by three 1.0-cm satellite lesions (Figure 1 Left). The dorsal aspect of his left hand was covered by a 5.2-cm × 4.2-cm indurated lesion, also surrounded by six small satellite lesions ranging in size from 0.1 to 0.5 cm. He was given oral isotretinoin, 1 mg/kg body weight in divided doses. Measurable tumor regression, beginning with the peripheral satellite lesions, was first seen after 2 weeks of therapy. Over the next 6 months, the skin lesions resolved completely. In January 1986, treatment was discontinued after a routine laboratory screening showed a serum creatine kinase level of 69.01  $\mu$ kat/L; the level returned to normal (0.33-3.17  $\mu$ kat/L) within 3 months. This patient has had healing of the skin grafts and remained free of disease for 13 months since therapy was stopped (Figure 1 Right).

## PATIENT 2

A 77-year-old white man was seen in 1985 for treatment of a large neck mass. In 1976 he had first noticed a small lump on the right aspect of his neck and another lump on his nose. In 1981 there was a short-lived response to radiation therapy of the neck lesion. The patient refused further treatment, and both lesions progressed. Biopsy samples later showed well-differentiated squamous cell carcinoma of the skin.

In December 1985, he had a massive, indurated, and erythematous 10-cm × 10-cm exophytic fungating lesion on the right side of his neck (Figure 2 Left), and complete destruction and erosion of the nose. He was given isotretinoin, 1 mg/kg body weight in divided doses. A remarkable regression of tumor bulk occurred within 3 weeks. At 6 months, only a nondiscrete, flat, residual lesion remained on his neck (Figure 2 Right) and the nasal lesion had regressed by 70%, accompanied by evidence of early facial remodeling. At the 11-month follow-up, his neck mass recurred. Chemotherapy with fluorouracil and cisplatin has induced a partial response after two cycles.

## PATIENT 3

From December 1983 to early 1985, an industrial waste inspector had several local excisions for recurrent keratoacanthomas on the dorsal aspect of his right hand. In May 1985 he developed a small nonhealing lesion on the dorsal aspect of the right thumb. This lesion was excised in July 1985 and found to be well-differentiated squamous cell carcinoma. The surgical margins were free of disease. In December 1985 the thumb lesion recurred, with bony involvement as shown by bone scan and biopsy. In March 1986 the right thumb was amputated. Pathologic evaluation confirmed well-differentiated squamous cell carcinoma with extensive granulomatous inflammation.



**Figure 1 Left.** Pretreatment photograph of Patient 1 showing extensive erythematous, indurated and ulcerated lesions on the dorsal aspect of both hands. Note the peripheral satellite lesions. **Figure 1 Right.** Response after 19 months of isotretinoin. Complete resolution of cutaneous lesions and healing of skin grafts has occurred.

Several weeks later the patient developed right shoulder and right axillary pain. A 2-cm subcutaneous mass was found in the right axilla. This mass was excised and diagnosed as moderately well-differentiated squamous cell carcinoma.

Despite local measures and systemic analgesics, the right shoulder pain became progressively severer. Computed tomography (CT) of the chest showed a 4-cm  $\times$  2.5-cm axillary soft-tissue mass at the level of the tracheal bifurcation. Radical surgery with amputation of the right shoulder and arm was recommended. The patient, now 54 years old, sought another medical opinion.

As an alternative to radical surgery, he was given isotretinoin (1 mg/kg body weight  $\cdot$  d) immediately. Within 3 to 4 weeks the patient reported that his right shoulder and axillary discomfort had resolved. Follow-up CT scans taken 8 weeks and 15 weeks after isotretinoin therapy was started showed that the mass in the right axilla had completely resolved.

#### PATIENT 4

In early 1986, a 69-year-old white man with a long history of sun-related skin changes (actinic keratosis, keratoacanthoma, and basal and squamous cell carcinoma) was referred for recurrent squamous cell carcinoma. Since 1979 several local excisions and electrodesiccation had been done.

Examination showed that the dorsal aspects of both hands were extensively involved with numerous lesions (1 cm or less in diameter), which were erythematous, papular, indurated, and, in some cases, centrally ulcerated. Treatment with oral isotretinoin (1 mg/kg body weight  $\cdot$  d) began in January 1986. After 6 weeks a 70% reduction had occurred in the area of cutaneous involvement. The dose was reduced to 40 mg every other day because of mucocutaneous toxicity. The disease progressed locally and a 1.5-cm right epitrochlear node developed. Treatment was discontinued. The node was excised and regional metastatic disease was confirmed. The patient received radiation therapy, 4500 rad, to a 15-cm field in the epitrochlear area. Upon completion of radiation therapy, isotretinoin was restarted. The cutaneous lesions on the dorsal aspects of his hands partially regressed once again and no new lesions had developed as of his last examination in January 1987.

#### Discussion

We used isotretinoin (1 mg/kg body weight  $\cdot$  d) to treat four patients with refractory cutaneous squamous cell carcinoma. All patients had major disease regression beginning within 4 weeks of starting therapy. Toxicity was generally mild and included reversible mucocutaneous

side effects and asymptomatic laboratory abnormalities.

The effects of retinoids on epidermal growth factor receptors support the use of this class of drugs for treating squamous cell carcinoma. It is well known that epidermal growth factor modulates cell proliferation (possibly through certain protein kinases) (10, 18-20). In certain human squamous cell carcinoma cell lines (such as A431), epidermal growth factor binding capacity correlates directly with growth inhibition (19, 20). Retinoic acid can induce significant increases in the number of epidermal growth factor receptors, and these increases also correlate with growth inhibition in certain cell lines (10, 18).

Other recent in-vitro and in-vivo data indicate that retinoid activity correlates directly with the degree of differentiation of transformed cells (10). The well-differentiated nature (keratin production, pearl formation, and intercellular bridges) of the patients' squamous cell carcinomas may help explain their responses to the retinoid.

Only 14 patients with advanced squamous cell carcinoma of the skin have been treated with three different oral vitamin A derivatives (21-24). The overall response rate was 10 of 14 patients, including four complete sustained remissions. Especially encouraging in the absence of any other effective systemic therapy (7, 8), these data suggest that retinoids deserve continuing trials, as this class of drugs may be an effective and well-tolerated therapy for advanced squamous cell carcinoma of the skin.

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**Figure 2 Left.** Pretreatment photograph of Patient 2 showing the massive (10-cm  $\times$  10-cm) exophytic lesion on the right side of his neck. **Figure 2 Right.** After 6 months of treatment with isotretinoin there was a remarkable tumor regression with only a nondiscrete, flat, residual lesion.

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