Aromatase inhibitors and their use in the sequential setting

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Abstract

Over the past decade several novel aromatase inhibitors have been introduced into clinical practice. The discovery of these drugs followed on from the observation that the main mechanism of action of aminoglutethimide was via inhibition of the enzyme aromatase thereby reducing peripheral levels of oestradiol in postmenopausal patients.

The second-generation drug, 4-hydroxyandrostenedione (formestane), was introduced in 1990 and although its use was limited by its need to be given parenterally it was found to be a well-tolerated form of endocrine therapy.

Third-generation inhibitors include vorozole, letrozole, anastrozole and exemestane, the former three being non-steroidal inhibitors, the latter being a steroidal inhibitor. All are capable of inhibiting aromatase action by >95% compared with 80% in the case of 4-hydroxyandrostenedione.

The sequential use of different generations of aromatase inhibitors in the same patients is discussed. Studies suggest that an optimal sequence of these compounds may well result in longer remission in patients with hormone receptor positive tumours.

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Introduction

The aromatase enzyme is a cytochrome P450-mediated enzyme complex responsible for the conversion of the androgens androstenedione and testosterone to oestrone and oestradiol respectively. The idea of treating oestrogen-dependent breast cancer with aromatase inhibitors has been around for several years. Aminoglutethimide was the first such compound shown to be clinically effective (Santen *et al.* 1978). Trials using aminoglutethimide in advanced breast cancer showed that responses occurred in between 20 and 40% of women so treated and the remission duration ranged from 6 to 12 months (Santen *et al.* 1978, Harris *et al.* 1983). A major feature that emerged was the toxicity of aminoglutethimide. Side effects, including skin rash, drowsiness and the inhibition of cortisol synthesis, necessitated the use of corticosteroids with their concomitant side effects. This led to various studies in which lower doses of aminoglutethimide were used in the treatment of patients with breast cancer (Harris *et al.* 1983, Stuart-Harris *et al.* 1985). However, the responses seen were generally lower and the duration of response was

reduced, although formal trials comparing different dose regimens and using sufficient numbers of patients to provide the necessary statistical power have not been adequately carried out. Before considering the impact of using the drugs in sequence, it is important to consider their effects when given alone.

Second-generation aromatase inhibitors: 4-hydroxyandrostenedione (formestane)

4-Hydroxyandrostenedione is a compound that has been shown to possess irreversible binding to the enzyme substrate-binding sites (Brodie *et al.* 1981). This suggests that the compound would cause permanent inactivation and a high degree of selectivity for aromatase. Prolonged inhibition of the enzyme would be likely to result, as recovery of activity is dependent on the rate of neosynthesis of the enzyme. Several studies have been carried out using 4-hydroxyandrostenedione over the past 13 years. Essentially these studies were initially conducted using a lyophilised microcrystalline material and given at a dose of 250 mg every 2 weeks. Peak levels were seen on the first and second day after injection with a fall to less

than 50% of peak levels by day 4. Thereafter the fall in serum 4-hydroxyandrostenedione was approximately log-linear with an apparent half-life of between 5 and 10 days.

4-Hydroxyandrostenedione is principally metabolised to the 4-hydroxyandrostenedione glucuronide which is found in the patients' urine at between 14 and 35% of the administered dose, and this explains why the drug is rapidly metabolised when administered by the oral route and needs to be administered parenterally. Major routes of metabolism are via dehydrogenation, reduction of the ketone functional groups, reduction of the C4/C5 double bond and hydroxylation at the C5 position (Poon *et al.* 1991).

Clinical studies began at the 250 mg dose every 2 weeks (Coombes *et al.* 1984). This dose selection was based on plasma oestrogen measurements in which we compared the suppression obtained with a single injection of 4-hydroxyandrostenedione at doses of 125-500 mg. Comparison of 250 mg and 500 mg showed equivalent degrees of initial suppression but there was an indication of minor recovery in the patients receiving the lower dose. The slightly lower pharmacological effectiveness was confirmed in studies using *in vivo* aromatisation in which the 250 mg dose reduced peripheral aromatisation to 15.2% of baseline in comparison with a reduction to 8.1% with the 500 mg dose ($P < 0.05$) (Jones *et al.* 1991). Serum oestrone levels measured by gas chromatographic mass spectrometer have been found to fall in parallel with oestradiol levels during intramuscular treatment. The dose of 250 mg every 2 weeks was chosen for clinical studies, as local side effects were much more pronounced for the 500 mg dose.

Other endocrine effects of 4-hydroxyandrostenedione were generally not seen. There are no significant effects on luteinising hormone, follicle-stimulating hormone, sex hormone-binding globulin, dehydroepiandrosterone sulphate, testosterone, 5-dihydrotestosterone or androstenedione when the drug is given intramuscularly. However, when the drug is given orally a small increase in dehydroepiandrosterone sulphate levels is seen. Oral administration of 4-hydroxyandrostenedione is also associated with a dose related fall in sex hormone-binding globulin (Dowsett *et al.* 1992) and this may be a reflection of the minor androgenic activity associated with the drug.

The drug is clinically very effective (Coombes *et al.* 1992). The overall complete and partial response rate was 26% in 136 patients who received therapy for at least 4 weeks. A major determinant of response was oestrogen receptor status of the primary tumour: 93% of objective responders whose oestrogen receptor was known had oestrogen receptor positive tumours. Prior successful therapy with endocrine therapy was also a determinant: only two of 35 patients who had failed to respond to other endocrine therapy responded. In these studies the drug was

well tolerated, with only a minority having any adverse effects. Thus 13% of patients on the 250 mg dose every 2 weeks complained of some local side effects, principally pain and inflammation at the site of the injection. Only one patient showed androgenic side effects, but anaphylactoid reactions occurred in five patients, presumed to be due to inadvertent intravenous administration.

4-Hydroxyandrostenedione has been given in combination with other endocrine agents. Encouraging results were obtained with a combination of 4-hydroxyandrostenedione and goserelin, the growth hormone-releasing hormone agonist currently used for medical ovariectomy. Goserelin is not able to affect peripheral aromatisation, but, in patients who respond to goserelin and then relapse, the subsequent addition of 4-hydroxyandrostenedione produces further reduction in oestradiol and subsequent response in a high proportion of patients (Stein *et al.* 1990). Others (Lonning *et al.* 1992) have also studied the combination of aminoglutethimide and 4-hydroxyandrostenedione in postmenopausal patients with breast cancer. Significant further falls in oestradiol, oestrone and oestrone sulphate were achieved on the addition of aminoglutethimide, with the greatest effect being on oestrone sulphate. Two patients achieved an objective tumour response on the further addition of aminoglutethimide.

4-Hydroxyandrostenedione has also been used in the neoadjuvant setting (Gazet *et al.* 1996). In this study patients with tumour size (clinical) T1-3 invasive breast cancer were assigned to pretreatment based on oestrogen receptor status. Although patients with hormone receptor negative tumours received chemotherapy, those with oestrogen receptor positive tumours received 4-hydroxyandrostenedione if they were postmenopausal. Treatment was continued for 3 months, and 34 patients received 4-hydroxyandrostenedione with an overall response rate of 35%. At the end of 3 months treatment patients had definitive surgery and/or radiation, depending on the 'T' stage of the primary tumour. Patients whose disease stabilised or responded to 4-hydroxyandrostenedione continued treatment for a total of 18 months. The 5-year survival rates of this study are the subject of a future paper. This suggests that 4-hydroxyandrostenedione could be used as a neoadjuvant therapy to reduce the size of large or unresectable primary breast carcinomas.

Third-generation aromatase inhibitors

New aromatase inhibitors include letrozole, anastrozole and vorozole, all of which are non-steroidal aromatase inhibitors, and exemestane, which is an example of a steroidal third-generation aromatase inhibitor.

Regarding the non-steroidal aromatase inhibitors, several clinical studies have now assessed their efficacy and tolerability. Johnston *et al.* (1994) studied vorozole at three separate doses (1, 2.5 and 5 mg) in 24 postmenopausal patients with breast cancer. Increasing doses of vorozole showed greater suppression of oestradiol, oestrone and oestrone sulphate. Eight of 24 patients achieved an objective response: these were principally patients who had responded to tamoxifen. Aside from a slight reduction in serum cortisol, no other endocrine changes were seen.

Vorozole has also been compared with aminoglutethimide in tamoxifen-treated patients. A total of 277 patients received vorozole and 279 patients received aminoglutethimide; responses were seen in 23 and 18% of patients respectively. Drug-related adverse events were seen in 31% of patients receiving vorozole and 53% of patients receiving aminoglutethimide (Bergh *et al.* 1997). Vorozole has also been compared with megace in tamoxifen-treated patients; complete and partial response rates were seen in 10.5% of vorozole and 7.6% of patients receiving megace but weight gain occurred in 14% of patients receiving megace compared with only 1% of those receiving vorozole (Goss *et al.* 1997).

Anastrozole was assessed in an early clinical study (Plourde *et al.* 1994) and this showed considerable suppression at doses between 1 and 20 mg. No other endocrine changes were observed. A study reported by Buzdar *et al.* (1997) compared anastrozole 1 mg, anastrozole 10 mg and megace 160 mg in 386 tamoxifen-treated patients. No differences in response rate were seen. However, side effects differed, with weight gain being more prevalent in megace-treated patients and gastrointestinal side effects in anastrozole-treated patients.

In a further study two different doses of letrozole (0.5 and 2.5 mg) were compared with aminoglutethimide at 500 mg daily, and more than 170 patients were accrued in each arm of the study. Complete and partial responses were seen in 16.7% of the patients receiving the lower dose of letrozole and 17.8% of those receiving the higher dose, whereas only 11.2% of aminoglutethimide-treated patients responded. Treatment-related adverse events were seen in 28, 32 and 45% respectively (Marty *et al.* 1997).

Exemestane (FCE 24304) was developed some 15 years ago. It causes a time-dependent inactivation of human placental aromatase and has a K_i of 26 nM, thus showing an affinity for the enzyme 2.6-fold higher than the substrate androstenedione. In preclinical studies, exemestane induced high rates of regression in Dimethylbenzanthracene (DMBA)-induced mammary tumours in rats (30% at 10 mg/kg and 73% at 50 mg/kg) and these dosages caused an 86 and 93% decrease in total ovarian aromatase activity respectively (Di Salle *et al.*

1989, Zaccheo *et al.* 1991). A phase I endocrine study of exemestane was carried out by Evans *et al.* (1992). Exemestane was given at doses between 0.5 and 800 mg to groups of between three and four patients. The minimal dose that produced a maximum suppression of plasma oestrogen was 25 mg. Although in this study there was evidence that some of the metabolites of exemestane interfered with some of the assays used, oestrone, oestradiol and oestrone sulphate were reduced to 35, 28 and 39% of basal values. No clinically adverse events were attributed to the drug during this study.

Subsequent to this, 27 postmenopausal heavily pretreated patients with metastatic breast cancer were selected for exemestane treatment (Di Salle *et al.* 1994). Exemestane was given again at between 5 and 600 mg daily to three or four subjects per dose and treatment was given for at least 12 weeks and continued until tumour progression. Minor side effects were seen including dizziness, headaches, hot flushes and nausea. Objective response was seen in eight (two complete responses and six partial responses) of the 24 evaluable patients (33%; 95% confidence intervals 18 to 53%). Mean duration of response was 42 weeks (12-72 weeks plus). These studies indicated that exemestane was an effective and relatively well-tolerated third-generation aromatase inhibitor, and other subsequent studies have confirmed that the drug is highly active (Di Salle *et al.* 1994).

Sequential administration of aromatase inhibitors

We have recently conducted an endocrine study in which patients receiving 4-hydroxyandrostenedione who were responding or stabilising were subsequently given vorozole for a 2 month period (during this time 4-hydroxyandrostenedione was discontinued), and both oestrone and oestradiol were measured sequentially during the course of treatment. The results indicated that the non-steroidal inhibitor vorozole resulted in a further sustained suppression which returned to pretreatment levels once the patients restarted 4-hydroxyandrostenedione treatment (Dowsett *et al.* 1999).

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 to >99% (Lonning *et al.* 1991, Jones *et al.* 1992, Lipton *et al.* 1995, Masamura *et al.* 1995, Geisler *et al.* 1996). 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 as randomised studies using different doses of letrozole have shown improved response rates at higher dosages (Dombernowsky *et al.* 1998).

A further study, carried out by our group (Stein *et al.* 1990), indicated that a stepwise suppression of oestradiol could result in 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 4-hydroxyandrostenedione on relapse and goserelin treatment was maintained. As a result of the introduction of 4-hydroxyandrostenedione, levels of oestradiol fell to similar levels to those observed in postmenopausal patients and the majority of patients obtained a further remission.

We have subsequently studied the clinical effects of giving anastrozole (1 mg) to 21 postmenopausal patients with advanced breast cancer who had already received 4-hydroxyandrostenedione and who had either responded and then relapsed or who had failed to respond. During 4-hydroxyandrostenedione therapy, 10% (2/21) achieved a partial response and 48% (10/21) were classified as stable disease (SD). Nine of these 12 patients showed a further SD on anastrozole with the remaining three showing clear evidence of progression. Seven of these nine patients had oestrogen receptor (ER) positive carcinomas. Four patients achieved SD with anastrozole despite failing to respond to 4-hydroxyandrostenedione. Three of these had ER positive carcinomas. The remaining five patients progressed on both treatments. Five patients stabilised on anastrozole for longer than 6 months, three had progressed on 4-hydroxyandrostenedione (one ER negative) and the other two had stabilised on 4-hydroxyandrostenedione but for less than 6 months (one ER negative). This suggests that sequential reduction in oestradiol in postmenopausal patients may be of benefit.

Several other groups have explored the sequential use of aromatase inhibitors. The administration of 4-hydroxyandrostenedione after aminoglutethimide and exemestane after aminoglutethimide have been reported. Both studies suggest that this approach could be of clinical benefit. The study of Murray & Pitt (1995) demonstrated that it was possible to obtain responses to 4-hydroxyandrostenedione after aminoglutethimide and these authors observed a 21% response rate for an average duration of 11 months. The study by Thurlimann *et al.* (1997), 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 from our 4-hydroxyandrostenedione-anastrozole study as aminoglutethimide and 4-hydroxyandrostenedione, used in the study of Murray & Pitt (1995), are approximately equipotent in terms of aromatase inhibition. In addition, the study by

Thurlimann *et al.* (1997) uses a steroidal inhibitor following a non-steroidal inhibitor, i.e. the reverse of the sequence used in the study that we conducted (Harper-Wynne & Coombes 1999).

In conclusion, much still needs to be learnt about the correct ways of using aromatase inhibitors. A systematic evaluation of response rates and time to progression with different sequences needs to be undertaken. In addition, randomised comparisons should be made of a stepwise approach to oestrogen degeneration versus immediate maximal degeneration. Only when we have this information will we be able to treat patients rationally in both the adjuvant and advanced settings.

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