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Original Paper

Anastrozole Shows Evidence of Activity in Postmenopausal Patients who have Responded or Stabilised on Formestane Therapy

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Formestane (Lentaron™) and anastrozole (Arimidex™) are in clinical use as second-line treatments for advanced breast cancer. Current practice is often to use an aromatase inhibitor only once before switching to third-line agents such as progestins. There are few clinical data on the sequential use of aromatase inhibitors. We therefore decided to study the clinical effects of anastrozole in postmenopausal patients with advanced breast cancer who had already received formestane. 21 patients were recruited. When receiving formestane 2/21 (10%) achieved a partial response (UICC criteria) and 10/21 (48%) stable disease. Of these 12 patients, 9 achieved further stable disease on anastrozole (78%; 7/9 oestrogen receptor positive). 4 of 9 patients who progressed on formestane also stabilised on anastrozole, of whom 3 had oestrogen receptor positive breast carcinomas. The explanation of this second stabilisation may relate to a further fall in oestradiol levels. We feel these results are of interest and warrant further clinical investigation. © **1999 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

PERIPHERAL AROMATISATION of androgens to oestrogens represents the principal source of endogenous oestrogen in postmenopausal women [1]. Aminoglutethimide, the earliest of these inhibitors, is a relatively non-specific aromatase inhibitor and is associated with several unwanted side-effects [2]. The newer agents are classified into type 1 and type 2. Type 1 includes formestane (4-hydroxyandrostendione, Lentaron™ and available only in Europe) and type 2 includes anastrozole (Arimidex™) vorozole and letrozole, all of which are in widespread clinical use as second-line treatment for advanced breast cancer [1].

We have recently conducted an endocrine study in which patients receiving formestane were subsequently given vorozole and both oestrone and oestradiol were measured sequentially during the course of treatment. The results indicated that the type 2 inhibitor vorozole resulted in a further, sustained, suppression which returned to pretreatment levels once the patients restarted formestane treatment (data not shown).

Previous studies in advanced breast cancer using the non-selective inhibitor aminoglutethimide as well as the newer agents have shown that *in vivo* aromatisation can be inhibited by 85–90% [3–8] and studies using anastrozole have demonstrated a greater degree of inhibition of aromatisation and consequently a greater suppression of plasma oestrone [8]. As yet, there is no clear correlation between these levels of suppression and clinical efficacy, but recent studies suggest that this may be the case since randomised studies using different doses of letrozole have shown improved response rates at higher dosages [9].

A further study, carried out by our group [10], indicated that a stepwise suppression of oestradiol was associated with more prolonged benefit for patients with metastatic breast cancer. In this study, premenopausal patients who had achieved either disease stabilisation or remission on goserelin treatment were given formestane on relapse and goserelin

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treatment was maintained. As a result of the introduction of formestane, levels of oestradiol fell to similar levels observed in postmenopausal patients and the majority of patients obtained a further remission. Another study showed that patients on formestane who received additional aminoglutethimide achieved further oestrogen suppression and clinical response [11]. This suggested to us that sequential reduction in oestradiol in postmenopausal patients using type 1 and then the more potent type 2 inhibitors may be of benefit. It was thus decided to carry out a prospective trial to examine the clinical effects of treating postmenopausal patients with advanced breast cancer who had previously received formestane with a type 2 aromatase inhibitor in the form of anastrozole.

PATIENTS AND METHODS

Postmenopausal patients (more than 1 year since last menstrual period or having had bilateral ovariectomy or ovarian irradiation) with metastatic or locally advanced breast cancer who had received formestane for advanced disease were eligible for the study. Prior histological or cytological proof of recurrent breast cancer was obtained in all patients. The disease had to be bidimensionally measurable by physical examination or radiological investigation. Only patients who had previously received tamoxifen and were considered resistant to further treatment with tamoxifen were eligible.

Patients who had extensive visceral metastases (i.e. renal or liver function tests > 2 times the upper limit of normal) were excluded from the study. No concomitant endocrine, steroid, cytostatic or other investigational therapy was allowed and all these therapies had not been used for 4 weeks prior to the study. Patients having radiotherapy were eligible providing the treatment was palliative and outside the area of clinically measurable disease. All patients had progressive disease.

If clinically suitable for further endocrine treatment, patients were started on treatment with anastrozole 1 mg/day to be taken orally. Patients were assessed for response each month using UICC criteria [12]. Stable disease was defined as no clinical change in bidimensional measurements over 3 months. Patients defined with stable disease at 3 months continued to have monthly clinical assessments with repeat radiological assessment at 6 months.

Table 1. *Patient characteristics*

	No. (%)
Total	21
ER status	
Positive	16 (76)
Negative	4 (19)
Unknown	1 (5)
Disease sites	
Soft tissue	13 (62)
Visceral and bone	8 (38)
Sequential treatment with anastrozole	
Yes	14 (67)
No	7 (33)
Response on formestane	
PR	2 (10)
SD	10 (48)
PD	9 (43)

ER, oestrogen receptor; PR, partial response; SD, stable disease; PD, progressive disease.

RESULTS

21 patients were recruited to the study between February 1996 and May 1997 from Charing Cross Hospital (London, U.K.). 16 (76%) of the 21 patients' tumours were oestrogen receptor positive, 19% (4/21) were oestrogen receptor negative and a single patient's tumour was irretrievable for assay. Sixty-two per cent (13/21) of patients had soft tissue disease involving skin and breast and the remaining 8 patients had disease in other sites, i.e. liver, lung and bone (Table 1). 14 of 21 (67%) patients received anastrozole 1 month after formestane with no intervening therapy. The remaining 7 received anastrozole after other interventions (e.g. chemotherapy) and their disease had subsequently progressed (Table 1).

During formestane therapy, 10% (2/21) achieved a partial response and 48% (10/21) were classified as stable disease. Of these 12 patients, 9 showed further stable disease on anastrozole with the remaining 3 showing clear evidence of progression. 7 of these 9 patients had oestrogen receptor positive carcinomas and 6 of the 9 had soft tissue disease. Of the 9 patients who had progressive disease on formestane, 4 achieved stable disease with anastrozole. 3 of these had oestrogen receptor positive carcinomas. The remaining 5 patients progressed on both treatments (Table 2). 5 patients stabilised on anastrozole for greater than 6 months: 3 had progressed on formestane (1 oestrogen receptor negative) and the other 2 had stabilised on formestane but for less than 6 months (1 oestrogen receptor negative).

DISCUSSION

Over recent years it has become accepted that aromatase inhibitors should be used in patients with metastatic breast cancer after failing on tamoxifen therapy, especially if the tumours are oestrogen receptor positive. The recent introduction of type 2 aromatase inhibitors which are orally active at lower dosage has meant that most clinicians now use these compounds in preference to type 1 (less active) agents such as aminoglutethimide and formestane.

We reasoned that if premenopausal patients on goserelin could respond to a subsequent reduction in oestradiol after

Table 2. *Results on anastrozole*

	No. (%)
Total	21
PR	0
SD	13 (62)
PD	8 (38)
PR/SD on formestane	
Total	12
PR	0
SD	9 (75)
PD	3 (25)
PD on formestane	
Total	9
PR	0
SD	4 (44)
PD	5 (56)

PR, partial response; SD, stable disease; PD, progressive disease.

the addition of formestane [10], and patients on formestane receiving additional aminoglutethimide showed further endocrine and clinical response [11], it was likely that postmenopausal patients could benefit from type 2 inhibitors if they had displayed resistance to formestane. Indeed, endocrine evaluation has suggested a stepwise fall in oestradiol using a highly sensitive oestradiol radioimmunoassay, confirmed by measurements of urinary oestrone [13].

Despite the fact that this cohort of patients was not ideal, as 43% (9/21) of patients had failed to respond with formestane, our study indicates that, providing patients had either responded or stabilised to the first-line aromatase inhibitor they could possibly benefit from a second-line aromatase inhibitor. There was also an indication that if the patient's tumour was oestrogen receptor positive it was possible that even patients with progressive disease may stabilise.

Several other groups have explored the use of sequential aromatase inhibitors [14, 15]. One group has reported the use of sequential formestane after aminoglutethimide [14] and another has recently reported the utilisation of exemestane after aminoglutethimide [15]. Both studies suggest that this approach could be of clinical benefit. The study of Murray and Pitt [14] demonstrated that it was possible to obtain responses to formestane after aminoglutethimide and these authors observed a 21% response rate for an average duration of 11 months. The study by Thurlimann and colleagues [15], in which 33 aminoglutethimide resistant patients and 39 aminoglutethimide responders were treated with exemestane 200 mg/day, resulted in a response rate of 12% and 33%, respectively. This study indicated that non-steroidal and steroidal aromatase inhibitors are not necessarily cross-resistant. However, the rationale for the former study is different to this group's, since aminoglutethimide and formestane, used in the Murray and Pitt study, are approximately equipotent in terms of aromatase inhibition. In addition, the study by Thurlimann and colleagues sequences a steroidal following a non-steroidal inhibitor, i.e. the reverse of the sequence used in the present study.

We feel our results are of interest and warrant further investigation in the form of a randomised study recruiting a larger number of postmenopausal patients, as they indicate that optimal treatment may not simply be to commence tamoxifen resistant patients on the most potent form of endocrine therapy *de novo*. A longer total period of remission may result from a sequence of more than one aromatase inhibitor. We hope these findings will answer the question of the usefulness of the second response with aromatase inhibitors.

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