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Brief report

Phase II study of Fenretinide (N-[4-Hydroxyphenyl]retinamide) in advanced breast cancer and melanoma

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Summary

Retinoids, the natural and synthetic analogs of vitamin A, are growth-inhibiting and differentiation-inducing agents and show clinical promise as chemopreventive and antineoplastic agents. Fenretinide, a new synthetic retinoid, has antitumor activity in certain *in vitro* and *in vivo* model systems and was relatively nontoxic in phase I trials. Based on these data, we designed a phase II study of Fenretinide involving 31 patients with advanced breast cancer [15] and melanoma [16], two cancers shown to be responsive to this agent in preclinical models. Fenretinide was inactive in patients with advanced disease. Toxicity was mild, and reversible. Mucocutaneous side effects occurred in 16 (52%) patients. Nyctalopia developed in three patients one of whom developed decreased B-wave amplitude of the scotopic electroretinogram. The minimal toxicity and significant activity in preclinical studies make this an attractive agent for future breast cancer chemoprevention studies.

Introduction

Retinoids, the natural derivatives and synthetic analogs of vitamin A, are differentiation-inducing and cytostatic anticancer agents. Chemical modification of the basic retinoid structure has produced analogs with enhanced target organ specificity, increased anticarcinogenic activity and reduced toxicity [1]. The retinamides are a new class of synthetic retinoids in which the terminal carboxyl group of retinoic acid is replaced by an N-substituted carboxyamide group [1]. *In vitro*, the retinamide Fenretinide has antitumor activity against ovary, lung, breast and melanoma tumor cells [1]. Studies in a rat mammary carcinogenesis model, Moon *et al.* showed that Fenretinide is effective as chemopreventive, primary, and adjuvant therapy, and augments the anticarcinogenic effects of tamoxifen and ovariectomy [2,3]. Further, Fenretinide was stored in breast tissue and was significantly less toxic than other retinoids [4], making Fenretinide ideal for long-term therapy.

Patients and methods

Thirty-one patients with advanced or metastatic breast cancer [15] or melanoma [16] were treated with Fenretinide, 300–400 mg/d (Table 1). Dosage modifications were based on toxicity levels [1], as follows:

Table 1. Patients treated with Fenretinide (300–400 mg/d)

Case	Age	Sex	Disease	Disease site	Prior therapy	Duration of therapy (days)	Response	Toxicities
1	48	F	Breast	Breast	---	15	PD	---
2	70	F	Breast	Breast, skin	HT[1,2,3],CT,RT	62	S	Dry skin, cholesterol 21%*
3	64	F	Breast	Skin	HT[1,2,3],CT,RT	10	PD	Cholesterol 13%
4	61	F	Breast	Bone, liver	HT[1,2,3],CT,RT	47	S	Cheilitis
5	46	F	Breast	Bone	HT[1,2],CT,RT	60	PD	Dry skin
6	58	F	Breast	Skin	HT[1,2],CT,RT	30	PD	Triglycerides 62%
7	58	F	Breast	Skin, SQ	HT[1],CT	15	PD	Dry skin
8	41	F	Breast	Bone, lung, brain	CT,RT	20	PD	Dry skin, cholesterol 21%
9	46	F	Breast	Bone	HT[1,2,3],CT,RT	80	S	Dry skin, fatigue, cholesterol 14%
10	63	F	Breast	Bone, lung	HT[1,2,3],CT,RT	45	PD	Fatigue, blurred vision
11	59	F	Breast	Skin, SQ	HT[1,2],CT,RT	45	MR	Dry skin
12	52	F	Breast	Bone	RT	70	PD	Dry skin, cholesterol 8%
13	34	F	Breast	Bone	HT[1],CT,BT	35	PD	Headache
14	66	F	Breast	Skin	HT[1],CT,RT	80	S	---
15	62	F	Breast	Bone, brain	HT[1,2,3],CT,RT	120	MR	Conjunctivitis, blurred vision, cholesterol 57%, triglycerides 10%
16	46	M	Melanoma	Skin	---	80	PD	---
17	79	M	Melanoma	Lung, brain	CT,RT,BT	22	PD	Dry skin
18	26	F	Melanoma	Skin, SQ	RT	26	PD	Dry skin, change in taste
19	61	F	Melanoma	Skin, SQ	BT	140	S	Nyctalopia
20	72	F	Melanoma	Liver	---	12	PD	Dry skin
21	55	F	Melanoma	SQ	CT,RT,BT	15	PD	---
22	46	M	Melanoma	Skin, SQ	CT	30	PD	Fatigue
23	72	F	Melanoma	Palate, orbit	CT,RT,BT	30	PD	---
24	73	F	Melanoma	Lung	BT	100	S	---
25	22	F	Melanoma	Skin, SQ, liver	BT	20	PD	---
26	32	M	Melanoma	Skin, SQ	BT	90	S	Dry skin, fatigue
27	67	M	Melanoma	Lung, brain	CT,RT,BT	15	PD	---
28	75	M	Melanoma	Lung	RT,BT	40	PD	Dry skin
29	43	M	Melanoma	Liver, pelvis	RT,BT	300	S	Dry skin
30	36	F	Melanoma	Skin, liver	BT	60	PD	Double vision
31	65	M	Melanoma	Skin, bone, lung, liver	CT,RT,BT	60	PD	Dry skin

HT = hormonal therapy; 1 = Tamoxifen; 2 = Megace; 3 = Aminoglutethimide; CT = Chemotherapy; RT = Radiotherapy; BT = Biological therapy; SQ = Subcutaneous nodules; *% rise over baseline; MR = Mixed response; S = Stable disease; PD = Progressive disease

1. Level I = no change for one month, then increase to 400 mg/day
2. Levels II and III = 50% decrease
3. Level IV = discontinue drug until level II toxicity, then reinstitute at 50% of initial dose.

Physical examination, toxicities and serum chemistries were assessed every two weeks for the first two months and then every month. Photopic- and scotopic-phase electroretinography (ERG) was performed to test retinal function.

Results

Patient characteristics are shown in Table 1. The median Karnofsky performance status was 80% (40–90%). Six of ten evaluable breast cancer pa-

tients were estrogen and/or progesterone receptor positive. There were no complete or partial responses. Two patients achieved mixed responses (6.7%), and eight (26.7%) had disease stabilization.

Reversible grade I–II mucocutaneous toxicities occurred in 52% of patients. Of the patients with breast cancer, 40% developed a rise in their serum cholesterol and 20% in their serum triglycerides, both of which returned to baseline 2–4 weeks after discontinuing therapy or decreasing dosage. Three patients developed reversible nyctalopia, one of whom had a decreased B-wave amplitude of the scotopic ERG.

Discussion

We observed that Fenretinide, like other retinoids, has limited activity as a single agent against advanced breast cancer and melanoma. Although recent data has shown a 41% Fenretinide response rate (22% complete response) when used as primary therapy of rat mammary carcinoma [3], we observed no partial or complete responses in our breast cancer patients.

The spectrum of Fenretinide toxicity which we and others [4] observed is similar to that of Isotretinoin, although the frequency and degree is less. The rise in serum triglyceride and cholesterol seen only in patients with breast cancer is difficult to explain. Nyctalopia occurred in three patients, one of whom displayed decreased B-wave microvoltage on the scotopic ERG. Another study evaluating Fenretinide's effect on the ERG reported that high-dose therapy (800 mg/day) produced reversible nyctalopia with elevated rod dark adaptation thresholds and depressed scotopic ERG in two of three basal cell carcinoma patients [5]. Costa *et al.* also found reversible night blindness in 1 of 25 patients treated at a lower dose (300 mg/d) over 6 months [4]. The visual side-effects of Fenretinide and other synthetic retinoids may be due to their interference with vitamin A metabolism. Our recent pharmacokinetic study, revealing a Fenretinide-induced reduction in serum retinol level supports this postulate [6].

The data from other breast carcinogenesis studies in animals and the low toxicity in this clinical trial support the need for further investigation of Fenretinide in the management of breast cancer. Furthermore, preclinical data showing that Fenretinide enhances tamoxifen efficacy [2] serves as a rationale for clinical studies of this drug combination in breast cancer.

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