Preliminary Study of the Treatment of Advanced Breast Cancer in Postmenopausal Women with the Aromatase Inhibitor CGS 16949A

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ABSTRACT

Thirty-one postmenopausal women with advanced breast cancer have been treated with the nonsteroidal competitive aromatase inhibitor CGS 16949A at p.o. doses of 0.3, 1, and 2 mg twice a day. All patients were assessed for response. Five patients, all treated with 1 mg twice daily, had objective evidence of response (two complete responses and three partial responses); disease stabilized in 17 patients.

Minor side effects were reported by ten patients. Two further patients treated with 2 mg twice a day experienced persistent nausea which improved after dose reduction, and one patient, treated with 0.3 mg twice daily, developed a vasculitic rash requiring discontinuation of CGS 16949A.

Estradiol levels measured in 24 patients were significantly suppressed 2 wk after starting CGS 16949A treatment at all doses used. Treatment with 2 mg twice a day lowered estradiol levels to a mean of 29% of pretreatment values which was significantly lower than the corresponding figure of 57% for patients treated with 0.3 mg twice daily. Aldosterone levels were significantly lowered below pretreatment values by the 1- and 2-mg twice daily doses. No clinically apparent cases of adrenocortical insufficiency occurred, although small changes in serum electrolyte levels were noted.

The results indicate that CGS 16949A is an effective aromatase inhibitor, requiring further evaluation in the treatment of advanced breast cancer. The optimal dose is likely to be 1 mg twice a day.

INTRODUCTION

Approximately one-third of human breast cancers are sensitive to hormonal manipulation. Reduction in the levels of circulating estrogens by inhibitors of the peripheral aromatization of adrenal androgens is an accepted method of treatment of advanced breast cancer in postmenopausal women (1). AG,[2] the only aromatase inhibitor currently in widespread clinical use, has been shown to have efficacy comparable to the antiestrogen tamoxifen in postmenopausal women in both the treatment of metastatic disease (2, 3) and as an adjuvant to primary surgery (4). Responses to endocrine treatments for advanced breast cancer are of limited duration. Both antiestrogens and aromatase inhibitors have a role in the management of advanced breast cancer, since it is frequently possible to induce multiple remissions as a result of consecutive treatments with hormonal agents of different classes (3, 5). A proportion of patients who fail to respond to one form of endocrine therapy subsequently experience a remission as a result of treatment with a different agent (3, 5).

Unfortunately AG has a number of undesirable characteristics; this has prompted a search for alternative aromatase inhibitors. The drug is poorly tolerated as a result of side effects

such as somnolence, nausea, and rash, although some of these are self limiting, and some can be minimized by adjustment of dosage (2–4). Furthermore, AG causes some nonspecific adrenocortical suppression at therapeutic doses, making the coadministration of replacement steroids advisable. 4OHA, a steroidal aromatase inhibitor which is more selective and better tolerated than AG, has been shown to be clinically effective in Phase I and Phase II studies (6–8). 4OHA, however, is rapidly inactivated by hepatic glucuronidation, and this may limit its usefulness as an aromatase inhibitor, especially when given p.o. (9, 10).

CGS 16949A is a novel nonsteroidal compound, which has been shown in vitro and in animal studies to be a potent competitive inhibitor of aromatase with no other significant endocrine effects described at pharmacological levels (11). CGS 16949A causes regression of tumors in the rat 7,12-dimethylbenz(a)anthracene-induced mammary carcinoma model which has been widely used in the testing of endocrine treatments of breast cancer (12).

CGS 16949A, in a Phase I dose escalation study in postmenopausal women with breast cancer, has been shown to be a specific inhibitor of aromatase without effect on other corticosteroids at doses below 4 mg daily, and to lack apparent side effects or toxic actions at doses of up to 16 mg daily (13).

In this paper, we report the results of a preliminary clinical study of CGS 16949A in the treatment of advanced breast cancer in postmenopausal women.

PATIENTS AND METHODS

Thirty-one patients with histologically or cytologically proven locally advanced or metastatic breast cancer were entered into the study between December 1987 and August 1988. The age range of patients was 51 to 90 (median, 70 years); one patient had undergone surgical ovariectomy 5 yr before entry, and the remainder were naturally postmenopausal. Fifteen patients were known to have ER-positive carcinomas (i.e., >15 fmol/mg cytosol protein by dextran-coated charcoal assay) (14); 2 patients were ER negative, and the ER status of the remaining 14 was unknown. Eighteen patients had received between one and 4 previous endocrine treatments of whom 11 had experienced at least one remission; 5 further patients had had adjuvant endocrine treatment only. Five patients had had prior chemotherapy. Previous treatments were discontinued at least 3 wk before entry, and all patients had progressive disease on entry.

Patients were fully staged on entry, at intervals of approximately 3 mo during treatment and on completion. Staging consisted of clinical examination, full blood count, measurement of liver function tests and serum calcium, chest radiograph, isotopic bone scan, radiographic limited skeletal survey, and liver ultrasound. Clinical examination, measurement of serum biochemical and haematological parameters, and toxicity assessment were repeated at least every 4 wk during treatment. Assessment of response was made according to standard criteria of the International Union against Cancer (15). All patients gave full informed consent, and the study was approved by St George's Hospital Ethics Committee.

CGS 16949A was supplied in tablets of 0.1 mg and 1 mg by Ciba-Geigy. Patients were treated with doses of 0.3, 1, or 2 mg twice a day.

Fourteen patients were randomized to initial treatment with either 0.3 or 1 mg twice a day for 14 days before crossing over to (maintenance) treatment at the other dose level. Blood was taken for estradiol and aldosterone measurement before CGS 16949A treatment and after 2 wk of treatment. Patients were ambulant when venesection was performed. A further group of 17 patients were similarly randomized to cross over between doses of 1 and 2 mg twice daily; endocrine assessment was also performed on these patients.

Serum estradiol levels were measured by a sensitive and specific radioimmunoassay which has previously been described in detail (7, 8). The assay was conducted after ether extraction of 2×200 μl of serum using an antibody raised to an estradiol-6-carboxymethyloxine-bovine serum albumin conjugate (Baxter Healthcare, Egham, Surrey, England) and estradiol-6-carboxymethyloxine-[2-^{125}I]iodohistamine (about 2000 Ci/mmol; Amersham International, Amersham, England). The sensitivity limit of the assay was 3.5 pmol/liter. The overall within assay coefficient of variation at a range of levels from 14 to 40 pmol/liter was 9.4%, and the between assay coefficient of variation at a level of 27 pmol/liter was 12.8%. Serum aldosterone levels were measured with the Biotecx Aldosterone Direct Radioimmunoassay Kit (Biogenesis, Bournemouth, England). The reference range (95% limits) for standing subjects for this assay is 83 to 370 pg/ml (230 to 1025 pmol/liter). The assay is highly specific, having a cross-reaction of <0.001% with any endogenous steroid. The sensitivity was 10 pg/ml. The intra- and interassay coefficients of variation were <10%.

Estradiol and aldosterone values were seen to be lognormally distributed. Therefore statistical analysis was performed on logarithmic values which required geometric rather than arithmetric means to be quoted. Comparisons of hormone levels over time were made using a split-plot analysis of variance model, while comparisons between doses at each time point were made using analysis of covariance with the baseline values for each patient as the covariate. In 4 patients the on-treatment level of estradiol was <3.5 pmol/liter (assay sensitivity limit) and in these cases the values were taken as being equal to 3.5 pmol/liter.

Electrolyte values were analyzed using the same statistical methods. Logarithmic transformation was not required to normalize values.

RESULTS

All thirty-one patients treated with CGS 16949A were assessed for response. The median duration of treatment was 6 mo with the maximum follow-up currently 19 mo. One patient (with stable disease) was withdrawn because of toxicity. All other patients were treated until disease progressed. Five patients (all treated with a maintenance dose of 1 mg twice daily) had objectively documented partial (3 patients) or complete (2 patients) responses. Response durations were 4, 5, 12, 18+, and 19+ mo. Disease stabilized for at least 2 mo in 17 patients, and stabilization continued for at least 6 mo in 12 patients; the median duration of disease stabilization was 9 mo. Response data according to CGS 16949A dose, ER status, and response to previous endocrine treatment are summarized in Table 1. The CGS 16949A dose was increased from 0.3 to 1 mg twice daily in 3 patients with stable disease and one patient with slowly progressive disease after between 3 and 7 mo of low-dose therapy because of concern that 0.3 mg twice a day might be an endocrinologically suboptimal dose; no improvements in response status occurred. No patient with an ER-negative carcinoma responded. Eight patients who had previously had treatment with multiple endocrine agents including in all cases both tamoxifen and other aromatase inhibitors were included in the study; of these patients, 2 had previously responded to a combination of tamoxifen, AG, and danazol, one had responded to AG, and 3 had responded and 2 stabilized on 4OHA treatment. None of these patients responded to CGS 16949A (no change, 4; progressive disease, 4 patients). The number of patients responding according to site of disease involvement

Table 1 *Response to CGS 16949A*

	Total	Complete or partial response	No change	Progressive disease
Overall	31	5	17	9
CGS 16949A maintenance dose (mg twice daily)				
0.3[a]	7	0	4	3
1	17	5	8	4
2	7	0	5	2
ER status				
ER positive	15	3	7	5
ER unknown	14	2	10	2
ER negative	2	0	0	2
Previous endocrine treatment and response				
Nil or adjuvant only	13	3	8	2
Antiestrogen only				
Response	5	1	2	2
No response	4	0	3	1
Not assessable	1	1	0	0
Multiple agents[b]				
Response	6	0	2	4
No response	2	0	2	0

[a] CGS 16949A dose increased to 1 mg twice daily in 4 patients for >4 wk without effecting response (no change, 3 patients; progressive disease, one).

[b] Includes antiestrogen and aromatase inhibitor treatment in all cases, in either sequence (6 patients) or in combination with danatol (2 patients), progesterone treatment (4 patients) and miscellaneous agents (1 patient).

and the number of patients with disease at each site were as follows: soft tissue, 4 of 24; bone, one of 7; liver, 0 of 2; lung and other viscera, 0 of 8.

All 31 patients, 30 of whom completed 2 or more wk of treatment at each of 2 dose levels, were assessable for CGS 16949A toxicity. Thirteen patients reported side effects which were for the most part mild and transient; these included nausea (6 patients), giddiness (4 patients), lethargy (one patient), headaches (one patient), hot flushes (two patients), dry mouth (two patients), and disturbance of taste (one patient). The number of patients experiencing side effects and the number of patients treated at each dose level were: 0.3 mg twice daily, 2 of 13; 1 mg twice daily, 9 of 31; 2 mg twice daily, 6 of 17. Two patients treated with 2 mg twice a day had troublesome nausea which improved with reduction of dose to 1 mg twice daily. One patient treated with 0.3 mg twice a day, who was also treated with silver sulfadiazine ointment, phenytoin, warfarin, and a number of other medicaments, developed a vasculitic skin rash after 6 wk of therapy, which resolved on discontinuation of CGS 16949A.

Serum estradiol levels were significantly suppressed after 2 wk of treatment with CGS 16949A at all 3 doses used. The mean (geometric) pretreatment serum estradiol levels were 23.5, 20.8, and 19.0 pmol/liter for the 0.3- ($n = 7$), 1- ($n = 11$), and 2-mg ($n = 6$) twice daily doses, respectively. After 14 days of treatment, those levels were significantly suppressed, respectively, to 55.7 (33.7 to 92.0), 41.1 (33.4 to 50.5), and 28.7 (18.4 to 44.7)% of pretreatment levels (geometric means and 95% confidence intervals of mean). The suppression achieved by 2-mg twice a day was significantly greater than that by 0.3 mg twice a day ($P = 0.015$), but there was no significant difference between that achieved by 0.3 and 1 mg twice a day, or between 1 and 2 mg twice a day.

Mean (geometric) levels of aldosterone were not significantly affected by 0.3 mg twice daily after 14 days [pretreatment, 715 (510 to 1000) pmol/liter; Day 14, 598 (429 to 834) pmol/liter; $P = 0.45$]. Significant suppression was found, however, with the two higher doses [1 mg twice daily, pre, 457 (360 to 576) pmol/liter; Day 14, 338 (271 to 418) pmol/liter; $P < 0.005$; 2 mg twice daily, pre, 341 (266 to 438) pmol/liter; Day 14, 169 (119 to 244) pmol/liter; $P < 0.001$]. No patient was treated

Table 2 *Changes in serum electrolyte levels after 14 days of treatment with CGS 16949A*

The mean change in serum electrolyte levels from Day 0 to Day 14 (paired data) and 95% confidence interval of the mean are shown. Positive values represent a rise, and negative values a fall in levels after 14 days of treatment.

CGS 16949A dose (mg/twice daily)	n	Day 14 to Day 0 mean			
		Sodium (mmol/liter)	Potassium (mmol/liter)	Sodium/potassium ratio	Urea (mmol/liter)
0.3	7	−1.8 (0.3 to −3.9)[a]	0.14 (−0.26 to 0.54)	−1.6 (2.3 to −5.5)	0.7 (−0.2 to 1.6)
1	13	−1.4[b] (0.0 to −2.8)	0.30[b] (0.03 to 0.57)	−3.2[b] (−0.6 to −5.8)	0.8[c] (0.2 to 1.4)
2	9	−2.7[c] (−0.9 to −4.5)	0.20 (−0.14 to 0.54)	−2.3 (1.0 to −5.6)	0.9[c] (0.2 to 1.6)

[a] Numbers in parentheses, 95% confidence interval of mean.
[b] $P < 0.05$.
[c] $P < 0.01$.

with an angiotensin-converting enzyme inhibitor or aldosterone antagonist or had a change in concomitant medication during the study period was likely to affect aldosterone levels.

Serum electrolyte levels were measured prior to treatment and regularly during treatment. Pretreatment values were: sodium, 140.1 (139.3 to 140.9) mmol/liter; potassium, 3.9 (3.8 to 4.0) mmol/liter; sodium/potassium ratio, 36.2 (34.9 to 37.5); urea, 5.3 (4.7 to 5.9) mmol/liter; ($n = 31$). The mean changes in these parameters from Day 0 to Day 14 at all 3 CGS 16949A dose levels are shown in Table 2. Small but significant changes occurred for all 4 parameters in the 1-mg twice daily group, and for sodium and urea levels in the 2-mg twice daily group. In all cases, changes in electrolyte levels were in a direction which was consistent with the effect of aldosterone suppression. There were no significant differences between the values of any parameters on comparing the 3 dosage groups after 14 days of treatment. The only significant difference found on comparison of electrolyte parameters between Day 14 and Day 28 was for the sodium/potassium ratio in the group crossed between 0.3 and 1 mg twice daily (mean difference: 1 to 0.3 mg twice daily, −1.9 (−0.2 to −3.6); $P = 0.028$). In only one patient did the sodium level fall to below the normal range, and there were no cases of hyperkalemia. Progressive change in electrolyte levels with continued treatment was not observed.

DISCUSSION

The clinical and endocrine data that we have presented show that CGS 16949A is an effective aromatase inhibitor, suitable for further evaluation in the treatment of advanced postmenopausal breast cancer.

The clinical efficacy of CGS 16949A is demonstrated by the 5 objective responses that we have documented. The overall response rate of 16% was slightly lower than the 25 to 35% previously reported for AG and for 4OHA (2, 3, 8). Similarly a larger proportion of patients had prolonged disease stabilization than is usually reported in endocrine studies of breast cancer. However, because of the Phase I/II nature of the study, the overall number of patients evaluated was small, a variable dose of CGS 16949A was used, and the patient population was heterogeneous. In particular, a number of patients who had had previous treatment with other aromatase inhibitors or who had ER-negative carcinomas were included. The number of patients falling into identifiable subgroups is therefore small. For these reasons, it is not possible to extrapolate the response pattern observed in the current study to more homogeneous groups of patients who might be treated with either CGS 16949A or other aromatase inhibitors, nor is it possible to comment on the relative clinical efficacy of the 3 doses of CGS 16949A that were used. Since CGS 16949A appears to be as effective an

inhibitor of aromatase as are AG and 4OHA, it is likely that the clinical results in larger studies with an endocrinologically satisfactory dose of CGS 16949A and a more clearly defined patient population will be similar to those found with other aromatase inhibitors.

The endocrine data that we have presented show that CGS 16949A at the higher doses used suppresses the dominant estrogen, estradiol, to an extent comparable with that reported for both AG and 4OHA (7, 16), demonstrating that CGS 16949A is an effective aromatase inhibitor in humans. The differences in suppression of estradiol detected at different CGS 16949A doses suggest that 0.3 mg twice a day may be suboptimal. The significance of the aldosterone suppression which we observed at the 1- and 2-mg twice daily doses is uncertain. The small but nevertheless significant changes in electrolyte values which we observed at the 2 higher doses are consistent with a degree of aldosterone suppression. Although there were no clinically apparent cases of adrenocortical insufficiency, it is possible that aldosterone suppression may prove to be problematic in some patients. This needs to be carefully monitored in future studies. Our endocrine data are in broad agreement with the results of Santen et al. (13), but the effect of CGS 16949A on serum aldosterone has not previously been reported. A full endocrinological profile of CGS 16949A is the subject of a separate report (17).

Side effects reported by patients were for the most part mild and transient, although a higher proportion of patients complained of symptoms than did those treated with 4OHA (6). There is a suggestion that there may be a greater incidence of side effects at higher doses. In particular, the occurrence of persistent nausea at the 2-mg twice daily dose in 2 patients which was ameliorated by dose reduction suggests that gastrointestinal side effects may be problematic at higher doses. The vasculitic skin rash affecting one patient is likely to have been idiosyncratic; other medications may have contributed.

Our preliminary study shows that CGS 16949A is sufficiently effective and well tolerated to merit further clinical study. While larger studies are required to define the optimal dose, on the basis of the toxicity and endocrinological data collected in this study, it appears that the optimal dose is likely to be 1 mg twice a day.

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