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Tolerability of the Synthetic Retinoid Fenretinide® (HPR)

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Abstract—*Fenretinide®, N-(4-hydroxyphenyl)retinamide (HPR), is a synthetic retinoid which has been proven effective in inducing cell differentiation and in inhibiting carcinogen induced mammary tumors in rodents. Because of its efficacy and low toxicity in animals, HPR has been proposed for chemopreventive evaluation in humans. Thus, a randomized trial has been conducted to select a dose which can be administered over a lengthy period of time and with acceptable toxicity. The retinoid was administered orally to patients already operated on for breast cancer in daily doses of* 100, 200 *and* 300 mg *for* 6 *months and subsequently at* 200 mg *for another* 6 *months. No acute toxicity was found. Dermatological toxicity was minimal and no liver function abnormalities were observed. Nausea and headaches were infrequent and always mild. Menstrual irregularities were recorded with similar frequency in the treatment and placebo groups and appeared to be more age related than drug dependent. After* 6 *months of treatment one of* 25 *patients taking* 300 mg *HPR daily experienced impaired night vision, confirmed by the electroretinogram, and resolved by interruption of treatment. Because the* 300 mg *daily dose is possibly associated with impaired dark adaptation, the recommended dose for chemoprevention trials of HPR is* 200 mg *per day.*

INTRODUCTION

VITAMIN A and a variety of natural and synthetic retinoids have important effects on the growth and differentiation of epithelial tissues.

Approximately 1500 different retinoids have been synthesized by modifying either the ring structure, the side chain or the terminal group of the molecule to obtain greater efficacy and less toxicity [1]. Among the many synthetic retinoids which have been tested in several experimental studies of cancer chemoprevention [2], HPR is one of the most promising agents for breast cancer because of its efficacy in laboratory models, its unique concentration in the mammary gland and fat tissues, and its apparent lack of toxicity [3–5]. The incidence of dermatological toxicity [6, 7] and impaired dark adaptation [8] has been carefully monitored in the current state of 101 patients previously operated on for breast cancer taking three different daily doses of HPR (100, 200 or 300 mg) or placebo.

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MATERIALS AND METHODS

The study is based on the follow up of 101 patients who underwent a modified mastectomy or quadrantectomy with axillary dissection and radiotherapy 1–3 years prior to the beginning of this study. The diagnosis of breast cancer was based on histological examination of the surgical specimen and nodes. None had lymph node metastases. The patients' ages extended from 35 to 65 years and they had no detectable relapse of their cancer at the time of the study. None had received other antineoplastic treatment or vitamin supplements.

The patients were randomized as follows: during the first 6 months of study the patients were divided into four groups (placebo, 100, 200 or 300 mg HPR). During the following 6 months they then all received 200 mg daily. HPR capsules (Fenretinide®), 100 mg per capsule, were supplied by McNeil Pharmaceutical, Spring House, PA, U.S.A.

Written informed consent in accordance with institutional guidelines was obtained from each patient prior to starting HPR. Women able to bear children were asked to use measures to avoid pregnancy during treatment because HPR is known to be teratogenic.

Previous or concomitant non-neoplastic conditions which could have been influenced by HPR

intake (hepatitis and/or hypertriglyceridemia) were appropriately investigated and recorded at the baseline. Physical examination and blood chemistries, including renal, hematologic and hepatic parameters, were performed every 2 weeks for the first 2 months and every 4 weeks for the remainder of 1 year.

Chest and skeleton X-rays were performed at baseline and every 6 months. Ophthalmologic evaluations, including visual acuity tests, were done at the baseline, every 4 weeks and as required by patient symptomatology. Dermatologic examination was performed at baseline, every 6 months and as clinically indicated. The study protocol required discontinuation of HPR if any severe toxicity such as hepatitis, impaired night vision or multiform erythema developed, or if metastatic disease occurred. After the first 6 months of study, it was decided to continue all patients on the 200 mg daily dose. Eighty-seven patients agreed to continue to participate in the study for another 6 months, six of them with an average drug interruption period of 2 months.

RESULTS

Out of the 101 randomized patients, 100 were evaluable at 6 months and 84 at 1 year, as shown in Table 1. Ten patients refused to continue the trial, one was taken off the drug because of impaired dark adaptation and three because of distant metastases. In the final evaluation, each sign and/or symptom was classified as episodic (present once only during the period of treatment), recurrent (present twice or more times during treatment) or continuous (always present during treatment). The data on adverse reactions are summarized in Table 2.

Episodic or recurrent nausea was present in 12 patients but it may have been related to the large size of the HPR capsules since it developed with similar frequency in the placebo-treated group.

Dermatologic complaints reported involved two main symptoms: pruritus and dryness. Pruritus was evident in 22 cases; 12 of them were episodic and 10 were recurrent. Skin dryness, especially of the limbs, easily controlled by using emollients, was observed in 16 cases. Cheilitis and mouth dryness appeared in four patients. Only two cases of peeling of palms and soles were evident, both in the group receving 200 mg and after 5 months of treatment. No cases of multiform erythema or skin rash were recorded and dermatological toxicity was never severe. Twenty patients complained of headaches: 17 were episodic and three recurrent but they were never severe. Four patients were referred to the opthalmologist because of visual disturbances, two in the group which initially took 300 mg HPR daily and two from the 200 mg group. After 6 months of therapy with 300 mg HPR daily one patient complained of marked visual difficulty at low levels of illumination. She had the typical corneal changes of patients taking Amiodarone but visual field examination was normal. The dark-adapted electroretinogram (ERG) showd a marked reduction of scotopic b-waves in both eyes. HPR was promptly discontinued after the ERG was performed. The visual symptoms disappeared completely 2 days

Table 1. HPR phase I trial: dose administration

Months 1–6			Months 7–12		
Daily dose (mg)	No. of patients Randomized	Evaluable	Daily dose (mg)	No. of patients Continuing	Evaluable
100	25	24(a)	200	21(b)	20(f)
200	26	26	200	25(c)	25
300	25	25	200	22(d)	21(g)
Placebo	25	25	200	19(e)	18(h)
Totals	101	100		87	84

Reasons for withdrawal			
	Refusal to continue	Metastases	Other reasons
(a)	—	1 lung and bone at 12 weeks	—
(b)	2	1 lung and bone at 24 weeks	—
(c)	1	—	—
(d)	2	—	1 impaired night vision
(e)	5	1 liver at 24 weeks	—
(f)	—	1 lung at 28 weeks	—
(g)	—	1 bone at 36 weeks	—
(h)	—	1 bone at 32 weeks	—

*Table 2. Adverse reactions in patients of HPR phase I trial**

Daily dose in mg (No. of evaluable patients)		Frequency†	Nausea		Headaches		Menstrual irregularities		Pruritus		Skin dryness		Impaired night vision	
months 1–6	7–12		6	12	6	12	6	12	6	12	6	12	6	12
Placebo (25)	200 (18)	1	2	0	5	3	1	1	3	2	0	2	0	0
		2	1	0	0	0	3	0	2	0	0	0	0	0
		3	0	0	0	0	0	0	0	0	0	0	0	0
100 (24)	200 (20)	1	1	0	3	2	1	0	4	0	3	3	0	0
		2	0	0	0	0	1	0	0	0	1	0	0	0
		3	0	0	0	0	0	0	0	0	0	0	0	0
200 (26)	200 (25)	1	0	4	0	2	0	1	0	3	0	3	0	0
		2	0	0	0	2	0	3	0	3	0	1	0	0
		3	0	0	0	0	0	0	0	0	0	0	0	0
300 (25)	200 (21)	1	1	1	0	2	1	1	3	1	0	0	1‡	0
		2	2	0	1	0	4	2	1	0	2	1	0	0
		3	0	0	0	0	0	0	0	0	0	0	0	0

*All the adverse reactions were mild, i.e. easily tolerated.
†1 = episodic, i.e. present once only during treatment; 2 = recurrent, i.e. present twice or more during treatment; 3 = continuous, i.e. present continuously during treatment.
‡After 24 weeks of treatment.

later. Nine days after the interruption of treatment, the rod b-wave of the dark-adapted ERG had completely recovered in the right eye and almost completely in the left. Another 11 ERGs were performed at random in patients taking HPR at different doses and no other cases of altered dark adaptation were recorded.

Since menstrual irregularities were all recorded in patients between the ages of 45 and 55, such symptoms appear to be more age related than drug dependent. No changes in red blood cell, white blood cell differential or platelet counts were seen. No significant alterations in SGOT, SGPT, alkaline phosphatase or total bilirubin values were found during the 12 months of treatment. Seven patients presented an increase from 2 to 4 times above the normal value (n.v. 5–25 u/l) in the gamma GT value: one episodic, four recurrent (two developed liver metastases) and two continuous. There were no alterations in creatinine or BUN. HPR treatment did not modify the values of serum cholesterol or tryglycerides. No alterations occurred in albumin, total proteins, LDH, uric acid, blood sugar or electrolyte values.

No local recurrences were recorded in the whole series; six patients had metastases between the 12th and the 36th week (one in lung, one in liver, two in bone and two in lung and bone).

DISCUSSION

Although retinoids have demonstrated efficacy in several experimental models, their potential utility in cancer patients needs to be further investigated [9]. Studies have been published on cervical [10], lung [11], head and neck [12, 13] and skin [14] cancer and oral [15] and vulvar leukoplakia [16]. HPR was selected for human breast cancer prevention because of its demonstrated efficacy and low toxicity in animal models. The aim of this study was to assess its toxicity and to identify an appropriate daily dosage for a long term intervention trial, originally designed by Umberto Veronesi, evaluating the effectiveness of HPR in preventing contralateral breast cancer [17].

Contrary to what has been observed with high dose HPR treatments, no major dermatological side-effects were recorded in doses ranging from 100 to 300 mg/day. Hepatic tolerance appears excellent. Menstrual irregularities have been recorded with other retinoids [18] but in our series they seemed to be age related rather than drug dependent. No changes were noticed in the psychological behavior [19]. Slight anemia (between 9–11 g/dl of hemoglobin) was observed in only one case in our series.

Abnormal retinal function has been associated with HPR at the dose of 800 mg daily *[8] and with other synthetic retinoids [20–22]. One of 25 patients receiving 300 mg HPR daily experienced impaired night vision after 6 months of treatment; this symptom was never recorded at 200 mg, even after 1 year of HPR intake. Recently, we have shown that HPR treatment in rats causes a significant reduction of their retinol serum levels [23]. The mechanism of this reduction, its relationship to HPR toxicity and/or activity should be further investigated.

In summary, no severe acute toxicity developed in patients given 200 mg HPR daily for up to 1 year. Although both chronic toxicity and also efficacy require further study, this retinoid appears to be an excellent candidate for long term chemoprevention studies in a variety of patient populations.

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