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FADROZOLE HYDROCHLORIDE, A NEW NONTOXIC AROMATASE INHIBITOR FOR THE TREATMENT OF PATIENTS WITH METASTATIC BREAST CANCER

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Summary—Eighty previously treated postmenopausal women with metastatic breast cancer were randomized to receive fadrozole (CGS 16 949A), a new aromatase inhibitor, 1 or 4 mg orally per day. Seventy eight patients were evaluable for toxicity and response. Only mild to moderate toxicity, namely hot flushes (28%), nausea and vomiting (13%), fatigue (8%) and loss of appetite (5%) occurred. Complete response was documented in 10% and partial response in 13% of patients with 45% having a no change status for at least 2 months. The median time to treatment failure is 4.1 months. The median survival is 23.7 months. The median survival is 23.7 months. The response and survival in patients with estrogen receptor positive and estrogen receptor unknown disease were not significantly different. Neither response nor survival was significantly different between the patients receiving 1 or 4 mg of fadrozole per day. Fadrozole is a well tolerated, effective second line treatment for women with metastatic breast cancer.

INTRODUCTION

Inhibitors of the aromatase enzyme system are used both to lower systemic estrogen levels and to inhibit intracellular conversion of androgens to estrogens by tumour cell aromatase. Aminoglutethimide (AG) was the first aromatase inhibitor to gain an established place in antiestrogenic treatment of hormone sensitive breast cancer in postmenopausal women [1]. AG however has been demonstrated to inhibit several enzymes involved in adrenal steroid biosynthesis other than aromatase [2, 3]. The glucocorticoid inhibitory properties of AG require glucocorticoid supplementation when larger doses are used. When low dose AG is used, careful observation of the patient for adrenal insufficiency is required [4]. When corticosteroids are given they can cause euphoria, insomnia and cushingoid symptoms. Apart from the adrenal effects, other toxicities associated with AG are lethargy in about 30% of patients and skin rash in about 20% of patients. In addition, occasional severe thrombocytopenia and leukopenia occur. The toxicity associated with the use of AG warranted the search for equally efficacious but less toxic alternatives.

A new class of aromatase inhibitors in the form of substrate analogues was developed. The first of these to enter clinical trials was 4-hydroxyandrostenedione which was found to be about 60-fold more potent than AG in inhibiting aromatase activity in placental microsomes [5]. One of the only drawbacks of this steroidal compound is sterile abscess formation at the site of injection with use of the parenteral formulation [6].

More recently, a nonsteroidal imidazole derivative, CGS 16 949A, (4-{5,6,7,8-tetrahydroimidazo-[1,5α]-pyridin-5-yl}benzonitrile monohydrochloride), fadrozole hydrochloride, has been shown to be a potent, highly specific inhibitor of aromatase activity. *In vitro* and animal studies of fadrozole have shown it to be about 200 to 1000 times more potent than AG [5, 7, 8]. Phase I studies showed that fadrozole is very well tolerated [9, 10]. The only side-effects encountered were occasional mild nausea, vomiting, decreased appetite, fatigue and leg cramps. Orthostatic hypotension was reported in patients who received high doses (16 mg daily) of fadrozole. At a daily dose of 2 mg of fadrozole, no significant changes in aldosterone, thyroid hormone, cortisol, adrenocorticotropic hormone (ACTH), androstenedione and testosterone levels were observed. Daily doses of 8 to 16 mg of fadrozole caused a drop in plasma aldosterone and blunting of cortisol and aldosterone responses to Cortrosyn. A recent report,

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however, has indicated that aldosterone levels could be suppressed at 2 mg of fadrozole per day [7]. Maximal estrogen suppression at 2 mg of fadrozole daily [9, 10]. This equals the estrogen suppression observed previously with 1000 mg of AG and 40 mg of hydrocortisone daily. These daily confirm *in vitro* and animal studies reporting a 300 to 1000-fold potency supremacy of fadrozole to AG.

It has been reported that approximately two thirds of human breast cancers contain measurable aromatase activity [11]. It is generally accepted that estrogen deprivation plays an important role in the endocrine treatment strategy for patients with breast cancer. Phase I studies indicate that appropriate doses of fadrozole for further study would be either 1, 2 or 4 mg per day. In order to more easily evaluate a difference in effect at different dosage levels, the 1 and 4 mg doses were chosen for the present study. The study reported here is an update of a study in postmenopausal patients with advanced breast cancer undertaken to investigate the therapeutic and the toxic effects of 1 vs 4 mg of fadrozole daily [12].

MATERIALS AND METHODS

Patient eligibility for entry into the study were: histologically confirmed advanced metastatic breast cancer. Patients had to have estrogen receptor (ER) positive or ER unknown breast cancer, measurable or evaluable disease, and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) [13] of 2 and less. The patients had to be postmenopausal. A bilirubin $\leqslant 3$ mg/dl, blood urea nitrogen $\leqslant 30$ mg/dl, serum creatinine $\leqslant 1.5$ mg%, white cell count >4000 per microlitre and a platelet count $>100{,}000$ per microliter were required. Baseline and follow-up investigations included measurement of all metastatic sites, chest X-ray, isotope bone scan, serum calcium, serum estradiol (E_2), follicle stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH) and serum electrolytes. Patients had to have received prior treatment for metastatic disease. (Patients who had received more than one prior cytostatic regimen or more than one hormone treatment or more than one combined cytostatic and hormone regimen were ineligible for the study.) All patients gave informed consent.

Patient ineligibility criteria included central nervous system metastases, lymphangitic pulmonary metastases, other dire disease and peritoneal metastases with ascites. Patients with a history of malignant neoplasms other than curatively treated basal cell carcinoma of the skin or carcinoma *in situ* of the cervix, and patients who were medical or psychiatric risks were considerable ineligible. Patients with prior exposure to AG were also considered ineligible. ECOG response and toxicity criteria were used [13].

Eighty women with metastatic breast cancer were entered on study. The patient factors were well balanced with no significant difference in the two randomized groups with regard to age, PS, ER status, number of metastatic sites, dominant site of metastases, menopausal status and prior treatment. Twenty eight patients had received prior hormone treatment, 12 prior cytostatic treatment and 40 both hormone and cytostatic treatment for metastatic disease.

Fadrozole was supplied as tablets containing 0.5 and 2 mg by CIBA-GEIGY. Patients were randomized to receive 1 or 4 mg orally daily. Treatment was continued until progressive disease was documented.

Statistical methods

Time to treatment failure (TTF) and survival were analysed using life-table analyses. Data that took the form of contingency tables were evaluated for statistical significance by Fisher's exact test [14]. The 95% confidence limits were calculated [15]. Repeated-measures analysis-of-variance techniques were used to compare TSH, FSH, LH, E_2 and serum electrolyte values over time. Results were considered to indicate significance at a P value of <0.05.

RESULTS

Eighty patients were entered on study. Thirty eight patients were randomized to receive fadrozole 0.5 mg orally twice a day and 42 patients to receive 2 mg orally twice a day. Two patients were not evaluable for toxicity, response or survival. One refused treatment after 14 days and did not come for follow-up. She died 1

Table 1. Hormone and electrolyte values in patients treated with fadrozole

	On study	3 Months
E_2	<5 pmol/l (59 patients)	$\leqslant 5$ pmol/l (All patients)
FSH	56 8 IU/l	67.1 IU/l
LH	37 7 IU/l	36.7 IU/l
TSH	1 7 mIU/l	1.3 IU/l

Electrolyte and Ca^{++} unchanged.

month after being entered on study. The other patient whose only measurable metastasis was a supraclavicular gland, had this lesion removed surgically 2 weeks after entry on study. This patient was removed from study, but is still being followed for survival.

Toxicity

No severe life threatening or lethal toxicity was encountered. In the 78 patients evaluable for toxicity, mild to moderate toxicity documented was as follows: hot flushes 22 patients, nausea and vomiting 10 patients, fatigue 6 patients and loss of appetite 4 patients. There was no difference in the toxicity documented at the two dose ranges used in this study. Possible treatment related side-effects that were seen were a maculo-papular skin rash in 1 patient, mild transient leukopenia in 1 patient and mild transient anemia in 1 patient.

There was no significant change in serum electrolytes, serum calcium, TSH, LH or FSH in any of the patients during the course of the study (see Table 1). It can be stated that neither the 1 or 4 mg daily dosage of fadrozole affected these biochemical parameters. Both dosage arms appear to be equally effective in suppressing serum E_2 levels. As virtually all patients were postmenopausal the on study E_2 levels were low. In most patients the measurements of E_2 values were below the sensitivity values of the radioimmunoassay used. In 21 patients with levels of $E_2 > 5$ pmol/l at the start of treatment, the value fell to 5 pmol/l or less within 2 months.

Response

Seventy eight patients are evaluable for response. Response by treatment regimen is shown in Table 2. Eight patients had a complete response and 10 patients had a partial response with an overall response rate of 23% (95% confidence interval 12–34%). If the patients with a no change status are included, 53 of the 78 patients (68%) benefited from treatment. The response rate in patients receiving 1 mg of fadrozole was 24% (95% confidence interval of 8–40%) and in patients receiving 4 mg, 22% (95% confidence interval 6–38%). With 78 evaluable patients on this study the power to detect a 30% difference in response rate between the 2 regimens is 80%.

Table 2. Response to fadrozole %

	Fadrozole			
	1 mg daily		4 mg daily	
Complete response	13	24	7	22
Partial response	11		15	
		73		64
No change	49		42	
Progression of disease	27		36	

The response in patients in the different prior treatment groups is similar. The patients who had received prior AG had a partial response (bone and soft tissue metastases). This patient experienced progression of her disease after receiving 4 mg fadrozole per day for 19 months. The patient with ER negative disease had a partial response.

Time to treatment failure (TTF)

The median time from one study to treatment failure is 4.1 months (0.4–27.5). With 1 mg daily it is 4.7 months (0.4–21), and with 4 mg daily is 3.7 months (0.5–27.5). This is not significantly different ($P = 0.84$). The median TTF by PS, age, number of metastatic sites and dominant site of metastases was not significantly different. The only patient factor significantly influencing TTF was ER status. Patients with ER unknown disease had a longer TTF than patients with ER positive disease, 5.3 months (0.4–27.5) vs 2.3 months (0.9–17.6), ($P = 0.008$). In a multivariate regression analysis patients with ER unknown disease had a significantly longer TTF ($P = 0.008$) (see Table 3). The TTF on the patient with ER negative disease is >21 months.

Survival

The median survival time was 23.7 months (2.3–33). For patients treated with 1 mg fadrozole daily it was 22.3 months (2.3–30.4), and for patients on 4 mg daily, 26.3 months (2.4–33) (see Fig. 1). The difference is however not statistically significant ($P = 0.36$). Factors that predicted for survival in a univariate analysis were 1 vs >1 site of metastases ($P = 0.003$), soft tissue dominant vs visceral dominant disease ($P = 0.01$), and osseous dominant vs visceral dominant disease ($P = 0.007$). In a multivariate

Table 3 Fadrozole: patient factors significantly predicting for TTF and survival

	TTF		Survival	
Patient factors	Univariate analysis *P*-value	Multivariate analysis *P*-value	Univariate analysis *P*-value	Multivariate analysis *P*-value
ER status	0.008	0.008	NS	NS
Number of metastatic sites	NS	NS	0.003	NS
Dominant site of metastases				
Soft tissue vs visceral	NS	NS	0.010	NS
Osseous vs visceral	NS	NS	0.007	0.03
Soft tissue vs osseous	NS	NS	NS	NS

NS = Not significant: fadrozole dose, performance status and age.

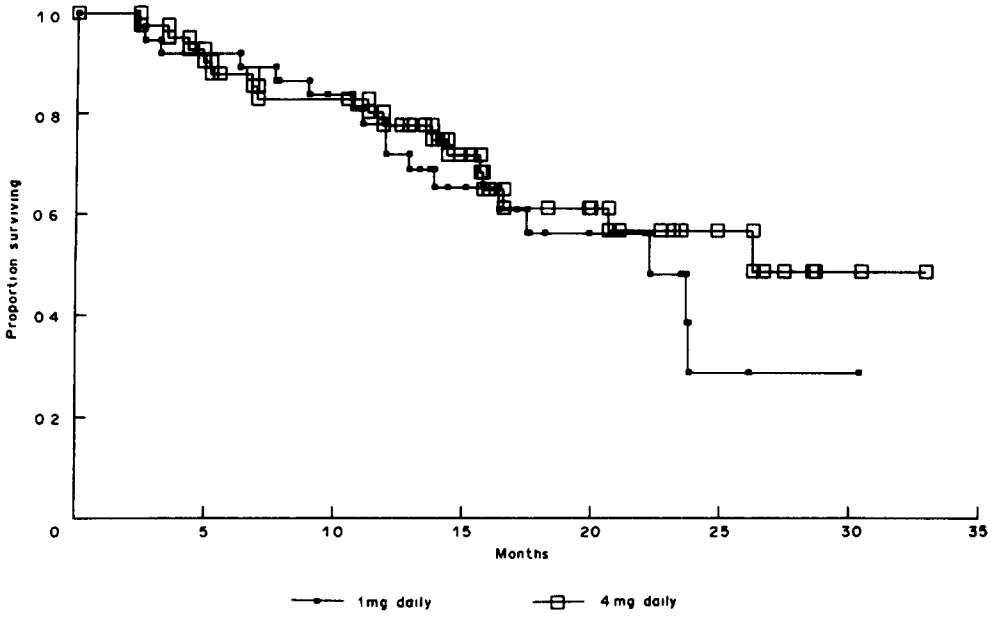

Fig. 1. Survival for patients on 2 doses of fadrozole was not significantly different ($P = 0.36$). Median survival on 1 mg per day was 22.3 months and on 4 mg per day 26.3 months.

regression analysis these factors lost their significance as predictors for survival except for bone vs visceral ($P = 0.03$) (see Table 3).

DISCUSSION

Estrogens provide the support for endocrine dependent human breast cancer cells. The main source of estrogen production in postmenopausal women is the extraglandular conversion of androstenedione to estrone. Androstenedione is converted to estrone in peripheral tissues via the multi-component aromatase enzyme complex. Estrone can either be conjugated into estrone sulphate to form a slowly turning over storage pool with a potential for back conversion to estrone, or be reduced to E_2, the major active estrogenic steroid [16]. Fat and muscle have been proved to contain the majority of extraglandular aromatase activity present in postmenopausal women [17, 18].

Hormone therapy with the aromatase inhibitor AG gives an objective response rate of 30% (range 4–52%) in unselected patients [19, 22], with the higher response rates occurring in patients who had responded to tamoxifen [20]. The new aromatase inhibitor fadrozole has greater specificity and was more effective in preclinical trials.

In the current study of fadrozole, only mild (grade 1) to moderate (grade 2) toxicity was documented among the 78 evaluable patients. The toxicity encountered consisted mainly of hot flushes. Toxicity was not significantly different among patients receiving either 1 or 4 mg of fadrozole per day. The drug was therefore extremely well tolerated as a second line treatment among these women with previously treated metastatic breast cancer.

The current study shows that this aromatase inhibitor gives a response rate of 23% in patients with previously treated metastatic breast cancer. The responses in the present study were seen in patients with good PS. Responses were seen mainly in patients with soft tissue dominant disease. The number of organ sites involved, receptor status and age did not have a significant effect. No difference in response rate was demonstrated between the doses of fadrozole used. When only the 57 patients who received >8 weeks of treatment are considered, the response rate was 32% with 8 of the 57 having a complete response.

Seven patients who are included in the evaluation were ineligible. One patient had ER negative disease, three were premenopausal, one had received more than one previous cytostatic regimen for metastatic disease, one had received a previous AG containing regimen for metastatic disease and one had bone marrow infiltration (considered dire disease) at the time of registration on study. The patient with ER negative disease responded to treatment for >21 months and the patient who had previously

received AG responded for 18 months. One of the 3 premenopausal patients responded to treatment.

A response rate of 28% was reported in pretreated patients, treated with the aromatase inhibitor 4-hydroxyandrostenedione [23]. The response rate in the current fadrozole study is comparable to that achieved with high dose medroxyprogesterone acetate [24]. Although the response rate in the present trial of fadrozole is not higher than the response rate expected with AG, there is much less toxicity among the patients treated with fadrozole.

A significantly longer TTF (and therefore time on study) and a better response rate for patients with ER unknown disease may indicate another mechanism of action. It is however, of note that the patients with ER unknown disease did not have a significantly longer survival than those with ER positive disease. Future clinical trials of fadrozole should not therefore exclude patients with ER unknown disease. The median survival time of 23.7 months for patients treated with fadrozole compares favourably with most trials of second line treatment for patients with metastatic breast cancer. The finding that the best response was seen in patients with soft tissue metastases and the best survival in patients with osseous metastases is the usual pattern seen in patients treated with hormones for advanced breast cancer.

It can be concluded that fadrozole is a worthwhile, particularly well tolerated second line treatment for patients with metastatic breast cancer who do not have dire disease.

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