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Original Paper

Third-Line Hormonal Treatment with Exemestane in Postmenopausal Patients with Advanced Breast Cancer Progressing on Aminoglutethimide: a Phase II Multicentre Multinational Study

B. Thürlimann,[1] R. Paridaens,[2] D. Serin,[3] J. Bonneterre,[4] H. Roché,[5] R. Murray,[6] E. di Salle,[7] S. Lanzalone,[7] M.G. Zurlo[7] and G. Piscitelli[7]
on behalf of the Exemestane Study Group

[1]Department of Internal Medicine C, Division of Oncology-Haematology, Kantonsspital, CH-9007 St. Gallen, Switzerland; [2]UZ Gasthuisberg Afdeling Gezwelziekten, Herestraat 49, 3000 Leuven, Belgium; [3]Clinique St. Catherine, Chemin du Lavarin, B.P. 846 84 082 Avignon Cedex; [4]Centre Oscar Lambret, rue Frederic Combemale, 59020 Lille Cedex; [5]Centre Claudius Regaud, 11 rue Piquemil, 31052 Toulouse, France; [6]Peter MacCallum Cancer Institute, Department of Endocrinology, St Andrews Place, Melbourne, Victoria, Australia; and [7]Pharmacia & Upjohn S.p.A., Via Robert Koch 1.2, 20152 Milan, Italy

In a European multicentre phase II study, 80 postmenopausal patients (pts) with advanced breast cancer progressing on aminoglutethimide (AG) at daily doses of ≥ 500 mg were enrolled. Seventy-eight received exemestane (200 mg daily orally), including 33 pts resistant to prior AG, 39 pts who had progressed after an initial response to AG, and 6 pts whose response to AG was either unavailable or not evaluable. Three pts were pretreated with AG only, 69 with tamoxifen and AG, and 6 with tamoxifen, AG and other hormone therapies; 55% had also previously received chemotherapy. The predominant site of disease was visceral in 34 cases, bone in 27 and soft tissue in 17. Based on Peer Review assessment, the overall objective response rate (CRs plus PRs) was 26% (12% in pts resistant to AG and 33% in AG-responsive pts). Disease stabilisation ≥ 24 weeks was achieved in an additional 13% of patients (15% of those resistant to AG and 13% of those AG-responsive), resulting in an overall success rate of 39% (28–50, 95% confidence interval). The median duration of objective response, overall success and median TTP were 59, 48 and 21 weeks, respectively. Toxicities were usually mild to moderate in severity, with hot flushes (21%), nausea (19%), dizziness (12%), weakness (12%), increased sweating (12%), androgenic symptoms (10%) and peripheral oedema (9%) as the most common side-effects. Only 2 pts (3%) discontinued treatment due to adverse events. These results are very promising considering that exemestane was administered as third- or fourth-line hormonal treatment in most cases and confirm previous observations about the lack of cross-resistance when steroidal aromatase inhibitors are sequenced with the non-steroidal aromatase inhibitor AG. © **1997 Elsevier Science Ltd.**

Key words: exemestane, breast cancer, aromatase inhibitors, endocrine treatment
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INTRODUCTION

VARIOUS ENDOCRINE therapies have been used in the management of postmenopausal patients with advanced breast cancer. First-line therapies in an unselected population produce an overall response rate of approximately 30% with a median duration of response ranging from 8 to 12 months [1]. The choice of drug is usually based on its tolerability and toxicity profile. For this reason tamoxifen is widely used as first-line therapy of potentially hormone-sensitive advanced breast cancer in postmenopausal women. The second-line endocrine treatment, following tamoxifen failure, usually

Correspondence to B. Thürlimann.
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involves the use of progestins or aromatase inhibitors. Progestins are generally well tolerated but are associated with fluid retention, arterial hypertension, vaginal bleeding and thromboembolism in 10–20% and weight gain in up to 50% of patients [2, 3]. Oestrogen deprivation through inhibition of aromatase (the enzyme responsible for conversion of androgens to oestrogens) represents an effective and selective treatment method for hormone-dependent breast cancer in postmenopausal patients. The major source of oestrogens in these patients comes from the conversion of the circulating androstenedione into oestrone and then into oestradiol, mainly in the adipose tissue, but also in the liver, muscle and in normal and cancerous glandular breast tissue.

Two types of aromatase inhibitors are known. Type I agents are steroidal compounds structurally related to the natural substrate, androstenedione. They irreversibly inhibit the aromatase enzyme in the presence of the cofactor NADPH via reactive intermediates which irreversibly bind to the active site. Type II agents are non-steroidal compounds which interfere with the haem group of the aromatase enzyme, and compete with the natural substrate. Formestane and aminoglutethimide (AG), respectively, represent the prototypes of the two classes of aromatase inhibitors.

AG was the only commercially available aromatase inhibitor for many years. Although it has been shown to induce a response rate at least as high as that of tamoxifen in postmenopausal metastatic breast cancer patients (30% in an unselected population), the high incidence of side-effects such as skin rash, ataxia and drowsiness are major drawbacks of this treatment [4]. Moreover, due to the lack of specificity, AG has an inhibitory effect on other steroid hydroxylases as it also interferes with the haem group of these enzymes. Inhibition of glucocorticoid synthesis may result in adrenal insufficiency requiring the addition of corticosteroids, especially when AG is used in doses higher than 500 mg daily [4, 5]. Furthermore, approximately one third of patients require mineralocorticoid replacement due to inhibition of aldosterone synthesis [6].

Formestane is currently available in a number of European countries: due to its poor bioavailability via the oral route, an intramuscular injection is required (250 mg fortnightly), which causes adverse reactions at the injection site in approximately 9% of cases [7]. The need for orally active, better tolerated, more specific aromatase inhibitors, led to the discovery of several compounds [6, 8, 9]. Among them, exemestane is the only Type I, orally active aromatase inhibitor in an advanced stage of development. Preclinical studies have shown that exemestane is a specific aromatase inhibitor [10, 11]. Early hormonal studies in breast cancer patients have indicated a maximal inhibition of oestrogens of up to 30% of baseline levels, starting from doses of 2.5–5 mg daily for exemestane [12–14]. Recently available results, obtained using a very specific and sensitive analytical method (HPLC-RIA), indicate that exemestane at daily doses of 10–25 mg suppresses plasma oestrogens down to 6–15% of pretreatment levels [15, 16], thus demonstrating an activity comparable to that observed with new Type II aromatase inhibitors such as letrozole and significantly more pronounced than that of formestane [8, 9]. Exemestane has been tested in several phase II studies as second- or third-line hormonal treatment in patients progressing on other endocrine therapies [16]. While sequential hormonal manipulations using drugs with varying types of actions (anti-oestrogens, progestins, aromatase inhibitors) represent an established approach for treatment of hormone-sensitive breast cancer, little is known about cross-resistance between drugs belonging to the same class. Early clinical evidence indicates that patients relapsing on AG may respond to formestane [17, 18]. The mechanism behind this apparent lack of cross-resistance between different types of aromatase inhibitors is poorly understood. It might be explained by enhanced suppression of circulating oestrogens or a differing effect on intratumour aromatase resulting from their different action mechanism.

We performed the present phase II multicentre multinational study in order to evaluate antitumoral efficacy, oestrogen inhibition and tolerability of exemestane, administered at a daily oral dose of 200 mg in postmenopausal patients with metastatic breast cancer who failed to respond or progressed after initial response to AG. The 200 mg dose, which is higher than the current standard dose (25 mg), was selected for this trial based on the preliminary clinical results from a phase I study with intrapatient dose escalation in breast cancer patients [15]. The results, available at the time this trial was initiated, indicated good antitumour efficacy and tolerability at this dose level.

PATIENTS AND METHODS

This was an open-label, uncontrolled, multicentre phase II study. The protocol was approved by the Ethics Committees of the participating centres. Postmenopausal patients with advanced breast cancer relapsing on AG after at least 8 weeks of treatment at a daily dose of ≥ 500 mg were eligible for the study. Postmenopausal status was defined as natural menopause with > 1 year since last menses, chemically induced amenorrhea > 3 years with biochemical evidence of postmenopausal status, or surgical or radio-castration. Additional eligibility criteria were: histological or cytological confirmation of breast cancer; positive oestrogen and/or progesterone receptor status or unknown receptor status for patients responsive to prior hormonal therapy (objective response or disease stabilisation lasting ≥ 6 months); prior treatment with no more than two hormonal agents, including AG (prior treatment with aromatase inhibitors other than AG was not allowed); no more than one chemotherapeutic regimen for metastatic disease with a ≥ 3 week interval since last dose and full recovery from toxicity; ECOG performance status ≤ 2; adequate haematological function (WBC $\geq 4000/\mu l$, neutrophils $\geq 2000/\mu l$ and platelets $\geq 100\,000/\mu l$); serum creatinine and ALT ≤ 1.5x and ≤ 3x upper normal limit for the institution, respectively. Patients had to have measurable or evaluable lesions. Prior treatment with bisphosphonates during the 8 weeks preceding study entry was not allowed in patients with evaluable bone lesions only. Patients with previous or concurrent malignancies, other than adequately treated cervix carcinoma *in situ* and basal or squamous cell carcinoma of the skin, were excluded as were patients with massive visceral disease and/or presence of brain metastasis. All patients gave their informed consent to the study.

Baseline assessments included a complete clinical history, physical examination, haematology, blood chemistry (total bilirubin, alkaline phosphatase, AST (aspartate aminotransferase), ALT (alanine aminotransferase), gamma-GT, total proteins, calcium, phosphorus, sodium, potassium, glucose, urea or BUN, creatinine), urinalysis and 12-lead ECG. Tumour assessments included chest X-rays, abdominal CT scan or ultrasound, liver imaging (if indicated), bone scan and bone X-rays (if bone scan abnormal). Patients were

evaluated every 4 weeks during the initial 8 weeks of therapy and every 8 weeks thereafter. Efficacy was firstly assessed at week 8 of therapy using WHO criteria. The US-NCI Common Toxicity Criteria were used to document side-effects. The iconographic material from patients achieving objective response or disease stabilisation ≥ 24 weeks was submitted for independent peer review.

Serum samples for oestrone-sulphate (E_1S) measurement were obtained at baseline, during therapy and at progression of disease in 45 patients. The method of assay (HPLC-RIA) has been previously described [15]. Briefly, a 2 ml serum sample, acidified with 1 ml of 2 M acetic acid, was loaded into a preconditioned Amprep C18 cartridge (500 mg, from Amersham, Arlington Heights, Illinois, U.S.A.), then washed with 4 ml of water and the fraction containing E_1S was eluted with 4 ml of 24% acetonitrile in water. E_1S was hydrolysed with arylsulphatase (*Helix Pomatia*, Merck, Darmstadt, Germany) at 45°C for 18 h and the deconjugated E_1 was further isolated with a C18 cartridge, then purified by reversed-phase HPLC (Nova Pack C18 column, 300×3.9 mm, mobile phase acetonitrile:water 35:65). The fraction containing deconjugated E_1 was collected and submitted to specific RIA ($[^{125}I]E_1$ RIA kits from Diagnostic System Laboratories, U.S.A.). The overall recovery of the procedure was $\approx 55\%$ and the detection limit was 22.2 pmol/l.

After checking confirmation of eligibility, patients were centrally registered and stratified according to prior response to treatment with AG as follows: (i) patients who did not respond to AG or showed disease stabilisation lasting less than 24 weeks (AG-resistant); (ii) patients who progressed while on AG after initial objective response or disease stabilisation of at least 24 weeks (AG-responsive); and (iii) patients for whom their response to AG was not evaluable or unavailable.

Eighty patients entered the study between October 1992 and August 1995. Treatment was not started in 2 patients who were found ineligible soon after registration (1 had brain metastasis and 1 had rapidly progressive liver disease); the remaining 78 patients received exemestane 200 mg orally as a daily single dose: at the cut-off date for the analysis, mean duration of exemestane treatment was 30.6 weeks (range 2.3–119.4). Exemestane treatment was initiated within 4 weeks from AG withdrawal in most patients (78%), the median wash-out period being 1 week.

Of the 78 treated patients, 33 were AG-resistant, 39 were AG-responsive and for 6 response to AG was unknown. Patients' baseline characteristics are detailed in Table 1. Median age was 62 years (range 42–88). Sixty-nine patients (88%) had ECOG performance status 0–1 at study entry. Fifty-seven patients (73%) had measurable disease, 18 patients (23%) had evaluable/non-measurable disease, while 3 patients (4%) had non-evaluable disease only. Oestrogen and/or progesterone receptor status was positive in 65 patients (83%), unknown in 11 (14%) and negative (neither positive) in 2 (3%). The predominant site of disease was visceral in 34 patients (44%), bone in 27 patients (35%) and soft tissue in 17 patients (22%). 3 patients (4%) had received one line of hormonal therapy (AG only), 69 patients (88%) had received two lines (tamoxifen and AG), and 6 patients

Table 1. Patients' baseline characteristics

	AG-resistant ($n=33$)	AG-responsive ($n=39$)	AG response unknown ($n=6$)	Total patients ($n=78$)
Age (years)				
median	63	59	69	62
range	46–88	42–84	54–82	42–88
PS				
median	1	1	1	1
0	13 (39%)	15 (38%)	3 (50%)	31 (40%)
1	16 (48%)	20 (51%)	2 (33%)	38 (49%)
2	4 (12%)	2 (5%)	1 (17%)	7 (9%)
3	—	1 (3%)	—	1 (1%)
unknown	—	1 (3%)	—	1 (1%)
ER/PgR status				
positive	26 (79%)	34 (87%)	5 (83%)	65 (83%)
unknown*	5 (15%)	5 (13%)	1 (17%)	11 (14%)
negative	2 (6%)	—	—	2 (3%)
Type of disease at study entry				
measurable	23 (70%)	30 (77%)	4 (67%)	57 (73%)
evaluable only	8 (24%)	8 (21%)	2 (33%)	18 (23%)
non evaluable	2 (6%)	1 (3%)	—	3 (4%)
Predominant site of disease				
visceral	15 (45%)	16 (41%)	3 (50%)	34 (44%)
bone	10 (30%)	17 (44%)	—	27 (35%)
soft tissue	8 (24%)	6 (15%)	3 (50%)	17 (22%)
Prior systemic treatment				
hormone therapy only	13 (39%)	19 (49%)	3 (50%)	35 (45%)
chemo- and hormone therapy	20 (61%)	20 (51%)	3 (50%)	43 (55%)
chemo- for advanced disease	15 (45%)	13 (33%)	—	28 (36%)
Type of hormone therapies				
AG only	—	2 (5%)	1 (17%)	3 (4%)
TAM + AG	29 (88%)	35 (90%)	5 (83%)	69 (88%)
TAM + AG + Others	4 (12%)	2 (5%)	—	6 (8%)

*Patients with receptor status unknown and responsive to prior hormonal therapy.

(8%) three lines (tamoxifen, AG and other hormonal treatment). Corticosteroid replacement therapy had been administered in association with AG in 52 patients (67%). Forty-three patients (55%) had also received prior chemotherapy, 28 (36%) for metastatic disease.

Statistical considerations

Treated patients were considered in the analysis. Descriptive statistics were used to summarise tumour response and toxicity results. Kaplan–Meier's method was used for the analysis of time to response, duration of response and time to progression (TTP); TTP and duration of response were calculated from start of treatment to documented disease progression in all treated patients and in the subset of responding patients, respectively.

As serum oestrogen levels in postmenopausal breast cancer patients have been shown to be log-normal distributed [19], serum E_1S levels were described as absolute and relative values (percentage of baseline values) using geometrical means with 95% confidence intervals (95% CI). Since the suppressive effect of AG on oestrogens levels is known to persist for approximately 24 h after discontinuation, E_1S results were analysed by grouping patients according to duration of wash-out from prior AG treatment, namely $\leq$ and $>$ 1 day from AG withdrawal.

RESULTS

Efficacy

Based on peer-review results, 2 patients achieved a complete response (CR) and 18 a partial response (PR), resulting in an objective response rate of 26% (95% CI: 16–37%). In addition, 27 of 78 patients (35%) had disease stabilisation (NC), lasting $\geq$ 24 in 10 cases (13%). Thus, the overall success rate (CR + PR + NC $\geq$ 24 weeks) was 38% (Table 2). Median time to objective response was 15.5 weeks, and the median duration of objective response and overall success were 59 and 48 weeks, respectively. For the study population as a whole, median time to progression (TTP) was 21 weeks.

In the subset of the 20 patients achieving an objective response, exemestane was administered as second-line hormonal treatment in 1 case, as third-line in 16 and as fourth-line in 3.

Patients resistant to AG had a poorer response to exemestane compared with AG-responsive patients: an objective response was achieved in 4 out of 33 patients (12%) compared with 13 out of 39 AG-responsive patients (33%). Furthermore, the median duration of objective response and the median TTP were shorter in patients resistant to AG compared with those who were AG responsive (Table 2).

Association of corticosteroids with AG did not seem to influence the response to exemestane (23% objective response rate versus 31%).

The objective response rate was poorer in patients treated with prior chemotherapy for advanced disease than in those patients who received prior hormone therapy only (14.3% versus 32%). However, the negative effect was limited to the AG-resistant patients: no objective responses were observed in these patients, compared to a 31% objective response rate in AG-responsive cases.

In patients with soft tissue as the predominant site of disease, the objective response rate was higher (47%) than in patients having bone or visceral disease as predominant sites (11% and 27%, respectively). 9 patients with predominant visceral disease achieved an objective response, only 1 being resistant to AG: 6 responded in viscera and 3 had stabilisation of visceral lesions with an objective response in soft tissue. Responding visceral sites were liver (three PRs), lung (three PRs) and visceral lymph nodes (one PR); furthermore, 3 patients had disappearance of pleural effusion.

Neither of the 2 patients with negative receptor status achieved objective response, but 1 had disease stabilisation lasting 6 months.

Mean baseline serum E_1S levels were 203 pmol/l in the 17 patients who started exemestane treatment within 1 day from AG withdrawal and 663 pmol/l in the 28 patients who received exemestane after a wash-out period longer than 1 day. At week 8 of therapy, E_1S levels were suppressed on average to 44% (95% CI: 30–64%) and 11% (95% CI: 8–15%) of baseline values in the two groups, respectively, although the extent of suppression in terms of absolute values

Table 2. Tumour response in treated patients

	AG-resistant (n = 33)	AG-responsive (n = 39)	AG response unknown (n = 6)	Total patients (n = 78)
Best response				
CR	1	1	0	2 (3%)
PR	3	12	3	18 (23%)
NC	13	13	1	27 (35%)
NC $\geq$ 24 weeks	5	5	0	10 (13%)
PD	12	10	2	24 (31%)
Not evaluable	4	3	0	7 (9%)
Objective response rate (CRs + PRs)	12%	33%	50%	26%
(95% CI)	(3–28)	(19–50)	(12–88)	(16–37)
Overall success rate (CR + PR + NC $\geq$ 24 weeks)	27%	46%	50%	39%
(95% CI)	(13–46)	(30–63)	(12–88)	(28–50)
Median time to objective response (weeks)	8.5	16	15	15.5
(range)	(7–17)	(7–34)	(9–24)	(7–34)
Median duration of objective response (weeks)	41	58	65	59
(range)	(33+–107+)	(24–120+)	(57+–65)	(24–120+)
Median duration of overall success (weeks)	35	49	65	48
(range)	(24–107+)	(24–120+)	(57+–65)	(24–120+)
Median time to progression (weeks)	16	24	44.5	21
(range)	(3–107+)	(2–120+)	(3–65)	(2–120+)

was similar in the two groups (72 and 82 pmol/l, respectively). The inhibitory effect was maintained with continued treatment, with no significant increase in E_1S levels at progression of disease (Figure 1).

Tolerability

The most common adverse events which were either of undeterminate cause or considered drug-related by the investigators were: hot flushes (21%), nausea (19%), dizziness (12%), weakness (12%), increased sweating (12%), androgenic symptoms (including hair loss in 10%, hypertricosis in 5%, hoarseness in 5% and acne in 4% of cases) and peripheral oedema (9%) (Table 3). Reported events were usually mild to moderate in severity, with only 1 patient reporting grade 3 toxicity (restless legs syndrome) which was deemed to be possibly drug-related and led to treatment discontinuation at week 52 of therapy. The incidence of treatment withdrawals was low, with only 2 patients (3%) discontinuing treatment due to adverse events (the above-mentioned case of restless legs syndrome and an additional case due to sural phlebitis of undeterminate cause at week 4). In both cases the symptomatology resolved after treatment discontinuation. There were 8 on-study deaths, none of which was considered as being drug related.

On average, no significant changes in the laboratory parameters tested were observed throughout the treatment period and no drug-related > grade 2 alterations in laboratory tests were recorded.

DISCUSSION

This study clearly showed that exemestane is an effective, well-tolerated treatment for postmenopausal patients with advanced breast cancer, as previously reported [12–16, 20].

Although it is well known that sequential endocrine treatment for patients with a continuous indication for hormonal therapy is a successful strategy, we did not expect so many patients progressing on a non-steroidal aromatase inhibitor to benefit from treatment with the steroidal aromatase inhibitor exemestane. Considering that most of the patients had received at least two prior endocrine therapies, the observed objective response rate (26%) is indeed unexpectedly high, particularly in patients who had benefited from prior AG treatment (33%). Stabilisation of the disease for a prolonged period provides a clinical benefit that has been shown to be similar to that of partial response [21–23]: if disease stabilisations ≥ 24 weeks are added to the objective responses achieved with exemestane, the overall clinical benefit rate reached in this study was 39% (46% in patients responding to prior AG). Prior chemotherapy for advanced disease did not seem to influence the response rate in patients benefiting from AG. As expected, the highest response rate was observed in patients with only soft tissue disease (47%), although disease remission was achieved in approximately one-quarter of patients with visceral involvement.

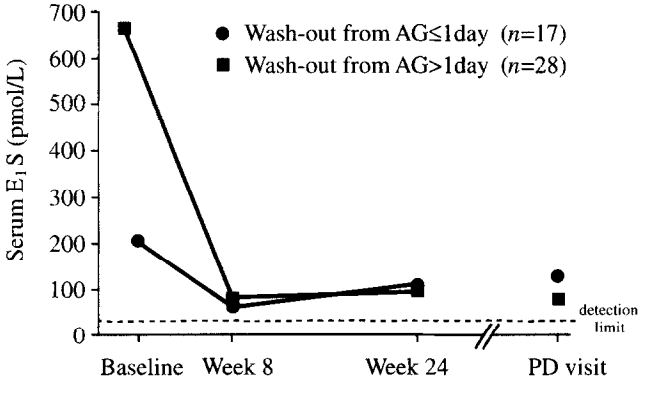

Figure 1. Effect of exemestane treatment on serum oestrone sulphate (E1-S) levels according to time interval from AG withdrawal. Results are expressed as geometric mean of absolute values (SDs are within the symbol of each data point).

The above results compare favourably with those reported by Murray and colleagues who investigated the activity of another steroidal aromatase inhibitor, formestane, in postmenopausal patients previously treated with AG (≥ 250 mg daily dose with or without steroid replacement therapy) and at least one other endocrine therapy [17, 24, 25]. Although the objective response rate reported for formestane (21%, duration 11 months) was similar to that which we observed with exemestane (26%, duration approximately 13 months), the rate of disease stabilisations was lower (22% versus 35%, any duration) and the percentage of failures higher (50% versus 31%). Furthermore, when the subset of patients pretreated with AG conventional dose plus concurrent glucocorticoid replacement is considered, the response rate obtained was approximately 12% compared with 23% with exemestane in our study.

As in our study, the response rate with formestane was higher in AG-responsive patients than in AG-refractory patients (26% versus 16%, respectively).

Our results provide further evidence that aromatase inhibition by steroidal and non-steroidal agents given sequentially can offer two different and not totally cross-resistant methods of endocrine treatment for advanced breast cancer in postmenopausal women. The reason for this is not fully understood.

It is possible that further responses to exemestane in patients relapsing on AG are related to further reduction of peripheral oestrogen levels. Studies demonstrating that additional suppression of serum oestradiol (by the same or a second oestrogen lowering agent) may result in further response to therapy have recently been discussed in this journal [26]. Treatment with AG usually results in a reduction of oestrogen

Table 3. Most frequent (> 5%) treatment emergent adverse events drug-related or of indeterminate cause

Adverse events	Percentage of patients with adverse events ($n = 78$) %
Any event	77
Hot flushes	21
Nausea	19
Sweating	12
Weakness	12
Dizziness	12
Alopecia	10
Peripheral oedema	9
Headache	6
Insomnia	6
Constipation	6
Hoarseness	5
Hypertrichosis	5
Rash	5
Pain	5
Paraesthesia	5

levels to approximately 40% of baseline values, whereas exemestane in postmenopausal patients is able to lower oestrogens into the range of the detection limit of highly specific and sensitive methods of measurement [15, 16]. In our study, exemestane inhibited E_1S to approximately 11% of baseline levels in patients with appropriate wash-out period from AG, and induced a further decrease in patients starting exemestane soon after AG discontinuation who still had serum E_1S suppressed (as indicated by comparing their baseline values with average values obtained with the same method of assay in basal samples from 200 postmenopausal breast cancer patients; geometric mean: 995 pmol/l, data not shown).

Better tissue penetration of the drug, especially into tumour tissue may also have contributed to the favourable results seen in our study. In a laboratory investigation of 247 primary breast cancers, 178 (72%) tumours showed evidence of aromatase activity. In a small subgroup of this patient population, including 23 patients treated with AG 1000 mg daily and hydrocortisone 40 mg daily, response was significantly associated with evidence of aromatase activity in the primary tumour. Eleven of the 18 patients with positive aromatase status showed a partial response, whereas all 5 patients with negative aromatase status failed to respond to aminoglutethimide [27].

Toxicity in our study was infrequent and usually mild, as expected. Hot flushes from oestrogen deprivation were most frequently observed. Mild alopecia and hypertricosis might be specific for the weak androgenic effect of exemestane seen in doses of >100 mg daily (data on file, Pharmacia and Upjohn, Milan, Italy, 1996). Another ongoing European multicentre study using a dose 8 times lower (25 mg daily) is also investigating the activity and tolerability in postmenopausal patients with breast cancer and failure of aminoglutethimide and other non-steroidal aromatase inhibitors. With the 25 mg daily dose, maximal peripheral oestrogen inhibition is achieved but the mild androgenic effects seen in our study are less likely to be seen (data on file, Pharmacia and Upjohn, Milan, Italy, 1996).

In conclusion, aromatase inhibition with exemestane is an effective treatment for postmenopausal women with advanced breast cancer, even in patients who have failed on multiple prior endocrine therapies including aromatase inhibition with the non-steroidal compound aminoglutethimide. Exemestane is associated with minimal toxicity and offers an additional tool in the management of breast cancer.

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APPENDIX

The following centres investigators (name underlined) and co-investigators participated in the trial and accrued at least 1 patient:

Australia

Investigators: R. Murray, J. Davison, S.L. McMahon. P. Pitt
Peter MacCallum Cancer Institute, Melbourne, Australia

Austria

Investigators: G. Steger, R. Jakesz
Univ. Klinik Innere Medizin I, Wien, Austria

Investigators: H. Samonigg, I. Kuss. R. Moser. F. Ploner
Medizinische Univ. Klinik Graz, Graz, Austria

Investigators: G. Reiner, M. Fangl, B. Ruckser
Snz-ost, Chirurgische Abteilung, Wien, Austria

Belgium

Investigators: R. Paridaens, J. Thomas, J. Menten, W. Van den Bogaert, L.J. Vanuytsel, I. Vergote, J. Wildiers
UZ Gasthuisberg, Leuven, Belgium

Investigators: J. Longueville, M.C. Berliere, Y. Humblet, M. Symann, A. Vereyen
U.C.L. St. Luc, Bruxelles, Belgium

Investigators: M. Beauduin, F. Majois, E.A. Tueni
Hopital de Jolimont, La Louvière, Belgium

Investigators: M. Lippens
Algemeen Ziekenhuis, Gent, Belgium

France

Investigators: H. Roché, M.C. Durand, J. Mihura
Centre Claudius Regaud, Toulouse, France

Investigators: D. Serin, L. Aymard, J. Brewer, S. Kirscher, E. Vuillemin
Clinique St. Catherine, Avignon, France

Investigators: J. Bonneterre, A. Adenis, J.M. Pion
Centre Oscar Lambret, Lille, France

Investigators: L Mauriac, P. Campo
Fondation Bergonié, Bordeaux, France

Investigators: J.L. Misset, E. Cvitkovic, C. Mita, M. Museteanu, M. Musset, L. Trandafir
Hopital Paul Brousse, Paris, France

Germany

Investigators: F. Jänicke, V.R. Seifert, C. Thomssen
Leitender Oberarzt Fraunkklinik der TU Munchen, Munchen, Germany

Investigator: K. Bremer
Augusta Kranken-Anstalt Bochum, Bochum, Germany

Switzerland

Investigators: B. Thürlimann, L. Bacchus, J. Greiner-Lang, D. Köberle, H.J. Senn, B. Späti, F. Weisser
Kantonsspital St Gallen, St Gallen, Switzerland

U.K.

Investigators: A.L Harris, J.P. Braybrooke, T.J. Littlewood, L. Long, J.D.S. Kay, L. McKinley, P.A. Philip, A.J. Salisbury, M.P. Saunders, N.S. Stoner, T.S. Ganesan, D.C. Talbot, R.M. Whitehouse
ICRF Clinical Oncology Unit, Churchill Hospital, Oxford, U.K.

Pharmacia & Upjohn Study group

Australia
P. Smith, D. Fontana

Austria
B. Valenta, A. Emberger

Belgium
J.P. Lobelle, K. De Belder, C. Weynants

France
E. Gilles, J.M. Suissa, A.Vaiman

Germany
S. Kerpel-Fronius, E. Beyer-Finkler

Switzerland
G. Herbert

U.K.
R. Miller

Italy
G. Piscitelli, M.G. Zurlo, A. Arkhipov, A. Polli, S. Lanzalone, A. Consonni, E. di Salle