Pergamon

European Journal of Cancer Vol. 32A, No. 3, pp. 393–395, 1996

Printed in Great Britain
0959–8049/96 $15.00+0.00

S0959-8049(95)00013-5

Editorial

New Aromatase Inhibitors: More Selectivity, Less Toxicity, Unfortunately, the Same Activity

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HORMONES, HORMONAL mechanisms and manipulations have made basic contributions to both our knowledge of the aetiology of breast cancer and the treatment of patients affected by this disease.

Just 100 years ago, Beatson [1] reported in the *Lancet* on the beneficial effect of oophorectomy in patients affected by breast malignancy. Some years later, Marshall and Jolly [2] recognised the hormonal function of the ovaries, inducing oestrus in castrated dogs by injecting them with ovary extracts removed from another dog during oestrus.

The biosynthesis of oestrogens is a multistep process in which the male sex hormones, androgens, are converted through aromatisation of the A-ring to form female sex hormones, oestrogens. In premenopausal women, aromatisation occurs principally in the ovaries, but after menopause this occurs mainly in the fat deposits (including the breast) and in the muscle tissue, the liver and in the brain.

The comparison of tissue oestradiol levels in pre- and postmenopausal patients shows that premenopausally, the plasma concentration is similar to the levels in tumour tissues, whereas in postmenopausal breast cancer patients, the concentration of oestradiol in the tumour cells and their nuclei is some 10–20 times greater than in plasma [3, 4]. This was also demonstrated in patients with negative oestrogen receptors, so that this gradient cannot be explained by the generally higher oestrogen receptor content of tumours in postmenopausal women, but rather supports the evidence that the tumour itself is producing oestrogens. The observation that oestrogen levels are generally higher in tumour cells than in plasma, leads to the hypothesis that higher levels of aromatase inhibition may better block the oestrogen synthesis within the tumour and therefore inhibit tumour growth more efficiently.

Advanced or metastatic breast cancer is an incurable disease. Therefore, the goal of treatment is, in most cases, palliation. The balance between the target of symptom relief, mostly reached by tumour remission, and treatment toxicity becomes of primary importance.

Since the first report on oophorectomy, many hormonal manipulations have been used for the therapy of advanced breast cancer, mainly because of their favourable therapeutic index, with generally acceptable toxicity profiles (when compared to chemotherapy) and remission rates of about 30% in unselected patients populations. Tamoxifen is the hormonal agent that is most frequently used in this situation, but its increasing application in the adjuvant setting has led to the need for second-line hormonal therapies for relapsing patients suitable for this approach. Progestins and aromatase inhibitors (mostly aminoglutethimide) have been widely used as a second-line hormonal therapy after tamoxifen failure. Due to their mechanism of action, aromatase inhibitors have been generally used in postmenopausal women because of the concern that, in premenopausal patients, a reflex rise in gonadotrophins may result in ovarian hyperstimulation with a consequent increase in oestrogen levels. The aromatase inhibitors currently available are, in fact, unable to block completely ovarian oestrogen production in premenopausal women.

Aminoglutethimide, a derivative of the hypnotic agent glutethimide, was introduced in the U.S.A. as an anticonvulsant in 1960. The observation of adrenal insufficiency in patients receiving the drug led to the discovery of its inhibition of the steroidogenesis.

In the 1980s, it was introduced in the "armamentarium" for the treatment of advanced breast cancer as an alternative to additive hormonal therapies or ablative manipulations (adrenalectomy, hypophysectomy). Its use has been limited due to its lack of specificity, with the consequent adrenal deficiency requiring the concomitant administration of glucocorticosteroids and, in some instances, also mineralocorticosteroids, and due to its side-effects including lethargy (in 9% of the patients), dizziness (15–20%), skin rashes (10–35%), and thyroxine synthesis blockade (5% of patients develop hypothyroidism) [5].

Great efforts have been invested in attempting to produce more selective aromatase inhibitors (steroidal and non-steroidal) with the hope of increasing their therapeutic index by increasing their activity and reducing their toxicity. A variety of compounds are currently under investigation or have recently been introduced in clinical practice.

Received 9 Jan. 1996; accepted 10 Jan. 1996.

4-hydroxy-androstenedione (Formestane) is a steroidal aromatase inhibitor, 30–60 times more potent than aminoglutethimide, but due to its conjugation by first-pass metabolism in the liver, it requires intramuscular administration (every 2 weeks). Lethargy, dizziness and skin rashes are less common than with aminoglutethimide and are reported in less than 7% of the patients [6]. The most common side-effects with this compound are local reactions at the injection site (7–13%).

The imidazole class of compounds has potent effects on a number of steroid hydroxylation steps [7] and has been introduced in the treatment of advanced breast cancer during the last decade. Fadrozole, a non-steroidal imidazole, 1000–3000 times more potent than aminoglutethimide, showed response rates of 20–30% in pretreated patients [8] and showed very favourable toxicity profiles in a recent study of the Swiss Group for Clinical Cancer Research comparing it to tamoxifen: hot flushes and thrombo-embolic complications were less frequent in patients treated with fadrozole [9].

Vorozole is about 1000 times more active than aminoglutethimide in the human placental aromatase system and is more selective than fadrozole, showing no suppression of aldosterone production. In a recently published phase II study of 27 evaluable patients, only 3 achieved the criteria for a partial remission, but an additional 14 experienced a disease stabilisation of 7–24 months duration [10]. A response rate of this level is low for second-line endocrine treatment in patients with positive or unknown hormone receptors, but it may be explained by the characteristics of the patients included in that small trial. The toxicity was considered mild and consisted mainly of oestrogen deprivation side-effects, such as hot flushes (14%) and dizziness (14%).

Anastrozole (Arimidex), 100–150 times more potent than aminoglutethimide, was shown to reach the maximum quantifiable suppression of serum oestrogen at a dosage of 1 mg/day in postmenopausal women with breast cancer. Remarkably, even a dose of 10 mg daily had no effect on adrenal or pituitary hormones or on response to ACTH challenge.

Results with aromatase inhibitors in advanced breast cancer are summarized in Table 1.

In this issue of the *European Journal of Cancer* (pages 404–412), Jonat and associates [11] reports on a very well conducted phase III clinical trial in postmenopausal breast cancer patients failing tamoxifen, that compares two dosages of anastrozole (1 and 10 mg/daily) with the standard second-line treatment, megestrol acetate (160 mg daily). There were two reasons for testing both doses of anastrozole: firstly, the dose–response relationships for the effects of anastrozole on serum oestradiol and on tumour growth might differ at different dosage, as, for example, if the tumour growth were more dependent on local oestrogen production than on circulating oestrogens. It is, therefore, possible that higher tissue concentrations of the drug may block oestrogen synthesis within the tumour more efficiently. Secondly, earlier phase II trials did not identify any significant toxicity for anastrozole with single doses up to 60 mg. In different efficacy trials, anastrozole at 1 mg daily reduced serum oestradiol to near or below the limits of detection of a sensitive oestradiol assay, and 10 mg daily had no greater effect. As the plasma elimination half-life of this compound is approximately 30–60 h and effects on serum oestradiol persist for up to 6 days after cessation of the treatment, anastrozole can be given once daily, making this treatment very simple, especially for older patients.

Table 1. *Results of clinical trials of aromatase inhibitors in advanced breast cancer*

Author	Compound	Percentage hormonally pretreated	Response %	Response duration
Brufman and Biran [13]	Aminoglutethimide 250–1000 mg/day	98%	34% CR/PR	9 months
Coombes and Stein [14]	Formestane 4-hydroxy-androstenedione 250 mg i.m./2 weeks	64%	33% CR/PR	12 months
Höffken *et al.* [15]	Formestane 4-hydroxy-androstenedione 500 mg i.m./2 weeks × 6 weeks then 250 mg i.m./2 weeks	80%	23% CR/PR 29% NC	3+ to 27+ months
Perez-Carrion *et al.* [16]	Formestane 4-hydroxy-androstenedione 250 mg i.m./2 weeks	Unknown	33% CR/PR	15 months
Thürlimann *et al.* [9]	Fadrozole (CGS 16949A) 2 mg/day	60%	16% CR/PR 24% at 1 mg/day	Time to treatment failure 5 months
Raats *et al.* [8]	Fadrozole (CGS 16949A) 1 mg/day or 4 mg/day	84%	22% at 4 mg/day CR/PR PR: 3/27 (11%)	Median survival all patients 23 months PR: 15 months
Goss *et al.* [10]	Vorozole (R 83842) 2.5 mg/day	100%	NC: 14/27 (52%)	NC: 12 months
Vinholes *et al.* [17]	Vorozole (R 83842) 2.5 mg/day	100%	30% CR/PR 2/21 patients PR 7/21 patients NC	10 months
Lipton *et al.* [18]	Letrozol (CGS 20267) 0.1–5 mg/day	Unknown	10% 1 mg 13% 10 mg (CR/PR)	Unknown
Jonat *et al.* [11]	Anastrozole 1 mg/day or 10 mg/day	100%	34% for both dosages considering also NC (≥6 months)	9 months for 1 mg/day not reached for 10 mg/day

i.m., intramuscular; PR, partial remission; CR, complete remission.

Endpoints of the study were time to progression, response rate and especially tolerability of the three treatments options. The UICC response criteria were strictly applied using a validated computer algorithm, preventing, in this way, potential subjective bias of investigators, and no partial remission definition was allowed for patients with unmeasurable disease (only complete response, stabilisation of the disease or progression). In addition, response rate was calculated for all randomised patients (intention to treat analysis). Quality of life aspects (physical and psychological symptoms and functional activity) were assessed using the Rotterdam Symptom Checklist and a prospective subjective symptoms score (for evaluation of analgesic use, pain and World Health Organization (WHO) performance status).

Response rates (complete remission (CR), partial remission (PR)) were quite low for all three treatment options (10.4% for anastrozole 1 mg/day, 12.7% for anastrozole 10 mg/day and 10.4% for megestrol acetate, respectively) and can be explained by the strict application of the UICC response definition. Another 21–23% of the patients experienced a prolonged stabilisation of the disease for more than 6 months. As expected, soft tissue lesions showed the highest response rates. Adverse events were similar for the three treatment options of the trial, with the exception of weight gain and oedema that were significantly more frequent with megestrol acetate.

What do we learn from this trial? From the methodological point of view, we learn that the strict application of the response criteria leads to much lower response rates than those expected and reported in the past. Anastrozole is quite well tolerated, and has a good therapeutic index, with slightly fewer side-effects than the standard second-line therapy with progestins.

Unfortunately, the antitumoral activity of anastrozole is not better than other hormonal manipulation, and even with a "superoptimal" dosage of 10 mg, the response rate does not increase. Higher tissue concentrations of aromatase inhibitors may block oestrogen synthesis within the tumour more efficiently, but the poor tolerability of the only available aromatase inhibitor, aminoglutethimide, has prevented the investigation of dosages higher than 1 g per day and therefore limited the testing of this interesting hypothesis. The present trial with a dosage of 10 mg anastrozole failed to demonstrate that increasing the dose also increases the oestrogen block within the tumour cells. We may hypothesize that the high oestrogen concentration within most of the tumours in postmenopausal patients may not be as important as we thought, and that there are other mechanisms which need to be investigated and are responsible for the lack of additional tumour shrinkage with higher aromatase inhibition.

Endocrine therapy of breast cancer has profoundly changed since the report by Beatson: ablative surgery and additive hormone therapy with their severe morbidity have been substituted by more precise and less toxic systemic approaches. Anti-oestrogens have played an important role and aromatase inhibition is another potential area of further development, especially after the introduction of more selective inhibition of aromatase with less toxic compounds. The next step in the progress of endocrine therapy of breast cancer may be the exploration of aromatase inhibitors in the adjuvant setting, and one of the tasks for basic research may be the better understanding of aromatase inhibition at the breast tissue level. In addition, highly selective aromatase inhibitors could have a future as chemopreventive agents against breast cancer as suggested by experimental models in rats [12], especially if their toxicity profile was more favourable than the currently investigated anti-oestrogens.

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