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Review

The therapeutic significance of aromatase inhibitors in endometrial carcinoma

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HIGHLIGHTS

- Aromatase inhibitors block aromatase activity that regulates levels of estrogen and can thereby exert anti-tumor effects in endometrial carcinoma.
- Aromatase inhibitors have shown promising effects in patients with early-stage endometrial carcinoma.
- Aromatase inhibitors have side effects that must be considered when devising a treatment plan for patients with endometrial carcinoma.

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ABSTRACT

Objective. To review recent studies about the application of aromatase inhibitors in endometrial carcinoma and the benefits and challenges of aromatase inhibitors in this regard.

Methods. Relevant studies and manuscripts were searched for in Pubmed using the following terms, either alone or in combination: aromatase, aromatase inhibitors, letrozole, anastrozole, endometrial cancer, breast cancer, endocrine, therapy, and side effects.

Results. Endometrial carcinoma is one of the most pervasive gynecological malignancies. Type I endometrial carcinoma is estrogen-dependent. Recent studies have demonstrated that aromatase inhibitors, which interfere with estrogen biosynthesis by inhibiting the activity of aromatase, can be used to treat endometrial carcinoma and its precancerous lesions to some extent. In early-stage endometrial carcinoma or atypical hyperplasia, a precancerous lesion of endometrial carcinoma, the effects of aromatase inhibitors were promising. However, in advanced or recurrent endometrial carcinoma, the application of aromatase inhibitors cannot solve the problem evidently. In addition, these inhibitors have limitations, like side effects and drug resistance. The need for a new generation of inhibitors with higher specificity and fewer side effects should be studied further.

Conclusions. Aromatase inhibitors show promise in the therapy of endometrial carcinoma, especially the early stage. Further studies should be conducted to develop next-generation aromatase inhibitors with higher specificity and fewer side effects.

Contents

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Introduction

Endometrial carcinoma (EC) is one of the most pervasive neoplasms in developed countries, and it affects an increasing number of women [1]. In the United States, 49,560 new cases and 8190 deaths were caused by this malignancy in 2013 [2]. A majority (>80%) of EC cases are estrogen-dependent while estrogens can stimulate the growth of the endometrium. Some studies have demonstrated that increased circulating estrogen levels can promote DNA strand breakage in endometrial tissue and upregulate the expression of methionine and hepatocyte growth factor (HGF) [3,4]. All these estrogen associated factors are relevant to endometrial carcinogenesis. Estrogens originate from the ovaries in premenopausal women. In postmenopausal women, androgens are converted to estrogen by aromatase to increase circulating estrogen levels in peripheral tissues [5]. The estrogens, especially estradiol, have been shown to contribute significantly to the growth and progression of estrogen-dependent tumors, like EC [6]. In addition, local levels of estrogens in EC tissue were higher than levels in normal endometrium and in circulation [7]. Thus, inhibiting circulating levels of estrogens, as well as local estrogens, may limit the progression of these estrogen-dependent tumors.

Many risk factors of EC, such as obesity and polycystic ovarian syndrome (PCOS) [8,9], induce the occurrence and progression of this prevalent gynecological cancer; however, the etiology of EC is not completely clear. In some studies, obesity was associated with poor prognosis for EC while women with PCOS were four times more likely to develop EC than those without PCOS [10,11]. Notably, these risk factors have a direct or indirect relationship with estrogen biosynthesis. Some clinical studies showed that aromatization of plasma androstenedione correlated positively with body weight, which may explain why obesity is a risk factor of EC [12]. And as for PCOS, its clinical features associated with EC mainly include elevated circulating concentrations of androgens, hyperandrogenism, insulin resistance, hyperinsulinemia and elevated levels of circulating luteinizing hormone (LH) [9]. A study by Lathi et al. demonstrated that insulin may have homeostatic functions at lower doses via the phosphatidylinositol-3-kinase (PI3-kinase) pathway and may predispose to cell proliferation at higher doses via the mitogen-activated protein kinase (MAPK) pathway [13]. Insulin can affect the endometrium through its own receptor or the structurally similar insulin-like growth factor (IGF) type I receptor and it can inhibit the biosynthesis of IGF binding protein I (IGFBP-1), produced by decidualized endometrial stromal cells [14]. The IGF system is a key participant in endometrial proliferation and development. Over-expression of LH/HCG receptors is also associated with endometrial carcinogenesis [15]. All this evidences suggest that EC is a risk in women with PCOS.

Aromatase, a member of the cytochrome P450 superfamily, plays an important role in the conversion of androstenedione and testosterone to estrone and estradiol [16]. This enzyme is present primarily in the placenta and ovaries, but can also be detected in other peripheral tissues, such as the testis, adipose, bone, skin, muscle, and brain [17]. Thus aromatase can increase the concentration of circulating estrogens in peripheral tissues, especially in postmenopausal women [5,18]. In addition, in premenopausal women, granulosa cells secrete higher levels of aromatase when the density of follicle stimulating hormone (FSH) rises. Likewise, an increase in luteinizing hormone (LH) also enhances the secretion of ovarian steroid hormones, especially the androstenedione. Thus, both of these hormones can increase the concentration of circulating estrogens [19].

Given the impact of aromatase on estrogen levels, blocking its activity with aromatase inhibitors may be regarded as a kind of endocrine therapy for EC. Several recent studies have provided important insight into the role of aromatase and aromatase inhibitors in EC. Therefore, in this review, we summarize these findings and discuss their implications.

Overview of aromatase and aromatase inhibitors

Aromatase and its activity in the human body

Aromatase is a key enzyme that catalyzes the biosynthesis of estrogens from androgens. In humans, aromatase is encoded by the gene CYP19. Interfering with the activity of this gene or inhibiting its products can block aromatase biosynthesis [18]. A polypeptide chain of 503 amino acid residues and a heme group constitute the basic structure of aromatase [20]. What makes aromatase unique among other P450 enzymes is a proline residue at position 308. The crystal structure of aromatase and its substrate androstenedione was elucidated successfully in 2009 [20]. Thus, the catalytic mechanism of aromatase and the discovery of its inhibitors can be understood more comprehensively.

The catalytic mechanism of aromatase may have three steps, and each requires 1 mol of O_2 and 1 mol of NADPH [21]. Among these three steps, the first two steps are C19-methyl hydroxylation and the third step can set aromatase apart from other P450s via aromatization of the steroid A-ring. The process of aromatization in the third step can be called androgenic specificity [20].

The history of aromatase inhibitors

Aromatase inhibitors suppress estrogen biosynthesis by blocking aromatase activity. Several studies reported that aromatase gene expression could be found in tumor tissues from 80% of postmenopausal patients with ER-positive breast cancer [22]. In addition, an isolated treatment with aromatase inhibitors produced better effects than tamoxifen [23]. The latter, which is a kind of selective estrogen receptor modulator, was first used in the 1970s as a treatment for breast cancer [24]. Anyway, it is still in use for breast cancer at present. Aromatase inhibitors have been studied extensively and have evolved through three generations of development. Based on their distinct mechanisms of action, these inhibitors are divided into two kinds: steroidal and non-steroidal. Steroidal aromatase inhibitors include testolactone (first generation), formestane (second generation), and exemestane (third generation). All of these agents have a structure similar to androgens, which are substrates of aromatase, thus facilitating competition with androgens. However, unlike androgens, these inhibitors bind aromatase irreversibly [25].

The first two generations of steroidal aromatase inhibitors have been eliminated gradually because of their limitations. For example, the first-generation inhibitor testolactone blocked the biosynthesis of epinephrine and other steroid hormones and, as a result, had to be administered concurrently with hydrocortisone. In clinical studies, the second-generation inhibitor formestane was not superior to tamoxifen, though formestane had relatively few side effects [26]. By contrast, the third-generation inhibitor exemestane is so far rather actively in use owing