Aromatase Inhibitors: A Safer Approach for the Treatment of Breast Cancer

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ABSTRACT

Breast cancer is the second leading cause of cancer death in women. About two-thirds of breast cancers are termed hormone-dependent breast cancer, which contains estrogen receptors (ER) and requires estrogen for tumor growth. Aromatase, the enzyme involved in the last step of the biosynthesis of estrogens from androgens, are potential targets for the prevention and treatment of this type of breast cancer. Aromatase inhibitors can markedly suppress plasma estrogen levels by inhibiting aromatase. However, these compounds inhibit aromatase activity in a global fashion and thus could adversely impact sites where estrogen is required for normal function. This drawback has encouraged researchers to develop new drugs that can selectively inhibit aromatase for breast cancer.

INTRODUCTION

There is a high mortality rate in women because of the Breast Cancer. **Breast cancer** is the Neoplasm of the breast Tissue. An Uncontrolled and abnormal growth in breast tissue. Signs of breast cancer may include a lump in the breast, a change in breast shape, dimpling of the skin, fluid coming from the nipple, or a red scaly patch of skin. In those with distant spread of the disease, there may be bone pain, swollen lymph nodes, shortness of breath, or yellow skin.

Risk factors for developing breast cancer include obesity, lack of physical exercise, drinking alcohol, hormone replacement therapy during menopause, ionizing radiation, early age at first menstruation, and having children late or not at all. About 5–10% of cases are due to genes inherited from a person's parents, including BRCA1 and BRCA2 among others.

But commonly develops in cells from the lining of milk ducts and the lobules that supply the ducts with milk. Cancers developing from the ducts are known as ductal carcinomas, while those developing from lobules are known as lobular carcinomas. There are more than 18 other sub-types of breast cancer. Some cancers develop from pre-invasive lesions such as ductal carcinoma in situ.

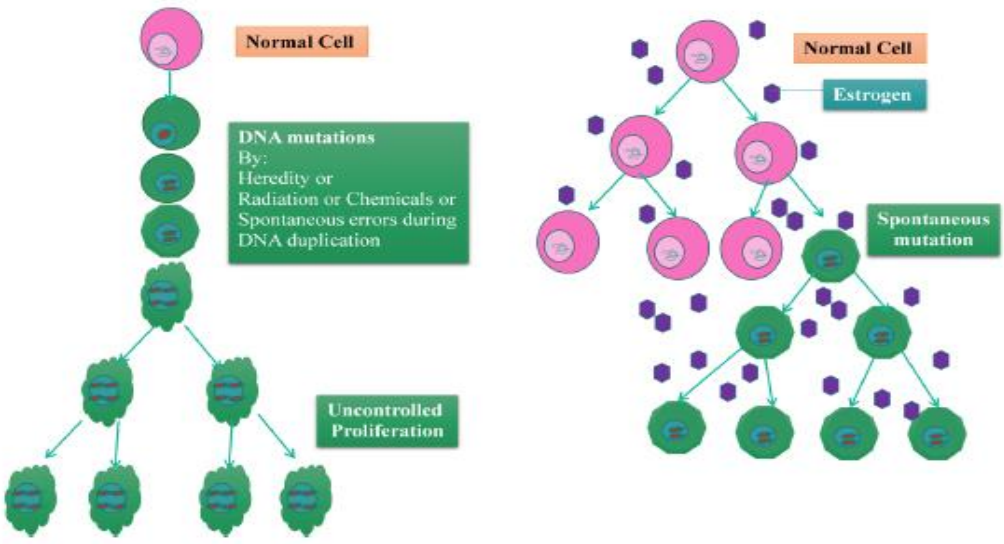

Fig. 1: Effect of Estrogen on the growth of cancer cells

The diagnosis of breast cancer is confirmed by taking a biopsy of the concerning lump. Once the diagnosis is made, further tests are done to determine if the cancer has spread beyond the breast and which treatments it may respond to.

MECHANISM OF ACTION OF AROMATASE ENZYME

Aromatase is the cytochrome P450 enzyme that converts androgens including androstenedione and testosterone to the estrogen products, estrone and estradiol respectively. This enzyme plays a key role in the regulation of these sex steroids. The aromatase gene, designated *CYP*19, encodes the cytochrome P450arom and consists of 10 exons, with the exact size of the gene exceeding 70 kilobases. The gene is located on chromosome 15q21.1. The full length cDNA of 3.4 kilobases encodes for a protein of 503 amino acids with a molecular weight of approximately 55,000 daltons. The enzyme complex is bound in the endoplasmic reticulum of the cell and is comprised of two major proteins. One protein is cytochrome P450arom and the other one is NADPH-cytochrome P450 reductase. Three moles of NADPH and three moles of oxygen are utilized in the conversion of one mole of androgen substrate into one mole of estrogen product (Fig. 1.1). Aromatization of androstenedione proceeds via three successive oxidation steps, with the first two being hydroxylations of the angular C-192 methyl group. The final oxidation step, whose mechanism remains unclear, proceeds with the aromatization of the A ring and loss of the C-19 carbon atom as formic acid.

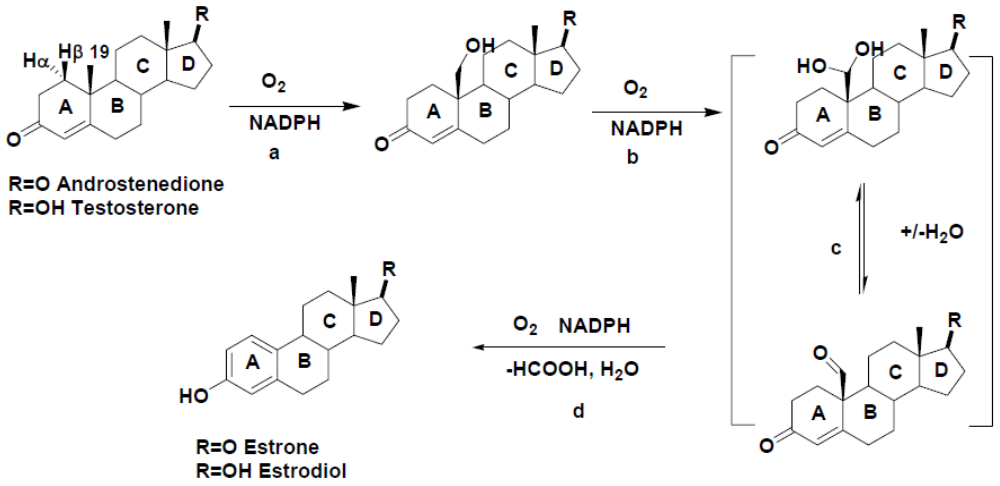

Figure 1.1. Reaction mechanism for estrogen biosynthesis by aromatase

AROMATASE INHIBITORS

Estrogen can influence the risk of breast cancer and also the growth of established tumours. Hormone-dependent breast cancer tumours depend on estrogen for growth. Two approaches treating these cases of breast cancer are either blocking the mechanism of action of estrogens or inhibiting its synthesis. These therapies are particularly helpful in postmenopausal women in whom hormone responsive is common and estrogen synthesis is primarily peripheral (adipose tissue, muscle and breast tissue) rather than in the ovary. A large number of aromatase inhibitors have been developed and utilized in clinical studies over the last 20 years. This development was prompted by the recognition that the cytochrome P450 inhibitor aminoglutethimide is an aromatase inhibitor and exerts its therapeutic effectiveness in postmenopausal women with advanced breast cancer via the inhibition of aromatase.

Aromatase inhibitors that have been used clinically can be categorized by generation and by mechanism of action. They are described as first-, second-, and third generation inhibitors according to the order of their clinical development. They can also be classified as type 1 and type 2 according to their mechanism

of action. Type 1 and type 2 inhibitors are also known as steroidal and nonsteroidal inhibitors, respectively.

- There is a 2 types of Inhibitors:-

1. Steroidal Inhibitors
2. Nonsteroidal Inhibitors

(1) Steroidal Inhibitors

This steroidal group includes inhibitors that act in a competitive manner and agents acting as enzyme in activators or suicide inhibitors. Competitive inhibitors are molecules that compete with the substrate androstenedione for noncovalent binding to the active site of the enzyme to decrease the amount of product formed. Steroidal inhibitors that have been developed to date build upon this basic androstenedione nucleus and incorporate chemical substituents at varying positions of the steroid (Fig. 1.4). These inhibitors bind to the aromatase cytochrome P450 enzyme in the same manner as the substrate androstenedione. The structure-activity relationships of those inhibitors have been well reviewed.

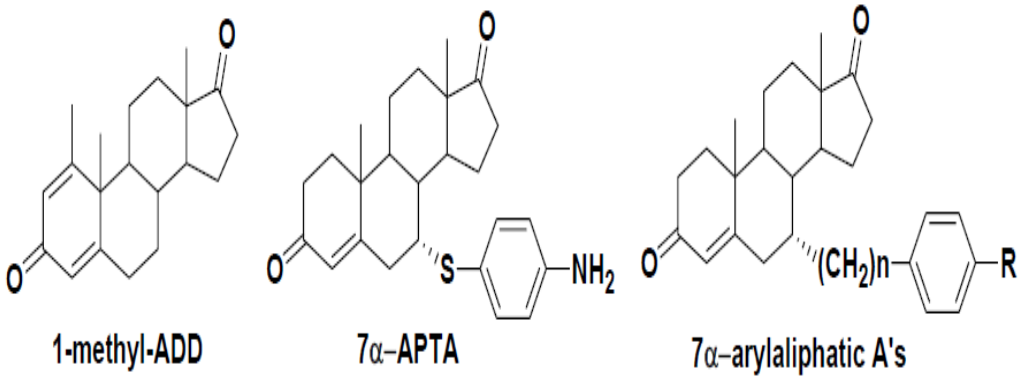

Figure 1.4. Competitive steroidal aromatase inhibitors.

Suicide inhibitors, also called mechanism-based inhibitors, require that the enzyme itself converts the inhibitor to a chemically reactive intermediate that binds irreversibly and covalently to the protein structure of the enzyme-substrate binding site. Thus, the individual enzyme molecule is irreversibly inactivated and the inhibitor molecule is no longer available to interact with other enzyme molecules (Fig. 1.5). These types of inhibitors have the potential for exquisite selectivity for the enzyme target and long-term effectiveness, since the recovery of enzyme activity depends on the re-synthesis of enzyme as well as on the pharmacokinetics of the drug. A larger number of mechanism based inhibitors have developed from more detailed biochemical investigations of several inhibitors originally thought to be competitive inhibitors. These inhibitors can be grouped into the general categories of 4-substituted androst-4-ene-3, 17-diones, substituted androsta-1, 4-diene-3, 17-diones, and 6-methylene- or 6-oxo-androst-4-ene-3, 17-diones.

The mechanism-based inactivation that occurs is due to irreversible, covalent binding of the inhibitors to the enzyme protein. However, the exact nature of the covalent bound(s), the chemical structures of the bound inhibitors, and the amino acids involved are yet to be elucidated. Additionally, the question of whether the inhibitors are oxidized at the C-19 position in a manner similar to the substrate androstenedione before irreversible binding and inactivation remains to be answered.

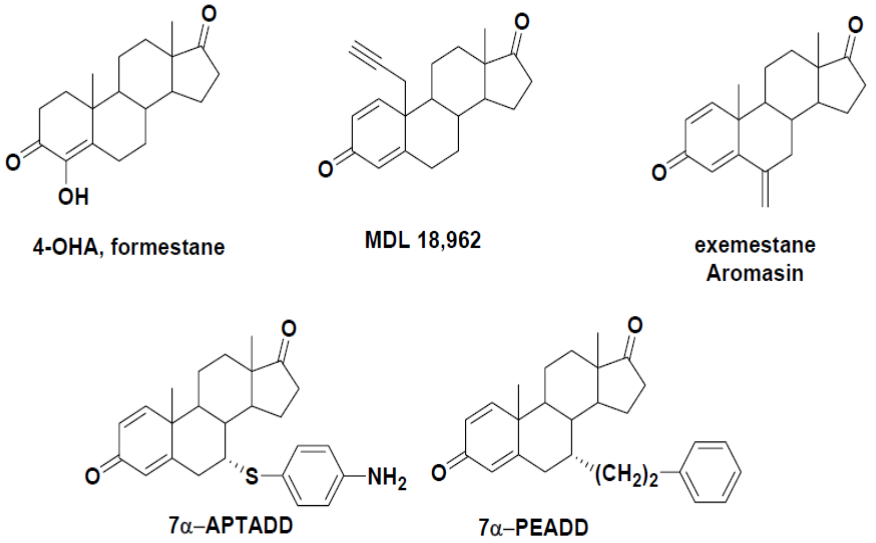

Figure 1.5. Suicide aromatase inhibitors

(2) Nonsteroidal Inhibitors

Nonsteroidal aromatase inhibitors are competitive and reversible in nature. These inhibitors have a basic nitrogen atom that allows them to interact with the iron atom of the heme prosthetic group of the enzyme. Their specificity for inhibition of the aromatase enzyme (as opposed to the very large number of other cytochrome P450 enzymes) is determined by the other structural aspects of the drugs and the way that these allow a close fit to the substrate-binding site of aromatase. This specificity results in high-affinity binding and limits the fit into the substrate-binding site of other enzymes. A full understanding of these molecular interactions has been restricted by the unavailability of a crystallized aromatase preparation for structural analysis of the inhibitor-enzyme interaction. These inhibitors produce a Type II binding spectra (λmin = 385-395 nm and λmax = 425-435 nm) as a result of coordination of the nitrogen heterocycle to the iron atom of the iron protoporphyrin IX at the active site of aromatase.

Aminoglutethimide is the prototype nonsteroidal inhibitor of aromatase. It was originally used as an antiepileptic agent, but this therapeutic use was discontinued due to serious side effects. It was later found that it can inhibit the aromatase enzyme, making this drug the first nonsteroidal first-generation aromatase inhibitor. Problems with the side effects of aminoglutethimide led to the development of the second-generation of nonsteroidal aromatase inhibitor. The realization that the nitrogen heteroatom of aminoglutethimide could coordinate with the heme group of aromatase prompted many groups to consider other nitrogen heterocycles. An obvious starting point is the imidazole ring, which led to the discovery of imidazole compound fadrazole (Fig. 1.6). Fadrazole is a potent competitive inhibitor of aromatase and is more selective than aminoglutethimide. However, this compound still has some nonselective inhibitory activity with respect to aldosterone, progesterone, and corticosterone biosynthesis.

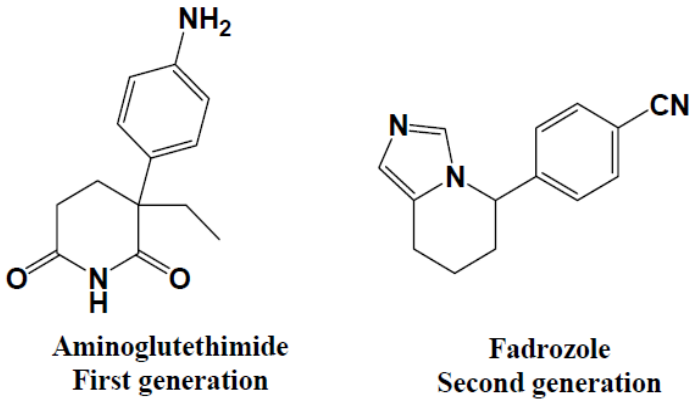

Figure 1.6. First and second generation of nonsteroidal aromatase inhibitors

Competitive nonsteroidal inhibitors can also be constructed with a triazole ring, which is found in the third generation of aromatase inhibitors (Fig. 1.7). The triazole derivative vorozole in its racemic form inhibits aromatization in human placental microsomes with an apparent *Ki* of 1.3 nM[55]. (-)-Vorozole is more potent than its enantiomer, (+)-vorozole, each having apparent *Ki* values of 0.7 nM and 18 nM, respectively. Neither the racemate nor the enantiomerically pure compounds had any effect on P450-dependent cholesterol biosynthesis, cholesterol side chain cleavage, 7α- hydroxylation, or 21-hydroxylase activity. Anastrozole is a potent aromatase inhibitor of human placental microsomes with an IC50 of 15 nM. In animals, it was also found to be selective for the aromatase enzyme with a maximal activity at about 0.1 mg/kg. Anastrozole displays no estrogenic, androgenic, progestrogenic, glucococorticoid or mineralocorticoid activity in rats making it suitable for the treatment of breast cancer. Letrozole is a potent inhibitor of aromatase with an IC50 of 11.5 nM in human placental microsomes. Letrozole suppressed both plasma and urinary levels of estrogen by about 95% and showed no compromise in cortisol and aldosterone output. The third-generation inhibitors possess a specificity that appears to be nearly complete at clinical doses with no effect on aldosterone, progesterone, corticosterone biosynthesis. Recent clinical studies have shown that aromatase inhibitors, specially the third-generation, are more effective than tamoxifen in postmenopausal patients with metastatic breast cancer.

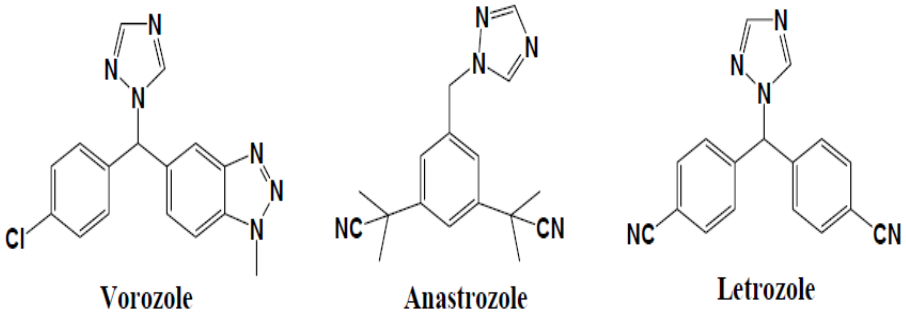

Figure 1.7. The third generation of nonsteroidal aromatase inhibitors

CONCLUSION

Aromatase Inhibitors are more selective and safer than the Estrogen Antagonist. Still there is plenty of work remained related to more efficacy and safety profile of drugs. And there should be more candidate to come across in this class of drugs.

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Dear god, I wonna take a minute,
Not to ask for anything from you,
But simply to say thank you for all I have.
"To mom and the dad, for their love, their humour, their ethics, their inspiration but also for their genes"

I would like to thank my parents Mr. Jagdishchandra N. Gohil and Mrs. Vanitaben J. Gohil for their love and support. The spirit of kindness and forgiveness that you deposited in me will be kept in my heart for all of my life.

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