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REVIEW

The Role of Aromasin in the Hormonal Therapy of Breast Cancer

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In the last 40 years tamoxifen and progestogens constituted the basis of hormonal therapy. Introduction of the third generation, selective, anti-aromatase agents added effective drugs of good tolerability to the anti-cancer armamentarium. Exemestane, an oral steroidal-type aromatase inhibitor – which irreversibly blocks aromatase – is very effective in the treatment of metastatic breast cancer. As a second line therapy, exemestane is more effective and causes less side effects than megestrol-acetate. Its administration as first line therapy gave promising results. The role of exemestane in adjuvant treatment has not yet been soundly established but trials are ongoing. It may be effective as neoadjuvant treatment in selected groups of patients. Future studies will clarify exemestane's role in chemoprevention and in the treatment of postmenopausal women administered together with cytostatic agents. (Pathology Oncology Research Vol 8, No 2, 87–92, 2002)

Keywords: exemestane, aromasin, hormonal therapy, breast cancer

Introduction

Successful therapy of breast cancer remains a challenge in the 21st century. Although the incidence of the disease shows significant geographical differences, it is the leading cause of morbidity and mortality among both the pre- and postmenopausal women.[1]

It is known for a long time that estrogen has an important role in the pathology of breast cancer. It was observed more than 100 years ago that ovariectomy slows the growth of metastases.[2] This method was followed by adrenalectomy[3] and hypophysectomy[4] in the treatment of metastatic postmenopausal breast cancer. A further development was the introduction the administration of estrogen, androgens and glucocorticoids,[5,6] later tamoxifen,[7] the first generation of active antiestrogen agents. Until now, tamoxifen remained the gold standard of endocrine therapy, together with the first generation anti-aromatase drug, aminogluthetimide.[8] These were followed by by the application of progestogens.[9] The mechanism of action of the progestogens is unknown (hypothetically they block the C21-C19 steroid pathway). The most widely used progestogens are megestrol-acetate and medroxyprogesterone-acetate. The first results with the second generation anti-aromatase inhibitor was published in 1984.[10] The initial slow development in the field of endocrine therapy of breast cancer has been accelerated since the 80-es. Currently 3 large groups of active agents exist: the group of selective estrogen modulators (SERM) including tamoxifen; the „pure" or steroidal anti-estrogens and the anti-aromatases.

Since the development of full therapeutic effect in hormonal therapy is slower than in chemotherapy, the hormonal therapy is used traditionally in patients whose progression of disease is moderate. It is very effective against bone metastases but good results can be achieved in metastases of other localizations. The response rate of hormonal therapy is 60-75% when the patients are both estrogen and progesterone receptor positive; 40-45% in progesterone receptor positive cases; 25-30% in estrogen receptor positive cases and less than 10% when both estrogen and progesterone receptors are negative.[11] CR + PR + SD≥24 weeks is characterized as clinical efficacy or full result. This parameter can be successfully used since it turned out that in 2 year survival during anastrosole therapy there is no difference between patients

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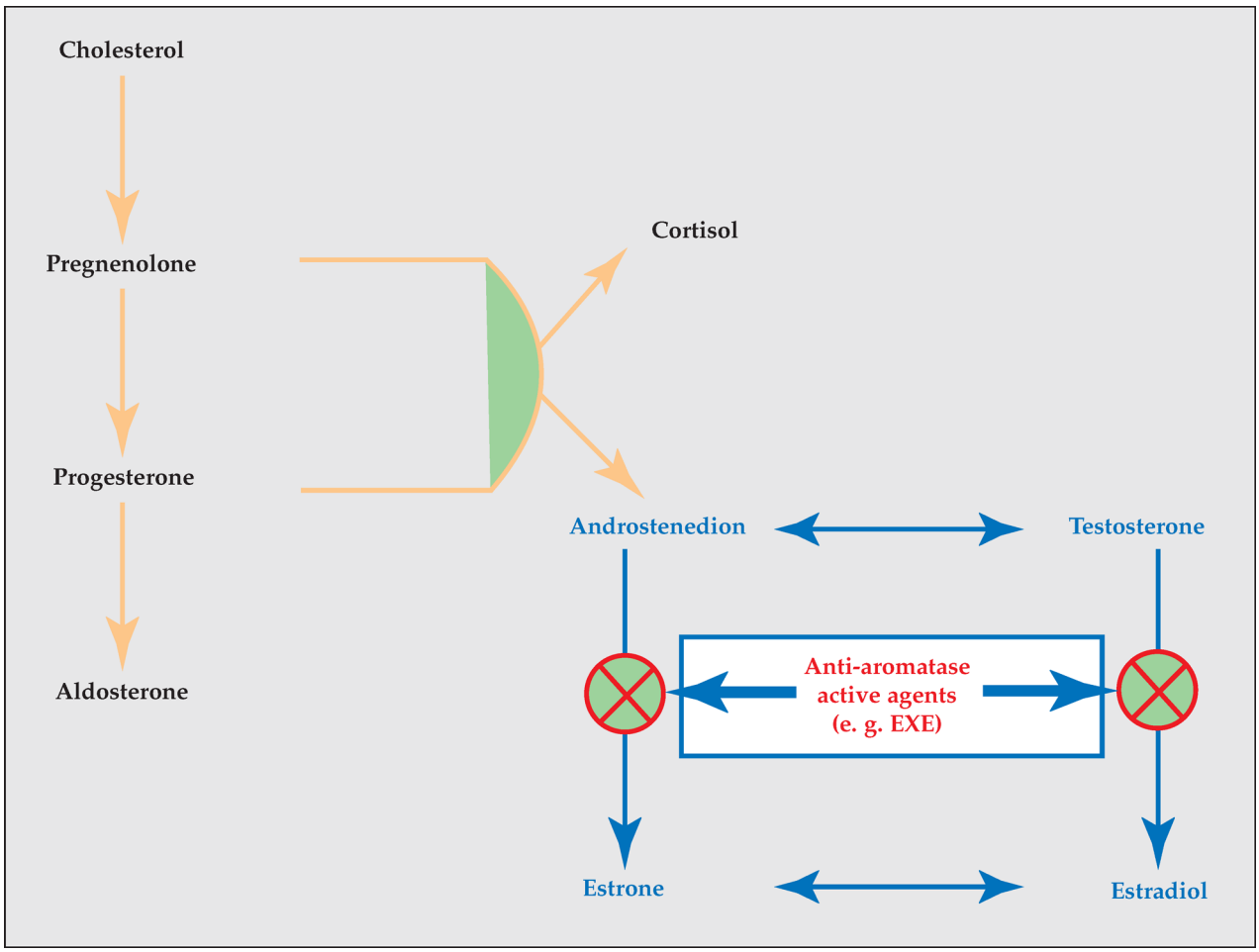

Figure 1. *Effect of anti-aromatase active agents on estrogen synthesis*

achieving OR or SD.[12] Resistance to one or two previous hormonal therapies do not mean that such therapy can not be effective any more. Different mechanisms of action of the agents make it possible to turn to an other hormonal treatment.

The anti-aromatase drug family

Anti-aromatase drugs inhibit the synthesis of estrogen by blocking the activity of aromatase *(Figure 1.)*. In postmenopause this enzyme is responsible for estrogen production. Aromatase activity is present in the fat tissue, in the muscles, in the breast and in many cases within the breast carcinoma as well.[13] There are 2 types of anti-aromatase drugs which differ in their chemical structures and mechanisms of action: steroidal type and non-steroidal type inhibitors (structures see in *Figure 2.*).

There are 3 generations of anti-aromatase agents. The so-called *first generation* agents are not used any more because of their toxicity. (Aminogluthetimide is the first representative of the non-steroids and testolactone is the first representative of anti-aromatase drugs). The *second generation* non-steroidal fadrosole is not used in the clinical practice whereas the rarely used, steroidal-type formestane can be administered only i.m. Currently the effective, *third generation*, so-called selective anti-aromatase drugs are in the focus of clinical practice. All of them inhibit the last step of estrogen synthesis (the androstendion – estrone and testosterone – estradiol transformations). Steroidal inhibitors mimic the natural substrate androstendion and bound covalently, irreversibly to the substrate binding site of aromatase enzyme. The enzyme gets inactivated this „suicidal" way and its level decreases. Non-steroidal inhibitors bind reversibly to the hem-group of the aromatase enzyme. This is not a covalent bound but the inhibition is prolonged until the inhibitor molecules are present. The enzyme is stabilized by the binding of the non-steroidal inhibitor which protects the enzyme from degradation, therefore the level of the enzyme increases.[14,15,16,17,18] Biochemical efficacy of the third generation anti-aromatase agents is about 98% based on the degree of aromatase inhibition.[19,20]

Exemestane – pharmacology and pharmacokinetics

Exemestane is an oral, steroidal-type aromatase inhibitor with a chemical structure resembling the natural substrate androstendion. The time-dependent aromatase inactivation by the drug is 40-156 times higher than that of caused by aminogluthetimide.[21,22] Exemestane interferes significantly with neither 5-alpha-reductase nor desmolase and does not bind to estrogen, progesterone or glucocorticoid receptors. The 17-hydroxy metabolite binds in a certain degree to the androgen receptors but it has no clinical importance during the administration of 25 mg daily doses.[21,22,23] Androgen agonist activity of this metabolite was observed in vitro and in patients who received a long-term therapy with large doses (200 mg/day). Absorption of the drug is rapid, peak-concentration develops within 2 hours after administration; half-life of the drug is nearly 24 hours. It decreases the levels of estrogen, estradiol and estrogen-sulfate in a dose-dependent manner. Maximum level of estrogen suppression develops in the third day of therapy. With the administration of daily 25 mg the level of estrogen, estradiol and estrogen-sulfate decreases by 85-95%.[24] When this result was compared to an other one showing that megestrol-acetate lowered the plasma estrogen level by 70-80% in postmenopausal women with breast cancer, it makes understandable that exemestane proved to be more effective in the clinical practice.[25]

Tolerability and side effects

In five phase I clinical studies altogether 107 patients participated. Higher doses (600 mg/day or 1200 mg/week) were tolerable. The drug has a wide therapeutic window. The most frequent side effects included flush (14%), gastrointestinal symptoms, mainly nausea (11,9%). Androgen-like side effects like alopecia (2%), dysphonia (1%) and hypertrichiosis (below 1%) could be observed in few patients (4,3%). The last two side effects appeared only when doses exceeded 100 mg. Estrogen deprivation has an effect on bone mineralization, inducing osteoporosis – and by this way – increasing the risk of pathological fractures. Although exemestane lowers the plasma estrogen concentration to an almost undetectable level, the incidence of fractures remains low. Adjuvant studies will provide answer to the question that how does exemestane therapy influence bone density? It is known that estrogen decreases the risk of cardiovascular diseases and has a positive effect on plasma cholesterol. During dose-escalation of

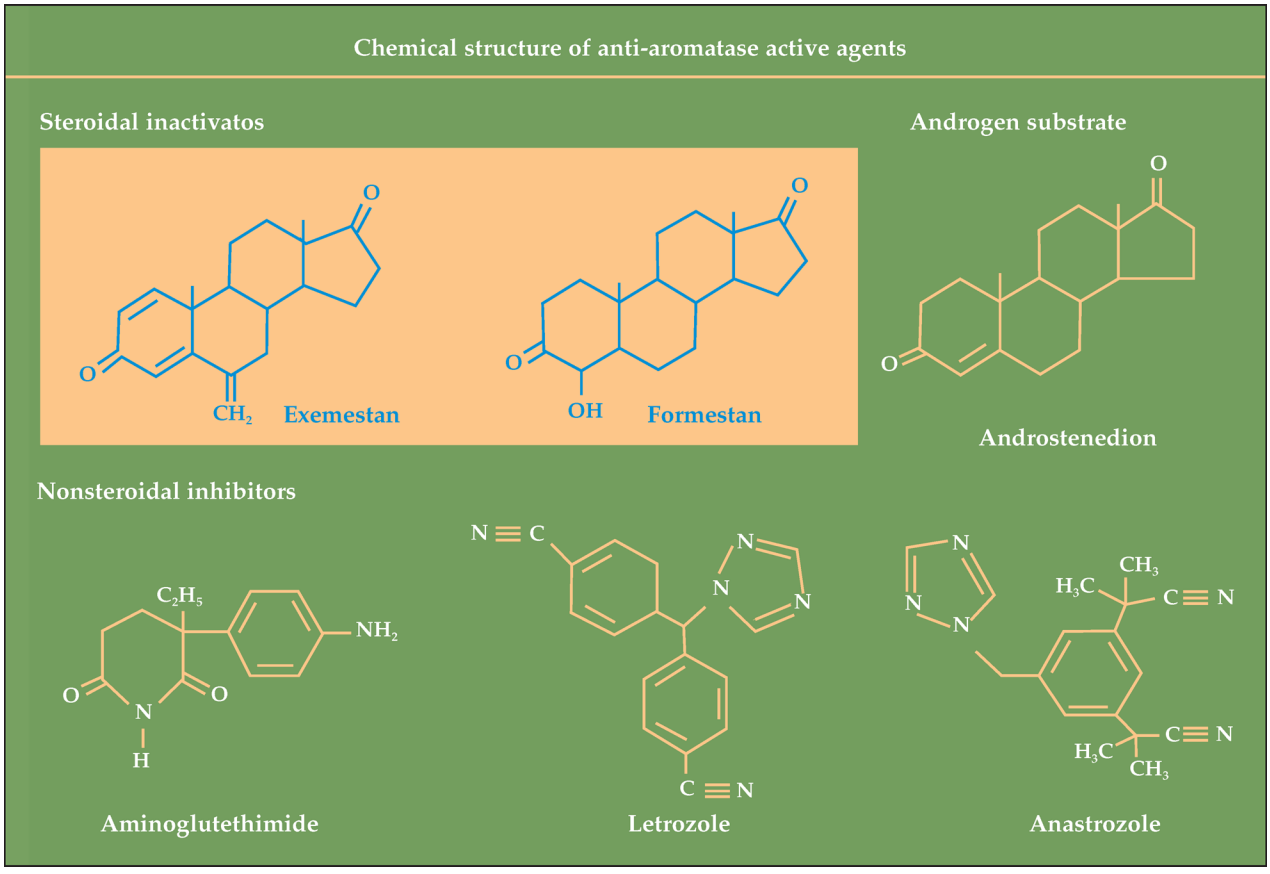

Figure 2. *Chemical structure of anti-aromatase active agents*

exemestane (5-200 mg during 12 weeks) decrease of total cholesterol level was observed together with a lower high-density lipoprotein cholesterol, apoA1 and triglycerol levels. It is important to note that the administration of exemestane does not elevate the incidence of thrombotic or thromboembolic complications.[26] Side effects observed during exemestane treatment is summarized in *Table 1.*

Exemestane – clinical application

Third line treatment

In a phase II study 80 patients received 200 mg/day exemestane. Patients were previously administered aminogluthetimide, tamoxifen and other endocrine treatments and/or chemotherapy. In 43% of patients visceral metastasis was present. The response rate was 26%, clinical efficacy (CR + PR + SD≥24 weeks) 39% and average period achieving objective response 52 weeks. The drop-out rate due to side effects was 3%.[27] During this study still high, 200 mg/day doses were given. Since it became evident that maximum estrogen suppression can be achieved with daily 25 mg dose, too, this dose was administered in further studies.

In another large international study 25 mg exemestane was administrered. Patients were previously treated with aminogluthetimide or other anti-aromatase (anastozole, letrozole). More than 90% received at least 2 courses of hormonal therapy. The clinical efficacy was 24,3% with an average duration of 37 weeks.[28] In 2 studies daily 25 mg exemestane was administered in relapse following tamoxifen and megestrol-acetate. The rate of objective response was 11% and 16%, whereas the clinical efficacy was 29% and 30%.[29,30] These studies provided evidence that exemestane is effective in the treatment of repeatedly pretreated metastatic breast cancer patients.

Second line treatment

In two studies patients with progressive disease – after tamoxifen treatment – were involved. The objective response rate was 23% and 28%, whereas clinical efficacy agreed in 47%.[31,32] In one study[30] positive receptor status and soft tissue metastases proved to be predictive factors in achieving better clinical efficacy. Efficacy of 25 mg/day exemestane and 160 mg/day megestrol-acetate was compared in a randomized, double-blind, phase III study in metastatic breast cancer patients who relapsed after tamoxifen treatment. Metastases developed after tamoxifen adjuvant treatment either within one year or they progressed during their tamoxifen treatment. Exemestane treatment resulted in a higher objective response rate than megestrol-acetate (15,0% vs 12,4%) but the difference was not significant. However, the following parameters were significantly different to the favor of exemestane group: average duration of the period of clinical efficacy (60,1 weeks vs 49,1 weeks, p = 0,025), duration of the period of time until tumor progression (20,3 weeks vs 16,6 weeks, p = 0,037) and the period of time until the drug loses its effectiveness (16,3 weeks vs 15,7 weeks, p = 0,042). The most important result was that survival was significantly better in the exemestane arm of the study.

Table 1. **Summary of grade 1-4 side effects during administration of 25 mg/day exemestane in phase I-II-III studies in 1058 patients**

Side effects – (NCI-CTG grade 1–4 (%)	*No. of patients (%)*
Side effects, total	503 (47,5)
Flush	148 (14)
Nausea	126 (11,9)
Fatigue	81 (7,7)
Dizziness	59 (5,6)
Increased perspiration	59 (5,6)
Headache	49 (4,6)
Cardiovascular	38 (3,6)
Insomnia	37 (3,5)
Pain	36 (3,4)
Rash	30 (2,8)
Abdominal pain	29 (2,7)
Musculosceletal pain	28 (2,6)
Anorexia	27 (2,6)
Vomitus	28 (2,6)
Depression	25 (2,4)
Reproductive system	21 (2,0)
Alopecia	21 (2,0)

NCI-CTC=National Cancer Institute Common Toxicity Criteria

In summary, the second line exemestane therapy decreases the risk of disease progression and the mortality in metastasized breast cancer by nearly 20%.[33] Furthermore the above study a quality of life assessment was performed. which gave better results in the exemestane study group. The pain and symptoms associated with the tumor decreased more during exemestane therapy than during megestrol-acetate treatment.[32]

Efficacy of exemestane in visceral metastases is reviewed in reference 34, which summarizes data from 5 clinical studies. In case of visceral metastases the objective response rate with exemestane is 14-29% and clinical efficacy 36,3% whereas with megestrol-acetate 30,0%.[34] It is interesting that exemestane is more effective in the treatment of visceral metastases than letrozole or anastrozole.[34]

First line therapy

Promising results were reported from a phase II study in which exemestane or tamoxifen was administered as first line therapy. Average period of time until progression was 8,9 months in the case of exemestane and 5,2 months in case of tamoxifen. The objective response rate in the

exemestane treatment group was 42% and in the tamoxifen group 16%. These data emphasizes the efficacy of exemestane now against tamoxifen in first line therapy of metastatic breast cancer.[35]

Adjuvant therapy

The most widely used current endocrine therapy in adjuvant treatment of postmenopausal breast cancer is tamoxifen. Its application can be limited by thromboembolic complications or by changes of the endometrium including development of endometrium carcinoma.[36] Hormonal therapies of the same or better efficacy and more favorable side effect profile may be introduced in the future. Anti-aromatase agents are promising possibilities in this area. In the ICCG (International Collaboration Cancer Group) study patients first were administered daily with 20 mg tamoxifen for 2-3 years then have been continuing their therapy either with daily 25 mg exemestane or 20 mg tamoxifen until the end of the 5th year.

In the NSABP (National Surgical Adjuvant Breast and Bowel Project) study patients started their therapy with tamoxifen for 5 years then switched either to exemestane or placebo treatment which is continuing for 2 years. Results of the above studies will be reported in the future.

Neoadjuvant treatment

Based on in vitro study results exemestane decreases aromatase activity both in the tumor and in normal tissues. During its neoadjuvant application in 13 postmenopausal patients with local, estrogen receptor positive breast cancer, PR developed in 10 patients and SD in 2 patients. One patient died but not because of toxic side effects of the treatment. In the future larger studies involving more patients are needed.[37]

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