Aromatase Inhibitors: An Overview for Surgeons

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Breast cancer is the most common cancer in women in the US and the second leading cause of cancer death in women. Over the past century, there have been many advances in the treatment of breast cancer, including radiation, chemotherapy, and endocrine therapy. Beatson[1] discovered in 1896 that oophorectomy could lead to regression of a breast tumor in an inoperable patient. Since that time, researchers have discovered what estrogen is, how its receptor functions, and how it is involved in breast cancer. Strategies have been developed to use this knowledge by manipulation of the estrogen receptor, most notably through tamoxifen. Tamoxifen is a selective estrogen receptor modulator that functions by competitively blocking the estrogen receptor. Tamoxifen has become the gold standard for endocrine therapy of the breast. It is used in estrogen receptor-positive (ER+) women in the adjuvant, advanced, and neoadjuvant phases of treatment. It is even being used in prevention of cancer. Another strategy in endocrine therapy has been developed that blocks synthesis of estrogen by inhibiting the aromatase enzyme. Aromatase inhibitors are proving to be an effective treatment in breast cancer and might even be superior to tamoxifen. Exposure of surgeons to aromatase inhibitors will become more common as these drugs are used increasingly in the neoadjuvant setting. Additionally, as more surgeons manage their patients' endocrine therapies postoperatively, they will need to add aromatase inhibitors to their treatment strategies. This article will review available evidence on the use of aromatase inhibitors in breast cancer.

MECHANISM OF ACTION

Aromatase is an enzyme of the cytochrome P-450 family. Its function is to convert either androstenedione to estrone, or to convert testosterone to estradiol. Aromatase is a key checkpoint in the synthesis of estrogen (Fig. 1). Aromatase is present in the granulosa cells of the ovary and in subcutaneous fat, adrenal, and breast tissue. Aromatase present in the ovary is dependent on gonadotropin stimulation. After menopause, the ovaries cease to be the main source of estrogen. Peripheral aromatase in the adipose tissue and adrenals produces the majority of estrogen in postmenopausal woman. Tamoxifen functions to competitively block the estrogen receptor, and aromatase inhibitors function by decreasing systemic levels of estrogen. Interestingly, studies have demonstrated that nearly two-thirds of breast cancer cells express aromatase. Aromatase levels are higher in breast tumors than in peritumoral fat. Additionally, peritumoral levels of aromatase are higher in the quadrant of the breast in which the tumor is located, compared with other quadrants, leading to an estrogen-rich microenvironment.[2-6] Aromatase inhibitors function to deprive breast tumors of both circulating and intratumoral estrogen.

There are two general types of aromatase inhibitors, based on their mechanism of action. Type I aromatase inhibitors are the steroidal aromatase inhibitors. Their structure resembles that of androstenedione, and they bind irreversibly to the substrate site of aromatase. These aromatase inhibitors are called "suicide inhibitors." Type II aromatase inhibitors, also called nonsteroidal aromatase inhibitors, bind reversibly to the heme moiety on the aromatase enzyme (Fig. 2). There are now three generations of aromatase inhibitors, based on the timing of their development (Table 1). Each generation has become more selective in its blockade of aromatase. Aminoglutethimide is the only first-generation aromatase inhibitor. It is a type II inhibitor, administered orally, which became available for breast cancer treatment in the 1970s and is nonselective in that it inhibits both glucocorticoid and mineralcorticoid synthesis. Patients who take this drug require steroid supplementation. Second-generation aromatase inhibitors include formestane and fadrozole, which are more selective. They demonstrated some efficacy in breast cancer treatment, but side-effect profiles of third-generation aromatase inhibitors were better.[7-10] Additionally, formestane is administered IV, making oral availability of third-generation inhibitors more desirable. Currently, third-generation

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Abbreviations and Acronyms

ABCSG = Austrian Breast and Colorectal Study Group
ARNO = Arimidex-Nolvadex Trial
ATAC = Anastrozole Tamoxifen Alone or in Combination Trial
DCIS = ductal carcinoma in situ
DFS = disease-free survival
ER+ = estrogen receptor-positive
IBIS = International Breast Intervention Study
IES = Intergroup Exemestane Study
OS = overall survival
PERCHE = Premenopausal Endocrine Responsive Chemotherapy Trial
SOFT = Suppression of Ovarian Function Trial
TEXT = Tamoxifen and Exemestane Trial

aromatase inhibitors have replaced the two earlier generations. Only three are available in the US. They include the type I inhibitor exemestane, and the type II inhibitors anastrozole and letrozole. All three have good oral bioavailability and are dosed daily. All three third-generation aromatase inhibitors suppress > 95% of estradiol levels. Letrozole has been shown to generate the greatest suppression, although it has not been proved to have a greater clinical response than the other two.[11,12]

Aromatase inhibitors have only been approved for use in postmenopausal patients. In the premenopausal patient, circulating gonadatropins stimulate the ovaries. The ovaries respond by synthesizing estrogen, which inhibits the pituitary's production of gonadatropins. By blocking estrogen synthesis, aromatase inhibitors disrupt this feedback loop in the premenopausal patient. Unopposed gonadotropin stimulation of the ovaries leads to enlargement of the ovaries and possibly cystic disease. Additionally, it is unclear whether aromatase inhibitors can completely suppress estrogen production in the premenopausal patient. Studies with aminoglutethimide and formestane demonstrated incomplete suppression of estrogen levels, but no studies have been performed with third-generation inhibitors.[13]

AROMATASE INHIBITORS IN ADVANCED CANCER

Aromatase inhibitors were initially compared with megestrol acetate for second-line therapy in advanced breast cancer. All three third-generation aromatase inhibitors were found to be as effective or superior to megestrol acetate. The objective response rates and time to progression were improved with use of aromatase inhibitors. There was no substantial increase in overall survival (OS) compared with megestrol acetate (Table 2). Common side effects with megestrol acetate are weight gain, dyspnea, and vaginal bleeding. An improved side-effect profile and tolerability were noted

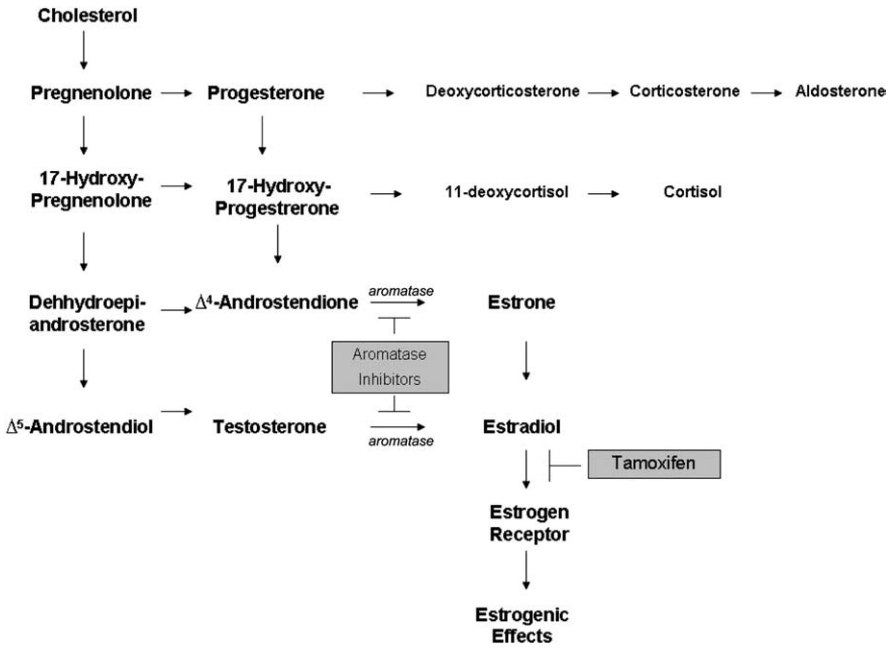

Figure 1. Estrogen synthesis pathway.