Eur J Cancer Clin Oncol, Vol. 18, No. 10, pp. 925–928, 1982.
Printed in Great Britain.

0277-5379/82/100925–04$03.00/0
Pergamon Press Ltd.

Phase II Trial of 13-*cis*-Retinoic Acid in Metastatic Breast Cancer

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Abstract—*Studies have suggested that both natural and synthetic retinoids have extensive chemopreventive activity against a variety of carcinogens* in vivo *and* in vitro. *We have previously shown that growth of human breast cancer cells can be inhibited by retinoids, and retinoic acid-binding proteins have been demonstrated in these cell lines and tumor biopsies. We studied the activity of* 13-cis-*retinoic acid in the treatment of 18 patients with advanced breast cancer refractory to standard cytotoxic and/or endocrine therapy. Patients began on* 0.5 mg/kg *and escalated to* 8 mg/kg *over a one-month period unless toxicity (dry skin, dry mucosa, cheilitis, conjunctivitis) forced dose reduction. All these toxicities responded promptly to dose reduction. Four patients exhibited drug related hypercalcemia, 2 complained of severe earache and several had nausea, vomiting and abdominal cramping. There were no objective responses as defined by standard criteria. One patient with thrombocytopenia secondary to documented marrow involvement demonstrated a recovery of platelet count from* 9000 *to* 110,000. 13-cis-*Retinoic acid is not of apparent value in women with heavily pretreated breast cancer.*

INTRODUCTION

VITAMIN A (retinol) and its natural and synthetic analogues (retinoids) have increasingly attracted attention over the last fifteen years for their capacity to prevent experimental carcinogenesis [1]. In rats, the premalignant lesions of vitamin A deficiency-induced squamous metaplasia are reversed by the administration of retinoids [2].

Newer retinoids such as the *N*-(4-hydroxyphenyl) retinamide or retinyl methyl ether have been shown to inhibit rat mammary carcinogenesis induced by 7,12-dimethylbenz(a)anthracene and by *N*-methyl-*N*-nitrosourea [3–6]. These retinoids are stored in the breast, not in the liver, as are the natural retinoids, and were found to cause less toxic effects than the natural retinoids. Furthermore, the growth of several human breast cancer cell lines is decreased by retinoic acid, retinol and retinyl acetate [7, 8].

The exact mechanism of action of retinoids is still unknown. Specific and distinct intracytoplasmic proteins which bind either retinol or retinoic acid have been identified in a variety of organs from rats [9] and in experimental tumors [9, 10].

Recently, similar binding proteins have been identified in the cytosol of MCF-7, Hs578T and ZR-75-B human breast cancer cell lines [8]. Retinoic acid-binding protein was found to be present in 3 out of 3 human breast cancer samples examined by Ong *et al.* [11], whereas it was absent in normal breast tissue. Recently, Huber *et al.* [12] expanded these data by showing that the cytoplasmic retinoic acid-binding protein was detectable in 15 out of 29 human mammary carcinomas and in 6 out of 14 cases of proliferative dysplasias, whereas it was absent in 32 cases of simple dysplasia with or without fibrosis.

Retinoids have been utilized therapeutically in man primarily for dermatological diseases, including skin cancer, and cutaneous disorders of keratinization [13]. For instance, 13-*cis*-retinoic acid was used in the treatment of patients with multiple basal cell carcinomas. Of 248 tumors in these patients, 16% underwent complete clinical remission, 65% decreased in size and 19% remained unchanged [14].

Accepted 12 May 1982.

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These studies suggest that retinoids could prove to be of therapeutic usefulness in several types of human malignancies. This paper reports on the effect of 13-*cis*-retinoic acid in patients with metastatic breast cancer.

MATERIALS AND METHODS

Selection of patients

Patients with a histologically proven metastatic breast cancer who had failed conventional chemotherapy and hormonal treatment were eligible. Evaluable disease, a Karnofsky index of greater than 40 and an expected survival without therapy of greater than two months were required. Eighteen patients were entered on the study—all were evaluable.

Drug administration

13-*cis*-Retinoic acid was administered orally on an escalating dose schedule, starting with 0.5 mg/kg/day and increased to a total of 8.0 mg/kg/day over a one-month period. The therapy regimen is shown in Table 1. This drug dose was then to be maintained for a total of 6 months, discontinued for a one-month period and recycled unless progressive disease intervened. Since safety data for long-term, continuous therapy did not exist at the time the study was initiated, the United States Food and Drug Administration required a rest period after six months of therapy.

Study parameters

Patients were continued on therapy as long as there was evidence of a tumor response (complete or partial remission—defined by standard criteria), marginal or mixed response or disease stabilization (no change). Patients with progressive disease were removed from the study.

Definitions of response: measurements of mass lesions in two dimensions were done at least every 4 weeks. Detailed response criteria have been published [15, 16]. In brief:

Complete response: complete disappearance of all objectively measurable disease. The appearance of no new lesions.

Partial response: equal to or greater than 50% decrease in the product of perpendicularly measured diameters of all measurable lesions: persisting for at least 30 days.

Stabilization: persistence for at least one month of less than 50% regression of disease and lack of progressive disease; appearance of no new lesions and no lesions could increase in size by greater than 25%.

Table 1. Treatment regimen for 13-cis-retinoic acid

Time		Total daily dose (mg/kg)
Days	1–2	0.5
	3–4	1.0
	5–7	2.0
	8–10	3.0
	11–14	4.0
	15–17	5.0
	18–20	6.0
	21–24	7.0
	25–28	8.0
Weeks	5–26	Continue at 8.0
	27–30	The drug is discontinued, then recycled from day 1 on week 31.

All patients received 13-*cis*-retinoic acid twice daily.

Progressive disease: equal to or greater than 50% increase in the product of diameters of any measurable lesions; appearance of any new lesion.

RESULTS AND DISCUSSION

Toxicity

Patients were seen in the clinic every two weeks and toxicities as observed by clinicians and/or reported by patients were recorded at that time.

The major side effects included dry skin seen in 16 out of 18 patients and in all patients receiving a dose above 4 mg/kg, and dry mucous membranes—mouth, lips—seen in 12 of the 18 patients (all but three patients were receiving doses above 3 mg/kg). These toxicities might have been seen at a lower dose had escalation proceeded more slowly [13]. Seven patients had some degree of conjunctivitis and nine of the patients had gastrointestinal complaints: mostly mild nausea and/or vomiting; however, two patients had severe abdominal cramping. Six patients had minor nose bleeds, four patients had dependent edema and there were two cases of otitis media. Changes in the blood chemistries included elevated creatinine (two patients) and evelated calcium (four patients), and these appear to be drug-related (see Table 2). These changes in blood chemistries as well as nausea and vomiting and otitis media were not seen in dermatologic patients [13].

In six cases reduction of the dose was necessary to minimize toxicity. All toxicities were completely reversible with cessation of the

Table 2. Toxicity seen with 13-cis-*retinoic acid in 18 patients*

Toxicity	*N*	%
Dry Skin	16	89
Dry Mucous Membranes	12	67
Conjunctivitis	7	39
GI Symptoms	9	50
Nose Bleeds	6	33
Dependent Edema	4	22
Otitis Media	2	11
↑ Ca	4	22
↑ Creatinine	2	11

drug. All but two patients tolerated daily doses up to 4 mg/kg with minimal side effects, most of the patients could be escalated to a dose of 7 mg/kg with side effects that were described as acceptable and seven patients were escalated to the total dose of 8 mg/kg and continued at that dose with side effects that were managed with lubricants and eye drops (see Table 3).

Response data

Based on the guidelines outlined above there were no objective responses in 18 patients to 13-*cis*-retinoic acid. Of these, three were discontinued at less than three weeks because of rapidly progressive disease. Three patients with skin lesions did show minor or mixed responses manifested by a less than 50% decrease in the size and/or inflammation of the skin disease, while at the same time bone or visceral lesions stabilized temporarily or increased in size or intensity. Eight of 18 patients had disease stabilization for at least 6 weeks (median 13 weeks, range 6–32 weeks). Progressive disease in this population included the appearance of new disease sites, as well as increasing intensity of disease in initial sites. Ten out of 18 patients were observed to have new lesions when they were taken off the study. The median time on study was eight weeks (see Table 3).

Table 3. Doses taken by patients on 13-cis-*retinoic acid*

Patient	Weeks on study	Maximum dose achieved/ maximum chronically tolerated dose*(mg/kg)
1	2	4/4
2	32	8/7
3	10	8/8
4	2	5/5
5	3	7/7
6	4	6/4
7	16	6/4
8	4	8/7
9	6	8/7
10	4	8/8
11	4	8/8
12	16	8/8
13	16	8/8
14	8	8/8
15	1	2/2
16	3	4/4
17	6	4/2
18	5	8/8

*Maximum chronically tolerated dose was the dose patients continued to take until off study. Reductions were based on toxicity.

One patient with thrombocytopenia secondary to documented marrow involvement with metastatic disease demonstrated a recovery of platelet count from 9000 to 110,000 over the six-month period. Per protocol, the drug was discontinued at the end of a six-month period and the platelet count fell to 29,000. When the drug was reinstituted after a one-month period the platelet count again increased to 62,000, at which time other disease sites became progressive and the drug was discontinued. Bone marrow biopsies during this period remained continuously positive for cancer.

We conclude that 13-*cis*-retinoic acid is not useful in advanced breast cancer, but further studies are necessary to determine its usefulness as a therapy in other diseases or as a prophylactic agent.

Pharmacologic studies on drug availability and metabolism were also performed as part of this study [17]. In brief, 13-*cis*-retinoic acid plasma levels showed variable times to reaching peak concentrations following oral administration, although there was an overall linear correlation of levels with increasing oral doses. During substantial periods of the day plasma concentrations were less than 10^{-6} M, a concentration required for maximal *in vitro* effectiveness. In addition, a metabolite which has not been fully characterized but which resembles a 4 oxo-metabolite accumulated over time at concentrations in excess of the parent compound. This metabolite may be as toxic without having the therapeutic properties of the 13-*cis*-retinoic acid.

Acknowledgement—The authors acknowledge the assistance of Hoffman-LaRoche, Inc., Nutley, NJ, for supplying the drug, 13-*cis*-retinoic acid.

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