Editorial ESGO

Recent data about endometrial carcinoma: potential of anti-aromatase agents

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Forty years of basic research and clinical experience have established medroxyprogesterone acetate (MPA) as the most potent cancericidal available for the treatment of endometrial adenocarcinoma. In advanced or recurrent disease, the objective response rate is approximately 50% when a medium dosage (1g per week) is administered orally or intramuscularly. A 5-year recurrence-free survival rate of a nearly 100% is achieved using MPA as an adjuvant therapy for primary endometrial adenocarcinoma [1]. Looking at it the other way however, MPA is ineffective in almost half of the advanced cases of the disease and even responsive carcinomas eventually escape control.

In the early eighties, tamoxifen administered at a daily dosage of 40 mg and used as a fist-line therapy of advanced endometrial adenocarcinoma, proved to induce a complete and objective tumour response rate of approximately 35%. The same dose in second-line therapy produces responses ranging between 25 and 75% [2].

Later on, combining therapies with both tamoxifen and MPA and incorporating various time and dose schedules opened up promising new clinical perspectives in the treatment of endometrial adenocarcinoma. Hormonal therapy of a fully hormone-dependent cancer (ER+, PR+) should start with medroxyprogesterone administration. MPA transforms the tumour into a slightly hormone-dependent ER+ PR– type which would then require tamoxifen treatment. In the ER+, PR– tumour, the combined oestro-anti-oestrogenic action of tamoxifen should depress the cytosolic ER content and induce synthesis of PR. In that way, tamoxifen treatment may induce responsiveness to further progestogen therapy. In the hormone-independent tumour ER–, PR– tamoxifen seems to act as an oestrogenic agent, stimulating both ER and PR synthesis. This effect will transform an autonomous tumour into a hormone-dependent one and will prime it in readiness for progestogen treament [3, 4].

More recently, anti-aromatase agents have been introduced as a novel hormonal approach in the treatment of breast cancer and probably of other oestrogen-dependent malignancies as the pre-eminently hormone-dependent endometrial adenocarcinoma.

All the third-generation anti-aromatase agents: exemestane, anastrozole and letrozole, available today in clinical practice, act to block oestrogen biosynthesis, which occurs as a series of steroidal hydroxylation steps in which cholesterol is converted to oestrogen. The last step is the conversion of androgens (androstenedione and testosterone) to oestrogens and is catalyzed by the aromatase enzyme. Aromatase is located in the endoplasmic reticulum, which is also associated with the drug metabolizing (cytochrome P450) system.

There are two types of anti-aromatase agents which differ structurally and in their precise mechanism of action.

Steroidal inactivators mimic the natural substrate androstenedione and are very specific for the aromatase enzyme. They bind covalently (irreversibly) to the substrate-binding site of the aromatase and are acted upon by the enzyme during the catalytic process. As a result, the enzyme is inactivated or 'commits suicide' and there is a marked decrease of the amount of aromatase present.

Lecture in a round table devoted to "recent data about endometrial carcinoma". During the fifth European Meeting of the French Society of Gynecology held in Paris october 14, 2000.

Non-steroidal inhibitors reversibly bind to the heme part of aromatase. They bind non covalently, thus decreasing the amount of oestrogen formed. The interaction between the enzymes and the inhibitor stabilizes aromatase and prevents its degradation. Since proteolytic degradation is blocked, there is an increase in the amount of aromatase present after administration of a non-steroidal inhibitor [5, 6, 7, 8].

The biochemical effect of anti-aromatase agents, as measured by aromatase inhibition is approximately 98% for each of the third-generation anti-aromatase agents. This value is reflective of the peripheral oestrogen suppression to the detection limit of the assay achieved with these agents for oestradiol, oestrone and oestrone sulfate.

Anti-aromatase agents exert their anatomo-pathological antitumour effects by decreasing cell proliferation, increasing apoptosis, increasing coagulative necrosis and extensive hyalinosis of the carcinoma cells in possible correlation with host reactions such as tumour infiltration by lymphocytes and/or macrophages or angiogenesis [9].

All anti-aromatase agents are superior to progestins in postmenopausal women with advanced breast cancer who experience failure of tamoxifen. Moreover, exemestane consistently offers improvement in time-dependent variables [10, 11, 12]. Emerging data suggest that exemestane is associated with superior activity and improved tolerability compared with tamoxifen in the first-line treatment of advanced breast cancer, Anastrozole does not appear to offer advantages over tamoxifen in this population [13, 14]. Based on the encouraging results in patients with advanced breast cancer, trials are underway to evaluate anti-aromatase agents in the adjuvant setting. Early neo-adjuvant data suggest that anti-aromatase agents may also have an important role in the neo-adjuvant setting. Anti-aromatase agents also hold great promise in the treament of early breast cancer and in chemoprevention.

Based on improved efficacy and safety documented in comparative clinical trials with exemestane, anastrozole and letrozole versus megestrol acetate, anti-aromatase agents have replaced progestins as the preferred therapy in women with advanced breast cancer who experience failure of tamoxifen. Currently tamoxifen is the hormonal therapy of first choice for patients with advanced breast cancer, but this role is being challenged in phase III studies comparing anti-aromatase agents with tamoxifen.

The anti-aromatase agents represent an inhibiting pathogenetic and thus, restrictive epidemiologic factor in the carcinogenesis of the endometrium. Otherwise, they could be useful in the systemic hormonal approach of peri- and postmenopausal patients with an estrogen-dependent – even malignant – uterine tumour.

The anti-aromatase agents inhibit cell-proliferation of tumour cells as indicated by blocking of (3H) thymidine incorporation stimulated by testosterone and by decreasing the Ki67 labeling index. However, treatment by means of anti-aromatase agents does not change the ER status of tumour cells in human endometrial carcinomas [9]. In that way, anti-aromatase agents block, by their indirect but simple antagonistic oestrogenic action, the impact of oestrogens on the uterus and do not stimulate uterine growth, producing on the contrary a significant and dose-dependent decrease of mean uterine weight, comparable to that induced by ovarectomy or a normalization of abnormally increased uterine weight [15-21]. Anti-aromatase agents have no in vivo oestrogen or androgen agonistic properties [20]. Even reduction of endometrial thickness and glandular atrophy are observed in patients treated by means of anti-aromatase agents [22]. Consequently, anti-aromatase agents, in congrast to tamoxifen, do not at all induce endometrial hyper- or neoplasia as a disturbing adverse event.

In endometriosis, adenomyosis, leiomyomas and endometrial cancer, oestrogens are probably synthesized and secreted at a local level. Aromatase is detected in the cytoplasm of glandular cells of normal and hyperplastic endometrium [25]. Oestrogens synthesized by aromtase in endometrial tissue may play a pivotal role in regulating growth [18].

There is evidence of increased aromatase activity in malignant endometrial tumours, representing an additional source of oestrogens in the developing tumour [26]. In endometrial stromal cells 17ß oestradiol from any source is known to markedly stimulate the production of prostaglandin E_2, which is the most potent known inducer of aromatase expression in endometriosis [27]. An autocrine positive feedback mechanism for the development of endometriosis favours the continuous production of oestrogens and prostaglandin E_2 in endometrial stromal cells [28]. The local oestrogen formation in endometriotic tissue may be as significant as the circulating oestrogen originating from the adipose tissue of the patient [27]. The autocrine and paracrine effects of prostaglandin E_2 in the target tissue amplify oestrogenic action in comparison with steroid hormones delivered through the circulation [29].

Anti-aromatase agents may be useful clinically as an endocrine chemotherapy for peri- and postmenopau-

sal women with uterine oestrogen-dependent tumours [25]. They dose-dependently inhibit oestrogen biosynthetase activities in human uterine tumours: adenocarcinomas, leiomyomas, adenomyosis and endometriosis, without stimulating oestrogen action [30]. Anastrozole demonstrated limited efficacy in a group of patients with advanced or recurrent endometrial cancer; however, most of these cancers were poorly differentiated or presenting an aggressive histology (clear cell carcinoma and papillary serous carcinoma) [31]. Therefore, further studies are awaited to determine definitely the use of anti-aromatase agens and especially the inactivator, exemestane, in the treatment of uterine adenocarcinoma, as they have potential for the regression of endometrial hyper- and neoplasias with fewer adverse effects associated with a severe hypo-oestrogenic state [18].

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