Anti-Cancer Drugs 1998, 9, pp. 675–683

Clinical paper

Safety, activity and estrogen inhibition by exemestane in postmenopausal women with advanced breast cancer: a phase I study

R Paridaens, J Thomas, J Wildiers, P Vermeiren, J-P Lobelle,[1] E di Salle,[1] G Ornati,[1] MG Zurlo,[1] A Polli,[1] S Lanzalone[1] and K de Belder[1]

UZ Gasthuisberg, Dienst Gezwelziekten, Herestraat 49, 3000 Leuven, Belgium. Tel: (+32) 16 34 69 02; Fax: (+32) 16 34 76 75. [1]Pharmacia & Upjohn, Milan, Italy.

Exemestane is an irreversible, steroidal, oral aromatase inhibitor under evaluation in postmenopausal women with advanced breast cancer. A phase I study was conducted in 27 postmenopausal patients who were candidates for hormone therapy because they had advanced breast cancer and estrogen receptor-positive or unknown status. Most patients were moderately or heavily pretreated. Cohorts of at least three patients received sequentially escalating daily oral doses of 5–600 mg. The median duration of exemestane treatment was 13 weeks (range: 3–166 weeks). The maximal tolerated dose was not reached because of lack of treatment-related grade 3 or 4 toxicity. The most common adverse events, including those not related to treatment, were mild to moderate headache (44% of patients), dizziness (33%), nausea (33%), hot flushes (30%) and tumor-related pain (30%). There were three complete and four partial responses for an objective response rate of 26% (95% CI: 11.1–46.3%) in the intent-to-treat population; the median duration of response was 74 weeks (95% CI: 48–99 weeks). Exemestane, at the dose of 25 mg, maximally suppressed estradiol, estrone and estrone sulfate serum levels to 13, 5 and 10% of baseline, respectively. Exemestane appears to suppress estrogen, be well tolerated and have antitumor activity in postmenopausal women with advanced breast cancer. A large, safe therapeutic window of up to 600 mg was defined. In view of its safety and estrogen-suppression profiles, the most favorable effects were observed at the 25 mg daily dose. [© 1998 Lippincott Williams & Wilkins.]

Key words: Advanced breast cancer, aromatase inhibitor, exemestane, phase I study, postmenopause.

Introduction

Hormonal therapy, which suppresses or antagonizes endogenous estrogens, plays an important role in the management of advanced breast cancer because of its clinical activity, especially in patients with positive estrogen receptors and safety profile.[1] While oophorectomy or other castration methods may be preferred for premenopausal women, the antiestrogen, tamoxifen, is conventionally first-line hormonal therapy for postmenopausal women.[1,2] Megestrol acetate[3] and aminoglutethimide[4,5] produce analogous response rates, but these agents are generally considered to be second-line therapy because of adverse events. The success of hormonal therapy has prompted a search for alternative agents for patients who are refractory to first- or second-line agents. Aromatase inhibitors are of interest because they inhibit the enzyme that mediates conversion of ovarian and adrenal androgen substrates to estrogens, and have potent antitumor effects in animal models.[6,7]

Aromatase inhibitors can be differentiated by their chemical configurations and pharmacological properties.[6,7] The first aromatase inhibitor, aminoglutethimide, has a non-steroidal configuration and inhibits many cytochrome P450-dependent enzymes. Its clinical role is limited by low potency, lack of specificity and adverse effects (e.g. skin rash, somnolence and, rarely, leukopenia, thrombocytopenia or thyroid insufficiency). Newer non-steroidal agents (e.g. anastrozole, letrozole and vorozole) are more potent inhibitors and more selective for the cytochrome P450 aromatase system than the previous generation of competitive inhibitors (e.g. fadrozole). In contrast with non-steroidal agents, steroidal agents (e.g. formestane and exemestane) are substrate analogs that bind covalently to the aromatase enzyme thereby inhibiting it in an irreversible manner.[6,7] While the exact implications of these biochemical differences are the subject of ongoing investigation,

This investigation was supported by Pharmacia & Upjohn, Milan, Italy.

Correspondence to R Paridaens

available data suggest that these differences may be clinically relevant. For example, the results of clinical studies[8,9] in which patients who were refractory to aminoglutethimide responded to formestane suggest a lack of cross-resistance between non-steroidal and steroidal aromatase inhibitors.

Exemestane (PNU 155971; FCE 24304) is a potent, irreversible inhibitor of aromatase in *in vitro* and *in vivo* models.[10,11] After both oral and s.c. administration, exemestane had antitumor activity in an animal model of postmenopausal mammary tumors, which were induced by DMBA in ovariectomized rats treated with testosterone.[12] A single oral dose suppressed plasma estrogen levels for up to 5 days in healthy postmenopausal volunteers.[13] This long-lasting endocrine effect was more consistent with irreversible aromatase inhibition than with the pharmacokinetic profile because, after reaching peak levels 2 h after oral administration, exemestane plasma concentrations declined with a terminal half-life of 18–24 h. Finally, single oral doses of exemestane ranging from 0.5 to 800 mg were well tolerated in healthy postmenopausal volunteers.[13] We conducted a phase I study to evaluate the endocrine and clinical effects of sequentially escalating doses of exemestane in postmenopausal women with advanced breast cancer. Preliminary results of this study were reported in abstract form.[14]

Patients and methods

Eligibility criteria

Postmenopausal patients were eligible for the study if they were candidates for endocrine therapy because they had locally advanced or metastatic and estrogen receptor-positive or receptor-unknown breast cancer. All patients had amenorrhea for at least 1 year, or follicle-stimulating hormone (FSH) level of >50 mIU/ml and luteinizing hormone (LH) level of 15–40 mIU/ml. Patients had to have at least one measurable lesion, predicted survival of at least 6 months and ECOG performance status of ≤ 2. Previous systemic antineoplastic therapy was permitted and had to be completed at least 4 weeks before study entry. Patients were excluded if any of the following conditions were present: contraindication to hormonal therapy (e.g. massive visceral disease), severe intercurrent illness, previous depot hormonal treatment, mental incapacity, abnormal renal or hepatic function, leukopenia, or thrombocytopenia. All patients gave written informed consent for participation in the study.

Study design

This was an open-label, dose-finding study. The protocol was approved by the ethics committees from the two participating centers in Belgium. Successive cohorts of three to six patients received exemestane once daily after breakfast in sequentially escalating doses of 5, 10, 25, 50, 100, 200, 400 and 600 mg.

Study parameters and response criteria

Pre-study evaluation included history and physical examination, assessment of adverse events, laboratory studies (i.e. hematology and chemistry studies, urinalysis, assessment of serum estrogens), and tumor evaluation. Physical examination and assessment of adverse events were repeated weekly for the first 6 weeks and then every 3 weeks for the rest of the first 12 weeks. Laboratory studies and assessment of drug compliance were performed every 3 weeks for the first 12 weeks. Beginning at the end of week 12, physical examination, and assessments of adverse events and drug compliance were repeated monthly; laboratory studies and tumor evaluation were performed every 12 weeks.

The maximal tolerated dose was defined as the first dose level at which more than half of the patients experienced new or increased toxicity. New toxicity was defined by the onset of the National Cancer Institute's (NCI's) Common Toxicity Criteria (CTC) for grade 2 or greater events affecting blood pressure, blood or bone marrow, skin (excluding alopecia); grade 2 or greater cardiac, genitourinary, hepatic or neurologic events; or grade 2 or greater diarrhea, nausea, vomiting, stomatitis, phlebitis or thromboembolism. New toxicity was also defined by the onset of CTC grade 3 or greater other than those listed above. Increased toxicity was defined by worsening of events present at baseline, which had to worsen by at least one CTC grade if they were listed above or by two grades if they were not listed.

Patients were evaluated for tumor response if they completed the initial 12 week treatment period without evidence of disease progression. Response was defined by World Health Organization (WHO) criteria. Assessments for complete (CR) and partial response (PR) were determined on two consecutive observations within the same 4 week period. CR was defined as the disappearance of all known disease. PR was defined by a 50% or greater decrease in total tumor load. No change was defined by inability to establish 50% decrease in total tumor size without a 25% increase for at least 4 weeks. Progressive disease

(PD) was defined by 25% or greater increase in measurable lesion(s) or appearance of new lesions.

Patients were continuously monitored for adverse events, which were defined as any undesirable clinical events regardless of relationship to treatment. Adverse events were elicited by check list, by open questionnaire and by asking the patients if they had experienced any adverse events since the last visit. The severity of adverse events was graded by NCI CTC; relationship to treatment was also recorded. Routine laboratory tests were performed by participating institutions, which provided normal values for use in this study. Unexpected toxicity was defined as an event not previously reported in association with exemestane, or a known toxicity that differed because of greater severity or specificity. Serious adverse events were defined as any of the following: fatal regardless of relationship to treatment, life-threatening, permanently disabling or requiring hospitalization.

Serum estrogen measurements

Blood samples for hormone measurements were obtained in the morning after an overnight fast and before drug administration. Serum was obtained by centrifugation. Serum samples were stored at $-20^{\circ}C$ until they were assayed at a central laboratory by one of the investigators (E di S). Estrogen concentrations (estradiol [E_2], estrone [E_1], and estrone sulfate [E_1S]) were measured by high-performance liquid chromatography (HPLC)-RIA.[15] The sensitivity limits for serum E_2, E_1, and E_1S were 0.7, 1.8 and 6 pg/ml, respectively.

Statistics

The sample size was based on a conventional, dose-escalating, cohort, phase I design. Study variables were summarized by descriptive statistics using SAS® system release 6.07. Actual hormonal values, percent variation from baseline and the corresponding geometric means were determined. Mean and SD were calculated for laboratory variables; the frequency of values outside normal limits was calculated.

Results

Twenty-seven patients were enrolled between May 1991 and November 1992. All patients received exemestane and took at least 80% of the prescribed dose. At least three patients received each dose; four received the 100, 400 and 600 mg doses. The median duration of treatment was 13 weeks (range: 3-166 weeks); the median duration of follow-up was 19.7 weeks (range: 3-166 weeks). Seven patients were withdrawn before the end of week 12 because of disease progression (n=5), refusal to continue treatment (n=1) and ineligibility (negative receptor status) discovered at week 5 (n=1). Of the remaining 20 patients, 19 were withdrawn after week 12 (range: 12-126 weeks) because of disease progression. The remaining patient continued to receive exemestane beyond the cut-off date for this analysis and was still on treatment as of December 1997.

Patient characteristics are listed in Table 1. Additional details, not found in Table 1, are summarized below. Estrogen and progesterone receptors were positive in 21 and 12 patients (78 and 44%, respectively). Of five patients in whom receptor status was unknown, three had responded to previous hormonal therapy. All but one patient had received

Table 1. Demographics in 27 postmenopausal women with advanced breast cancer

Characteristic	No. of patients (%)[a]
Median age in years (range)	60 (37-77)
Median ECOG performance status (range)	1 (0-2)
Median number of years since menopause (range)	7 (1-27)
Disease evaluability	
measurable lesion(s)	24 (89)
evaluable disease	2 (7)
not evaluable	1 (4)
Predominant disease site at study entry	
soft tissue only	8 (30)
bone ± soft tissue	9 (33)
visceral ± other	10 (37)
Receptor status (estrogen, progesterone or both)	
positive	21 (78)
unknown	5 (19)
negative	1 (4)
Previous locoregional treatment(s)	
Surgery, radiotherapy and systemic therapy	21 (78)
Radiotherapy and systemic therapy	5 (19)
Surgery and radiotherapy	1 (4)
Previous systemic therapy	
hormonal therapy and chemotherapy (adjuvant and advanced)	12 (44)
hormonal therapy only (adjuvant and advanced)	10 (37)
adjuvant hormonal therapy only	3 (11)
adjuvant chemotherapy only	1 (4)
none	1 (4)
Median duration of first disease-free interval in months (range)	40 (2-170)

[a]Unless otherwise stated.

previous systemic therapy, which usually consisted of both adjuvant therapy and treatment for advanced disease, either as hormonal therapy alone or combined with chemotherapy. Previous hormonal therapy consisted of tamoxifen in 15 patients (56%); tamoxifen and aminoglutethimide in three (11%); tamoxifen and medroxyprogesterone in one (4%); and tamoxifen, aminoglutethimide and medroxyprogesterone in six (22%).

Most patients (96%) had previous or concomitant medical conditions, of which the most common were skeletal problems (85%), cardiovascular diseases (54%), gastrointestinal conditions (48%) and genitourinary conditions (48%). Eighteen patients (67%) received a wide variety of concomitant medications; six (22%) received analgesics. Most patients (93%) reported at least one sign or symptom at study entry, which were of mild (grade 1) and moderate (grade 2) severity in 52 and 41% of patients, respectively. The most common symptoms were pain at tumor site in 13 patients (48%), gastrointestinal disturbances in eight (30%) and hot flushes in six (22%).

Safety

Although the dose was increased up to 600 mg daily, the maximal tolerated dose was not reached. There was no clear relationship between dose and the distribution of adverse events with grade 2 or greater toxicity during the first 12 weeks of treatment (Table 2). There were no grade 4 adverse events. Only one patient experienced a grade 3 adverse event of indeterminate cause. After 4 weeks of treatment with exemestane, this 69-year-old patient, who had cardiomegaly, sinus arrhythmia and hypertension, experienced atrial fibrillation followed by cardiac decompensation. She recovered fully upon discontinuation of exemestane and was successfully retreated with exemestane for up to 24 weeks.

Overall, 26 patients experienced at least one adverse event during the first 12 weeks of treatment, regardless of relationship to treatment (Table 3). The most common adverse event was headache, which occurred in 44% of patients. The next most common adverse events, dizziness, nausea, hot flushes and tumor-related pain, each occurred in approximately one-third of patients.

Less common adverse events, which occurred in less than three patients each, were not included in Table 3. Adverse events that occurred in only two patients during the first 12 weeks of treatment each were insomnia, pharyngitis, rhinitis and urinary tract infection. Adverse events that occurred in only one

Table 2. Adverse events with grade 2 or greater toxicity, which were related to drug or of indeterminate cause and which occured during the first 12 weeks of treatment

Dose in mg (no. of patients)	No. of patients (adverse event)	
	Grade 2 toxicity	Grade 3 toxicity
5 (3)	2 (weakness [n=2], dizziness [n=1], nausea [n=1], mood changes [n=1])	0
10 (3)	0	0
25 (3)	1 (hot flushes)	1 (atrial fibrillation and cardiac decompensation)
50 (3)	1 (hot flushes)	0
100 (4)	1 (fever)	0
200 (3)	1 (sweating)	0
400 (4)	0	0
600 (4)	2 (hot flushes [n=1], vomiting [n=1], mood changes [n=1])	0

Table 3. Adverse events occurring in three or more patients during treatment with exemestane

Adverse event	Percent of patients with adverse event[a]	
	⩽12 weeks (n=27)	⩾12 weeks (n=13)
Any	96 (78)	100 (100)
Maximal severity		
grade 1	44 (44)	8 (38)
grade 2	37 (30)	69 (54)
grade 3	15 (4)	23 (8)
grade 4	0 (0)	0 (0)
Headache	44 (37)	62 (54)
Dizzinesss	33 (30)	54 (38)
Nausea	33 (22)	38 (31)
Hot flushes	30 (30)	54 (54)
Tumor-related pain	30 (0)	15 (0)
Weakness	22 (11)	23 (15)
Constipation	19 (15)	31 (31)
Mood changes	19 (15)	15 (8)
Sweating	19 (11)	46 (23)
Peripheral edema	15 (15)	38 (38)
Dyspepsia	15 (11)	15 (15)
Vomiting	15 (7)	31 (8)
Paresthesia	11 (11)	31 (23)
Abdominal pain	11 (4)	15 (8)
Viral infection	11 (0)	38 (0)
Insomnia	8 (4)	23 (23)
Bronchitis	4 (0)	23 (0)
Pain (no otherwise specified)	0 (0)	23 (8)

[a]Percent with any adverse event is shown first, followed in parentheses by the percent with adverse events that were treatment related or of indeterminate cause.

patient each were rash, arthritis, back pain, hyperkinesia, leg cramps, earache, anorexia, increased appetite, diarrhea, dry mouth, gastroenteritis, esophagitis, cardiac failure, atrial fibrillation, dyspnea, bronchitis, breast pain, vaginal hemorrhage, vaginitis and fever. Thirteen patients continued exemestane beyond 12 weeks. One received 5 mg of exemestane, two each received 10 and 25 mg, three received 50 mg, one received 100 mg, and two each received 200 and 400 mg. All patients experienced at least one adverse event at some time during treatment (see last column of Table 3), which was drug-related or of indeterminate cause and was of mild to moderate severity. The only grade 3 event reported during follow-up, which was related to treatment or of indeterminate cause, occurred in the previously described patient who had continuation of cardiac decompensation. The other two grade 3 events, which were not related to treatment, were pain (not otherwise specified) and aggravated angina. New adverse events emerged when patients continued exemestane beyond 12 weeks. Except for the two previously described cases of pain and aggravated angina, all new adverse events were of mild or moderate severity. Androgenic effects [i.e. hypertrichosis (n=2), dysphonia (n=2) and alopecia (n=1)] were reported in two patients who received the 400 mg dose. Pain was the only new adverse event that emerged in three patients. New adverse events that emerged in two patients each were arthralgia, coughing and fatigue. New adverse events that emerged in one patient each were skin discoloration, skin ulceration, arthrosis, pathologic fracture, myalgia, migraine, neuralgia, hyporeflexia, nervousness, somnolence, aggravated angina pectoris, cardiac fibrillation, phlebitis, sinusitis and inflicted injury. None of the patients withdrew from the study because of toxicity, although one patient refused to continue treatment with the 400 mg dose because of a variety of mild events, including headache, sweating, cold nose and gastrointestinal disturbances.

Nine patients (33%) experienced grade 1 or 2 weight loss; two (7%) experienced grade 1 or 3 weight gain. The cause of weight change was usually indeterminate. The grade 3 weight gain was attributed to general improvement.

Most abnormal laboratory findings were grade 1 or 2 (Table 4). Of the nine patients who developed grade 3 or 4 lymphocytopenia, all had grade 2 abnormalities at baseline. Elevated hepatic enzymes were at least partly due to disease progression. For example, elevated γ-GT was disease related in two of three patients with grade 3 abnormalities, who received 100 and 600 mg daily, respectively, and was of indeterminate cause and transient in the remaining patient with grade 3 abnormality, who received 100 mg daily. Most of the clinically relevant abnormal laboratory values resolved spontaneously or were attributable to underlying disease. Exemestane was not discontinued in any patient because of abnormal laboratory values.

Clinical activity

Seven patients achieved objective responses (26%; 95% CI: 11.1-46.3%), including three CR and four PR (Table 5). The median time to objective response was 12 weeks (95% CI: 12-24 weeks). The median duration of response was 74 weeks (95% CI: 48-99 weeks). The patient who continued exemestane therapy beyond completion of this study achieved a CR, which was sustained for 166 weeks at the cut-off date for the study (30 April 1996) and for an additional 21 months when this manuscript was written (December 1997). Clinical outcome did not appear to be related to the dose of exemestane. There were two objective responses (one CR and one PR) each in the 10 and 50 mg cohorts, one CR in the 400 mg cohort, and one PR each in the 100 and 200 mg cohorts. Seven patients were not evaluable for tumor response because of ineligibility due to negative receptor and perimenopausal status (n=2), non-evaluable bone lesions (n=2), refusal to continue treatment beyond week 3 (n=1), disease progression at week 2 (n=1), and prolonged dosing error (n=1). When these patients were excluded, there were seven objective

Table 4. Abnormal laboratory findings

Parameter	Percent of patients	
	Any	Grade 3 or 4
Anemia	15	0
Thrombocytopenia	4	0
Leukopenia	22	0
Neutropenia	12	0
Lymphopenia	46	35
Elevated serum glutamic oxaloacetic transaminase (SGOT)	37	0
Hyperbilirubinemia	4	0
Elevated GT	37	11[a]
Elevated lactic dehydrogenase	44	0
Elevated alkaline phosphatase	44	0
Elevated serum calcium	19	0
Elevated serum creatinine	30	0
Abnormal plasma glucose	67	0

[a]Seven percent of GT elevations were tumor related; 4% were indeterminate

Table 5. Tumor response according to modified WHO criteria

Patient group	No. of patients with objective response/no. evaluable (%)	
	All patients	Evaluable patients
All patients	7/27 (26)	7/20 (35)
Dose (mg)		
5	0/3 (0)	0/1 (0)
10	2/3 (67)	2/3 (67)
25	0/3 (0)	0/2 (0)
50	2/3 (67)	2/2 (100)
100	1/4 (25)	1/4 (25)
200	1/3 (33)	1/2 (50)
400	1/4 (25)	1/3 (33)
600	0/4 (0)	0/3 (0)
Predominant disease site		
soft tissue only	4/8 (50)	4/8 (50)
bone ± soft tissue	3/9 (33)	3/7 (43)
visceral ± other	0/10 (0)	0/5 (0)
Receptor (ER, PgR or both) status		
positive	6/21 (29)	4/16 (38)
unknown (and response to previous hormonal therapy[a]	1/3 (33)	1/3 (33)
Successful response to previous hormonal therapy[a]	4/10 (40)	4/7 (57)

[a]Success was defined as complete response, partial response or stable disease for at least 24 weeks.

responses in 20 evaluable patients (35%; 95% CI: 15.4–59.2%).

Serum estrogen concentrations

Three patients, one each in the 5, 25 and 600 mg cohorts, were not evaluable for endocrine effects because of insufficient samples, perimenopausal status and concomitant androgen therapy, respectively. Week 12 results from an additional patient in the 5 mg cohort were excluded because of prolonged dosing error (administration of 25 mg dose for 37 days beginning at week 10).

Exemestane reduced serum estrogen levels at the first (3 week) observation period and throughout the 12 week observation period (data not shown), regardless of dose. E_2 and E_1 levels were suppressed below the limits of detection of the assay in 20 and nine of 23 patients (87 and 39%), respectively. E_1S levels remained detectable in all patients.

Figure 1 illustrates the maximal suppression of estrogen levels, defined as the lowest mean value at any time during the 12 week treatment period,

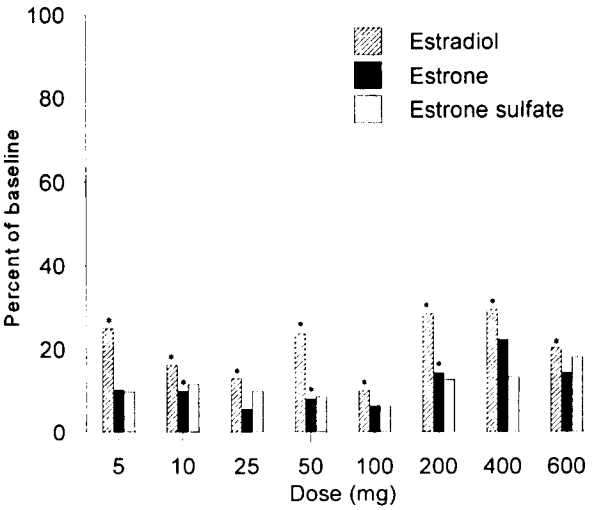

Figure 1. Maximal suppression of serum estrogens during treatment with exemestane in 24 postmenopausal patients with advanced breast cancer. *The calculated percentage of baseline underestimated the effect because the absolute levels approached or were below the detection limits of the assay.

expressed as a percentage of baseline. The mean maximal suppression of estrogen levels occurred at the lowest dose for E_2.

The mean E_2 value was suppressed to the lower limits of assay sensitivity (0.7 pg/ml) at all doses (Table 6), except the 400 and 600 mg doses. Therefore, the calculated percentages of the baseline level underestimated the suppressive effect because the value of the detection limit was used in most of these calculations. Maximal suppression of E_1 appeared at the 25–200 mg doses, which, however, was underestimated. Maximal suppression of E_1S occurred at the 5 mg dose (mean value: 17.9 pg/ml). Finally, the two highest doses did not appear to suppress estrogen as well as lower doses, except for E_1S at the 400 mg dose.

Discussion

The results of our phase I study indicate that exemestane is well tolerated, has clinical activity in postmenopausal women with advanced breast cancer, and has a profound inhibitory effect on blood estrogen production and subsequent levels at all doses tested in this study. All doses were well tolerated. Objective responses occurred in 26% of patients and were nearly evenly distributed across the dosing range. Estrogen levels often fell below the

Table 6. Maximal serum estrogen suppression during exemestane treatment in 24 postmenopausal patients with advanced breast cancer

Dose (mg) (no. of patients at baseline)	Mean value (pg/ml) at baseline and during treatment					
	Estradiol (E_2) (0.7 pg/ml)[a]		Estrone (E_1) (1.8 pg/ml)		Estrone sulfate (E_1S) (6 pg/ml)	
	Baseline	Lowest[b] (% of baseline)	Baseline	Lowest (% of baseline)	Baseline	Lowest (% of baseline)
5 (n=2)	2.8	<0.7 (25.0)[c]	28.8	3.3 (10.1)	230.1	17.9 (9.7)
10 (n=3)	4.6	<0.7 (16.2)[c]	32.0	<3.2 (9.9)[c]	302.9	35.1 (11.6)
25 (n=2)	4.7	<0.7 (12.9)[c]	42.6	2.6 (5.4)	250.5	24.1 (9.9)
50 (n=3)	3.0	<0.7 (23.7)[c]	24.5	<1.9 (7.9)[c]	263.9	22.4 (8.5)
100 (n=4)	4.4	<0.7 (10.0)[c]	28.8	2.1 (6.2)	303.4	22.2 (6.1)
200 (n=3)	2.4	<0.7 (29.5)[c]	17.6	<2.5 (14.3)[c]	147.3	18.5 (12.6)
400 (n=4)	2.7	<0.9 (28.3)[c]	15.0	3.2 (22.2)	113.4	15.1 (13.2)
600 (n=3)	4.0	<0.8 (20.2)[c]	29.8	4.2 (14.2)	185.6	33.7 (18.1)

[a]Lower limits of detection by HPLC-RIA.
[b]Lowest geometric mean value at any time during the 12 week treatment period.
[c]The calculated percent of baseline underestimated the effect because the levels approached or were below the detection limits of the assay.

level of assay sensitivity, which may have obscured any dose relationship. The extent of tolerability, clinical activity and endocrine effects across this broad dosing range makes it difficult to identify the optimal dose of exemestane.

The maximal tolerated dose of exemestane was not reached although the daily dose was increased from 5 to 600 mg in this study. None of the patients experienced grade 3 toxicity that was related to exemestane. None of the adverse events observed in our study were unexpected and some were directly attributable to the pharmacologic activity of exemestane. The most common treatment-related adverse events were headache, dizziness, nausea and hot flushes, which were of only mild to moderate severity, and did not interfere with treatment. In fact, patients appeared to develop tolerance to the gastrointestinal disturbances when treatment was continued beyond 12 weeks (data not shown). Some of the new symptoms that emerged after 12 weeks at the 400 mg dose (e.g. hypertrichosis, dysphonia and alopecia) have also been described during long-term therapy with exemestane[15] and may have been due to the formation of 17-hydroexemestane metabolite, which has mild androgenic activity, at a very high dose of exemestane. While not problematic in our study, adverse events associated with long-term treatment disappeared after reducing the dose from 200 to 100 mg in another study.[15] Aside from these androgenic effects, the frequency of adverse events did not appear to be related to the dose of exemestane, which has been reported previously in a single-dose study.[13]

The 26% objective response rate and 74 week median duration of response are encouraging in view of the extent of previous treatment in the present series (see Table 1). Our results are consistent with preliminary findings from larger, phase II studies of postmenopausal patients with advanced breast cancer. Kvinnsland *et al.*[16] reported an objective response rate of 22% and a median duration of response of 68 weeks in patients who received exemestane 25 mg after failing tamoxifen. Thürlimann *et al.*[17] reported an objective response rate of 28% and a median duration of response of 58 weeks in patients who received exemestane 200 mg daily after progressing on tamoxifen and aminoglutethimide. We documented objective responses in a wide variety of patients with advanced breast cancer including those with unknown receptor status and metastatic disease involving soft tissue or bone. Others also documented objective responses in patients with visceral disease[17] and in patients who were refractory to previous tamoxifen[16] or aminoglutethimide therapy.[17]

The relationship between exemestane dose and estrogen inhibition was not evident in this study as the lowest dose, 5 mg, was markedly suppressive. In addition, the trend toward less pronounced inhibition at the highest doses, particularly for E_1 and E_1S, has been reported previously,[15] and is likely due to interference of exemestane metabolites in the assay procedure.

Unfortunately, the limited number of patients treated at each dosage level yielded substantial differences in baseline estrogen values (see Table 6) and therefore failed comparisons between the groups,

which was also a confounding factor in dose-finding studies of other aromatase inhibitors.[18–21] In our study, this confounding factor was most evident for E_1S because the baseline value in the 400 mg cohort (113 pg/ml) was less than half that in the 5–100 mg cohorts (230–303 pg/ml). This low baseline value may have contributed to the very low absolute value observed during treatment with exemestane 400 mg. The baseline variability can be minimized by expressing the estrogen level as percent of baseline. In fact, a similar degree of E_1S suppression was observed in the dose range of 5–100 mg (range: 11.6–6.1% of baseline).

Because baseline estrogen values were less variable for E_2 and E_1, absolute values can also be used to identify the optimal dose. In fact, use of absolute values may be preferable for E_2 because exemestane 5–200 mg suppressed this estrogen below the level of assay sensitivity. Furthermore, calculation of percent of baseline value would have suggested between-group differences based entirely on baseline values. Maximal suppression of E_1 appeared to be dose related up to 50 mg; however, the absolute values were similar in the 25–200 mg cohorts. Although neither absolute values nor percent of baseline is ideal for conveying effects on all three estrogens, consideration of both indicates that endocrine effects appeared to be optimal at 25 mg of exemestane at which E_2, E_1 and E_1S were suppressed to 13, 5 and 10% of baseline, respectively. Evans *et al.*[13] also concluded that 25 mg was the minimally effective single dose of exemestane that produced maximal estrogen suppression.

The extent of inhibition associated with exemestane approximates that reported in other phase I studies of postmenopausal women with advanced breast cancer who were treated with exemestane,[15] letrozole[22] or anastrozole.[18] Exemestane appears to suppress estrogen better than formestane regardless of whether it is administered orally[19] or parenterally.[20,21]

The promising safety profile, antitumor activity and endocrine effects of exemestane observed in this phase I study merit further evaluation. Phase II and III studies are being conducted to compare the activity of exemestane with that of other hormonal therapies, such as tamoxifen as first-line therapy or megestrol acetate as second-line therapy.

References

1. Vogel CL. Hormonal approaches to breast cancer treatment and prevention: an overview. *Semin Oncol* 1996; **23** (suppl 9): 2–9.
2. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. *Lancet* 1992; **339**: 1–15 and 71–85.
3. Muss HB, Wells HB, Paschold EH, *et al.* Megestrol acetate versus tamoxifen in advanced breast cancer: 5-year analysis—a phase III trial of the Piedmont Oncology Association. *J Clin Oncol* 1998; **6**: 1098–106.
4. Harvey HA, Lipton A, White DS, *et al.* Cross-over comparison of tamoxifen and aminoglutethimide in advanced breast cancer. *Cancer Res* 1982; **42** (8 suppl): 3451s–3s.
5. Smith IE, Harris AL, Morgan M, *et al.* Tamoxifen versus aminoglutethimide in advanced breast carcinoma: a randomized cross-over trial. *Br Med J (Clin Res Edn)* 1981; **283**: 1432–4.
6. Brodie AMH, Njar VCO. Aromatase inhibitors and breast cancer. *Semin Oncol* 1996; **23** (suppl 9): 10–20.
7. Harvey HA. Aromatase inhibitors in clinical practice: current status and a look to the future. *Semin Oncol* 1996; **23** (suppl 9): 33–8.
8. Geisler J, Johannessen DC, Anker G, *et al.* Treatment with formestane alone and in combination with aminoglutethimide in heavily pretreated breast cancer patients: clinical and endocrine effects. *Eur J Cancer* 1996; **32A**: 789–92.
9. Murray R, Pitt P. Aromatase inhibition with 4-OH-androstenedione after prior aromatase inhibition with aminoglutethimide in women with advanced breast cancer. *Breast Cancer Res Treat* 1995; **35**: 249–53.
10. Di Salle E, Briatico G, Giudici D, *et al.* Novel aromatase and 5 α-reductase inhibitors. *J Steroid Biochem Mol Biol* 1994; **49**: 289–94.
11. Di Salle E, Giudici D, Briatico G, *et al.* Novel irreversible aromatase inhibitors. *Ann NY Acad Sci* 1990; **595**: 357–67.
12. Zaccheo T, Di Salle E. Effect of the irreversible aromatase inhibitor FCE24304 on DMBA-induced mammary tumors in ovariectomized rats treated with testosterone. *Cancer Chemother Pharmacol* 1989; **25**: 98–8.
13. Evans TRJ, Di Salle E, Ornati G, *et al.* Phase I and endocrine study of exemestane (FCE 24304), a new aromatase inhibitor, in postmenopausal women. *Cancer Res* 1992; **52**: 5933–9.
14. Thomas J, Paridaens R, Wildiers J, *et al.* Phase I study of exemestane (FCE24304), a new suicide aromatase inhibitor, in metastatic breast cancer (MBC). *Proc Am Soc Clin Oncol* 1993; **12**: 100 (abstr 202).
15. Johannessen DC, Engan T, Di Salle E, *et al.* Endocrine and clinical effects of exemestane (PNU 155971), a novel steroidal aromatase inhibitor, in postmenopausal breast cancer patients: a phase I study. *Clin Cancer Res* 1997; **3**: 1101–8.
16. Kvinnsland S, Anker G, Dirix LY, *et al.* Antitumor efficacy of exemestane, a novel, irreversible, oral, aromatase inhibitor in postmenopausal patients with metastatic breast cancer (MBC), failing tamoxifen (TAM). *Breast Cancer Res Treat* 1997; **46**: 55 (abstr 217).
17. Thürlimann B, Paridaens R, Serin D, *et al.* Third-line hormonal treatment with exemestane in postmenopausal patients with advanced breast cancer progressing on aminoglutethimide: a phase II, multicenter, multinational study. *Eur J Cancer* 1997; **33**: 1769–73.

18. Geisler J, King N, Dowsett M, *et al.* Influence of anastorole (Arimidex), a selective, non-steroidal aromatase inhibitor, on in vivo aromatisation and plasma oestrogen levels in postmenopausal women with breast cancer. *Br J Cancer* 1996; **74**: 1286–91.
19. Dowsett M, Mehta A, King N, *et al.* An endocrine and pharmacokinetic study of four oral doses of formestane in postmenopausal breast cancer patients. *Eur J Cancer* 1992; **28**: 415–20.
20. Dowsett M, Cunningham DC, Stein RC, *et al.* Dose-related endocrine effects and pharmacokinetics of oral and intramuscular 4-hydroxyandrostenedione in postmenopausal breast cancer patients.*Cancer Res* 1989; **49**: 1306–12.
21. Dowsett M, Goss PE, Powles TJ, *et al.* Use of the aromatase inhibitor 4-hydroxyandrostenedione in postmenopausal breast cancer: optimization of therapeutic dose and route. *Cancer Res* 1987; **47**: 1957–61.
22. Demers LM. Effects of fadrozole (CGS 16949 A) and letrozole (CGS 20267) on the inhibition of aromatase activity in breast cancer patients. *Breast Cancer Res Treat* 1994; **30**: 95–102.

(Received 28 May 1998; accepted 9 June 1998)