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New Endocrine Agents in the Treatment of Breast Cancer

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INTRODUCTION

THE HORMONE responsive tumours include breast cancer, endometrial cancer and prostate cancer, all common cancers and in Denmark five-year survival for these are approximately 60, 70 and 25%, respectively. Quantitatively and qualitatively, therefore, these tumours represent a significant challenge to the treatment of solid tumours. This review will relate to the treatment of breast cancer. It will briefly mention the available endocrine therapies and then present new groups of drugs recently developed.

AVAILABLE ENDOCRINE THERAPIES

The available endocrine therapies aim at reducing the level of circulating oestrogens or their binding to the oestrogen receptor which is present in approximately two-thirds of primary breast cancer cases. The clinical rationale for this approach is the early demonstration of tumour response following the surgical removal of endocrine glands such as the ovaries, the adrenals and the pituitary [1].

Oestrogens are produced by aromatisation of androgens (androstenedione) by the enzyme aromatase. Pre- and postmenopausal women have distinct sites of oestrogen production [2], the former in the ovary under luteinising hormone (LH) and follicle-stimulating hormone (FSH) control, and the latter in the extra glandular tissue (e.g. fat tissue or liver) under the influence of various agents including ACTH, glucocorticoids and several growth factors [3].

The available endocrine treatment modalities include ablative therapy, additive therapy, competitive therapy and inhibitive therapy.

Ablative therapy with oophorectomy significantly reduces the levels of circulating oestrogens.

The mechanism of action of additive therapy with progestins remains controversial, but part of its effect is probably mediated via inhibition of the synthesis of pituitary hormones, thus leading to suppression of the synthesis of sex steroids in the ovary and in the adrenals. They may also act as "physiological" antiproliferative agents through progesterone or androgen receptors or they may act by decreasing synthesis of oestrogens or androgens [4].

Competitive therapy with antioestrogens seems to exert its action by antagonism of oestrogen action at the oestrogen receptor level [5]. Binding of oestrogen to its specific receptor stimulates the secretion of growth factors exerting autocrine or paracrine control of growth, and it has been argued that tamoxifen may exert part of its action by increasing the secretion of transforming growth factor-beta [6]. However, the antioestrogen also binds to other sites, but the potential role of these additional bindings sites in the mediation of the antiproliferative effect is largely unknown [1].

Inhibitive therapies include aromatase inhibitors and analogues of gonadotrophin-releasing hormone (GnRH). The aromatase inhibitors act through the inhibition of the conversion of androgen, primarily androstenedione, to oestrogen. Aminoglutethimide in addition inhibits cortisol biosynthesis [2]. The GnRH analogues work indirectly by inhibition of the secretion of the pituitary hormones [7].

With the endocrine therapies available today, approximately one-third of unselected patients, and one-half of women with oestrogen-receptor positive tumours will respond [1, 8], with no major advantage as regards efficacy associated with any of the modalities.

NEW ENDOCRINE AGENTS

Recent years have seen the development of new drugs, especially aimed at achieving an enhanced suppression of circulating levels of oestrogens (new aromatase inhibitors), and enhanced interaction at the oestrogen receptor level (new antioestrogens) or an action on the progesterone receptor (antiprogesterones).

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NEW AROMATASE INHIBITORS

Recently, several new highly specific aromatase inhibitors have been developed and introduced in the clinical practice.

These include both suicide and competitive inhibitors. Suicide inhibitors compete with the natural substrate for binding to the active site of the enzyme and irreversibly inactivate the enzyme. Competitive inhibitors bind reversibly to and inactivate the enzyme only as long as the inhibitor occupies the catalytic site. Whereas suicide inhibitors are exclusively steroids, competitive inhibitors consist of both steroidal and non-steroidal compounds [2].

Substances in the former group include lentarone [9], and exemestane, and in the latter group fadrozole [10], vorozole [11], letrozole [10], and arimidex [12]. Compared with aminoglutethimide, these agents achieve a more pronounced suppression of circulating oestrogens.

NEW ANTIOESTROGENS

The success of tamoxifen in the treatment of breast cancer has stimulated the development of a series of new compounds in the search for drugs with enhanced antioestrogenic activity, less intrinsic agonist action and improved antitumour effect.

Among these new agents, clinical efficacy has been demonstrated in humans in trials with toremifene [13] and droloxyfene [14], which are both drugs with a higher antagonistic/agonistic ratio than with tamoxifen. Preliminary data have also demonstrated activity associated with treatment with the pure antioestrogen ICI 182780 [15].

The clinical relevance of the agonistic effect of an antioestrogenic compound like tamoxifen is demonstrated by the risk, during prolonged treatment, of developing endometrial carcinoma. There is, however, also the potential for positive effects on calcium metabolism and on cardiac morbidity. Whether this also relates to antioestrogens with less pronounced agonistic and more antagonistic effects remains to be demonstrated in comparative trials.

ANTIPROGESTINS

A new group of compounds, the antiprogestins, including mifepristone and onapristone, have recently been developed and have demonstrated activity in animal models [16]. These drugs bind to the progesterone receptor, but there is evidence that the mechanism of antitumour effect may not depend on a classical antihormonal mechanism [16]. The drugs are now being introduced into clinical practice and preliminary data have demonstrated efficacy in patients [17].

CONCLUSION

Several new agents have been introduced in the treatment of advanced breast cancer. Provided these drugs demonstrate activity superior to presently available therapies (especially tamoxifen), the next step might be to introduce them in the adjuvant setting.

In this context, potential long term effects, associated with these very potent antioestrogenic compounds (interference with calcium and lipid metabolism), are especially relevant and will require careful assessment.

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