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Original Report

Double-blind, Randomised, Multicentre Endocrine Trial Comparing Two Letrozole Doses, in Postmenopausal Breast Cancer Patients

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Letrozole is an orally competitive aromatase inhibitor. This double-blind, randomised, multicentre trial was carried out to evaluate the endocrine effects of two doses of letrozole, 0.5 mg versus 2.5 mg orally daily, in postmenopausal advanced breast cancer patients progressing after tamoxifen. The pharmacokinetics of letrozole was also assessed. 46 patients entered the trial, 22 on letrozole 0.5 mg and 24 on 2.5 mg. A significant suppression of oestrone and oestradiol levels was achieved by both letrozole doses. Neither letrozole dose induced any changes in cortisol and aldosterone production at rest or after Synacthen stimulation. Androstenedione, testosterone, 17α-OH progesterone, triiodothyronine (T3) thyroxine, (T4) and thyroid-stimulating hormone (TSH) plasma levels did not show any significant changes. Sex hormone binding globulin (SHBG), follicle-stimulating hormone (FSH) and luteinising hormone (LH) levels increased significantly over time. Plasma letrozole concentrations increased until reaching steady-state values after 1 month at the dose of 0.5 mg and after 2 months at 2.5 mg. In conclusion, both letrozole doses suppressed oestrogen levels without affecting adrenal activity.

Key words: oestrogens, Synacthen test, aromatase inhibitors, letrozole, breast cancer
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INTRODUCTION

LETROZOLE, FADROZOLE, vorozole and anastrozole are third-generation aromatase inhibitors, which are currently considered highly promising drugs for advanced breast cancer treatment [1, 2]. In experimental and animal models, these drugs have shown greater selectivity and potency than aminoglutethimide and formestane, the latter being the first selective aromatase inhibitor widely used in clinical practice [3–5].

Letrozole (Femara®, CGS 20267) is an orally potent and selective aromatase inhibitor. In animal models, it has been shown to have a better selectivity index than anastrozole (0.02 versus 0.6 μmol/l) and to decrease rat uterine weight to the same levels obtained with oophorectomy [6]. A marked suppression (90%) of plasma oestrone (E1), oestradiol (E2), and oestrone sulphate (E1S) levels was achieved with letrozole, within 24 h after the first dose, of between 0.1 and 5.0 mg once daily in 23 heavily pretreated breast cancer patients [7]. There were two partial responses and seven cases of stable disease. Similar results were obtained in another trial using 0.5 mg/day given to 14 postmenopausal patients previously treated with either endocrine therapy or chemotherapy [8]. Letrozole induced a decrease in E1 of more than 86% and in E2 of approximately 67%. One patient achieved a complete response and 4 achieved partial responses, for an objective response rate of 36% [95% confidence interval (CI): 13–65].

The endocrine and clinical activity of letrozole was evaluated in a phase II trial [9], in which 64 postmenopausal

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breast cancer patients were randomly given 0.5 mg (33 patients) or 1 mg daily (31 patients). During treatment E1 levels were maintained below the detection limit (2.5 pg/ml) and sustained E2 suppression was observed, with levels near to the detection limit (1 pg/ml). No changes were observed in aldosterone, cortisol, follicle-stimulating hormone (FSH), luteinising hormone (LH), testosterone or androstenedione levels. The tumour responses were peer reviewed and the overall response was 28% in the 0.5 mg group and 38% in the 1 mg group.

On the basis of the available pharmacological and clinical data, a double-blind, randomised, multicentre, endocrine trial was carried out in order to evaluate the effects of two daily letrozole doses (0.5 mg versus 2.5 mg) on oestrogen levels and adrenal function by means of Synacthen stimulation, measuring changes in cortisol, aldosterone and 17α-OH progesterone levels. The profile of other hormones was also evaluated, as well as the pharmacokinetics, antitumour activity and tolerability of the two doses.

PATIENTS AND METHODS

Patients

The eligible patients included postmenopausal women with a histologically or cytologically proven breast carcinoma that was oestrogen receptor (ER) and/or progesterone receptor (PgR) positive at either the primary tumour or metastatic site, or whose ER and PgR status was unknown. All patients had locally advanced and/or metastatic breast cancer with documented measurable and/or evaluable disease and their performance status was 0, 1 or 2 according to World Health Organisation (WHO) criteria [10]. Previous endocrine therapy with tamoxifen as adjuvant or first-line therapy for recurrent disease was allowed. Adjuvant tamoxifen had to have been given for more than 6 months and the interval between the discontinuation of adjuvant anti-oestrogen treatment and relapse had to have been at least 12 months. The patients may have had prior adjuvant chemotherapy and/or one regimen of cytotoxic therapy for advanced disease. Postmenopausal status was defined by one of the following criteria: (a) no spontaneous menses for at least 5 years; (b) spontaneous or chemically induced amenorrhoea ≥ 1 year but < 5 years with gonadotropin levels within the postmenopausal range (40 IU/l); (c) bilateral oophorectomy; or (d) radiation castration with amenorrhoea for at least 3 months. Patients were ineligible if they had endocrine disorders such as diabetes mellitus, hypothyroidism, hyperthyroidism, Addison's disease or Cushing's syndrome, or if they had any other concurrent malignant disease. Metastases occupying more than one-third of the liver, inflammatory breast carcinoma, lymphangitic pulmonary metastasis or brain dissemination were considered exclusion criteria. Patients with significant renal or hepatic dysfunction (creatinine > 1.5 times the upper limit of normal, bilirubin ≥ 1.5 times the upper limit of normal, and/or transaminases ≥ 2.6 times the upper limit of normal) or calcium ≥ 2.75 mmol/l were excluded. Likewise, patients were considered ineligible if they had haemoglobin < 10 g/dl, neutrophils $< 1.5 \times 109$/l or platelets $< 75 \times 109$/l.

A wash-out period of at least 3 weeks after previous anticancer treatment was mandatory prior to entry into the study and no concomitant treatment with glucocorticoids was permitted. All patients gave their written informed consent and the study was approved by the local ethics committees. Upon entry, the patients were evaluated for disease extent by means of a full clinical examination, chest X-rays, bone scan, skeletal X-rays, liver ultrasound, whole blood cell counts and blood chemistry.

Study design

Between June 1993 and January 1995, 46 patients were enrolled in this double-blind, multicentre, endocrine trial and randomly allocated to receive letrozole 0.5 mg or 2.5 mg once daily by the oral route (Figure 1). The drug was supplied by Ciba-Geigy (Basel, Switzerland) in the form of 0.25 mg and 2.5 mg tablets. The double-dummy technique was used to ensure double-blind conditions: the patients received two 0.25 mg letrozole tablets once daily in the 0.5 mg dose group, and one 2.5 mg letrozole tablet and one placebo tablet once daily in the 2.5 mg group. The drug was taken between 9.00 and 10.00 am.

Each patient was treated for at least 12 months, providing no severe adverse effects and/or signs of disease progression appeared. Physical examination, complete blood cell counts and serum chemistry test were repeated monthly for 12 weeks, and then every 3 months. Overall tumour response (complete remission, CR; partial remission, PR; no change, NC; progressive disease, PD) was assessed at 3-monthly intervals according to International Union Against Cancer (UICC) criteria [11]. Toxicity was evaluated at each visit according to NCI (National Cancer Institute, Bethesda, Maryland, U.S.A.) criteria [12].

At the end of the study, still responding patients continued on the treatment in open conditions.

Endocrine investigations

For the measurement of all of the hormones, 15 ml of blood (venipuncture) was taken after the patient had been in

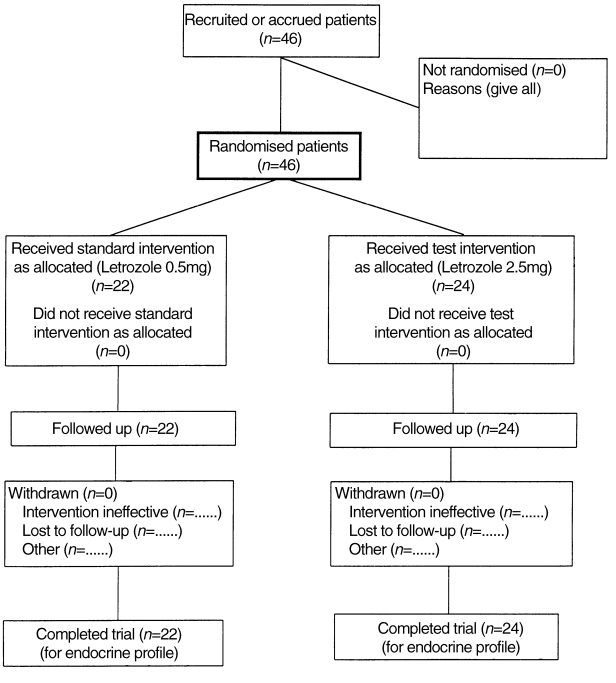

Figure 1. Flow chart of the progress of patients through the trial. (Adapted from Begg C, Cho M, Eastwood S, *et al.* Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *JAMA* 1996, 276, 637–639.)

the supine position for at least 30 min. The blood was collected into plain tubes, allowed to clot and centrifuged at 3000 rpm for 5 min at + 4°C. The serum was split into two labelled tubes and stored at a temperature of − 18°C or less. All blood samples were taken between a 9.00 and 10.00 am before drug intake.

Two samples were taken to measure oestrogen levels: one on the day before starting the trial (day − 1) and the other before the first drug intake (day 0). The endocrine variables were measured at baseline, on day 14 and then at 1, 2 and 3 months. E1 and E2 plasma levels were analysed as described previously [13, 14].

Plasma cortisol, aldosterone, 17α-OH progesterone, androstenedione and testosterone levels were measured at the same times. LH, FSH, sex hormone binding globulin (SHBG) and serum thyroid-stimulating hormone (TSH) were assessed at baseline and after 1 and 3 months.

LH and FSH were analysed using a Roche Cobas Core one-step sandwich immunoassay. TSH and aldosterone were measured using immunoradiometric assay kits obtained from Serono Diagnostic (Milan, Italy). Cortisol, androstenedione and 17α-OH progesterone were measured by means of radioimmunoassay kits (Biogenesis, Bournemouth, U.K.).

A Synacthen® stimulation test was performed immediately after the collection of the blood samples, at baseline and after 1 and 3 months. The adrenal response (cortisol, aldosterone and 17α-OH progesterone) was assessed 30 and 60 min after Synacthen injection [0.25 mg intramuscularly (i.m.)].

Pharmacokinetics

At baseline (day 0), after 14 days and then at 1, 2, 3, 6, 9 and 12 months, 3 ml of blood was collected for the measurement of plasma letrozole levels between 9.00 and 10.00 am, before drug intake. The blood was collected into ice-cooled ethylenediamine tetraacetic acid (EDTA) ®Venoject, citrate or heparin tubes and immediately centrifuged at 3000 rpm for 5 min at + 4 °C. The supernatant plasma was siphoned off, split and transferred to 5 ml polypropylene tubes, immediately frozen and stored at − 20 °C or less.

Bioanalytic and Pharmacokinetic Units (Laboratories Ciba-Geigy, Rueil Malmaison, France) carried out the appropriate analyses.

Statistical methods

The sample size was calculated on the basis of the proportion of patients in each dose group with E1 levels below the detection limit at 1 month, i.e. approximately 20% of the patients on letrozole 0.5 mg/day and 70% on letrozole 2.5 mg/day. A sample size of 18 patients in each dose group was necessary to detect such a difference as statistically significant at the 5% level ($\alpha = 0.05$) with a power ($1 - \beta$) of 80%. Since the loss to follow-up and/or withdrawal rate at 1 month was expected to be less than 10%, the sample size was adjusted upwards to allow for approximately 10% unavailable E1 measurements at one month. Based on these assumptions, recruitment of a minimum of 40 patients was required (20 in each treatment group). The randomisation was performed using a block size of 4 patients.

RESULTS

Patient characteristics

46 patients with advanced breast cancer entered the trial; 22 received letrozole 0.5 mg and 24 received letrozole 2.5 mg. The main patient characteristics are shown in Table 1, from which it can be seen that the two treatment groups were well balanced.

Endocrine results

All patients were evaluated for endocrine profile. At baseline, the mean E1 value was 71.7 pmol/l (range 16.0–210.0) in the low-dose group, and 85.7 pmol/l (range 29.0–423.5) in the high-dose group; the mean E2 value was 28.8 pmol/l (range 10.0–64.0) and 33.4 pmol/l (range 8.9–87.0) in the two groups, respectively (Figure 2). By day 14, both E1 and E2 levels were markedly suppressed in both dose groups and the reduction from baseline was significant ($P = 0.0001$) after 2 weeks. At this time 73% of the patients reached an E1 level below the limit of detection in the 0.5 mg dose group (mean 11.6 pmol/l; range 9.9–29.0) and 86% in the 2.5 mg dose group (mean 11.2 pmol/l; range 9.9–36.0), with no statistical difference between them ($P = 0.226$). Similarly, for E2, 24% in the low-dose group (mean 5.2 pmol/l; range 2.9–14.0) and 28% in the high-dose group (mean 4.9 pmol/l; range 2.9–21.0) had levels below the limit of detection.

Changes in plasma cortisol and aldosterone plasma levels are shown in Figure 3. There was no statistically significant effect on basal cortisol levels over time, nor any difference between the two dose groups (Figure 3a,b). After stimulation with Synacthen, a statistically significant ($P = 0.015$) decrease in the peak value (maximum value after stimulation) was observed, with no significant difference between the two dose groups; however, the peak cortisol values were close to the limit of the normal range.

Table 1. *Patient characteristics*

Characteristics	Letrozole 0.5 mg ($n = 22$)	Letrozole 2.5 mg ($n = 24$)
Median age (range)	62.5 (44–81) years	64.9 (45–80) years
Postmenopausal status		
Spontaneous	17	20
Oophorectomy	3	0
Induced amenorrhoea	2	4
Performance status (ECOG)		
Grade 0–1/2	11/11	9/15
ER		
Positive	17	16
Unknown	5	8
PgR		
Positive	10	11
Unknown	8	9
Negative	4	4
Median disease-free interval (range)	3.5 (0–20) years	4 (0–15) years
Sites of progression		
Soft tissue	3	3
Bone	6	8
Viscera	6	4
Dominant site of disease		
Soft tissue	3	3
Bone	10	11
Viscera	9	10
Number of disease sites		
1	15	15
> 2	7	9

ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; PgR, progesterone receptor.

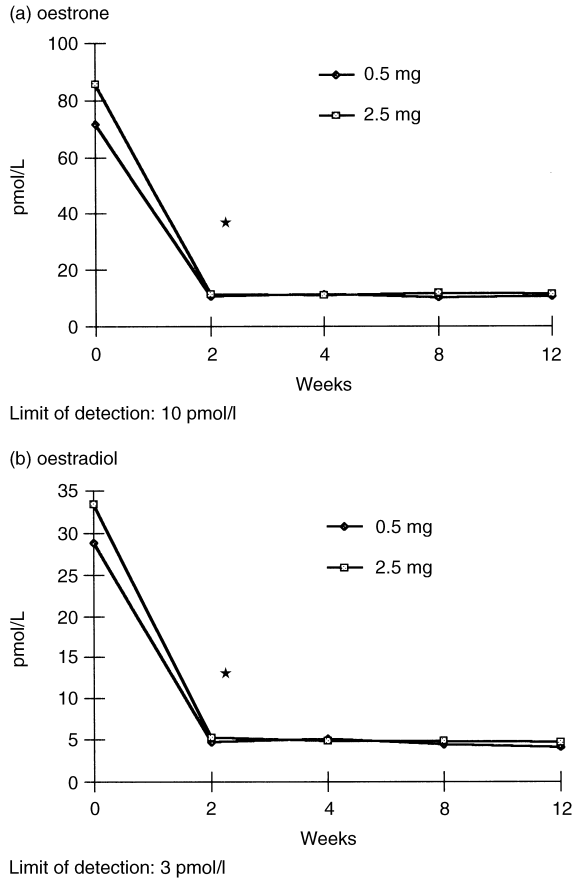

Figure 2. (a) Oestrone (E1) and (b) oestradiol (E2) plasma levels in each dose group during the trial (geometric mean). *$P = 0.0001$.

There was a statistically significant ($P = 0.025$) increase in post baseline aldosterone values with no significant difference between doses (Figure 3c,d). After Synacthen stimulation, there was a slight increase in the peak value in the low-dose group (Figure 3c) and a decrease in the high-dose group, which was reflected by a significant statistical interaction ($P = 0.04$; Figure 3d).

No changes were observed in basal or post stimulation 17α-OH progesterone levels over time and there was no difference between dose groups (data not shown).

Plasma FSH, LH and SHBG levels significantly ($P = 0.0001$) increased over time, with no differences between doses; these changes were expected and can be explained by the withdrawal of previous anti-oestrogen treatment (data not shown).

There was no significant time or treatment effect on triiodothyronine (T3). Plasma thyroxine (T4) levels were higher at baseline in the high-dose group and thereafter decreased; they remained stable in the low-dose group (data not shown). Thus, a statistically significant ($P = 0.046$) time-×treatment interaction was observed. Plasma TSH levels were higher at baseline and during treatment in the high-dose group, once again leading to a significant ($P = 0.04$) time-×treatment interaction. However, there was no significant change over time in either dose group.

Pharmacokinetics

Figure 4 shows the mean plasma letrozole concentrations. In the 0.5 mg dose group, these increased until reaching a steady-state value of approximately 50 nmol/l (range 38.4–63.4 nmol/l) after 1 month. The maximum mean level was observed after 2 months (63.4 nmol/l). In the 2.5 mg dose group, plasma letrozole concentrations progressively increased, reaching a steady-state value of 400 nmol/l after 2 months. For each dose the interpatient variability was generally below 35%.

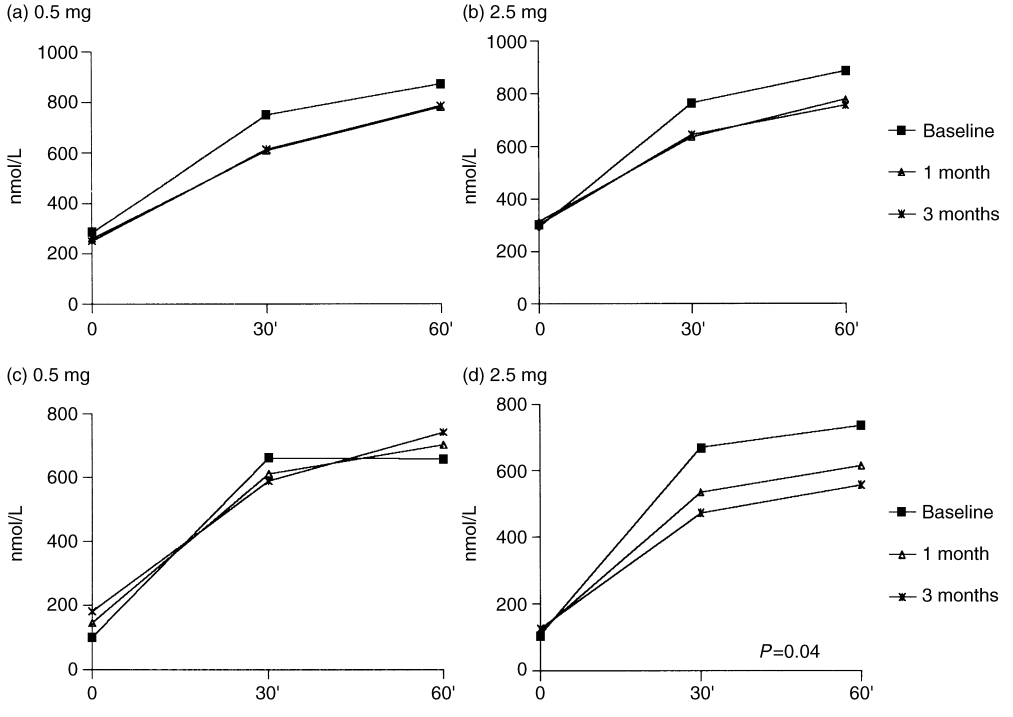

Figure 3. (a,b) Cortisol and (c,d) aldosterone plasma levels in each group, at baseline and after Synacthen stimulation geometric mean (1 and 3 months).

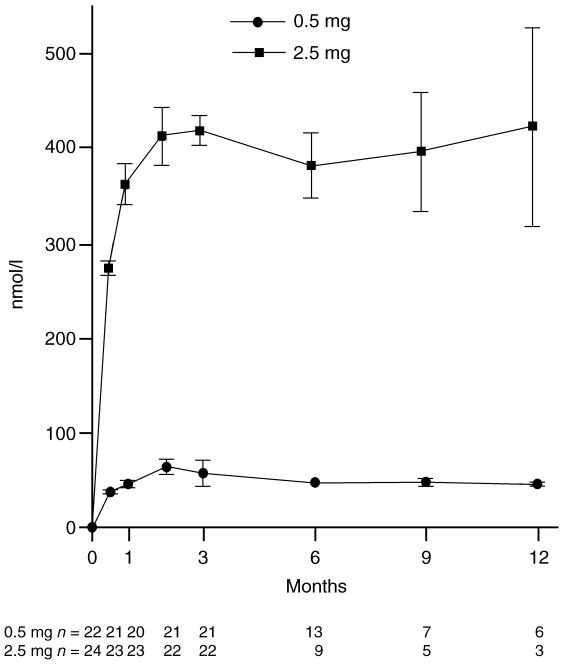

Figure 4. Mean plasma concentration (± SEM) of letrozole in each dose group.

Tumour response

40 cases were evaluable for antitumour activity, 20 in each dose group. 6 patients were considered unevaluable by an independent tumour review board (one oncologist and one radiologist): 2 on 0.5 mg (because of no evaluable disease) and 4 on 2.5 mg (one because of no evaluable disease and three because of major protocol violations).

6 patients achieved an objective response (13%, 95% CI 5–26% in the intent-to-treat analysis and 15%, 95% CI 6–30% in the drug efficacy analysis) (Table 2). In terms of clinical benefit (CR + PR + NC $\geq$ 6 months), the response rate was acceptable (intent-to-treat analysis 33%; drug efficacy 37.5%). All responding patients had only one site of lesion and were both ER and PgR positive (except for one patient who was PgR negative). The site of response was soft tissue in 4 (3 CR and 1 PR) and viscera in 2 patients (1 CR and 1 PR).

The median time to progression (TTP) was 94 days, as was the time to treatment failure. 11 of the 15 responding patients were still responding at the end of the trial and so the duration of their response could not be calculated; of the 4 remaining patients, 2 in the 0.5 mg group for 177 and 494 days, and 2 in the 2.5 mg group for 170 and 184 days.

Table 2. Tumour response

	Letrozole 0.5 mg *n* (%)	Letrozole 2.5 mg *n* (%)
Intent-to-treat analysis	*n* = 22	*n* = 24
CR	2 (9)	2 (8)
PR	2 (9)	0
CR + PR	4 (18)	2 (8)
NC	5 (23)	4 (17)
PD	11 (50)	14 (58)
Not assessable	2 (9)	4 (17)
Standard analysis	*n* = 20	*n* = 20
CR	2 (10)	2 (10)
PR	2 (10)	0
CR + PR	4 (20)	2 (10)
NC	5 (25)	4 (20)
PD	11 (55)	14 (70)

Toxicity

No difference was seen in the adverse event profile between the two letrozole doses and no deaths occurred. A total of 38 adverse events was reported in 17/46 patients (37%), 21 in the 0.5 mg dose group (45%) and 17 in the 2.5 mg group (29%). Among the 38 reported adverse events, 14 (37%) were considered as at least possibly related to letrozole therapy, 9 in the 0.5 mg and 5 in the 2.5 mg group. The most frequent adverse events were diarrhoea (one case in each treatment group) and hot flushes (two cases in each treatment group). The other related adverse events reported only once were: alopecia, sleep disorder, somnolence, nausea and vomiting in the 0.5 mg dose group and appetite and weight increase in the 2.5 mg group. Of these 38 events, 9 were of grade 3 severity (4 in the 0.5 mg and 5 in the 2.5 mg group). Only 1 patient in the 2.5 mg group was withdrawn from treatment owing to the onset of jaundice; a diagnosis of a second cancer was considered but not confirmed. One patient in the 0.5 mg group experienced a transient increase in liver enzymes. It should be pointed out that this elevation of liver enzymes occurred after a change in concomitant medication and that liver metastases were detected approximately 1 month after the onset of this adverse event.

DISCUSSION

The use of new-generation aromatase inhibitors for treating postmenopausal breast cancer patients with oestrogen-dependent tumours is currently increasing. These drugs appear to be safer and more potent than aminoglutethimide, the reference aromatase inhibitor widely studied but seldom used in clinical practice because of its poor tolerability [15]. Unlike fadrozole, which can affect plasma aldosterone levels [13], letrozole, anastrozole and vorozole are highly selective for aromatase enzymes.

The results of this study confirmed that both letrozole doses are equally effective in suppressing oestrogen levels and demonstrate the selectivity of the drug on adrenal function. Unlike formestane and exemestane, which are aromatase inhibitors with a steroidal structure, letrozole is capable of suppressing oestrogen levels to below the limit of detection. It is widely accepted that oestrogen supply is necessary for tumour cell growth, and so it should follow that the greater the suppression of circulating oestrogens, the greater the antitumour response. However, no correlation between oestrogen suppression and antitumour response has yet been demonstrated. There is considerable evidence that circulating plasma oestrogen suppression does not account completely for the mechanism of action of aromatase inhibitors. Peripheral conversion of oestradiol increases with increasing age and no feedback mechanism on aromatase has ever been demonstrated for any peripheral tissue [16]. The interest in intratumoral aromatase activity is increasing because this could be an important source of oestrogen synthesis and, thus tumour growth. Formestane is capable of penetrating tumuor cells, blocking intratumoral aromatase activity and decreasing DNA α-polymerase activity [17], but this characteristic has not yet been demonstrated for the new aromatase inhibitors, although some animal data support this hypothesis [18].

The Synacthen test demonstrated the selectivity for both letrozole doses. A similar test was carried out [19] on a smaller number of patients, but using low letrozole doses (0.1 and 0.25 mg/po/day) and without assessing changes after 1 month of therapy. The changes in aldosterone levels observed after 3 months of treatment are of little clinical significance and remain within the normal range. However, they suggest that doses of letrozole of more than 2.5 mg/day could reduce selectivity, as is the case with fadrozole [20], although doses up to 10 mg/day have been used in a neo-adjuvant setting with satisfactory clinical results [21]. Nevertheless, clinical data from two international multicentre trials confirm that a letrozole dose of 2.5 mg/day is significantly more effective than megace 160 mg and improves patient survival in comparison with aminoglutethimide [22, 23].

Although the number of patients studied in the present trial was small and was planned for endocrine evaluations, the antitumour response was satisfactory and in agreement with the results of a recently published trial. Letrozole was evaluated as third-line hormonal therapy in 91 advanced breast cancer patients receiving either 0.5 mg or 2.5 mg/day. At the lower dose, 9 patients (20%) achieved an objective response and, at the higher dose, 10 patients (22%), with 2 complete responses. The median time to progression was 97 days for the lower dose and 154 days for the higher dose [24].

In conclusion, this study profiled the selectivity and efficacy of letrozole in postmenopausal breast cancer patients after tamoxifen failure. Further biological studies are warranted in order to improve our understanding of the mechanism of action of aromatase inhibitors and, in particular, their intratumoral aromatase activity, which could be the most important source of oestrogens for the tumour and, thus the most important target for inhibition.

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