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Aromatase inhibitors and inactivators for breast cancer treatment

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While ovarian oestrogen synthesis ceases at the menopause, the ovaries and, in particular, the adrenals, synthesise androgens (androstenedione and testosterone) that may be converted into oestrogens (oestrone and oestradiol, respectively) by so-called aromatisation [1]. Thus, circulating androgens are taken up and converted into oestrogen in most body compartments, including benign as well as malignant breast tissue.

Aromatase inhibitors and inactivators are compounds that inhibit the aromatase enzyme. While 'first' and 'second-generation' compounds like aminoglutethimide, fadrozole and formestane inhibited total body oestrogen synthesis by approximately 85–90% [2], the novel 'third-generation' compounds anastrozole, letrozole and exemestane cause 97–99% inhibition [3,4]. The compounds belong to two different classes: the non-steroidal (also termed 'reversible') inhibitors, and the aromatase inactivators, also termed 'steroidal' or 'irreversible' inhibitors. The inactivators bind irreversibly to the aromatase enzyme, and there is a need to synthesise novel aromatase enzyme protein to restore the enzyme function.

An interesting observation is the lack of complete cross-resistance between compounds belonging to the two classes (see Ref. [5] for references and details). Clearly, this cannot be explained as a 'dose–response' effect only, and suggests the drugs of the two classes may have differential effects at the cellular level (see detailed discussion in Ref. [6]).

While the data from the individual studies are somewhat at variance (and may, at least partly, be due to statistical chance), the five phase III studies comparing anastrozole, letrozole and exemestane to megestrol acetate in second-line therapy [7–10] revealed superiority or equality for each of these novel compounds with respect to time to progression (TTP), overall survival and/or response rates. In addition, one study revealed superiority for letrozole compared with aminoglutethimide [11]. No study revealed superiority for the control treatment arm with respect to any of the endpoints. While the results for exemestane are the most consistent (superiority with respect to TTP, time to treatment failure (TTF) as well as overall survival), notably as long as any direct head-to-head comparison has not been conducted, we may not claim superiority for any of these novel compounds compared with the other two. The overall impression, therefore, is that these compounds revealed clinical superiority compared with conventional therapy. In addition, they consistently revealed an improved toxicity profile compared with conventional therapy. The result of a trial comparing anastrozole with letrozole is awaited in the near future.

Data from two mature phase III studies comparing anastrozole with tamoxifen as first-line therapy have been reported [12,13], and the preliminary data from a smaller study has been given in abstract form [14]. A more detailed interpretation of these results are given elsewhere [5]. Notably, in the largest study (the European multinational one), more than 50% of the patients had unknown receptor status (for oestrogen receptor (ER) as well as progesterone receptor (PgR)); in this study, no significant difference between the two arms were recorded in the total material or in the subgroup that had a known receptor positivity [12]. In contrast, the American study revealed a superiority for anastrozole [13]. Combined analysis of these two studies has shown a superiority for anastrozole in the subgroup of ER-positive patients, but not in the total population [15]. At this stage, we may conclude that anastrozole is 'at least as good as' tamoxifen as first-line therapy, but we cannot claim its superiority.

In contrast, a large phase III study comparing letrozole with tamoxifen as first-line therapy revealed a superiority for letrozole with respect to TTP, TTF as well as response rate [16]. Importantly, while approximately one-third of the patients enrolled in this study had an unknown receptor status, sub-group analysis revealed superiority for letrozole in all of the subgroups analysed (total material, patients with known receptor-positive tumours and patients not exposed to tamoxifen in the adjuvant setting).

Exemestane is currently being compared with tamoxifen in a phase III study. While the preliminary results suggest a superiority for exemestane [17], the number of

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evaluable patients are still too few for any conclusions to be drawn.

Based on the encouraging results in metastatic disease, anastrozole, letrozole and exemestane, administered as different regimens, are currently being evaluated in the adjuvant setting. The results available for anastrozole are promising [18], but there is a need for longer follow-up. Also, we need safety data [19] to provide a basis for the further development of these compounds in early disease, but also in breast cancer prevention.

While aromatase inhibitors and inactivators have earned their place as therapeutic agents for metastatic breast cancer in postmenopausal women, several questions remain to be addressed:

- Will aromatase inhibitors/inactivators replace tamoxifen as standard adjuvant therapy for postmenopausal patients? If so, which compound should be used? And should we use monotherapy, combinations (with a SERM) or sequential treatment, and what is the optimal duration of treatment?
- What is the explanation for the lack of complete cross-resistance between aromatase inhibitors and inactivators, and how may we take maximum advantage of this in clinical practice?
- Could 'maximal oestrogen suppression' (a luteinising hormone-releasing hormone (LH-RH) analogue and an aromatase inhibitor/inactivator in concert) offer a therapeutic advantage in premenopausal patients?
- What is the optimal sequence of the different compounds (inhibitors versus inactivators), and what is the current place for tamoxifen in advanced breast cancer?

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