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Editorial

Aromatase Inhibitors for Breast Cancer—Further Progress

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MORE THAN a century after the demonstration of the regression of advanced breast cancer following oophorectomy [1], oestrogen deprivation remains the rationale for the endocrine treatment of this disease. Suppression of oestrogen can be achieved in various ways including ablation of the source of oestrogens (oophorectomy, pelvic irradiation, adrenalectomy), removal or inhibition of gonadotrophins (hypophysectomy, gonadotrophin-releasing hormone agonists, danazol, progestogens), blocking the oestrogen receptor (tamoxifen) or inhibition of synthesis of oestrogen from androgen precursors (aromatase inhibitors). After the menopause, the adrenal cortex is the principal source of oestrogen production and so total oestrogen suppression is potentially attainable by bilateral surgical adrenalectomy. However, this approach has been obsolete for many years because of important advances in endocrine treatment. Interest in the possibility of achieving ablation of adrenal function medically arose with the introduction of aminoglutethimide. Its use at first was based on an understanding that it inhibited the desmolase enzyme responsible for converting cholesterol to pregnenolone in the adrenal cortex so interfering with the production of all adrenocortical hormones [2]. Hence, with the early use of this drug it had to be combined with the prescription of cortisol. Subsequent work showed that the principal action of the drug was to inhibit the aromatase enzyme which converts C19 androgens to C18 oestrogens [3], an effect achieved at concentrations of the drug that do not inhibit desmolase. Furthermore, inhibition of the aromatase enzyme also prevents the peripheral synthesis of oestrogens from androgens in adipose tissue, the liver and in breast carcinomas [4]. This research has prompted the development of specific aromatase inhibitors, the administration of which does not require concomitant replacement cortisol.

Two classes of aromatase inhibitors are now available for therapeutic use. Type I compounds are exclusively steroidal molecules which compete with the natural substrates (androstenedione and testosterone) and bind irreversibly to the catalytic site of the aromatase enzyme; they include formestane (4-hydroxyandrostenedione) and exemestane. Type II inhibitors are predominantly non-steroidal agents which bind reversibly to cytochrome P-450, the coenzyme for steroid hydroxylation. The type II compounds are less specific than the steroidal drugs and include aminoglutethimide, fadrozole, letrozole, vorozole and anastrozole.

Formestane is the type I inhibitor which has been studied most extensively. It blocks oestradiol production and has no detectable oestrogenic, anti-oestrogenic or anti-androgenic properties [5]. Because of extensive first-pass metabolism in the liver, the preferred route of administration for clinical use is intramuscular injection, but formestane is also active orally. Pooling the data from a variety of phase II studies utilising various doses and either method of administration, the objective regression rate in postmenopausal women with breast cancer who had received prior endocrine treatment was approximately 20% [6]. In this issue of the *European Journal of Cancer,* Thurlimann and associates (insert pages—1017–1024) report a randomised phase III comparison of formestane with megestrol acetate in postmenopausal patients who had failed prior tamoxifen, given either as postoperative adjuvant treatment or for the treatment of relapse. The response rate in each arm of the trial was 17% with virtually identical confidence intervals. Median time to treatment failure, approximately 4 months, was not significantly different between the two arms. There were, however, differences in the toxicity profiles. Formestane was associated with exacerbation of menopausal symptoms, while weight gain and serious cardiovascular adverse effects were seen more frequently with megestrol acetate, on which drug deep venous thrombosis occurred in 5 of 81 cases. These results reaffirm the efficacy of formestane as second-line endocrine treatment for which it provides an objective response frequency similar to other methods of endocrine treatment. However, its toxicity profile is favourable which provides certain advantages over progestogens and aminoglutethimide, although this may be offset by the inconvenience and occasional adverse consequences of intramuscular rather than oral administration.

Aminoglutethimide remains the standard type II aromatase inhibitor, although its place is being challenged by several new agents. Certain side-effects have interfered with tolerance to aminoglutethimide in some patients and these include rashes, drowsiness and fatigue, nausea and, rarely, ataxia. However, in low doses, 500 mg a day or less, which result in aromatase inhibition, but with relatively little effect on desmolase, the incidence of serious side-effects is low and can be lessened further by the concomitant prescription

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of cortisol. Nevertheless, data from trials of newer, more specific agents which do not require concomitant cortisol administration are steadily accumulating. In a randomised phase II study of three different doses of fadrozole, an objective response rate of 17% was reported in women who had failed prior tamoxifen [7], an effect identical to the current report from Thürlimann and associates. Similar levels of efficacy are emerging for letrozole [8] and vorozole [9], both these agents having the added advantage of needing only once daily administration for maintained oestrogen suppression. Another agent given only once daily is anastrozole which, as in the study of Thürlimann and colleagues, has been compared with megestrol acetate in a randomised phase III trial [10]. Again this was in patients whose disease had progressed on tamoxifen and objective response rates were not significantly different for the two agents. Gastrointestinal side-effects were more common with anastrozole, but weight gain was less of a problem with this agent compared with the progestogen. Similar results have been reported for randomised comparisons of fadrozole [11] or vorozole [12] against megestrol acetate.

Preliminary reports have now appeared of direct comparisons of vorozole and letrozole with aminoglutethimide [13, 14]. Although these new non-toxic aromatase inhibitors are ultimately likely to replace aminoglutethimide, until data from direct comparisons have been formally reported and corroborated, aminoglutethimide will continue to have a significant place in the treatment of metastatic breast cancer. For the present, the selection of endocrine treatment should continue to be based on judgements of the likelihood of a response in the context of prior treatments and, most importantly, in relation to those side-effects which are most important to avoid in an individual patient.

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