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Short communication

A clinical study of nafazatrom in advanced human breast cancer

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Summary. Prostaglandins (PGs) have been shown to inhibit tumour metastases in experimental animal systems. Nafazatrom is a pyrazolinone derivative that increases endogenous prostacyclin (PGI_2) and has experimental anticancer activity. In the present study, nafazatrom was given to 47 women with advanced breast cancer; objective remission of metastases was seen in 2 patients and stabilisation of disease in 1 case. Nafazatrom was safe and well tolerated.

Introduction

Experimental evidence suggests that prostaglandins (PGs) may play a role in the control of tumour growth and dissemination. PGE_2 has inhibited the replication of B16 melanoma cells in vitro [14], and systemic administration of 16-16 dimethyl PGE_2 to mice transplanted with B16 melanoma has resulted in tumour-growth delay and prolonged survival [15]. It has also inhibited the growth of human colorectal cancer xenografts in immune-deprived mice [16]. Honn et al. [5, 7] have demonstrated PGA_1 and PGA_2 to be effective inhibitors of DNA synthesis in Harding Passey melanoma cells.

Prostacyclin (PGI_2) is a potent inhibitor of platelet aggregation [11, 12] and has also been shown to inhibit experimental metastases [6]. Gasic et al. [2] demonstrated that circulating tumour cells aggregated platelets and suggested that such platelet aggregation contributed to enhanced tumour-cell survival in the circulation and promoted dissemination. Following this reasoning, Honn et al. [6] and Menter et al. [9] argued that prostacyclins have antimetastatic activity. These authors demonstrated the inhibition of tumour-cell-induced platelet aggregation in vitro and the reduction by 70% of lung-colony formation in mice inoculated intravenously with B16 melanoma. Nafazatrom, a pyrazolinone derivative, has increased PGI_2 biosynthesis in vivo and inhibited its degradation, thereby resulting in elevated circulating PGI_2 levels [1]. In vivo, nafazatrom has inhibited tumour growth and the development of metastases in several animal-tumour systems [6].

We undertook a phase II study of nafazatrom given to patients with progressive, locally recurrent or metastatic cancer of the breast.

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Patients and methods

A total of 47 women with histologically proven carcinoma of the breast were treated with nafazatrom. The protocol was approved by the hospital's ethical committee and all patients gave informed verbal consent. In all, 14 patients had local recurrence only, 26 had visceral metastases and 7 had metastatic disease in soft tissue and/or bone only. Most patients had received prior treatment for metastatic disease; 30 women had received one endocrine treatment (range, 0–2) and 14 had undergone chemotherapy. An interval of at least 3 weeks had elapsed since prior therapy. The age range was 39–79 years (mean, 66.4 years). Overall, 42 patients were postmenopausal and 4 were perimenopausal. Oestrogen receptor (ER) status was known in 21 patients; 17 were ER-positive and 4, ER-negative. Patients with renal dysfunction (blood urea of >8 mmol/l), hepatic dysfunction (bilirubin, >17 μmol/l) or cardiac failure were excluded.

Nafazatrom (Bayer) was given orally: of 41 women who were treated with 1,600 mg b.i.d., 4 were subsequently treated with 1,600 mg qd; 6 patients commenced treatment with 1,600 mg qd. All patients were assessed before treatment by clinical examination, full blood count, serum biochemistry and liver function tests, chest X-ray and limited skeletal survey. Blood tests were repeated every 3 weeks and radiological assessment, every 6 weeks during treatment. Response was assessed according to UICC criteria [4].

Statistical considerations. A partial response was seen in 1 of the first 14 women; therefore, extra patients were recruited to assess response. The number of patients required for the rejection of a therapeutic effectiveness in 10% of patients with a B-error of 10% is 29; the number required for the rejection of a 10% response rate with a B-error of 10% is 22. In all, 33 women with metastatic disease were included, as were 14 with local disease.

Table 1. Results of treatment

	Nafazatrom all patients	Nafazatrom (1,600 mg b.i.d.)	Nafazatrom (1,600 mg qd)
Patients treated (*n*)	47	41	6
Time on treatment (weeks):			
Mean	15.4	16	11.8
Range	1–104	2–104	1–28
Patients dying or stopping treatment within 4 weeks (response not assessable)	6	5	1
Patients dying on treatment with progressive disease	5	4	1
Patients remaining alive with progressive disease on treatment	26	23	3
Patients with stabilisation of disease on treatment for:			
9–12 weeks	4	4	0
12–24 weeks	3	2	1
>24 weeks	1	1	0
Patients exhibiting regression of disease on treatment (partial or complete response):	2 (1 CR) (1 PR)	2 (1 CR) (1 PR)	0

CR, complete response; PR, partial response

Results

The results of treatment are summarised in Table 1. The mean duration of treatment at 1,600 mg b.i.d. was 16 weeks (range, 2–104 weeks), and that at 1,600 mg qd was 11.8 weeks (range, 1–28 weeks). All patients eventually discontinued treatment because of progressive disease; six discontinued treatment within 4 weeks and were not evaluable for response. Response was seen in 2 women receiving 1,600 mg b.i.d.: one complete and one partial response. Four patients showed stabilisation of disease for >12 weeks, and one of these had stable disease for 69 weeks. There was no response to dose escalation from 1,600 mg b.i.d., to 1,600 mg qd in four patients. The histories of the two women who achieved remission are summarised below.

Patient 2

A 77-year-old woman with ulcerated local recurrence (ER-positive), lytic bone disease and pulmonary metastases was treated with nafazatrom at 1,600 mg b.i.d. for 72 weeks. After 26 weeks she showed partial remission of local disease, with re-epithelialization of the ulcerated area (Fig. 1). Skin metastases almost completely regressed and lung metastases cleared completely on chest X-ray. There was also sclerosis and healing of the bone metastases. The response was maintained for 63 weeks, after which the local disease progressed. Nafazatrom was increased to 1,600 mg qd for a further 22 weeks, but there was no response to the increased dose.

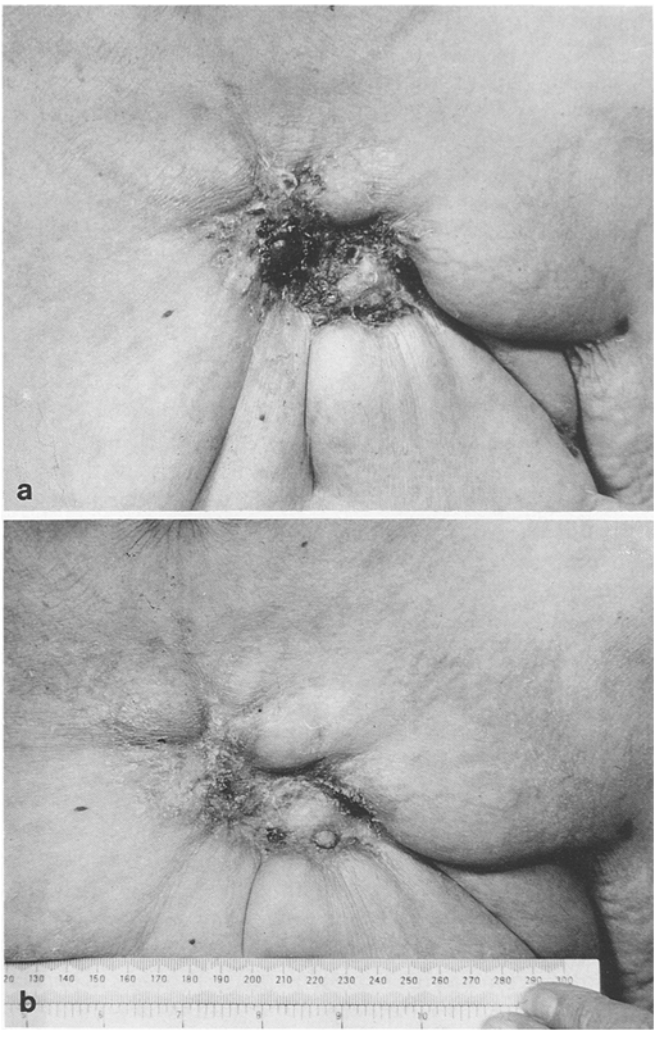

Fig. 1 a, b. An ulcerated, locally recurrent breast cancer in patient 2 **a** before treatment and **b** after 20 weeks' treatment with nafazatrom (1,600 mg b.i.d.)

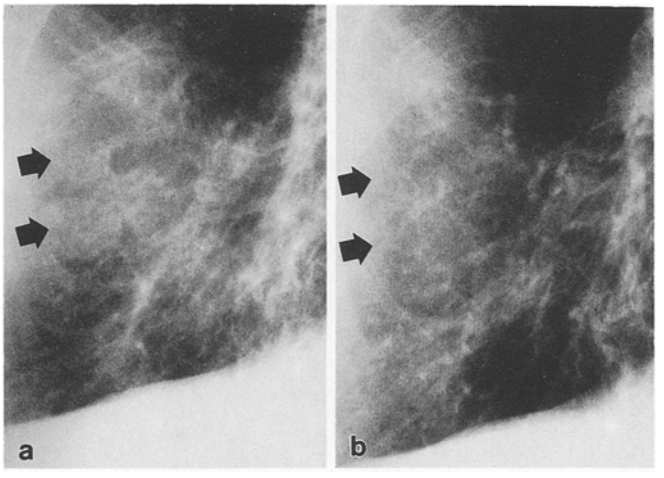

Fig. 2 a, b. Pulmonary secondaries (*arrows*) from breast cancer in patient 19 **a** before treatment and **b** after 16 weeks' treatment with nafazatrom (1,600 mg b.i.d.)

Patient 19

A 57-year-old woman with lung metastases (ER status unknown) was treated with nafazatrom at 1,600 mg b.i.d. After 16 weeks she showed the complete regression of metastases on chest X-ray and whole-lung tomography (Fig. 2). The response was maintained for a further 18 weeks, after which the pulmonary disease progressed.

Toxicity

None of the patients stopped treatment because of toxicity. Mild lethargy was seen in three cases; oedema, in one; and a skin rash, in two. Five patients experienced nausea; in one of these treatment was temporarily interrupted. There were no changes in blood count or serum biochemistry at either dose. Alkaline phosphatase and gamma-glutamyl transferase levels increased during treatment, but these minor elevations were considered to represent progression of known bone and/or hepatic metastases.

Discussion

The prevention and treatment of distant metastases is a major problem in cancer management. Prostaglandins and drugs that increase their production can inhibit metastases in animals, possibly by affecting interactions between platelets and tumour cells and preventing cells from forming established metastases in the microvasculature.

Nafazatrom has been tested in phase I studies in cancer patients at doses of between 30 and 4,000 mg/m^2 daily [3, 12, 16]. Oral nafazatrom produced serum levels of 50–100 mg/ml at these doses [3]. No objective anticancer responses were seen, although some patients had stable disease on treatment. There were no consistent effects on the products of arachidonate metabolism or on platelet function and survival or coagulation parameters. This indicates that no biological parameter has been defined to measure the activity of nafazatrom in vivo. In our phase II study in pre-treated patients, we observed an objective response in 2 of 41 evaluable patients (4.8%) and stabilisation of disease in 4/41 (9.7%). Toxicity with chronic oral administration was mild and easily controlled. The low response rate does not support the use of nafazatrom in the treatment of advanced breast cancer. However, nafazatrom has biological activity in vivo, and the use of prostaglandins and agents that affect their synthesis may play a role in cancer management.

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