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Clinico-pharmacological aspects of different hormone treatments

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Abstract

During the last decade, several new drugs and classes of drugs have become available for breast cancer treatment. Thus, in addition to tamoxifen we have got several new selective oestrogen receptor modulators (SERMs) with a partially different pharmacological profile. The first generation aromatase inhibitor, aminoglutethimide, has been replaced by more potent and less toxic inhibitors belonging to the triazole class (anastrozole and letrozole) and, more recently, the steroidal aromatase inactivator exemestane [1–3]. These drugs have all revealed a better toxicity profile and, in general, an improved antitumour activity, compared with conventional therapy. Faslodex, the first representative of the so-called 'pure' oestrogen antagonists, has shown beneficial effects in patients resistant to tamoxifen [4].

Keywords: Breast cancer; Endocrine therapy; Drugs

An interesting observation is that patients may respond to oestrogen deprivation independent of their pretreatment plasma oestrogen level. Thus, pre- as well as postmenopausal patients may respond to castration or use of an aromatase inhibitor, respectively, and there is evidence that patients previously exposed to hypophysectomy or adrenalectomy as well as patients on therapy with a low-potent aromatase inhibitor may respond to further treatment with more potent drugs, references in [5]. Another interesting observation is the lack of cross-resistance to different treatment options like tamoxifen, progestins, aromatase inhibitors and 'pure' anti-oestrogens [4,6,7]. Even more striking is the lack of cross-resistance between different compounds belonging to the same class of drugs. While toremifene resembles tamoxifen in chemical structure, and there seems to be complete cross-resistance between the two compounds [6], evidence suggests a lack of cross-resistance between tamoxifen and third generation SERMs [8]. There seems to be lack of complete cross-resistance between non-steroidal aromatase inhibitors and steroidal aromatase inactivators [5], which may not be fully explained by a different efficacy with respect to oestrogen deprivation. Oestrogens administered in pharmacological doses were abandoned following the introduction of contemporary therapy with tamoxifen. However, in a recent study we obtained durable objective responses to diethylstilboestrol administered as 5 mg t.i.d. to women with advanced breast cancer exposed to $\geqslant 3$ previous endocrine regimens [9]. Previous studies evaluating aminoglutethimide and tamoxifen concomitantly for breast cancer treatment revealed no improvement in response rate compared with monotherapy, reviewed in [10]. However, aminoglutethimide induces the metabolism of tamoxifen, suppressing drug levels by approximately 70% [11]. Currently, combined use of an aromatase inhibitor and tamoxifen is evaluated for adjuvant therapy. While neither letrozole nor anastrozole influenced the plasma levels of tamoxifen [10,12], tamoxifen was shown to suppress plasma levels of letrozole by approximately 35% [13]. Whether a similar effect may occur with anastrozole, is currently not known. Lack of cross-resistance between different endocrine treatment regimens suggests endocrine therapy may be improved in the advanced as well as adjuvant setting, and sequential therapy with tamoxifen followed by an aromatase inhibitor as well as use of both drugs together is currently compared with tamoxifen monotherapy for adjuvant therapy. However, careful pharmacokinetic evaluation is necessary before implementing any regimen involving different drugs in combination.

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An overview of the use of non-steroidal aromatase inhibitors in the treatment of breast cancer

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Abstract

A number of potent and selective non-steroidal aromatase inhibitors are now available for the treatment of advanced breast cancer in postmenopausal women. In particular, anastrozole represents a significant advantage over earlier agents, such as aminoglutethimide and formestane, in terms of both efficacy and tolerability. These agents are now established as the second-line therapy of choice in postmenopausal women with advanced disease progressing on tamoxifen and, furthermore, data are now available on the efficacy and tolerability of anastrozole as first-line treatment of advanced breast cancer compared with tamoxifen. The full potential of the new-generation aromatase inhibitors in the treatment of breast cancer is currently being investigated in a large programme of clinical trials, including evaluation as neoadjuvant treatment in postmenopausal women with newly-diagnosed locally-advanced or large operable breast cancers, as first-line treatment of advanced breast cancer in postmenopausal women. Aromatase inhibitors have been available for over 20 years; the ability of these compounds to reduce circulating oestradiol levels has been shown to produce clinical benefit in postmenopausal women with advanced breast cancer. Early aromatase inhibitors, however, such as aminoglutethimide and formestane, were not specific for the aromatase enzyme and resulted in significant side-effects.

Keywords: Breast; Aromatase inhibitors; Treatment

Within the last decade we have seen the development of a new-generation of triazole aromatase inhibitors that are better tolerated with more convenient dosage regimens than these earlier agents. This new class of drugs, which are potent, orally active, non-competitive, selective, non-steroidal aromatase inhibitors, includes anastrozole, the first of these agents to become commercially available for advanced breast cancer in postmenopausal women failing on tamoxifen therapy.

Anastrozole is the most widely used of the new-generation aromatase inhibitors [1], but its use so far has been restricted to the treatment of advanced breast

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